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IJMS

International Journal of Medical Students

Year 2025 | Months Apr-Jun | Volume 13 | Issue 2

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- Ending Nuclear Weapons, Before They End Us.

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- Sculpting the Science: Teaching Anatomy of the Facial Muscles to Medical Students

  Evaluating a Low-Fidelity Anesthesiology Simulation for Airway Management and Cardiac Arrest in Medical Students

  Exploring Wonder in Medical School Admissions: Correlations with Admissions Decisions
- A Nationwide Evaluation of U.S. Geriatric Fellowship Websites: Assessing Program Information Availability
- Comparative Cross-Sectional Study on the Prevalence of Impostor Phenomenon in Medical and Non-Medical Students of Lahore City.
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- Diagnostic Performance of Western Blot for Congenital Toxoplasmosis: A Systematic Review and Meta-Analysis
- Effects of Blood Pressure Variability and Its Association With Dementia and Cognitive Impairment: A Systematic Review

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- Medical Student Perspective on Gender Disparity: Challenges, and Discrimination Faced by Women in Surgical Fields in Pakistan
- Integrating Health and Education: A Medical Student's Teaching Experience in a Government School

IJMS INTERNATIONAL JOURNAL *of* MEDICAL STUDENTS

International Journal of Medical Students
The International Journal of Medical Students (IJMS) is a peer-reviewed open-access journal (ISSN 2076-6327) created to share the scientific production and experiences of medical students and recently graduated physicians worldwide.

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Year 2025 - Volume 13 - Issue 2

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IJMS INTERNATIONAL JOURNAL of MEDICAL STUDENTS

The *International Journal of Medical Students* (IJMS) is an open-access, peer-reviewed scientific journal (ISSN 2076-6327) that publishes original research in all fields of medicine. The Journal was created in 2009 to share the scientific production and experiences of medical students (*i.e.*, MBBS students, MD students, DO students, MD/MSc students, MD/PhD students, etc.) and recently graduated physicians (<3 years into practice) from all over the world. Our objective is to be the primary diffusion platform for early-career scientists, using standards that follow the process of scientific publication.

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The *IJMS* also strive towards the training of a new generation of Editors and Peer-reviewers promoting different training strategies among our Editorial Team that includes the Web of Science Academy courses and the Committee on Publication Ethics (COPE) courses available to its members (*IJMS* is a member of COPE).

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IJMS INTERNATIONAL JOURNAL of MEDICAL STUDENTS

Editorial

Uniting for Peace Through Science: A Call to Action from the IJMS and the 4th WCMSR

Chloe Carrington,[1] Hana Kabil,[1] Moses Stefanus,[2] Elaine Liang,[3] Sohil Aryal,[4] Sahil Aryal,[4] Sajjad Ahmed Khan,[5] Mihnea-Alexandru Găman,[6] Francisco J. Bonilla-Escobar.[7]

Introduction

"Peace cannot be kept by force, it can only be achieved by understanding"- Albert Einstein

In a year marred by economic turmoil and conflict, health crises are exacerbated by lack of access to healthy food, water, basic sanitation, and essential health services. According to the World Health Organization's (WHO) Health Emergency Appeal of 2025, an estimated 305 million people are in acute need of emergency humanitarian medical care, many in crisis zones like the Democratic Republic of the Congo, Myanmar, Haiti, Gaza, Ukraine, Iran, Israel, Sudan, and Syria.[1] Beyond these emergencies, over 1.6 billion people live amid displacement and conflict–the highest number in recorded history. Conflicts and displacement fracture the foundation of community stability, leaving populations vulnerable to disease outbreaks and prolonged health crises due to collapsed health systems. Without peace, health cannot thrive whether it be in its physical, mental, social or economic aspect.

To face these global health challenges, the International Journal of Medical Students (IJMS) aims to unite medical students around the globe to serve as catalysts for peace through research. Scientific research is a universal language that transcends cultural and political barriers through the shared pursuit of advancing human health. From our smartphones that we use to view this editorial to medications that have been our allies in defeating illnesses, these innovations all can be traced directly or indirectly to scientific research and discovery. At IJMS, we advocate the transformative power of science for the advancement of humanity and improving lives. Our goal is twofold: to serve as a global platform for medical students to share and grow scientific knowledge, and to cultivate peace by recognizing our shared humanity across borders, cultures, and beliefs. Our mission is to empower the next generation of globally conscious physicians to dream boldly, tackle urgent medical challenges with creativity, and champion global solidarity through science and health.

However, realizing this mission requires confronting unique challenges that medical students face around the globe. Medical students living in conflict-affected regions face major disruptions to their daily lives including losing access to essential resources which severely restrict their movement. They face constraints on their ability to engage in focused study as survival takes precedence over academic pursuits like research. In Sudan, 59% of medical schools in conflict zones were attacked and looted resulting in a complete halt on curriculum delivery. Despite this, 60% of these attacked schools eventually restored their educational processes through online methods, relocating medical students to safer locations, or collaborating with other medical universities in Sudan and abroad.[2] Meanwhile in Syria, medical students face additional hurdles in contributing to research due to very limited Internet access, lack of funding for conducting their studies, lack of consistent and reliable patient data due to constant patient displacement, and limited training in research.[3] In Lebanon, the constant fear of being victimized, grief, and concerns about deportation forced many students to forfeit their classes.[4]

Conflict generates turmoil and displacement that jeopardizes diversity in the medical profession as the destruction of medical infrastructure cripples preventing students of vulnerable communities from completing rigorous medical training. Additionally, after the completion of training, many physicians flee to safer and economically stable countries leading to medical brain drain.[5] Patients tend to have higher trust in physicians who

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come from similar backgrounds, so decreased physician representation from these diverse communities compounds existing health inequities.[6,7]

Beyond conflict, the global COVID-19 pandemic significantly restricted opportunities for medical students worldwide to meaningfully contribute to medical research. Studies conducted in Turkey, Poland, France, Switzerland, Saudi Arabia, and China demonstrated a concerning trend of medical students suffering from worsening mental health largely due to isolation and economic instability during the pandemic.[8,9,10,11,12] This discouraged extracurricular pursuits like research and volunteering as hospitals were inundated with patients, in-person opportunities were halted, and basic needs were difficult to attain. The pandemic emphasized the pre-existing deficits prevalent in access to care within communities and across borders. Much of the deficits were alleviated by global collaboration among scientists, physicians, and public health specialists eager to resolve the outbreak. Development of effective vaccination measures and methods of prevention involving social distancing were implemented reducing patient cases.

A shift in focus towards the promotion of public health and medical advancement brought to light the decline of physician scientists and the lack of safe spaces to pursue research. Research done by medical students, physicians, and scientists with the help of international collaboration saves millions of lives, especially in times of disease outbreak. Scientific accomplishments and public health successes such as the eradication of Polio, creation of pacemakers, and the development of Malaria and COVID vaccines are all examples of international collaborative efforts to advance global health.

Similarly, medical students have contributed a fair share of their discoveries through research conducted early on in their careers despite the occasional lack of resources or security throughout history. Among them, Jay Mclean, a second-year medical student at Johns Hopkins University who first discovered heparin, a common medication for thrombosis while in his second year of medical school in 1916. Another medical student from France, Augusta Klumpke, would be the first to diagnose what is now dubbed Klumpke paralysis associated with Horner's syndrome near the brachial plexus in 1885.[13] These contributions to peace and medicine would not be possible without the space to enable creativity, collaboration, and research among budding clinicians on an international scale.

With few journals tailored to medical students, the IJMS was born out of the need to foster medical research literacy, encourage the development of presentation and peer review skills, and promote mutual understanding among the international medical student community. The journal provides a space to present research, engage with experts from various specialties, and publish innovative solutions to current medical issues. We train medical students to analyze, edit, and review research conducted by their fellow peers. We support medical students' early exposure to different cultures, perspectives, methodologies, and research aiding in the development of evidence-based medicine that is grounded in empathy and cultural humility. Medical students who engage with global peers and research early in their training are better equipped to think critically and approach patient care with nuance drawing on a broader understanding of both scientific evidence and human experience.[14]

Thus far, we have brought together medical students from over 30 countries and counting. In 2022, we hosted the first of our annual World Conference of Medical Student Research (WCMSR), a virtual conference inviting medical students from around the world to present and collaborate with each other in all aspects of medical research. The IJMS has enabled researchers since then to connect and exchange scientific ideas bringing unity and peace amid tumultuous times.[15,16] Our growing impact and engagement are illustrated in ***Table 1.***

Table 1. The Diversity and Impact of the IJMS Conference of World Student Research from 2022 to 2024.

Year	Number of Countries	Number of Authors Presenting	Website engagement on the day of conference	Youtube Views
2022	22	40	N/A	3,754
2023	17	38	604	2,196
2024	19	35	1,073	1,993

Legend: The journal and conference committee hopes to continue fostering a sense of unity and provide even more innovative ways for students to engage with their global peers.

We are excited to announce the upcoming fourth annual WCMSR to be held virtually on November 15th and 16th, from 8 AM to 5 PM EST. Viewers of the conference can expect two days of groundbreaking medical student research featuring global presenters and judges with diverse expertise. Abstract topics that are encouraged for submission include but are not limited to: clinical medicine and its subspecialties, surgery and its subspecialties, public health and epidemiology, basic science in medicine, medical ethics, medical education, and other interdisciplinary medical fields.

The first day of the conference will feature forty oral research presentations, followed by a second day dedicated to presenting digital posters. This is our first year expanding the WCMSR to include a second day for poster presentations reflecting our ongoing commitment to broadening research and presentation opportunities for global medical students.

Abstracts may be submitted to the following submission link: https://ijms.info/IJMS/submission/wizard until the deadline of September 30th, 11:59 PM EST. The results of the submissions will be released on October 20th.

The submission fee per abstract is based on the World Bank's country income classifications:

- Low-Income Countries (LICs): $10
- Lower-Middle-Income Countries (LMICs): $20
- Upper-Middle-Income Countries (UMICs): $30
- High-Income Countries (HICs): $40

IJMS Student Editors are eligible for a 50% fee reduction and fee waivers or reductions may be requested with proper justification.

Further information regarding the submission process and guidelines are available at the conference section of the IJMS webpage: https://ijms.info/IJMS/Conference/welcome. If authors have further questions, the conference team can be contacted by email at conference@ijms.info.

You can follow us as we prepare for the upcoming conference by connecting with us on our socials. We are on LinkedIn @International Journal of Medical Students (IJMS), X @TheIJMS, YouTube @IJMS, Instagram @Ijms.official, and Facebook @ijms.official.

Conclusion

In a world stricken with prolonged conflict, division, and health crises, medical students are uniquely positioned to lead transformative, peace-building efforts through global health research. The IJMS is dedicated to empowering medical students to become global agents of peace and future leaders of global health. By creating an international platform for medical students of all backgrounds to share, learn, and connect with fellow peers, the IJMS aims to bring about a more peaceful, compassionate, and healthy future.

Our fourth annual WCMSR reaffirms science as not only a tool for exploration, but also a powerful bridge between cultures and ideologies. As we will unpack during our conference, we aim to emphasize how research conducted by medical students and early career physicians advances global health equity, peace, and unity. This theme will be explored through presentations ranging from clinical medicine to medical educational research highlighting an urgent need for global collaboration and interventions. The core values of the IJMS to promote the research of medical students and early career physicians worldwide and empower their emerging voices will be ever present at this year's conference. We strive to continue fostering this sense of unity and explore innovative ways for students to engage with their global peers.

In This Issue

This issue showcases trailblazing medical student research in the domains of editorial, original research, short communications, reviews, case reports, and experience, many of which are the product of international collaboration. Within the editorials featured, we discuss several topics including how the power of medical student research can bring about peace and our commitment to support this aim through the announcement of our fourth annual World Conference of Medical Student Research. The original research in this issue covers many topics in various fields of medicine including using sculpting to advance medical education, the evaluation of U.S. geriatric fellowship websites for information availability, and the prevalence of imposter syndrome in medical students compared to non-medical students in a community in Pakistan. [17,18,19] Our short communications section addresses the impact of predisposing conditions on the outcomes of hypoglossal nerve stimulation for patients with obstructive sleep apnea. [20] One of the systemic reviews uncovers effects of blood pressure variability and the connection with dementia and cognitive impairment while one of the featured case reports poses how a positive rapid strep test could muddy the waters in the diagnosis of serum sickness-like reaction. [21,22] Finally, we conclude with two experience-based essays regarding gender-based disparities and challenges faced by female, Pakistani surgeons and a medical student's experience teaching at a government school. [23,24] The culmination of this diverse research highlights our call to action that the global medical student community unites, collaborates, and engages in scientific discovery to bring about peace.

References

1. World Health Organization. WHO health emergency appeal 2025: Snapshot. Available from: https://cdn.who.int/media/docs/default-source/documents/emergencies/2025-appeals/who-health-emergency-appeal-2025-snapshot.pdf. Cited Jun 26, 2025.
2. Mahgoub EAA, Khairy A, Osman S, Haga MB, Osman SHM, Hassan AMA, et al. War and education: the attacks on medical schools amidst ongoing armed conflict, Sudan 2023. Confl Health. 2024;18(23).
3. Saadi TA, Abbas F, Turk T, Alkhatib M, Hanafi I, Alahdab F. Medical research in war-torn Syria: medical students' perspective. Lancet. 2018;391(10139),2497-2498.
4. Zgheib NK, Sabra R. How a sudden war affected our medical school: reflections and lessons learned on adaptability and equity while preserving academic standards. BMC Med Educ. 2025 May 30;25(1).
5. Kollar E, Buyx A. Ethics and policy of medical brain drain: a review. Swiss Med Wkly. 2013;124:w13845.
6. Cao W, Fang Z, Hou G, Han M, Xu X, Dong J, et al. The psychological impact of the COVID-19 epidemic on college students in China. Psychiatry Res. 2020 Mar 20;287(112934).
7. Street R, O'Malley KJ, Cooper LA, Haidet P. Understanding concordance in patient-physician relationships: personal and ethnic dimensions of shared identity. The Annals of Fam Med. 2008;6(3):198-205.
8. Aslan I, Ochnik D, Çınar O. Exploring Perceived Stress among Students in Turkey during the COVID-19 Pandemic. Int J Environ Res Public Health. 2020 Dec 2;17(23):8961.
9. Rogowska AM, Kuśnierz C, Bokszczanin A. Examining Anxiety, Life Satisfaction, General Health, Stress and Coping Styles During COVID-19 Pandemic in Polish Sample of University Students. Psychol Res Behav Manag. 2020 Sep 28;13(1):797–811.

10. Husky MM, Kovess-Masfety V, Swendsen JD. Stress and anxiety among university students in France during Covid-19 mandatory confinement. Compr Psychiatry. 2020 Oct;102(152191):152191.
11. AlAteeq DA, Aljhani S, Altheyabi I, Majzoub S. Mental Health among Healthcare Providers during Coronavirus Disease (COVID-19) Outbreak in Saudi Arabia. J Infect Public Health. 2020 Sep;13(10).
12. Elmer T. Students under lockdown: Comparisons of students' social networks and mental health before and during the COVID-19 crisis in Switzerland. PLoS ONE. 2020 Jul 23;15(7):e0236337.
13. Dawadi P, Khadka S. Research and Medical Students: Some Notable Contributions Made in History. JNMA J Nepal Med Assoc. 2021;59(233):94-97.
14. Charnell AM, Dennis CA. Enhancing diversity in medical education: Bridging gaps and building inclusive curricula. Med Educ. 2025; 59(5): 460-462.
15. Mujanovic, A., Kipkorir, V., Mercalli, C., Dhali, A., Shah, P., Velandia, C, et al. The IJMS World Conference of Medical Student Research and an Overview of the IJMS Volume 10 Issue 2. Intl J Med Stud. 2025 June 30;13(2), 115–118.
16. Liblik K, Garcia-Espinosa P, Nahian A, Chatterjee S, Găman MA, Egan C, et al. Medical Student Research Journals: The International Journal of Medical Students (IJMS) Legacy. Intl J Med Stud. 2020;10(1):9-14.
17. Toni Chiappini, Janine C. Correia, Adam M. Taylor, Jan van der Merwe, Quenton Wessels. Sculpting the Science: Teaching Anatomy of the Facial Muscles to Medical Students. Int J Med Stud. 2025; 13(2):126-132.
18. Courtois E, Lahti J, Varkey T, Agarwal N. A Nationwide Evaluation of U.S. Geriatric Fellowship Websites: Assessing Program Information Availability. Int J Med Stud. 2022; 13(2):154-161.
19. Raashed L, Liaqat A, Nasir M, Tariq M, Omer Z. A Comparative Cross-Sectional Study on the Prevalence of Impostor Phenomenon in Medical and Non-Medical Students of Lahore City, Pakistan. Int J Med Stud. 2025; 13(2):162-168.
20. Adwer L, Nelson T, Carlson K, Samson K, Schmoker S, Thomas S. V, et al. Evaluating Hypoglossal Nerve Stimulation Outcomes in Obstructive Sleep Apnea: Impact of Predisposing Conditions in a Retrospective Cohort. Int J Med Stud. 2025; 13(2):182-186.
21. Pitliya A, Jaimalani A, Patel M, Parulkar A, Kumar M, Batra V, et al. Effects of Blood Pressure Variability and Its Association With Dementia and Cognitive Impairment: A Systematic Review. Int J Med Stud. 2025; 13(2):192-202.
22. Chatzigrigoriadis C, Eleftherakis G, Gyftopoulos K, Assimakopoulos S. F. To Test or Not to Test? How a Positive Rapid Strep Test May Perplex the Diagnosis of Serum Sickness-Like Reaction in a Case Report. Int J Med Stud. 2025; 13(2):208-212.
23. Akhtar A, Gillani M, Shariff Y, Inayat A, Bahrawar M. Challenges and Gender Disparities Faced by Women in Surgery in Pakistan. Int J Med Stud. 2025; 13(2):213-215.
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Editorial

Ending Nuclear Weapons, Before They End Us

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This May, the World Health Assembly (WHA) will vote on re-establishing a mandate for the World Health Organization (WHO) to address the health consequences of nuclear weapons and war.[1] Health professionals and their associations should urge their governments to support such a mandate and support the new UN comprehensive study on the effects of nuclear war.

The first atomic bomb exploded in the New Mexico desert 80 years ago, in July 1945. Three weeks later, two relatively small (by today's standards), tactical-size nuclear weapons unleashed a cataclysm of radioactive incineration on Hiroshima and Nagasaki. By the end of 1945, about 213,000 people were dead.2 Tens of thousands more have died from late effects of the bombings.

Last December, Nihon Hidankyo, a movement that brings together atomic bomb survivors, was awarded the Nobel Peace Prize for its "efforts to achieve a world free of nuclear weapons and for demonstrating through witness testimony that nuclear weapons must never be used again".[3] For the Norwegian Nobel Committee, the award validated the most fundamental human right: the right to live. The Committee warned that the menace of nuclear weapons is now more urgent than ever before. In the words of Committee Chair Jørgen Watne Frydnes, "it is naive to believe our civilisation can survive a world order in which global security depends on nuclear weapons. The world is not meant to be a prison in which we await collective annihilation."[4] He noted that our survival depended on keeping intact the "nuclear taboo" (which stigmatises the use of nuclear weapons as morally unacceptable).[5]

The nuclear taboo gains strength from recognition of compellingevidence of the catastrophic humanitarian consequences of nuclear war, its severe global climatic and famine consequences, and the impossibility of any effective humanitarian response. This evidence contributed significantly to ending the Cold War nuclear arms race.[6,7]

While the numbers of nuclear weapons are down to 12,331 now, from their 1986 peak of 70,300,[8] this is still equivalent to 146,605 Hiroshima bombs,[9] and does not mean humanity is any safer.[10] Even a fraction of the current arsenal could decimate the biosphere in a severe mass extinction event. The global climate disruption caused by the smoke pouring from cities ignited by just 2% of the current arsenal could result in over two billion people starving.[11]

A worldwide nuclear arms race is underway. Deployed nuclear weapons are increasing again, and China, India, North Korea, Pakistan, Russia and UK are all enlarging their arsenals. An estimated 2,100 nuclear warheads in France, Russia, UK, US and, for the first time, also in China, are on high alert, ready for launch within minutes.[8] With disarmament in reverse, extensive nuclear modernisations underway, multiple arms control treaties abrogated without replacement, no disarmament negotiations in evidence, nuclear-armed Russia and Israel engaged in active wars involving repeated nuclear threats, Russia and the US deploying nuclear weapons to additional states, and widespread use of cyberwarfare, the risk of nuclear war is widely assessed to be greater than ever. This year the Doomsday Clock was moved the closest to midnight since the Clock's founding in 1947.[10]

Led by Ireland and New Zealand, in late 2024, the United Nations General Assembly (UNGA) voted overwhelmingly to establish a 21-member independent scientific panel to undertake a new comprehensive study on the effects of nuclear war,[12] with its final report due in 2027. Noting that "removing the threat of a nuclear war is the most acute and urgent task of the present day", the panel has been tasked with examining the physical effects and societal consequences of a nuclear war on a local, regional and planetary scale. It will examine the climatic, environmental and radiological effects of nuclear war, and their impact on public health, global socioeconomic systems, agriculture and ecosystems.

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The resolution calls upon UN agencies, including WHO, to support the panel's work, including by "contributing expertise, commissioned studies, data and papers". All UN Member States are encouraged to provide relevant information, scientific data and analyses; facilitate and host panel meetings, including regional meetings; and make budgetary or in-kind contributions. Such an authoritative international assessment of evidence on the most acute existential threat to humankind and planetary health is long overdue. The last such report dates from 1989. It is shameful that France, UK and Russia opposed this resolution.[13]

In 1983 and 1987,[14] WHO convened an international committee of scientists and health experts to study the health effects of nuclear war. Its landmark, authoritative reports were influential and an excellent example of WHO fulfilling its constitutional mandate "to act as the directing and coordinating authority on international health work". In 1993, WHO produced an additional shorter report on the health and environmental effects of nuclear weapons, which included discussion of the production chain of nuclear weapons, including processing, testing and disposal.[15]

However, despite WHA having mandated WHO to report periodically on relevant developments, no further work was undertaken and in 2020 WHO's mandate on nuclear weapons and health lapsed.

The Marshall Islands, Samoa and Vanuatu, supported by seven co-sponsoring states and International Physicians for the Prevention of Nuclear War (IPPNW), are working to renew WHO's mandate. They are seeking wide support for a resolution on the health effects of nuclear weapons/war at this year's WHA in Geneva on 19-27 May.[1] WHO would then re-establish a programme of work on this most critical threat to health, and be able to lead strongly in providing the best health evidence to the UN panel.

Health professionals are well aware how crucial accurate and up-to-date evidence is to making good decisions. We and our organisations should support such a renewed mandate by urging our national WHA delegates to vote in support and commit the modest funds needed to re-establish WHO's work programme, especially now, as the organisation faces severe financial strain with the US decision to withdraw its membership.

Our joint editorial in 2023[16] on reducing the risks of nuclear war and the role of health professionals, published in over 150 health journals worldwide, urged three immediate steps by nuclear-armed states and their allies: adopt a “no first use” policy, take their nuclear weapons off hair-trigger alert, and pledge unequivocally that they will not use nuclear weapons in any current conflicts they are involved in. We also urged nuclear-armed states to work for a definitive end to the nuclear threat by urgently starting negotiations for a verifiable, timebound agreement to eliminate their nuclear arsenals, and called on all nations to join the Treaty on the Prohibition of Nuclear Weapons.[17]

It is an alarming failure of leadership that no progress has been made on these needed measures, nor on many other feasible steps away from the brink, acting on the obligation of all states to achieve nuclear disarmament. Nine states jeopardise all humanity and the biosphere by claiming an exclusive right to wield the most destructive and inhumane weapons ever created. The world desperately needs the leaders of these states to freeze their arsenals, end the modernisation and development of new, more dangerous nuclear weapons, and ensure that new technology such as artificial intelligence can never trigger the launch of nuclear weapons.

The UN scientific panel and a renewed mandate for WHO’s work in this area can provide vital authoritative and up-to-date evidence for health and public education, evidence-based advocacy and policies, and the mobilised public concern needed to trigger decisive political leadership. This is a core health imperative for all of us.

References

1. World Health Organization. Effects of nuclear weapons and war on health and health services. Available from: https://apps.who.int/gb/ebwha/pdf_files/EB156/B156_CONF10-en.pdf. Last updated Feb 5, 2025; cited Apr 3, 2025.
2. Tomonaga M. The atomic bombings of Hiroshima and Nagasaki: a summary of the human consequences, 1945–2018, and lessons for Homo sapiens to end the nuclear weapon age. J Peace Nucl Disarm. 2019;2(2):491–517.
3. NobelPrize.org. The Nobel Peace Prize 2024. Available from: https://www.nobelprize.org/prizes/peace/2024/summary/. Last updated 2024; cited Feb 25, 2025.
4. NobelPrize.org. Award ceremony speech. Nobel Prize Outreach; Available from: https://www.nobelprize.org/prizes/peace/2024/ceremony-speech/. Cited Feb 25, 2025.
5. Tannenwald N. The Nuclear Taboo: The United States and the Normative Basis of Nuclear Non-Use. Int Organ. 1999;53(3):433–68.
6. Robock A, Xia L, Harrison CS, Coupe J, Toon OB, Bardeen C. Opinion: How fear of nuclear winter has helped save the world, so far. Atmos Chem Phys. 2023;23(12):6691–6701.
7. Helfand I, Haines A, Ruff T, Kristensen H, Lewis P, Mian Z. The growing threat of nuclear war and the role of the health community. World Med J. 2016;62(3):86–94.
8. Kristensen H, Korda M, Johns E, Knight M, Kohn K. Status of world nuclear forces. Federation of American Scientists. Available from: https://fas.org/initiative/status-world-nuclear-forces/. Cited Mar 18, 2025.
9. Norwegian People's Aid. Nuclear weapons ban monitor 2024. February 2025. Available from: https://banmonitor.org/. Cited Mar 25, 2025.
10. Science and Security Board. Closer than ever: It is now 89 seconds to midnight. 2025 Doomsday Clock Statement. Bulletin of the Atomic Scientists; 2025 Jan 28. Available from: https://thebulletin.org/doomsday-clock/2025-statement/. Cited Mar 4, 2025.
11. Xia L, Robock A, Scherrer K, et al. Global food insecurity and famine from reduced crop, marine fishery and livestock production due to climate disruption from nuclear war soot injection. Nat Food 2022; 3: 586–96.

12. United Nations General Assembly. Nuclear war and scientific research. A/C.1/79/L.39. 2024 Oct 15. Available from: https://reachingcriticalwill.org/images/documents/Disarmament-fora/1com/1com24/resolutions/L39-.pdf. Cited Mar 4, 2025.
13. https://reachingcriticalwill.org/images/documents/Disarmament-fora/1com/1com24/votes-ga/408DRXVII.pdf. Cited Mar 4, 2025.
14. World Health Organization. Effects of nuclear war on health and health services, 2nd ed. Geneva: WHO; 1987. Available from: https://iris.who.int/handle/10665/39199. Cited Mar 4, 2025.
15. World Health Organization. Health and environmental effects of nuclear weapons. WHA46/30. 1993 Apr 26. Available from: https://iris.who.int/bitstream/handle/10665/175987/WHA46_30_eng.pdf?isAllowed=y&sequence=1. Cited Mar 4, 2025.
16. Abbasi K, Ali P, Barbour V, et al. Reducing the risks of nuclear war. BMJ. 2023; 382:1682
17. United Nations. Treaty on the Prohibition of Nuclear Weapons. 2017. Available from: https://www.icanw.org/tpnw_full_text. Cited Mar 9, 2025.

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Original Article

Sculpting the Science: Teaching Anatomy of the Facial Muscles to Medical Students

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Abstract

Background: Clay-modeling in anatomy education is an engaging activity that complements cadaveric dissections. The post-COVID-19 cadaver shortage further necessitates alternative practical modalities. **Methods:** A student-centred clay-modeling practical activity was developed towards the study of the muscles of facial expression due to a shortage of cadaveric material. Student feedback in the form of a questionnaire with closed- and open-ended questions. **Results:** Thematic analysis was manually performed to generate the primary and secondary themes associated with the open-ended questions. Four themes were generated: fun, collaboration, active learning, and bittersweet. Closed-ended questions revealed that respondents found the activity motivational and enjoyable. Feeling around the disassembly of students' anatomical models was of particular interest. Some students expressed emotions of sadness and others stated that they felt devastated. **Conclusion:** The outcome of this study presents the opportunity for further work to link discussions around the humanistic considerations of anatomy and the study of human remains, utilizing clay modelling as a crucial resource.

Introduction

The muscles of facial expression are particularly difficult to dissect, as well as time-consuming to study in formalin embalmed cadavers.[1] This holds particularly true in instances where cadaveric material presents with decreased skeletal muscle mass, central adiposity,[2] and facial fat atrophy.[3] Furthermore, the global shortage of cadaveric material due to the COVID-19 pandemic necessitates alternative approaches to the delivery of anatomy as a subject.

One such alternative is clay-modeling.[4] Studies have shown that teaching anatomy through art activities increases the observational skills and memory of students as well as encourages engagement in the learning process.[5] An 8-week first-year course of 'Art in Medicine' has been implemented at Brighton and Sussex Medical School and has proven successful according to student feedback.[5] Clay models are especially used as an alternative to classical cadaveric dissections or as an adjunct[2]. Globally, there are institutions without access to cadaveric material and animal specimens, are used for routine dissections and surgical training.[6] Furthermore, dissection is not a uniform learning experience and complementary innovative learning methods, such as clay modeling, should be incorporated.[7]

The use of clay-modeling helps students to broaden their horizons past the traditional methods of dissecting and written tests. Studies have shown that the use of clay-modeling helps enhance the students' self-confidence, participation, and memory of anatomical musculature.[8] The use of clay-modeling has also shown an increase in learners' ability to understand spatial relationships as well as understand the relationships and transition between 3D to 2D structures, such as converting clay models into cross-sectional anatomical images.[9,10] Furthermore, Correia et al,[4] found that students perceived that collaborative learning in clay-modeling enhanced their skills, such as problem-solving, communication and creative thinking. Another alternative to the traditional methods is the use of laboratory animals which was demonstrated in 2009. In this study, Motoike et al, employed 181 students and demonstrated that clay-modeling is more effective compared to cat dissections for the delivery of anatomy.[11] It is important to note that using animal models within the current context is an alternative to human cadaveric material.

The purpose of anatomical clay-modeling is to mimic anatomical visualization in a similar way to what would be seen during dissections and to gain a three-dimensional understanding of the human body. Clay-based modeling is a unique learning tool and the experience gained from physically constructing, rather than destructing an anatomical model is invaluable.[4] Kooloos and colleagues found that students performed better in anatomical knowledge assessment when they had an opportunity to build clay models compared to those who only watched a video tutorial on the same topic.[2] The rationale for students' improved

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performance relates to their increased concentration, engagement, and the novel aspect of cognitive stimulation.[2] Furthermore, Oh and colleagues noted that the majority of students who participated in clay-modeling as a supplement to conventional study modes reported a positive experience. Students' positive experiences were related to their improved understanding of the three-dimensional structure, improved interest and active participation.[9]

The current study presents a cost-effective and participatory innovation to the practical learning of the muscles of facial expression through clay-modeling. Furthermore, the study also explores the value of clay-modeling as a potential alternative to cadaveric dissection to facilitate students' learning of the muscles of facial expression.

Methods

A cross-sectional study design was followed involving second-year medical students at the University of Namibia. The intervention was presented as part of students' practical laboratory session on the muscles of facial expression and was necessitated by a shortage of cadaveric material due to the COVID-19 pandemic. White concrete skulls were made after obtaining silicone cake molds ***(Figure. 1).*** The silicone molds were first secured in wet sand, serving as a master mold and to prevent distortion, before the cement slurry was added ***(Figure. 1).*** Once cured, the casts were removed and sprayed with white paint ***(Figure. 1).***

The practical sessions followed theoretical lectures on the embryology of the face and muscles of facial expression. During the practical session, groups of students were provided with one concrete skull cast between them, a practical worksheet, and resources ***(Figure. 1).*** The resources consisted of an anatomy atlas, and a laminated worksheet with the respective muscles, their functions, and origins and insertions. Artistic sculpting clay (circa 400g) was provided for each group of four students. A total of nine groups (73 students in total) participated in the practical sessions. The first cohort of 36 students was tasked with a practical laboratory session to model the muscles of facial expression ***(Table 1).*** This activity was duplicated for the second cohort on the same day and totaled 37 students (one group had 5 students). An outline of each session and the duration of each phase is provided in ***Table 1*** and each session lasted one hour and 50 minutes. This afforded all staff 10 minutes to prepare for the next session. Lecturing staff served as facilitators during each practical session and rotated among the groups of students

Student feedback in the form of a questionnaire with closed- and open-ended questions was used. The questionnaire used was developed to promote critical reflection ***(Table 2).*** Only volunteering participants, after recruiting and providing written consent completed the questionnaire. Ethical approval for the data collection was obtained through the Namibian Ministry of Health and Social Services (Ref#TC2022). Data associated with the closed-ended questions were analyzed for measures of central tendency. Next, responses to the open-ended questions were subjected to thematic analysis. An inductive approach for latent themes was followed.[12] Thematic analysis (TA) was manually performed to generate the primary and secondary themes associated with the open-ended questions.[13] The generation of

Figure 1. Practical Clay-Modeling Setup.

Legend: A: Casting cement slurry into a silicone cake mold. B: The cured concrete skull after being sprayed with white paint. C: Students working in groups during the practical laboratory session. D: Work-in-progress demonstrating the muscles of facial expression and muscle fascicle direction.

Table 1. An Outline of the Practical Session and Expected Outcomes.

Phase (duration)	Activity
Phase 1 (10 minutes)	Familiarization with the practical task and planning.
Phase 2 (70 minutes)	Execution: *Use the resources provided to model the muscles of facial expression.* *Model the branches of the facial nerve.* *In a table, indicate which specific branch of CN VII innervates which muscles.*
Phase 3 (10 minutes)	Peer assessment and feedback (informal)
Phase 4 (10 minutes)	Disassembly and cleaning of the workstations.

Table 1. Survey Questions Assessing Medical Students' Perceptions of the Facial-Muscle Clay-Modeling Activity.

Do you feel that the activity allowed you to perform the tasks independently?
Did you find the activity motivational? In what way? If not, please explain.
Did you find the activity enjoyable? In what way? If not, please explain.
Were the resources provided adequate? If so, in what way? If not, please explain.
Did you find the activity was easy to follow independently? Please explain.
Would you recommend the activity? Why or why not?
Did you find this to be an effective learning experience? In what way? If not, please explain.
Did you learn something new?
Would you like to do something similar when studying anatomy?
Do you think the students will benefit from modeling in clay? In what way? If not, please explain.
What could change? What would you do differently next time?
What were your thoughts and experiences when you had to dismantle the model? i.e. remove the clay?

primary and secondary themes followed a similar approach to the work of Radzi et al.[14] TA was used to identify and analyze patterns of meaning within the questionnaire responses by identifying latent themes and to understand the attitudes and perceptions of first-year medical students' first exposure to a cadaver.[12,13,15] A reflexive approach was adopted where the researchers were immersed in data familiarization, coding, and theme development, rather than coding reliability and using a codebook approach.[13,16]

Results

A total of 21 students completed the questionnaire, yielding a response rate of 27.8%, and all provided written informed consent. The majority of participants (21/22; 95%) reported being able to perform the tasks independently, while one respondent (5%) indicated limited hands-on participation due to working in a group setting. All participants (22/22; 100%) found the activity to be both motivational and enjoyable. Most respondents (21/22; 95%) considered the available resources sufficient; one participant noted that the paper-based diagrams were less helpful without access to accompanying textbooks. Similarly, 21 participants (95%) stated they had learned something new through the activity, while one participant, although not identifying new knowledge, acknowledged gaining appreciation for the anatomical complexity of facial expression. All respondents (22/22) expressed positive feedback overall, with several suggesting the extension of this activity format to other anatomical regions, such as the muscles of the hand.

The themes generated from the students' responses are shown in ***Figure 2*** and four themes were generated: Fun, Collaboration, Active Learning, and Bittersweet.

Theme 1: Fun

Respondents overwhelmingly commented that the practical session with clay modeling was enjoyable. Students also noted that they were actively playing while learning the muscles of facial expression.

"It showed that learning could be fun instead of stressful"

"It was motivational as it gave me the chance to learn as well as have fun at the same time"

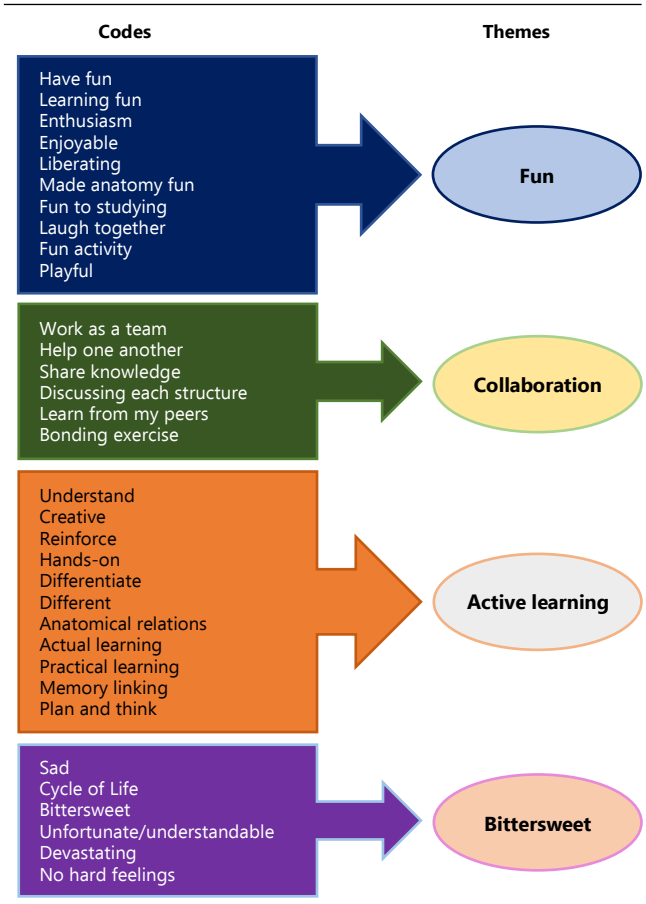
"It triggered my creativity and enthusiasm"

"We had the opportunity to link having fun to studying in a way"

A participant also mentioned that they wanted to spend more time on the activity.

Participants self-declared that the clay-modeling session inspired their creative side and felt that they were actively playing and having fun while learning the muscles of the face. Clay-modeling permitted creativity and allowed students to put theory into practice and form linkages.

Figure 2. The Four Themes that were Generated were Based on Thematic Analysis of the Open-Ended Survey Questions.



Theme 2: Collaboration

Collaborative learning experiences, in the form of practical teams, helped encourage communities of practice in learning and foster deeper learning approaches.

"I had the opportunity to learn from my peers"

"It allowed us to work as a team, share knowledge, and laugh together"

"The teamwork, having to plan and think creatively was very fun"

Respondents perceived the group work as being valuable in their learning experience. The participants recognized that such strategies increased their motivation and enhanced their engagement while learning anatomy.

Theme 3: Active Learning

The students perceived that the active and engaging learning strategy of clay-modeling can be used as a constructive learning tool in anatomy.

"It was a new experience learning about the muscles from a superficial to deep layer"

"It helped me differentiate between the different facial muscles from deep to superficial"

"It was different from just looking at 2D pictures in a textbook"

"It helps a student to think about the anatomy of the muscles (in relation to each other)"

Some participants commented on the fact that creating the anatomical clay models reinforced the learning of that structure. Students can physically manipulate and mold the clay to create a more accurate representation, which can help them remember the structure better.

"By modeling the muscles and learning their anatomical relations to one another, it makes it easier to retain the knowledge"

"Now there will also be a memory linking the information which will make it memorable"

The clay models also allowed the students to express their creativity and artistic abilities while learning about anatomy.

"Learn the muscles of the face in a more creative manner"

"Express my creativity and gave me a platform to freely learn without any external pressure"

Participants commented on the fact that creating the models allowed them to learn through hands-on experience. This can be particularly helpful for students who are tactile learners and prefer to learn by doing.

"it was a hands-on exercise and that makes it hard to forget"

"(...) practical way of learning facial muscles and not just memorizing them from an atlas"

"I find I prefer hands-on learning more than just being told about it"

In a learning system of parrot-fashion memorization, muscle actions, origin and insertion of facial muscles have little context and, thus, are less relevant to students and become difficult to learn and remember. Rather, interacting in a hands-on manner with clay-based modeling can help students better visualize the facial muscle.

Theme 4: Bittersweet

The students had conflicting emotions regarding the building and the breaking down of the clay models after the session was completed.

"It was a bittersweet moment"

"It felt emotional because we put in a lot of effort"

"I was sad because my group and I worked hard on it. We even named our clay model"

A participant even stated that the clay-modeling process of building and breaking down reminded them of the cycle of life and death.

Discussion

Clay-based modeling is the construction of anatomical models that emulate the three-dimensional structure of an organ or system.[9] Through this hands-on, interactive approach, the building of clay models allows for an improved understanding of spatial relationships between structures and the precise location of structures. This form of anatomy teaching is creative and fun, allowing students to actively enhance their long-term retention of anatomical knowledge in an enjoyable, positive environment.

Student involvement was increased during this study and students' grasp of the anatomical relationships in the human body was improved by using clay-modeling, an active, tactile learning tool.[4] Research has shown that, for effective learning, students must actively participate in the learning process.[17] Furthermore, in this study, the active learning process was employed when the students were required to build and manipulate the models.[18] However, research suggests that clay-modeling does not improve anatomical knowledge compared to students who only employed video material.[2] The most important pedagogical advantage of clay-modeling, as noted by Kooloos and colleagues, is active involvement.[2]

The building of anatomical clay models additionally adds a tactile approach to learning, which offers an alternative approach to the comprehension and retention of information. Furthermore, respondents from the current study also commented that they would prefer different colors of clay. According to Akle et al, adding color-coding structures may also supplement the learning effect as there have been correlations between color recognition and the recall of information.[19] A possible solution within the current context would be to add a color pigment to the clay. Furthermore, on a technical note, we found that artistic clay is excellent compared to plasticine in that it is easy to clean from the casts and workstations. This in turn optimizes the time students can spend learning and reduces the time between sessions spent by staff on recalibrating stations, enabling them to focus on other aspects of student learning, such as questions.

Other, more pragmatic factors make clay models a useful educational tool. For example, clay specimens are convenient to store, odorless, easy to handle and relatively cost-effective.[20] Clay modeling allows students to construct models rather than spend hours dissecting and potentially damaging important structures, which is of benefit in an educational climate that is seeing reduced contact hours for anatomy education.[21,22] Furthermore, clay-modeling allows for the re-use of both the clay and skull

template. The proposed concrete alternative as presented in the current study serves as a cost-effective modality in resource-constrained settings. This alternative has the potential to permit students to model the muscles of facial expressions remotely and thus serve as an extracurricular activity. Therefore, to a degree, clay models make an excellent complement to traditional dissection and a potential alternative where cadaveric material is not feasible due to scarcity or affordability issues. However, Curlewis and colleagues noted that clay-modeling cannot serve as a complete substitute for human tissue as it lacks detailed anatomy.[18]

Other potential advantages, such as students being able to work on the anatomical variability that occurs with muscle and nerve courses. The dissection room provides exposure to some of these normal variants, but it is not always present in each donor cohort and therefore clay modeling may provide a useful adjunct to students looking to convert the 2D presentation they see in textbooks into 3D resources. The challenges of observing nerves such as the facial nerve, or chorda tympani in the dissecting room are well documented and clay-modeling may present a resource that enables students to visualize the course and relationship with neighboring structures without having to dissect for prolonged periods in the hope that they can observe all the necessary structures and their relationships.[23] The importance and value of clay in increasing student performance on peripheral nervous structures has been shown by DeHoff and colleagues in undergraduate anatomy class.[17] One possible drawback within the current study relates to the anatomical accuracy of the casts that were used. However, staff ensured that the necessary anatomical landmarks were present, and all students found them identifiable enough to permit completion of the task at hand, as evidenced by student feedback, with no reference to issues relating to origin or insertion points.

This study shows the value of clay-modeling for medical students in their learning of anatomy. It has also recently been shown that clay-modeling is a valuable tool to postgraduate students as a revision resource to increase their confidence in pelvic anatomy knowledge amongst obstetrics and gynecology residents, demonstrating that clay-modeling has longevity in learning and revision across the healthcare spectrum.[20]

Our findings also highlight the importance of collaboration among students. The importance of collaborative learning in anatomy is well-documented and includes students' ability to learn communication and leadership skills.[24] From our findings, we noticed that students were forced to plan in a group during the planning phase of the activity, grappling with translating theoretical knowledge into practice. They had to think of the layering of the muscles (superficial to deep) and the associated origin and insertion of each. The alignment and portrayal of muscle fascicles was another element students had to compete with and portray in their clay model. The peer assessment and feedback phase provided a further opportunity for collaboration. The sharing of knowledge, though informal, is encouraged and is advantageous even if not formally included in the learning outcomes.[25] In hindsight, a formal peer-assessment checklist could be used to further foster collaborative learning and could include specifics such as muscle fascicle orientation, anatomical accuracy for the origin and insertion, and muscle layering.

Finally, and certainly an interesting finding, students' experiences associated with the disassembly of the models revealed feelings of loss and grief among some respondents. Dueñas and colleagues highlight the lack of research on coping strategies employed by students and staff when faced with stressors within an anatomy practical laboratory.[26] Our findings reflect varied responses associated with the activity of disassembly of students' clay models. Gross anatomy laboratories elicit emotional responses, and much understanding has been gained around students' first experience with death.[27–29] It should be noted that students within the current study have had prior exposure to cadavers and cadaveric material. However, the varied emotional responses ranging from "sad" to "devastating" further support the need to bolster humanistic considerations in anatomy education. The emotional responses from our respondents were associated with clay-modeling and not linked to the cadaveric material. These responses highlight the need to be actively cognizant of students' emotional well-being at all times. The incorporation of reflective writing is one possible approach to better understanding students' emotional responses and personal experiences within the gross anatomy laboratory.[30] An interdisciplinary and formal approach to dealing with death is not new and exists within many anatomy programmes.[31,32]

Critical reflection by the participants presents the opportunity for further work to link discussions around the humanistic considerations of anatomy and the study of human remains, such as "ownership", morality, ethics, loss, and grief. Clay-modeling presents a resource which can allow for the development of multiple skills as well as knowledge acquisition in the presence and absence of traditional cadaveric dissection.

Summary – Accelerating Translation

Main Problem to Solve:

Traditional methods of studying facial muscles, such as cadaveric dissections, are time-consuming, resource-intensive, and affected by global shortages of cadaveric material due to the COVID-19 pandemic. Finding effective alternatives to teach anatomy, particularly the intricate muscles of facial expression, is crucial.

Aim of Study:

This study aimed to assess the effectiveness and student perceptions of using clay modeling as an alternative method for learning the muscles of facial expression among medical students. The study also sought to explore the emotional responses associated with this learning approach.

Methodology:

A cross-sectional study design was employed involving second-year medical students at the University of Namibia. Due to a shortage of cadaveric material, white concrete skull casts were made using silicone molds. Practical sessions were conducted where students, working in groups, modeled the muscles of facial expression using artistic sculpting clay. A questionnaire with closed- and open-ended questions was used to gather feedback from participants.

Results:

Twenty-one students participated in the study, with overwhelmingly

positive feedback. Participants found the activity motivational, enjoyable, and conducive to learning. The themes from the responses included enjoyment, collaboration, active learning, and bittersweet feelings associated with disassembling the clay models.

Conclusion:
Clay modeling emerged as a cost-effective, enjoyable, and effective method for teaching facial muscle anatomy. It fostered collaboration, active learning, and creativity among students. The emotional responses observed during the disassembly phase highlight the need for considering students' emotional well-being in anatomy education. Clay modeling shows promise as a valuable complement or alternative to traditional cadaveric dissections, particularly in resource-constrained settings or during times of cadaveric material shortages.

References

1. Cotofana S, Lachman N. Anatomy of the facial fat compartments and their relevance in aesthetic surgery. J Dtsch Dermatol Ges. 2019;17(4):399–413.
2. Kooloos JGM, Schepens-Franke AN, Bergman EM, Donders RART, Vorstenbosch MATM. Anatomical knowledge gain through a clay-modeling exercise compared to live and video observations. Anat Sci Educ. 2014;7(6):420–429.
3. Talmor M, Hoffman LA, LaTrenta GS. Facial atrophy in HIV-related fat redistribution syndrome: anatomic evaluation and surgical reconstruction. Ann Plast Surg. 2002;49(1):11–18.
4. Correia JC, Baatjes KJ, Meyer I. Student-perceived value on the use of clay modelling in undergraduate clinical anatomy. Adv Exp Med Biol. 2022;1388:153–170.
5. Bell LTO, Evans DJR. Art, anatomy, and medicine: is there a place for art in medical education? Anat Sci Educ. 2014;7(5):370–378.
6. Aboud E, Suarez CE, Al-Mefty O, Yasargil MG. New alternative to animal models for surgical training. Altern Lab Anim. 2004;32 Suppl 1B:501–507.
7. Ghosh SK. Cadaveric dissection as an educational tool for anatomical sciences in the 21st century. Anat Sci Educ. 2017;10(3):286–299.
8. Nicholson LL, Reed D, Chan C. An interactive, multi-modal anatomy workshop improves academic performance in the health sciences: a cohort study. BMC Med Educ. 2016;16(1):7.
9. Oh C-S, Kim J-Y, Choe YH. Learning of cross-sectional anatomy using clay models. Anat Sci Educ. 2009;2(3):156–159.
10. Remmele M, Martens A. Using stereoscopic visualizations as templates to construct a spatial hands-on representation—is there a novelty effect? Adv Physiol Educ. 2019;43(1):93–98.
11. Motoike HK, O'Kane RL, Lenchner E, Haspel C. Clay modeling as a method to learn human muscles: a community college study. Anat Sci Educ. 2009;2(1):19–23.
12. Burnard P, Gill P, Stewart K, Treasure E, Chadwick B. Analysing and presenting qualitative data. Br Dent J. 2008;204(9):429–432.
13. Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol. 2006;3(2):77–101.
14. Radzi S, Chandrasekaran R, Peh ZK, Rajalingam P, Yee Yeong W, Mogali SR, et al. Students' learning experiences of three-dimensional printed models and plastinated specimens: a qualitative analysis. BMC Med Educ. 2022;22(1):1–10.
15. Joffe, H. Thematic Analysis. In Qualitative Research Methods in Mental Health and Psychotherapy: A Guide for Students and Practitioners; Harper, D., Thompson, A.R., Eds.; Wiley-Blackwell: Oxford, UK, 2011; pp. 209–223.
16. Braun V, Clarke V. Reflecting on reflexive thematic analysis. Qual Res Sport Exerc Health. 2019;11(4):589–597.
17. DeHoff ME, Clark KL, Meganathan K. Learning outcomes and student-perceived value of clay modeling and cat dissection in undergraduate human anatomy and physiology. Adv Physiol Educ. 2011;35(1):68–75.
18. Curlewis K, Leung B, Perera M, Bazira PJ, Sanders KA. Clay-based modeling in the anatomist's toolkit: a systematic review. Anat Sci Educ. 2021;14(3):252–262.
19. Akle V, Peña-Silva RA, Valencia DM, Rincón-Perez CW. Validation of clay modeling as a learning tool for the periventricular structures of the human brain. Anat Sci Educ. 2018;11(2):137–145.
20. Chong W, Tran N, Bui A. Effectiveness of a clay pelvic model: a hands-on approach to understanding pelvic floor anatomy. Obstet Gynecol. 2022;140(1):94–98.
21. Drake RL, McBride JM, Lachman N, Pawlina W. Medical education in the anatomical sciences: the winds of change continue to blow. Anat Sci Educ. 2009;2(6):253–259.
22. Ahmed K, Rowland S, Patel VM, Ashrafian H, Davies DC, Darzi A, et al. Specialist anatomy: is the structure of teaching adequate? Surgeon. 2011;9(6):312–317.
23. Liu L, Arnold R, Robinson M. Dissection and exposure of the whole course of deep nerves in human head specimens after decalcification. Int J Otolaryngol. 2012;2012:418650.
24. Pawlina W. Professionalism and anatomy: how do these two terms define our role? Clin Anat. 2006;19(4):391–392.
25. Laakkonen J, Muukkonen H. Fostering students' collaborative learning competencies and professional conduct in the context of two gross anatomy courses in veterinary medicine. Anat Sci Educ. 2019;12(2):154–163.
26. Dueñas AN, Kirkness K, Finn GM. Uncovering hidden curricula: use of dark humor in anatomy labs and its implications for basic sciences education. Med Sci Educ. 2020;30(2):345–354.
27. Dinsmore CE, Daugherty S, Zeitz HJ. Student responses to the gross anatomy laboratory in a medical curriculum. Clin Anat. 2001;14(4):231–236.
28. Talarico EFA. A change in paradigm: giving back identity to donors in the anatomy laboratory. Clin Anat. 2013;26(2):161–172.
29. Williams AD, Greenwald EE, Soricelli RL, DePace DM. Medical students' reactions to anatomic dissection and the phenomenon of cadaver naming. Anat Sci Educ. 2014;7(3):169–180.
30. Ferguson KJ, Iverson W, Pizzimenti M. Constructing stories of past lives: cadaver as first patient: "Clinical summary of dissection" writing assignment for medical students. Perm J. 2008;12(2):89–92.
31. Tuohimaa P, Tamminen T, Fabrin V. Is it appropriate to speak of death during a dissection course? Teach Learn Med. 1993;5(3):169–173.
32. Rizzolo LJ. Human dissection: an approach to interweaving the traditional and humanistic goals of medical education. Anat Rec. 2002;269(3):242–248.

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Author Contributions

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Original Article

Evaluating a Low-Fidelity Anesthesiology Simulation for Airway Management and Cardiac Arrest in Medical Students

Kendra L. Walsh,[1] Christopher Samuel,[2] Shyamal Asher.[3]

Abstract

Background: Low-fidelity simulations are cost-effective, accessible tools for medical education. This study describes the development and initial implementation of a low-cost, easy-to-run simulation, assesses participant performance in airway management and ACLS, and reviews qualitative feedback to refine future iterations. **Methods:** This single-center, prospective observational study piloted a low-fidelity simulation on difficult airway management and intraoperative cardiac arrest for fourth-year medical students in a three-hour workshop. Participant demographics, simulation performance, and post-simulation feedback were analyzed using proportions and Fisher's exact test. **Results:** A total of eleven medical students participated in the simulation, with most participants scoring in the higher range. No statistically significant findings using the Fisher's exact test were detected between student performance and past experiences in related fields of anesthesiology, critical care medicine, or emergency medicine. Learners had the most difficulty with adherence to ACLS pathways when managing a simulated cardiac arrest, scoring on average 4.5 ± 1.6 points out of 8. Six of the eleven participants completed the post-simulation survey (55% response rate), primarily giving positive feedback, with all responses indicating agreement that low-fidelity simulations are beneficial learning opportunities for medical students, citing them as helpful to review knowledge. **Conclusion:** Low-fidelity simulations provide an underutilized yet effective means for skill development in medical education. ACLS performance gaps may stem from limited practice or situational stress. This simulation requires minimal resources and personnel, making it easily adoptable. Future improvements include a larger sample size, clearer questions, and preparatory materials.

Introduction

The use of clinical simulations to hone routine skills in a safe environment and practice for rare events is ubiquitous across many medical specialties, especially anesthesiology.[1] A large body of literature exists on simulations in anesthesiology, with most of these activities indicated for resident training.[2-6] Anesthesiologists regularly encounter high-risk scenarios that can be rehearsed using simulation to minimize the potential for patient harm.[7] Within teaching hospitals, it is feasible to consider extending the participants of these simulations to medical students entering anesthesiology and related fields of critical care medicine and emergency medicine.[8] Several recent anesthesiology simulations that include medical students have stressed a need for continued research and development of these educational activities for this audience.[9-13]

According to a 2014 survey by the Association of American Medical Colleges (AAMC), nearly all medical schools accredited by the Liaison Committee on Medical Education (LCME) reported having a physical simulation center.[14] Yet, although the infrastructure is present, the use of simulation in medical school is limited by real-world factors such as time, faculty or staff availability for running simulations, and operating costs.[15,16] Technologically sophisticated, expensive, high-fidelity simulations are often touted as the best instructive experience, but Massoth et al. found that medical students randomized to one such high-fidelity simulation did not outperform their peers assigned to a low-fidelity simulation focusing on Advanced Cardiovascular Life Support (ACLS) and were even noted to overestimate their abilities.[17] In other literature, a low-fidelity "CardioSim" that employed role play between third- and fourth-year medical students noted that all participants had improved confidence in the management of myocardial infarctions after the activity.[18] Similarly, 75% of fourth-year medical students who took a two-week residency preparation course voted "agree" or "strongly agree" to the value of a virtual, low-fidelity critical care simulator; likewise, nearly 80% felt the activity helped apply and reinforce textbook knowledge.[19] Thus, low-fidelity simulations could be considered nearly equivalent and may be more accessible to institutions that either lack adequate simulation spaces or are located in resource-scarce settings.[20]

Based on this review of the literature, it is hypothesized that low-fidelity simulations are an effective tool for teaching critical

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concepts in anesthesiology to medical students. The objective of this project is to describe the development and initial use of a low-fidelity, minimal-cost, easy-to-run simulation that was designed to prepare graduating fourth-year medical students for the start of internship. Specific goals of this preliminary trial were to analyze participant performance on key principles of airway management and ACLS as well as review qualitative feedback that will help guide future iterations of this educational tool.

Methods

This single center, prospective observational study was performed at The Warren Alpert Medical School of Brown University with fourth-year medical students who voluntarily enrolled in the clinical elective "IPC 4318: Common Topics in Anesthesia," a one-time, three-hour workshop held on February 7, 2024 within the institution's "internship preparation courses." Subjects covered include advanced airway management techniques such as fiberoptic intubation; intravenous (IV) and central line access techniques; basic point-of-care ultrasound (POCUS) examinations including cardiac, lung and gastric; as well as common regional anesthesia nerve blocks. The low-fidelity simulation was included as one of several stations that students rotated through.

Simulation Development

The simulation was developed using references from The Open Critical Care Project with a focus on difficult airway management and intraoperative cardiac arrest resuscitation tailored to the expected knowledge of a medical student.[21] These topics were selected because of their applicability to general anesthesiology practice as well as their alignment with Accreditation Council for Graduate Medical Education (ACGME) minimal residency practice requirements. Primary learning objectives for the simulation (*Table 1*) were adapted from Levels 1-2 of the Anesthesiology Milestones from the ACGME; because this simulation does not include hands-on practice, these objectives are for cognitive domains only.[22] By the end of the simulation, the goal was to have students attempt to perform the following: basic preoperative chart review; anesthetic planning; identification and live interpretation of American Society of Anesthesiologists (ASA) standard monitoring criteria to inform next steps in patient care; and management of expected and unexpected events during anesthetic care following the ASA Practice Guidelines for Management of the Difficult Airway[23] as well as the American Heart Association (AHA) ACLS Adult Cardiac Arrest Algorithm.[24] No specific preparation materials were required for learners; however, familiarity with these guidelines could improve performance. Inclusion criteria consisted of enrollment in the course; there were no prespecified exclusion criteria.

Simulation Execution

The overarching flow of the simulation occurs over three parts, which are anesthesia induction, airway management, and intraoperative cardiac arrest (*Table 2*, *Supplements 1* and *2*). Throughout the entire experience, the medical student learner acts as an attending anesthesiologist supervising a trainee. Briefly, each part includes several questions for the student to answer regarding the simulated anesthetic case along with live interpretation of vital signs presented on an iPad running a mock anesthesia monitor app, SimMon (Castle+Andersen ApS; Copenhagen, Denmark). Using both narrative information and vital signs data, the student essentially reasons through their management of a patient undergoing a common surgery that develops several complications. As the case progresses and the patient's vital signs become increasingly unstable until the point of cardiac arrest, the student must recognize this acute change and plan their next steps. Importantly, this simulation is designed to continue as written even if the questions are answered incorrectly—there are no discrete branch points. If the learner does not answer all components of a multipart question, partial credit may only be awarded if this is stated in the facilitator guide. Otherwise, the question is marked as wrong, and the simulation continues. All scoring was completed by one researcher to avoid any possible inter-rater differences in this pilot study. Furthermore, the researcher achieved consistency in scoring by continually referencing the answer key's guidelines for half or full credit and did not deviate from these stipulations.

Simulation Scoring and Analysis

Prior to initiating the simulation, all participants completed an anonymous, written, multiple-choice basic demographics form that also included what medical specialty they were applying into (Supplement 3). After the workshop concluded, an online, anonymous post-simulation survey created using Qualtrics was distributed to students via their school email accounts (Supplement 4). The survey was developed referencing similar post-simulation evaluation tools published in the literature.[4,5] Questions focused on students' perceptions of the simulation experience and their opinions on low-fidelity simulations in general. To compare opinions on the airway management versus the intraoperative cardiac arrest portions of the simulation, two identical blocks of questions were presented. Scoring utilized a Likert scale from 1-5 (1 = Strongly Disagree, 2 = Disagree, 3 = Neutral, 4 = Agree, and 5 = Strongly Agree). Two questions required a "Yes" or "No" answer followed by the ability to elaborate on their choice. Survey participants were also presented with an optional chance to provide comments on the entire simulation experience.

All analyses were performed using Stata/SE 17.0, StataCorp LLC. Numerical student scores were categorized as "low" (0 to 7.5 points, inclusively) or "high" (8 to 15 points, inclusively) to perform comparisons with other categorical variables using the Fisher's exact test given the small sample size. Statistical significance was set at $p < 0.05$ with a concurrent understanding of the limitations of p-value analyses when drawing conclusions. Qualitative feedback was divided into the groupings of positive, neutral, or negative comments depending on the text content to form proportions. For questions that utilized a 5-point Likert scale, means and standard deviations were generated to note

overall trends. All authors attest to the accuracy of the data and fidelity of statistical analyses. This study was declared as curriculum review, not requiring formal informed consent of participants, and consequently exempt from the Brown University Institutional Review Board. This determination has been made according to the definition of research provided in Title 45 CFR Part 46.102(l).

Results

In this pilot study, a total of eleven fourth-year medical students enrolled in IPC 4318 and completed the simulation activity. Basic demographics and intended medical specialty reported from the pre-simulation questionnaire are described in ***Table 3.*** Participants consisted of seven male-identifying and four female-identifying students, with all but one applying to a single specialty. Most students were white/Caucasian and non-Hispanic/Latino or Spanish origin. Approximately half of the group desired to practice in a non-surgical specialty, which consisted of psychiatry, anesthesiology, emergency medicine, and internal medicine. Represented surgical fields included OB/GYN, otolaryngology, neurosurgery, plastic surgery, and general surgery. Simulation scores had a mean ± standard deviation of 9.3 ± 2.3 points with a median of 9 and mode of 10.5; the range was from a low of 6 points to a high of 14 (***Table 4***). Regarding subsection performance, it can be observed that the lowest scoring portion was the third part on intraoperative cardiac arrest; on average, participants scored about 4.5 ± 1.6 points out of 8. The opening scenario and initial questions resulted in middle-range scores, approximately 3 ± 1.2 points out of 5. Learners generally scored close to full credit in the second section with 1.7 ± 0.6 points, which had two questions on airway management and a maximum score of 2. A breakdown of each question and the proportion of students who answered correctly is described in ***Table 5.***

As detailed in ***Figure 1.*** participants had a mix of experiences taking electives or subinternships in anesthesiology, ICU/critical care medicine, or emergency medicine. The initial demographics survey inquired about shadowing experience in each respective field, as well as enrollment in the anesthesiology pre-clinical elective offered at The Warren Alpert Medical School, but due to the small sample size and lack of positive responses to those questions, the focus was shifted to enrollment in clinical electives only. Some students had experiences in two categories, but no single person had experiences in all three

Most students achieved simulation scores in the high category; of this group, the average score was 10.3 ± 1.9 points. Within the low category, the average score was 6.7 ± 0.8 points, and it can be noted that poor performance in the cardiac arrest section primarily drove their score classification. Due to the small sample size, a one-sided Fisher's exact test was performed to assess any meaningful relationship between score category and experience in anesthesiology, ICU/critical care medicine, or emergency medicine. All three tests did not lead to statistically significant p-values.

Table 1. Simulation Primary Learning Objectives and Anesthesiology Milestones from the Accreditation Council for Graduate Medical Education (ACGME).

Learning Objective	Residency Milestone
Performs basic chart review	Patient Care 1: Pre-Anesthetic Evaluation, Level 1
Identifies the components of an anesthetic plan and pain management plan	Patient Care 2: Peri-Operative Care and Management, Level 1
Identifies standard monitors and interprets standard monitoring data	Patient Care 3: Application and Interpretation of Monitors, Level 1
Manages expected events during anesthetic care, with supervision	Patient Care 4: Intra-Operative Care, Level 2
Participates in management during crisis situations	Patient Care 7: Situational Awareness and Crisis Management, Level 2
Recognizes when a patient is critically ill	Patient Care 9: Critical Care, Level 1
Demonstrates knowledge of pharmacology of medications routinely used in anesthetic care	Medical Knowledge 1: Foundational Knowledge, Level 2

Table 2. Simulation Flow, Sample Narratives, and Summary of Each Section's Questions. Full text in Supplements 1 and 2.

	Narrative	Vital Signs Monitor	Questions
Section 1: Induction	Introduces 45-year-old patient undergoing laparoscopic cholecystectomy with several factors increasing the risk of a difficult airway. *At section end:* The case proceeds with simulated induction and an attempt to intubate with an endotracheal tube.	• HR 85 [normal sinus rhythm] • SpO_2 100% on room air • BP 130/88 • RR 14	Anesthesia concerns, identification of monitoring devices, process of inducing general anesthesia.
Section 2: Airway Management	There are difficulties in securing an airway for this patient. *At section end:* After multiple tries, the patient is successfully intubated.	• HR 120 [sinus tachycardia] • SpO2 85% on room air • BP 90/60 • RR 0	Basic reasoning though a difficult airway, how to recognize unintentional esophageal intubation.
Section 3: Intraoperative Cardiac Arrest	The patient's pulse is suddenly lost.	• HR 160 bpm [ventricular tachycardia] • SpO2 76%, intubated, 100% FiO2 • BP 60/40 • RR 0	Live cardiac rhythm interpretation, key steps in the ACLS Adult Cardiac Arrest Algorithm, medication options, reversible causes of cardiac arrest.
Wrap-Up	Return of spontaneous circulation is achieved and the operation is cancelled. The patient is transferred to the ICU with stable vital signs. Calculate the learner's score, then debrief the simulation. Review answers and offer an opportunity to ask any questions.		

Legend: HR, heart rate; SpO_2, oxygen saturation; BP, blood pressure; RR, respiratory rate; ACLS, Advanced Cardiovascular Life Support.

Figure 1: Participant Clinical Experiences Prior to Simulation.

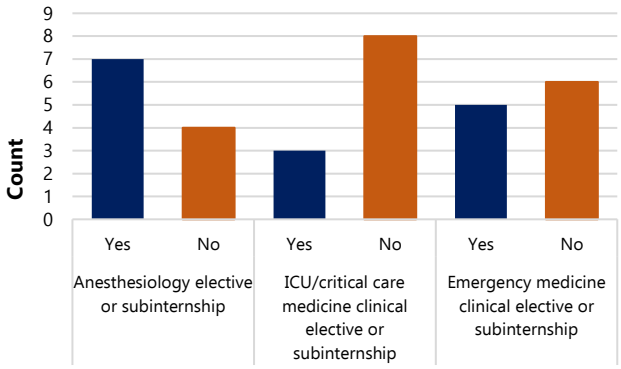

Table 3. Participant Demographics and Specialty Selection.

		n	%
Gender Identity	Male	7	64%
	Female	4	36%
Age Category	24 to 26 years	3	27%
	27 to 29 years	3	27%
	30 to 32 years	2	18%
	33 years or older	3	27%
Race	Black/African American	1	9%
	White/Caucasian	9	82%
	Other	1	9%
Ethnicity	Hispanic/Latino or Spanish origin	1	9%
	Not Hispanic/Latino or Spanish origin	10	91%
Intended Specialty* (*n* = 12)	Anesthesiology	1	8%
	Emergency Medicine	2	17%
	General Surgery	1	8%
	Internal Medicine	2	17%
	Neurosurgery	1	8%
	OB/GYN	2	17%
	Otolaryngology	1	8%
	Plastic Surgery	1	8%
	Psychiatry	1	8%

Legend: *One participant applied to both internal medicine and emergency medicine. All categories use n = 11 except where noted. Data are presented as counts and percentages. Total percentages may not equal 100% due to rounding.

Table 4. Participant Clinical Experiences and Simulation Scores.

ID	Section 1 score (Max 5)	Section 2 score (Max 2)	Section 3 score (Max 8)	Total Score (Max 15)	Score Category
1	1.5	2	2.5	6	Low
2	2.5	0	4	6.5	Low
3	3.5	2	2	7.5	Low
4	5	2	7	14	High
5	1.5	2	5.5	9	High
6	4	1.5	5	10.5	High
7	2	2	4	8	High
8	3	2	6	11	High
9	4	2	5	11	High
10	4	1.5	3	8.5	High
11	2.5	2	6	10.5	High
Score±SD	**3±1.2**	**1.7±0.6**	**4.5±1.6**	**9.3±2.3**	

Legend: SD, Standard Deviation. Score categories were defined as Low for scores from 0 to 7.5 (inclusive) and High for scores from 8 to 15 (inclusive).

Six of the eleven students that participated in the simulation completed the optional, anonymous, emailed online post-simulation survey, a 55% response rate. Summary data regarding perception of the simulation and its content is presented in ***Table 6.*** In general, participants provided positive feedback on the simulation, with all responses indicating agreement with a statement on low-fidelity simulations being beneficial learning opportunities for medical students, citing them as helpful to review knowledge. Of the six responses, five agreed with the proposed idea that all medical students should be required to participate in low-fidelity simulations as part of their school's clinical curriculum. Regarding this proposal, one respondent commented, "Ward time constitutes a fair amount of wasted time, and classroom knowledge isn't readily applicable without applying it to at least a few simulations throughout training."

Viewing Likert scale data, responses to general statements such as "The simulation was a valuable learning experience," and "The simulation was applicable to my upcoming responsibilities as an intern," averaged 4 ± 0.9 points and 4.3 ± 1 points respectively, which correspond to "Agree." When asked if "The simulation felt realistic," and "I felt it was fine that the simulation was not hands-on," responses tended to aggregate around 3.5 ± 1.4 and 3.5 ± 0.5 points correspondingly, equaling "Neutral" to "Agree" on the Likert scale. Duplicate question sets were presented for the airway management and the intraoperative cardiac arrest portions of the simulation to compare answers. Both blocks had mean Likert scores ranging from 4 to 4.7, with no obvious differences in responses for each section. Of note, the cardiac arrest portion was apparently more stressful (4 ± 1.3) than the difficult airway portion (4.5 ± 0.5); differences in mean scores indicate less agreement with the statement, "This portion was not overly stressful." The lowest average Likert scores for these question blocks was regarding the statement, "This portion enhanced my confidence and clinical decision-making skills for the future," where the difficult airway was 3.8 ± 1.3 points and the cardiac arrest was 3.5 ± 1.2 points, primarily clustering in the "Neutral" to "Agree" categories.

Discussion

This study describes the initial use of a low-fidelity simulation for fourth-year medical students that focuses on the steps one would take to manage both a difficult airway and cardiac arrest while in the operating room. Additionally, specific goals of this pilot test were to analyze participant performance and review qualitative feedback to guide future iterations of this educational tool. In the post-simulation follow-up survey, participants generally provided positive observations on the experience and felt the simulation was a good refresher on airway management and ACLS.

A unique component of this simulation is the live interpretation of data from a simulated anesthesia monitor to inform the participant of the patient's immediate status. Simulations are known to be more challenging than written exams, but offer learners a more lifelike environment to demonstrate their knowledge

Table 5. Aggregated Participant Responses by Question.

	Question	Full Credit (*n*, %)	Partial Credit (*n*, %)	No Credit (*n*, %)
Section 1: Induction	Based on the patient's chart, are there any concerns you have about this anesthetic? If so, name at least one factor.	9 (82%)	0 (0%)	2 (18%)
	What are the five standard ASA monitoring devices you should use?	1 (9%)	0 (0%)	10 (91%)
	How should you start the induction?	5 (45%)	0 (0%)	6 (55%)
	Name at least two medications that may be used during induction and briefly describe each's basic mechanism of action.	6 (55%)	4 (36%)	1 (9%)
	Which airway device should you pick?	9 (82%)	1 (9%)	1 (9%)
Section 2: Airway Management	How would you like to proceed? Besides direct laryngoscopy, name at least one other option to use with a suspected difficult airway?	11 (100%	0 (0%)	0 (0%)
	Name at least two signs that you would expect if the esophagus was intubated by mistake.	8 (73%)	2 (18%)	1 (9%)
Section 3: Intraoperative Cardiac Arrest	What is this cardiac rhythm?	9 (82%)	0 (0%)	2 (18%)
	What is your first step in managing this acute change?	9 (82%)	0 (0%)	2 (18%)
	What are your next steps?	11 (100%)	0 (0%)	0 (0%)
	What is the dose of epinephrine for cardiac arrest?	7 (64%)	0 (0%)	4 (36%)
	How is amiodarone dosed for cardiac arrest?	1 (9%)	0 (0%)	10 (91%)
	Name at least two causes of reversible cardiac arrest.	6 (55%)	2 (18%)	3 (27%)
	Given the patient's advanced airway, how often are they ventilated?	0 (0%)	0 (0%)	11 (100%)
	If the patient's rhythm were to change to asystole, what is the main difference to your management?	6 (55%)	0 (0%)	5 (45%)

Legend: ASA, American Society of Anesthesiologists. Full credit = 1 point; partial credit = 0.5 points; no credit = 0 points. Data are presented as counts and percentages out of 11 participants. Totals may not equal 100% due to rounding.

Table 6. Aggregated Participant Responses by Question.

	Question Stem	Positive Feedback	Neutral Feedback	Negative Feedback	Mean ± SD Likert Scale Scores
Overall Simulation Experience	The simulation was a valuable learning experience.	4 (67%)	2 (33%)	0 (0%)	4 ± 0.9
	The simulation was at an appropriate level of difficulty.	5 (83%)	1 (17%)	0 (0%)	4.5 ± 0.8
	The simulation was at an appropriate level of stress.	6 (100%)	0 (0%)	0 (0%)	4.7 ± 0.5
	I found the material included in the simulation interesting.	5 (83%)	1 (17%)	0 (0%)	4.3 ± 0.8
	The simulation was applicable to my upcoming responsibilities as an intern.	4 (67%)	2 (33%)	0 (0%)	4.3 ± 1
	This simulation enhanced my confidence and clinical decision-making skills for the future.	3 (50%)	2 (33%)	1 (17%)	3.8 ± 1.3
	The simulation felt realistic.	4 (67%)	1 (17%)	2 (33%)	3.5 ± 1.4
	I felt it was fine that the simulation was not hands-on (e.g., not intubating the mannequin myself).	3 (50%)	3 (50%)	0 (0%)	3.5 ± 0.5
Part 2: Airway Management	I had adequate preparation through my coursework or rotations to answer the questions.	4 (67%)	2 (33%)	0 (0%)	4.3 ± 1
	This portion was at an appropriate level of difficulty.	6 (100%)	0 (0%)	0 (0%)	4.7 ± 0.5
	This portion was not overly stressful.	6 (100%)	0 (0%)	0 (0%)	4.5 ± 0.5
	This portion was applicable to my upcoming responsibilities as an intern.	4 (67%)	2 (33%)	0 (0%)	4.2 ± 1
	This portion enhanced my confidence and clinical decision-making skills for the future.	3 (50%)	2 (33%)	1 (17%)	3.8 ± 1.3
Section 3: Intraoperative Cardiac Arrest	I had adequate preparation through my coursework or rotations to answer the questions.	5 (83%)	0 (0%)	1 (17%)	4.2 ± 1.2
	This portion was at an appropriate level of difficulty.	6 (100%)	0 (0%)	0 (0%)	4.5 ± 0.5
	This portion was not overly stressful.	4 (67%)	1 (17%)	1 (17%)	4 ± 1.3
	This portion was applicable to my upcoming responsibilities as an intern.	5 (83%)	1 (17%)	0 (0%)	4.5 ± 0.8
	This portion enhanced my confidence and clinical decision-making skills for the future.	2 (33%)	3 (50%)	1 (17%)	3.5 ± 1.2

Legend: Full credit = 1 point; partial credit = 0.5 points; no credit = 0 points. Data are presented as counts and percentages out of 11 participants. Totals may not equal 100% due to rounding.

and abilities while simultaneously presenting rare disease states or situations that may otherwise not be encountered in regular practice.[25] With this population consisting of medical students at the cusp of graduation and intern year, this simulation may be considered a readiness assessment and can help identify areas for improvement within the medical school curriculum. Given the comment from one participant mentioning that time on a hospital ward does not guarantee learning opportunities, simulations such as the one used in this study represent efficient teaching tools for students' often busy schedules.

Although students generally performed well, as only three (27%) individuals scored in the low range, there are clear opportunities for growth, mainly regarding application of the ACLS Adult Cardiac Arrest Algorithm. As noted in *Table 5,* two questions proved especially challenging: "How is amiodarone dosed for cardiac arrest?" (one correct answer, 9%) and "Given the patient's advanced airway, how often are they ventilated?" (zero correct answers, 0%). There were also difficulties in realizing asystole is a non-shockable rhythm, with only six (55%) individuals answering the question correctly. However, this contrasts with consistently accurate identification of ventricular tachycardia ("What is this cardiac rhythm?") on the simulated monitor, as only one (9%) student failed to do this at the start of the third section. Other difficult questions included knowing specific drugs and dosages used in cardiac arrest ("What is the dose of epinephrine for cardiac arrest?"; "How is amiodarone dosed for cardiac arrest?"), the use of preoxygenation at the start of an anesthetic ("How should you start the induction?"), and identification of standard intraoperative monitoring devices ("What are the five standard ASA monitoring devices you should use?"). On more than one occasion, learners did not fully address all aspects of in-hospital cardiac arrest care such as administering medications, instead focusing on compressions and rescue breaths.

Despite immediately noticing auditory cues and alarms, learners had trouble analyzing the live vital signs data in an efficient manner to determine their next steps in the case. It is likely that medical students are unaccustomed to viewing monitors and forming rapid assessments in their clinical training; instead, they are often given vignettes on tests or in case discussions, pointing out an educational benefit from this type of simulation. Alternatively, the stress of the simulation could have impacted their ability to clearly reason through the case; Anton et al. studied physiological and psychological markers of anxiety and found a negative correlation between higher stress levels and simulation performance.[26] A possible improvement for the future would be to provide students with a brief handout or reference on common monitoring devices used in anesthesia and rapid cardiac rhythm recognition so they could best understand the data presented to them and experience less pressure.

It is well-established in the literature that medical students seldom have adequate experiences applying ACLS pathways outside of dedicated training courses, which is problematic when they graduate and are expected to serve as a code team leader.[27,28] Research has pointed to the benefits of high-fidelity simulations[25] over standard, non-lifelike simulations to improve medical student performance and increase confidence in running codes.[29] However, certain metrics within ACLS algorithms such as timing of compressions and defibrillation were comparable between groups in Ko et al., suggesting that some benefits may be conferred even without the use of advanced mannequins and simulation equipment.[29] Given the participants tended to have neutral Likert scale ratings for enhancing confidence and clinical decision-making skills, this may be related to previous findings that low-fidelity simulations may not adequately instill self-assurance in learners. As noted by Nacca et al., supplementation of a computer-based low-fidelity simulation within a high-fidelity mannequin-based simulation ACLS course for medical students resulted in quicker, accurate decision-making when compared to the mannequin-only group; yet, once more, the low-fidelity simulation group tended to feel less confident in their actions, even if correct.[30] When considering these findings, it appears that low-fidelity simulations may have an important role as adjunctive teaching tools within a comprehensive ACLS course that includes elements of realism.

Unlike the cardiac arrest portion, students generally excelled with the difficult airway questions in the simulation. These findings could be explained by the inherent variable steps one may take to manage a difficult airway, such as switching a laryngoscope blade or utilizing a videolaryngoscope versus trying a different airway device, whereas ACLS requires set drug dosing, timing of interventions, and ordered actions. Moreover, with only two questions to answer, students had greater chances of performing well. This portion of the simulation was also highly simplified, with the student not physically attempting to intubate a mannequin, which could lead to increased stress and impaired thinking. Comparable studies have noted that students can achieve higher proficiencies in the setting of uncomplicated instructional pathways, as was the case with Ambardekar et al., who found that following a simplified difficult airway aid resulted in less cognitive burden and better performance outcomes.[31] It is also important to highlight that interactive discussions of how to manage a difficult airway, essentially what was done within this simulation, provides benefits to learners; in effect, physical practice is not required to optimize education on this topic.[32]

Strengths of this simulation are that it does not require an expensive setup, it can be conducted with as few as one facilitator, and on average, it takes no more than 15 minutes to perform. At minimum, it can be carried out with the medical student learner and a primary facilitator, who may be an anesthesia resident or attending. Minimum necessary supplies include the patient scenario (Supplement 1) for the learner, the facilitator guide (Supplement 2) for running and scoring the simulation, and an iPad or comparable device (e.g., smartphone) controlled by the primary facilitator to display live vital signs on a simulator app, of which a variety of paid and free options are

available. Specific dialogue is included in the simulation to maintain consistency across repeat trials; no additional dialogue or questions outside of the written case should be stated.

Ideally, a secondary facilitator, either an anesthesia resident or attending, can be present to act as an anesthesia provider that can perform the tasks to make the simulation more engaging, if this is done, additional equipment includes a mannequin that can be intubated, standard airway equipment (e.g., adult facemask, oral airway, endotracheal tube, laryngeal mask airway, laryngoscope with Mac and Miller blades, Ambu bag, bougie), mock medications, and a mock defibrillator with pads. Essentially, the primary facilitator will be running the case and asking questions while the secondary facilitator will provide periodic updates on the situation as it is acted out. Having a third facilitator would allow for distribution of the primary facilitator's responsibilities, such as a dedicated person to operate the iPad. This pilot study was conducted using two facilitators for one medical student learner, reflected here in the methods *(Table 2)*, and in the facilitator guide. Additionally, the role of the anesthesia trainee does not need to exclusively be clinical anesthesia year 1 resident (CA-1) as it is written in the materials.

Some limitations to this study include the small sample size, which greatly limited abilities to detect significant associations with the Fisher's exact test, potentially masking true relationships between variables. If this simulation were to be repeated with a larger group of students, experiences in critical-care related fields and scoring trends could be explored with correlation analyses. With medical students having earlier exposure to anesthesiology through preclinical electives, it is feasible that a moderate number of individuals could have familiarity with the subjects covered in this simulation as they near graduation, bringing into question possible self-selection bias for individuals already primed to perform well.[33] This was also the first-time use of this simulation, which led to unforeseen challenges related to defining unclear terminology and answering learners' clarifying questions. Scoring accuracy may also be increased by providing more partial credit for questions, especially those that require multiple responses, such as identifying the five standard ASA monitoring devices. A large proportion of students could identify three or four, but since they did not name all five, no credit was awarded. Future iterations could give a half point if at least three devices are correctly named. Lasty, as this study was conducted at a single center, this particular student population could risk not being representative of all medical students in the United States.

Conclusion

Low-fidelity simulations represent an underutilized tool in medical education that can provide learners with an effective experience to practice skills and demonstrate knowledge. This preliminary trial of one such simulation focusing on a challenging intubation leading to intraoperative cardiac arrest for fourth-year medical students was generally well-received, with most participants earning higher-range scores. Of note, learners found the subsection on ACLS to be the most challenging as it had the lowest mean total scores and was reported to be the most subjectively stressful portion of the simulation. Whether these results were due to lack of practice or stress remains an area for forthcoming investigation. This simulation can be run with limited supplies and personnel in under 15 minutes per trial, allowing easy adoption and use at peer institutions. Future trials of this simulation include obtaining a larger sample size, improving the clarity of questions, and providing preparatory reading material to refresh participants' knowledge on the tested topics.

Summary – Accelerating Translation

Title: Preliminary Trial of a Low-Fidelity Anesthesiology Simulation on Airway Management and Intraoperative Cardiac Arrest for Fourth-Year Medical Students

Simulations in healthcare are valuable learning opportunities and are used across many medical specialties, including anesthesiology. Low-fidelity simulations are inexpensive, accessible, and can be helpful in educating medical students. The objective of this work was to pilot a low-fidelity simulation and evaluate student performance plus opportunities for improvement of this learning tool.

This study was completed at one medical school and was designed to prospectively observe fourth-year medical student performance on the simulated patient case. A total of eleven fourth-year medical students participated in the simulation, with the majority scoring well. No relationship between student experience in anesthesiology or related fields and simulation score was noted. Six of the eleven participants completed the post-simulation survey (55% response rate), primarily giving positive feedback, with all responses indicating agreement that low-fidelity simulations are beneficial learning opportunities for medical students, citing them as helpful to review knowledge.

Low-fidelity simulations represent an underutilized tool in medical education that can provide learners with an effective experience to practice skills and demonstrate knowledge. This simulation can be run with limited supplies and personnel in under 15 minutes per trial, allowing easy adoption and use at peer institutions.

References

1. Singh H, Kalani M, Acosta-Torres S, El Ahmadieh TY, Loya J, Ganju A. History of simulation in medicine: from Resusci Annie to the Ann Myers Medical Center. Neurosurgery. 2013;73 Suppl 1:9-14.
2. Dorfling J, Hatton KW, Hassan ZU. Integrating echocardiography into human patient simulator training of anesthesiology residents using a severe pulmonary embolism scenario. Simul Healthc. 2006;1(2):79-83.
3. Altun D, Ozkan-Seyhan T, Camci E, Sivrikoz N, Orhan-Sungur M. Learning Curves for Two Fiberscopes in Simulated Difficult Airway Scenario with Cumulative Sum Method. Simul Healthc. 2019;14(3):163-168.
4. Yu CJ, Rigueiro F, Backfish-White K, Cartwright J, Moore C, Mitchell SA, et al. Cricothyrotomy in Acute Upper Gastrointestinal Bleed: A Difficult Airway Simulation Case for Anesthesiology Residents. MedEdPORTAL. 2024;20:11378.

5. Hong BE, Myo Bui CC, Huang YM, Grogan T, Duval VF, Cannesson M. Implementing COVID-19 Simulation Training for Anesthesiology Residents. MedEdPORTAL. 2022;18:11215.
6. Asselin M, Lafleur A, Labrecque P, Pellerin H, Tremblay MH, Chiniara G. Simulation of Adult Surgical Cricothyrotomy for Anesthesiology and Emergency Medicine Residents: Adapted for COVID-19. MedEdPORTAL. 2021;17:11134.
7. Chang CH. Medical simulation is needed in anesthesia training to achieve patient's safety. Korean J Anesthesiol. 2013;64(3):204-211.
8. Chakravarthy B, Ter Haar E, Bhat SS, McCoy CE, Denmark TK, Lotfipour S. Simulation in medical school education: review for emergency medicine. West J Emerg Med. 2011;12(4):461-466.
9. Nguyen W, Fromer I, Remskar M, Zupfer E. Development and Implementation of Video-Recorded Simulation Scenarios to Facilitate Case-Based Learning Discussions for Medical Students' Virtual Anesthesiology Clerkship. MedEdPORTAL. 2023;19:11306.
10. Ellis TA, Bracho DO, Krishnan S. Responding to a Respiratory Complication in the Recovery Room: A Simulation Case for Anesthesiology Students. MedEdPORTAL. 2017;13:10529.
11. Krishnan S, Kumar N, Diaz E, Thornton I, Ghoddoussi F, Ellis TA 2nd. Anesthesiology Handoff Simulation Case: A Handoff from Intensive Care Unit to Operating Room for Anesthesiology Learners. MedEdPORTAL. 2020;16:10887.
12. Quick J, Murthy R, Goyal N, Margolis S, Pond G, Jenkins K. Malignant Hyperthermia: An Anesthesiology Simulation Case for Early Anesthesia Providers. MedEdPORTAL. 2017;13:10550.
13. Ellis TA, Edberg JL, Kumar N, Applefield DJ. Delayed Emergence from Anesthesia: A Simulation Case for Anesthesia Learners. MedEdPORTAL. 2017;13:10628.
14. Association of American Medical Colleges. Simulation Center Use at Medical Schools. Available from: https://www.aamc.org/data-reports/curriculum-reports/data/simulation-center-use-medical-schools. Last updated 2014; cited April 25, 2024.
15. Senvisky JM, McKenna RT, Okuda Y. Financing and Funding a Simulation Center. Treasure Island: StatPearls; 2024.
16. Hippe DS, Umoren RA, McGee A, Bucher SL, Bresnahan BW. A targeted systematic review of cost analyses for implementation of simulation-based education in healthcare. SAGE Open Med. 2020;8:2050312120913451.
17. Massoth C, Röder H, Ohlenburg H, Hessler M, Zarbock A, Pöpping DM, et al. High-fidelity is not superior to low-fidelity simulation but leads to overconfidence in medical students. BMC Med Educ. 2019;19(1):29.
18. Philp N, Omran A, Otorkpa MJ, Kirk A. Medical Students' Confidence After "CardioSim": A Low-Fidelity, Peer Role-Play Simulation. Cureus. 2024;16(8):e67192.
19. Kassutto S, Clancy C, Bennett N, Tsao S. Virtual Simulations to Enhance Medical Student Exposure to Management of Critically Ill Patients. ATS Sch. 2024;5(2):242-246.
20. Delisle M, Hannenberg AA. Alternatives to High-Fidelity Simulation. Anesthesiol Clin. 2020;38(4):761-773.
21. The OpenCriticalCare.org Project. Anesthesia & Critical Care Simulation Scenarios for Resource Constrained Settings. Available from: https://opencriticalcare.org/resources/anesthesia-critical-care-simulation-scenarios-for-resource-constrained-settings/. Last updated: September 7, 2022; cited April 25, 2024.
22. The Accreditation Council for Graduate Medical Education. Anesthesiology Milestones. Available from: https://www.acgme.org/globalassets/pdfs/milestones/anesthesiologymilestones.pdf. Last updated: November 2020; cited April 25, 2024.
23. Apfelbaum JL, Hagberg CA, Connis RT, Abdelmalak BB, Agarkar M, Dutton RP, et al. 2022 American Society of Anesthesiologists Practice Guidelines for Management of the Difficult Airway. Anesthesiology. 2022;136(1):31-81.
24. Panchal AR, Bartos JA, Cabañas JG, Donnino MW, Drennan IR, Hirsch KG, et al. Part 3: Adult Basic and Advanced Life Support: 2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2020;142(16_suppl_2):S366-S468.
25. Strom SL, Anderson CL, Yang L, Canales C, Amin A, Lotfipour S, et al. Correlation of Simulation Examination to Written Test Scores for Advanced Cardiac Life Support Testing: Prospective Cohort Study. West J Emerg Med. 2015;16(6):907-912.
26. Anton NE, Rendina MA, Hennings JM, Stambro R, Stanton-Maxey KJ, Stefanidis D. Association of Medical Students' Stress and Coping Skills with Simulation Performance. Simul Healthc. 2021;16(5):327-333.
27. Langdorf MI, Strom SL, Yang L, Canales C, Anderson CL, Amin A, et al. High-fidelity simulation enhances ACLS training. Teach Learn Med. 2014;26(3):266-273.
28. Promes SB, Chudgar SM, Grochowski CO, Shayne P, Isenhour J, Glickman SW, et al. Gaps in procedural experience and competency in medical school graduates. Acad Emerg Med. 2009;16 Suppl 2:S58-S62.
29. Ko PY, Scott JM, Mihai A, Grant WD. Comparison of a modified longitudinal simulation-based advanced cardiovascular life support to a traditional advanced cardiovascular life support curriculum in third-year medical students. Teach Learn Med. 2011;23(4):324-330.
30. Nacca N, Holliday J, Ko PY. Randomized trial of a novel ACLS teaching tool: does it improve student performance?. West J Emerg Med. 2014;15(7):913-918.
31. Ambardekar AP, Rosero EB, Bhoja R, Green J, Rebal BA, Minhajuddin AT, et al. A Randomized Controlled Trial Comparing Learners' Decision-making, Anxiety, and Task Load During a Simulated Airway Crisis Using Two Difficult Airway Aids. Simul Healthc. 2019;14(2):96-103.
32. Myatra SN, Kalkundre RS, Divatia JV. Optimizing education in difficult airway management: meeting the challenge. Curr Opin Anaesthesiol. 2017;30(6):748-754.
33. Walsh KL, Yadav A, Cradeur M, Huang H, Lee D, Owusu-Dapaah H, et al. Impact of a Preclinical Medical Student Anesthesiology Elective on the Attitudes and Perceptions of Medical Students Regarding Anesthesiology. Adv Med Educ Pract. 2023;14:1347-1355

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Author Contributions

Conceptualization: KW, SA. Data Curation: KW, CS, SA. Formal Analysis: KW, SA. Investigation: KW, CS, SA. Methodology: KW, SA. Supervision: SA. Validation: KW, CS, SA. Visualization: KW, CS, SA. Writing - Original Draft: KW. Writing - Review Editing: KW, CS, SA.

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Supplementary Material

Supplementary Material 1

Simulation Scenario (Student Version)

You are ready to start the anesthesia induction for a case of a 45-year-old male named Gerald Anderson with past medical history of gout, type 2 diabetes mellitus, hypertension, and obesity (BMI 40) who is about to undergo laparoscopic cholecystectomy for acute cholecystitis. His medications include allopurinol, metformin, and irbesartan; he has no allergies; social history is notable for smoking a half pack of cigarettes per day along with recreational cannabis on the weekends.

His physical exam is notable for a Mallampati 3 airway, limited reck extension, and RUQ tenderness; cardiopulmonary exam reveals lungs CTAB and heart RRR. The patient is in NAD on the operating room table, and you will now assume care of him. Assessment, optimization, and room setup have already been performed—you do not need to repeat these steps.

Supplementary Material 2

Simulation Scenario (Facilitator Version)

Section 1: Induction

Provide the learner with a copy of the Student Version to review upon initiating the simulation. Vital signs on the monitor are heart rate 85 bpm [normal sinus rhythm]; oxygen saturation 100% on room air; blood pressure 130/88 mmHg; and respiratory rate 14 breaths/min. When the learner is ready to begin, ask the following prompts:

1. Based on the patient's chart, are there any concerns you have about this anesthetic? If so, name at least one factor.
2. What are the five standard ASA monitoring devices you should use?
3. How should you start the induction?
4. Name at least two medications that may be used during induction and briefly describe each's basic mechanism of action.
5. Which airway device should you pick?

Section 1 Scoring (1 point each, maximum 5 points)
1. Identifies at least one difficult airway risk factor based on the patient's chart. Options include obesity, Mallampati score, or limited neck motion.
2. Identifies standard ASA monitors: pulse oximeter, EKG, noninvasive blood pressure device, temperature probe, and end-tidal CO2.
3. Starts induction with preoxygenation.
4. At least two of any anxiolytic, hypnotic, paralytic, or analgesic drugs can be identified and each's basic mechanism of action is described. Half-credit may be awarded for identifying medications without knowing the pharmacodynamic activity.
5. Identifies an appropriate airway device for a general anesthetic case such as an endotracheal tube.

The case proceeds with simulated induction and an attempt to intubate with an endotracheal tube.

Section 1 Score: ____

Section 2: Airway Management

The secondary facilitator tells the learner "I am having difficulty visualizing the patient's airway. There's also changes on the monitor you should see." Vital signs on the monitor are heart rate 120 bpm [sinus tachycardia]; oxygen saturation 85% on room air; blood pressure 90/60 mmHg; and respiratory rate 0 breaths/min.

1. How would you like to proceed? Besides direct laryngoscopy, name at least one other option to use with a suspected difficult airway?
2. Name at least two signs that you would expect if the esophagus was intubated by mistake.

Section 2 Scoring (1 point each, maximum 2 points)
1. Options include optimizing positioning; change laryngoscopy blade; utilize a bougie; obtain a videolaryngoscope; perform external laryngeal manipulation; or call for skilled help.
2. The learner identifies at least two of the following: no breath sounds on auscultation; absent chest rise/fall with ventilation; no misting or fogging of the endotracheal tube; or no ETCO2 waveform on monitor.

The secondary facilitator informs the learner, "It took three tries, but I've successfully intubated the patient."

Section 2 Score: ____

Section 3: Intraoperative Cardiac Arrest

The secondary facilitator tells the learner, "I can't get a pulse on the patient!" Vital signs on the monitor are heart rate 160 [ventricular tachycardia]; oxygen saturation 76% while intubated on 100% FiO2; blood pressure 60/40 mmHg; and respiratory rate 0 breaths/min.

1. What is this cardiac rhythm?
2. What is your first step in managing this acute change?
3. What are your next steps?
4. What is the dose of epinephrine for cardiac arrest?
5. How is amiodarone dosed for cardiac arrest?
6. Name at least two causes of reversible cardiac arrest.
7. Given the patient's advanced airway, how often are they ventilated?
8. If the patient's rhythm were to change to asystole, what is the main difference to your management?

Section 3 Scoring (1 point each, maximum 8 points)
1. Identifies the rhythm as pulseless ventricular tachycardia.
2. Defibrillates the patient given the shockable rhythm.
3. Correctly identifies that CPR will be provided for 2 minutes, followed by rhythm checks for possible repeat defibrillation, along with epinephrine administration every 3-5 minutes. Also, can mention the use of second-line medications such as amiodarone or lidocaine if needed.
4. States 1 mg epinephrine.
5. States amiodarone boluses are 300 mg for the first dose and 150 mg for the second dose.
6. The learner identifies at least two of the following "H's and T's": hypovolemia, hypoxia, hydrogen ion (acidosis), hypo/hyperkalemia, hypothermia, tension pneumothorax, cardiac tamponade, toxins, or pulmonary/coronary thrombosis.
7. States one breath every 6 seconds or 10 breaths/minute.
8. Identifies that asystole is a non-shockable rhythm.

Section 3 Score: ____

End of Simulation Wrap-Up

Total Score: ____

Return of spontaneous circulation is achieved and the operation is cancelled. The patient is transferred to the ICU with stable vital signs.

The maximum score for the simulation is 15 points. Calculate the learner's total, then debrief the simulation. Review answers and offer an opportunity to ask any questions

Supplementary Material 3

Sociodemographic questions

1. What is your gender identity?
a. Female
b. Male
c. Transgender Female
d. Transgender Male
e. Nonbinary
f. Other
g. Prefer not to say

2. What is your age?

a. Under 18 years
b. 18 to 20 years
c. 21 to 23 years
d. 24 to 26 years
e. 27 to 29 years
f. 30 to 32 years
g. 33 years or older

3. What is your race?
a. Asian
b. Black/African American
c. Native American
d. Pacific Islander
e. White/Caucasian
f. Other (please specify)

4. What is your ethnicity?
a. Hispanic/Latino or Spanish origin
b. Not Hispanic/Latino or Spanish origin

5. What medical specialty are you applying into?
a. Anesthesiology
b. Dermatology
c. Emergency Medicine
d. Family Medicine
e. General Surgery
f. Internal Medicine
g. Medicine-Pediatrics
h. Neurology
i. OB/GYN
j. Pathology
k. Pediatrics
l. Physical Medicine & Rehabilitation
m. Psychiatry
n. Radiation Oncology
o. Radiology
p. Other

6. For the following statements, please indicate "Yes" if they apply to you or "No" if not:
a. I have had prior anesthesiology shadowing experience
b. I took the anesthesiology pre-clinical elective in my first or second year of medical school
c. I have taken an anesthesiology clinical elective (e.g., 2- or 4-week; pediatric anesthesia)
d. I have had prior ICU/critical care shadowing experience
e. I have taken an ICU/critical care clinical elective or subinternship
f. I have had prior emergency medicine shadowing experience
g. I have taken an emergency medicine clinical elective or subinternship

Supplementary Material 4

Post-Simulation Survey

Thank you for completing the simulation portion during IPC 4318: Common Topics in Anesthesia. This following survey will anonymously assess students' perceptions of this specific activity ONLY.
As a reminder, the simulation scenario focused on inducing general anesthesia for a patient with several risk factors for a difficult airway and asked how to progress through the ASA Difficult Airway algorithm. Due to issues with intubating, the patient suffered an intraoperative cardiac arrest requiring ACLS resuscitation.
Please rate your agreement with the following statements regarding the overall simulation station ONLY during IPC 4318: Common Topics in Anesthesia.

The simulation was a valuable learning experience.
• Strongly Disagree (1)
• Disagree (2)
• Neutral (3)
• Agree (4)
• Strongly Agree (5)

The simulation was at an appropriate level of difficulty.
• Strongly Disagree (1)
• Disagree (2)
• Neutral (3)
• Agree (4)
• Strongly Agree (5)

The simulation was at an appropriate level of stress.
• Strongly Disagree (1)
• Disagree (2)
• Neutral (3)
• Agree (4)
• Strongly Agree (5)

I found the material included in the simulation interesting.
• Strongly Disagree (1)
• Disagree (2)
• Neutral (3)
• Agree (4)
• Strongly Agree (5)

The simulation was applicable to my upcoming responsibilities as an intern.
• Strongly Disagree (1)
• Disagree (2)
• Neutral (3)
• Agree (4)
• Strongly Agree (5)

This simulation enhanced my confidence and clinical decision-making skills for the future.
• Strongly Disagree (1)
• Disagree (2)
• Neutral (3)
• Agree (4)
• Strongly Agree (5)

The simulation felt realistic.
• Strongly Disagree (1)
• Disagree (2)
• Neutral (3)
• Agree (4)
• Strongly Agree (5)

I felt it was fine that the simulation was not hands-on (e.g., not intubating the mannequin myself).
• Strongly Disagree (1)
• Disagree (2)
• Neutral (3)
• Agree (4)
• Strongly Agree (5)

Please rate your agreement with the following statements regarding the difficult airway portion of the simulation station ONLY during IPC 4318: Common Topics in Anesthesia.

I had adequate preparation through my coursework or rotations to answer the questions.
• Strongly Disagree (1)
• Disagree (2)
• Neutral (3)
• Agree (4)
• Strongly Agree (5)

This portion was at an appropriate level of difficulty.
• Strongly Disagree (1)
• Disagree (2)
• Neutral (3)
• Agree (4)
• Strongly Agree (5)

This portion was not overly stressful.
• Strongly Disagree (1)
• Disagree (2)
• Neutral (3)
• Agree (4)
• Strongly Agree (5)

This portion was applicable to my upcoming responsibilities as an intern.
• Strongly Disagree (1)
• Disagree (2)
• Neutral (3)
• Agree (4)
• Strongly Agree (5)

This portion enhanced my confidence and clinical decision-making skills for the future.
• Strongly Disagree (1)
• Disagree (2)
• Neutral (3)
• Agree (4)
• Strongly Agree (5)

Please rate your agreement with the following statements regarding the cardiac arrest / ACLS portion of the simulation station ONLY during IPC 4318: Common Topics in Anesthesia.

I had adequate preparation through my coursework or rotations to answer the questions.
• Strongly Disagree (1)
• Disagree (2)
• Neutral (3)
• Agree (4)
• Strongly Agree (5)

This portion was at an appropriate level of difficulty.
• Strongly Disagree (1)
• Disagree (2)
• Neutral (3)
• Agree (4)
• Strongly Agree (5)

This portion was not overly stressful.
• Strongly Disagree (1)
• Disagree (2)
• Neutral (3)
• Agree (4)

• Strongly Agree (5)

This portion was applicable to my upcoming responsibilities as an intern.
• Strongly Disagree (1)
• Disagree (2)
• Neutral (3)
• Agree (4)
• Strongly Agree (5)

This portion enhanced my confidence and clinical decision-making skills for the future.
• Strongly Disagree (1)
• Disagree (2)
• Neutral (3)
• Agree (4)
• Strongly Agree (5)

"Low-fidelity simulations" do not utilize the most realistic equipment or closely replicate real-world conditions as compared to "high-fidelity simulations." Given this brief description, do you feel that low-fidelity simulations such as the one piloted in this course are beneficial to student learners? Please indicate Yes or No in the appropriate box and provide any comments as you see fit.
• Yes Comments:
• No Comments:

Do you believe all medical students should be required to participate in low-fidelity simulations like the one you completed during this course as part of the clinical curriculum? Please indicate Yes or No in the appropriate box and provide any comments as you see fit.
• Yes Comments:
• No Comments:

Please feel free to add any comments regarding the simulation here:

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Original Article

Exploring Wonder in Medical School Admissions: Correlations with Admissions Decisions

Eojin Choi,[1] Maria W. Merritt,[1] Gail Geller.[3]

Abstract

Background: The capacity for wonder (CfW), which has been proposed as an important personal disposition for clinicians, may provide a meaningful picture of medical school applicants. The purpose of our study was to explore experiences of wonder among applicants and their association with components of the admissions process. **Methods:** The Johns Hopkins School of Medicine asks applicants to submit an essay about a time they experienced wonder in their everyday life. Among applicants who were interviewed in the 2021-2022 cycle, we analyzed an anonymized 50% random sample of essays (n = 224). Essays were coded using the validated CfW scale and categorized by topic. Standard bivariate statistical tests were used to assess whether the extent of wonder was associated with admissions decisions and interview scores. **Results:** Among applicants who were admitted, 80% had scores reflecting "high wonder," 62% had "medium wonder" scores, and 27% had "low wonder" scores. Applicants' extent of wonder was significantly associated with their admissions decisions ($p < 0.0002$), mean interview scores ($p = 0.00025$), and mean scores in research portfolio ($p < 0.0001$). Six broad essay topics were identified: connecting with others, engaging in art, experiences in nature, engaging in wellness, the pursuit of knowledge, and sports/exercise. **Conclusion:** Applicants' capacity for wonder may be a relevant consideration in the admissions process. Future research should verify our findings at other institutions, investigate other components of the medical school application that may be associated with the capacity for wonder, and explore interventions to cultivate wonder throughout medical education

Introduction

Authentic consideration of applicants' personal qualities is an ongoing challenge in medical school admissions. A large body of literature identifies factors to consider during the admissions process.[1-3] Albanese et al. found that the literature identifies 87 different personal qualities as relevant to the practice of medicine, and Koenig et al. identified nine core personal competencies rated by stakeholders as being especially important for entering medical students.[1,2] Prober & Desai have argued recently that assessment of factors like empathy and communication skills should replace selection criteria that overweigh standardized test scores[3] Although there is agreement about why/how these factors are relevant to excellence in clinical practice, merely assessing each factor discretely may fail to provide a genuine reflection of the applicant as a whole person. It is also challenging to select and measure personal qualities in a cost-effective and logistically feasible manner.[1,3]

The capacity for wonder—that is, the propensity to experience states of wonder in response to aspects of daily life—may underlie many desirable characteristics in medical professionals.[4] Indeed, researchers have linked the capacity for wonder to several personal characteristics that are necessary for clinical excellence—empathy, humility, tolerance for uncertainty, courage, curiosity—and have proposed it as an important personal disposition that can support and encourage character development in students aspiring to become physicians.[5] For example, the capacity for wonder enables people to show genuine interest in others, listen carefully, and acknowledge other perspectives, all behaviors that are foundational to empathy. Although empathy is crucial in healthcare, research shows that it often diminishes during medical school and residency.[6] Encouraging wonder in medical students may help counteract the decline of empathy and foster related traits in medical students.

Over the past decade, philosopher H. M. Evans wrote about the importance of wonder in clinical settings.[7-9] In 2012, he suggested that a sense of wonder can be a personal resource to the professional clinician and even described it as a "ubiquitous ethical source and a timely recalling of the embodied agency of both patient and clinician".[7] His work emphasizes the value of wonder in encouraging attentiveness and an appreciation of the human experience, even in routine or familiar clinical encounters.[7-9]

Wonder is a feeling of intense attentiveness and appreciation of an aspect of everyday life seen in a new light, which can be accompanied by reflection, exploration, and a change in perspective and motivation.[7,10,11] Wonder is distinct from curiosity

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and awe. Curiosity, a primarily cerebral experience, is an interest and motivation to explore something within an accepted framework.[11] On the other hand, awe is more of a spiritual experience associated with a sense of feeling small in response to "perceptually vast stimuli that overwhelm current mental structures".[12] Wonder might include cerebral and spiritual components, but its most distinctive features are affective and relational. The experience of wonder draws people in and engages them emotionally,[5] experiential sensibilities that are important for clinicians.

Considering the importance of wonder in academic and clinical settings,[5,6,13] Geller and colleagues developed and validated a measure of students' capacity for wonder (CfW) using a mixed-methods approach. Their work established a 10-item CfW scale, which contains two subscales representing "perspective shifting" and "emotional reawakening." This scale correlates with related constructs of humility, tolerance for ambiguity, curiosity, and empathy.[5]

Geller and colleagues administered their scale to medical students at a top tier medical school and found that second year students had the lowest mean CfW scores compared to students in other years.[13] The authors call for further investigation into what may occur during the second year of medical school to trigger a loss of wonder, and what interventions might mitigate this effect. They also hypothesize that applicants to medical school might vary in their capacity for wonder, a phenomenon worth studying.

To the extent that the capacity for wonder can serve as a proxy for several desirable personal characteristics, it may be fruitful and efficient to consider wonder in the admissions process. As a first step, this study aims to explore experiences of wonder among medical school applicants and their association with various aspects of their application. Our intention was to seek proof of concept that a qualitative elicitation of applicants' capacity for wonder would offer a meaningful portrayal of who they are relative to admissions criteria.

Methods

We conducted a mixed methods analysis of a secondary dataset consisting of a sample of Johns Hopkins medical school applications.

Data Collection

After review and exemption by the Institutional Review Board, the admissions office provided us with an anonymized dataset of applications from applicants interviewed in the 2021-2022 cycle. We formed subgroups based on gender and whether the applicants were accepted or rejected, then randomly selected a 50% sample of applications within each subgroup (n = 224). We excluded applications that did not include secondary essays or were withdrawn before an admissions decision was made.

Starting in 2019, the Johns Hopkins School of Medicine has asked applicants to write an essay in response to the following prompt: *"Wonder encapsulates a feeling of rapt attention… it draws the observer in. Tell us about a time in recent years that you experienced wonder in your everyday life. Although experiences related to your clinical or research work may be the first to come to mind, we encourage you to think of an experience that is unrelated to medicine or science. What did you learn from that experience?"*

Applicants submitted these essays as a part of the school-specific secondary application, which included other essays, and were aware that reviewers would potentially evaluate the essays for admission to medical school. These essays were the primary focus of our dataset, which also included admissions decisions and interview scores in four categories: clinical exposure, research portfolio, leadership experience, and community service. Our team obtained interview scores from two interviewers and ranged from 1 to 5, with 1 being the best and 5 being the lowest. We only used essays from applicants had interviews, and we conducted our analysis after the conclusion of the admissions cycle.

Data Analysis

We uploaded the dataset to NVivo, read all the essays on wonder and coded them both qualitatively and quantitatively. In our qualitative analysis we categorized the essays by topic. For the quantitative analysis, we assigned discrete codes to each of the 10 items in the validated CfW scale ***(Table 1)*** and applied the codes to relevant segments of text in the essays. We trichotomized the number of codes assigned to each essay and created a variable called "extent of wonder". We classified essays with three or fewer items as "low wonder," essays with 4-6 items as "medium wonder," and essays with more than 6 items as "high wonder."

Admissions decisions were grouped into three categories: accepted, waitlisted, and rejected. For our quantitative analysis, using R, we conducted a Fisher's exact test to assess the association between extent of wonder and admissions decisions. The purpose of Fisher's exact tests is to assess whether there is a statistically significant difference between the proportions in two categorical variables. To assess the association between extent of wonder and each of the different interview scores, we used one-way ANOVA, a statistical method of comparing the means of multiple groups.

Results

As shown in ***Table 2***, out of our sample of 224 applications, there was a fairly even distribution by gender (approximately 56% female and 44% male). The overwhelming majority of applicants were 20 to 25 years old. Around 55% of applicants who wrote these essays were accepted, 3% were waitlisted, and 42% were rejected after being interviewed.

Table 1. Items in the CfW Scale and Sample Quotes from Medical School Applicants Corresponding to Each Code.

CfW Scale Items	Quotes
W1: Find yourself drawing new connections between things in the world	"Since the tree was able to grow despite its isolation and the cliff's poor growing conditions, I thought it reflected people's resilience and resourcefulness during the hardships of the pandemic."
W2: Take to heart experiences that challenge your understanding of the world	"Maintaining a garden has taught me to appreciate the unexpected joys of cultivating organic (and, by extension, unpredictable) growth and that some of the most meaningful of insights can come from the unlikeliest sources."
W3: Be described by others as inquisitive	N/A
W4: Find yourself pausing to reflect	"I stared at my peanut butter and jelly sandwich, wondering at the deep meaning that this simple sandwich has to me, sticking with me through various achievements and obstacles."
W5: Move among several different perspectives on the same situation like a camera or microscope lens zooming in and out	"I can't help but find the excess beautiful and disturbing. I indulge my eyes, my nose, and my mouth in more fruit than I could eat in a lifetime, taking a single bite out of the ripest peaches and tossing them to the ground before grabbing the next. I am intoxicated by the mellow, tangy pulp that crescendos into a deep sweetness on my tongue; yet at the same time, the taste bitters as I feel like an accomplice to food waste, insecurity, and world hunger."
W6: Experience familiar things as if for the first time	"It's a song I had heard in the car many times in my life but putting my full attention into it, I felt as though I was hearing it for the first time."
W7: Feel amazement during the ordinary course of events	"I grew familiar with the perpetual noises of the city, from public transit announcements and traffic jams to phones ringing incessantly and the rapid footsteps of working professionals. But I never ceased to be amazed by these 'seemingly mundane' everyday moments."
W8: Feel personally engaged by an experience that takes your breath away	"It wasn't just that Carson wrote in such beautiful prose for literary arguments; her words seemed to capture and articulate everything swirling in my mind about the nature of human desire and connection, and why century after century we continue to write about it. Simply put, her writing moved me as I breathlessly read page after page in wonder."
W9: See the world with an interest of a child	"I looked with wonder and childlike awe, as I saw the light of a million dying stars. If we wished upon a star within a starry night, this would undoubtedly be the night when dreams would come to life."
W10: Experience surprise	"The shock came when an actor took the stage and began signing, captions of which filled the televisions in the shop windows. This struck a personal note."

Essay Topics

Essays were categorized by the six distinct topics shown in ***Figure 1***. The majority of essays (28%) focused on connecting with others, such as volunteering, religious communities, and relationships with friends and family. This was followed by engaging in art (such as painting, photography, and music; 23%) and experiences in nature (such as hiking or going to the beach; 20%). Less common topics included engaging in wellness (such as cooking, gardening, meditation, and journaling; 11%), the pursuit of knowledge (such as exploring topics in history and philosophy; 10%), and sports and exercise (such as going to sporting events, working out, and playing individual or team sports; 8%).

Coding of "Wonder" Essays

Table 1 shows the 10 codes in the validated CfW scale as well as sample quotes that correspond to each code. The two most prevalent codes in our analysis were "Take to heart experiences that challenge your understanding of the world," followed by "Find yourself drawing new connections between things in the world."

Association between extent of wonder and admissions status

Table 3 provides the frequency distributions for extent of wonder and its association with admissions status. Approximately 28% of essays had 3 or fewer items ("low wonder"), 56% had 4-6 items ("medium wonder"), and 16% had more than 6 items ("high wonder"). There was an association between applicants' extent of wonder and whether or not they were admitted to medical school. Out of 62 applicants with "low wonder," about one quarter were accepted and two thirds were rejected by the end of the application cycle. Among the 126 applicants with "medium wonder," twice as many applicants (62%) were accepted than were rejected (36%). Among the 36 applicants with "high wonder," over 80% were accepted. This association was statistically significant ($p < 0.0002$).

We also found a significant association of extent of wonder with mean interview scores ($p = 0.00025$) and mean scores in research portfolio ($p < 0.0001$). However, we did not find a significant association between extent of wonder and the three other interview scores (clinical exposure, leadership experience, and community service).

Table 2. Characteristics of Medical School Applicants.

Characteristic	TOTAL (N=224) N (%)
Gender	
Female	126 (56%)
Male	98 (44%)
Other	0 (0%)
Age	
20-25	198 (88%)
>25	26 (12%)
Admissions Decisions	
Accepted	124 (55%)
Waitlisted	6 (3%)
Rejected	94 (42%)

Discussion

To our knowledge, this is the first study to explore the capacity for wonder among applicants to medical school. Our results point to a significant correlation between medical school applicants' extent of wonder, applicants' interview scores, and ultimately, admissions decisions. We were not surprised by the associations of extent of wonder with mean interview scores or mean scores on research portfolio. Interviews inherently involve relational qualities, and the capacity for wonder may be a motivating factor for engaging in research. However, we expected a positive association between extent of wonder and interview scores for leadership and community service because both require strong interpersonal skills and a certain level of engagement. Perhaps the scoring of leadership and community service was based more on the number of hours devoted to leadership and community service activities rather than some estimate of quality, impact, or personal growth. This may indicate that leadership and community service scores reflect external accomplishments rather than qualities such as empathy and wonder.

Figure 1. Categorization of Essay Topics Among Medical School Applicants.

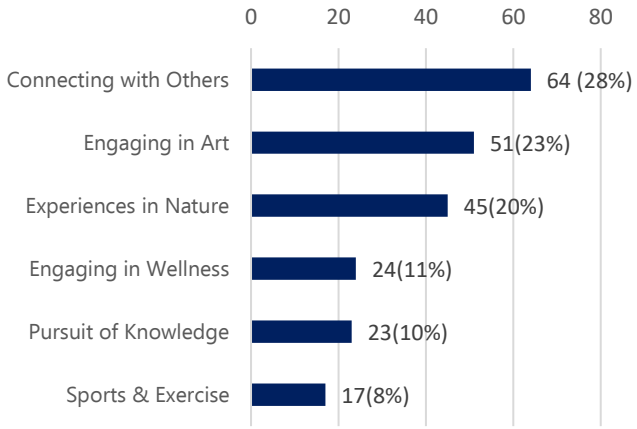

Table 3. Association Between Wonder Extent, Admissions Decisions, and Interview Scores Among Medical School Applicants.

Extent of Wonder	Total	Admissions Status			Mean Interview Scores	
		Rejected	Accepted	Waitlisted	Mean Interview Scores	Mean Scores in Research Portfolio
Low: ≤3						
CfW items	62	43 (69.4%)	17 (27.4%)	2 (3.2%)	1.75	1.74
Med: 4-6						
CfW items	126	45 (35.7%)	78 (61.9%)	3 (2.4%)	1.55	1.39
High: >6						
CfW items	36	6 (16.7%)	29 (80.6%)	1 (2.8%)	1.50	1.31
			$p < 0.0002$		$p = 0.00025$	$p < 0.0001$

Another notable finding was that many medical school applicants in our sample described experiences of wonder as connecting with others. This finding supports theoretical evidence that the experience of wonder is affective and relational.[12] The findings that many applicants also wrote about engaging in art and self-reflection in their wonder essays supports empirical evidence that arts-based education in medical school is associated with increased capacity for wonder scores, can foster professional identity formation, and can be transformative for students.[14]

Limitations

Our current study has several limitations. First, our sample only includes applicants who were interviewed. We do not know whether we would have categorized essays the same way or associated them with other aspects of the application (such as whether applicants received an interview) if our data had included students not invited for interviews. Second, there was a sole reader for these essays since this work was conducted as part of a project that a medical student led. As such, there may be potential biases, as the sole reader's perspectives or interpretations might have influenced the coding process. Although all co-authors discussed and agreed on codes in advance, we do not have a formal assessment of inter-rater reliability, which limits the rigor of the analysis. Due to time and financial constraints, we could not recruit additional coders, which would have reduced the risk of bias and improved reliability. We also did not use a deductive coding approach due to these constraints.

In addition, we did not have a way to control for the quality of the writing. Some applicants may have received help while brainstorming, writing, or editing their essays, which could have influenced the topic they chose to write about or the extent of wonder reflected in the essay. There are considerable differences in applicants' access to support and privilege, including their undergraduate institution, paid services, and social contacts. In turn, these socioeconomic factors could influence the topics, content, and quality of essays.[15] Since the quality of writing is likely to influence admissions decisions, it may have been a confounding variable in our analysis.

Moreover, there may be potential cultural biases in the CfW scale. Interpretations of wonder may vary across demographics, potentially influencing the topics applicants consider relevant to the prompt or how they describe experiences of wonder. These biases may also affect the content and perceived quality of essays. Lastly, we used data from only one institution, as Johns Hopkins is currently the only medical school that asks students to write essays on wonder.

Implications and Future Directions

Our study describes an early-stage initiative at a single institution that is both conceptually and methodologically innovative and may lay the groundwork for considering the role of wonder in the admissions process on a larger scale. Although the relationship we identified between the extent of wonder and admissions decisions was correlational, not causal, our findings provide proof of concept that the capacity for wonder may have a useful role to play; additional research is needed. To supplement our quantitative analysis, it would be interesting to conduct a qualitative content analysis of wonder essays to help us better understand and characterize applicants' experiences of wonder and explore the degree to which these qualitative experiences predict medical school admissions decisions. Incorporating wonder could align admissions with calls for innovations in the admissions process that emphasize empathy, compassion, communication, and other skills and qualities over standardized test scores, thus supporting more holistic student assessments.[3]

It may be useful to examine how the capacity for wonder may supplement or relate to some of the core personal competencies that schools identify as important for entering medical students, including ethical responsibility to self and others, service orientation, resilience and adaptability, and teamwork.[2]

To be clear, we do not propose that schools use or even calculate a quantitative assessment of the extent of wonder as part of the admissions process at this time. While it is important to consider applicants' personal qualities and experiences, quantifying these characteristics may have unintended consequences, as there is often a tension between expected and genuine responses when addressing essay questions in the admissions process.[16] For example, applicants may tailor their responses or even exaggerate details to include more items in the capacity for wonder scale if they believe that reviewers will score their essays for extent of wonder. Instead of using extent of wonder solely as a quantitative assessment tool, it is important to understand applicants' personal experiences of wonder and consider how to use them to learn about applicants more holistically.

This exploratory study points toward several fruitful directions for subsequent research. First, our findings should be verified at other institutions. This would require other schools to consider including an essay about wonder in their secondary application and could potentially lead to future multi-institutional studies. Comparing wonder across different medical school settings and exploring how cultural background and identity influence experiences and interpretations of wonder would provide deeper insights. In addition, it would be useful to know whether essays about wonder influence, consciously or unconsciously, the screeners' recommendations regarding which applicants to interview. Other components of the medical school application—such as undergraduate studies (i.e., whether and to what extent applicants studied the humanities), personal statements, and responses to other questions in the secondary application (including experiences applicants may have had during a gap year)—may also be associated with the capacity for wonder. Using artificial intelligence and language processing programs would make it possible to code essays more efficiently and include more variables for an in-depth qualitative analysis.

The capacity for wonder may have broader applicability to medical education than just the admissions process. Exploring interventions that support this capacity could benefit medical students at various stages of their education. For example, new curricular initiatives and programs that involve the arts and humanities could help sustain students' capacity for wonder.[17] This may be particularly important for second-year medical students, who one study found to have the lowest mean CfW scores.[13] Considering high burnout rates among medical students, future research could also explore whether cultivating the capacity for wonder may be protective against burnout.18 Additionally, longitudinal studies could examine associations between capacity for wonder and success and flourishing throughout medical training, providing insight into its lasting impact beyond the admissions process

References

1. Write Albanese MA, Snow MH, Skochelak SE, Huggett KN, Farrell PM. Assessing personal qualities in medical school admissions. Acad Med. 2003;78(3):313-321.
2. Koenig TW, Parrish SK, Terregino CA, Williams JP, Dunleavy DM, Volsch JM. Core personal competencies important to entering students' success in medical school: what are they and how could they be assessed early in the admission process? Acad Med. 2013;88(5):603-613.
3. Prober CG, Desai SV. Medical School Admissions: Focusing on Producing a Physician Workforce That Addresses the Needs of the United States. Acad Med. 2023;98(9):983-986.
4. Geller G, Caldwell M, Merritt MW. The Cultivation of Wonder in the Premedical Learning Environment: Nurturing Ethical Character in the Early Formation of Health Professionals. J Coll Character. 2018;19(3):229-235.
5. Geller G, Steinman C, Caldwell M, Goldberg H, Hanlon C, Wonnell T, et al. Development and Validation of a Capacity for Wonder Scale for Use in Educational Settings. J Psychoeduc Assess. 2020;38(8):982-994.
6. Pedersen, R. Empathy development in medical education – A critical review. Med. Teach. 2010, 32(7), 593–600.
7. Evans HM. Wonder and the clinical encounter. Theor Med Bioeth. 2012;33(2):123-136.
8. Evans HM. Wonder and the Patient. J Med Humanit. 2015;36(1):47-58.
9. Evans HM. Medicine, the body and an invitation to wonder. Med Humanit. 2016;42(2):97-102.
10. Carlsen A, Sandelands L. First passion: Wonder in organizational inquiry. Manag Learn. 2015;46(4):373-390.
11. Opdal PM. Curiosity, Wonder and Education seen as Perspective Development. Stud Philos Educ. 2001;20(4):331-344.
12. Shiota MN, Keltner D, Mossman A. The nature of awe: Elicitors, appraisals, and effects on self-concept. Cogn Emot. 2007;21(5):944-963.
13. Geller G, Shin S, Goldberg H, Merritt MW. Capacity for wonder among medical students: Assessment and educational implications. Med Teach. 2023;45(1):68-72.
14. Tackett S, Eller L, Scharff S, Balhara KS, Stouffer KM, Suchanek M, et al. Transformative experiences at art museums to support flourishing in medicine. Med Educ Online. 2023;28(1):2202914.
15. Wright S. Medical school personal statements: a measure of motivation or proxy for cultural privilege? Adv Health Sci Educ. 2015;20(3):627-643.
16. White J, Brownell K, Lemay JF, Lockyer JM. "What Do They Want Me To Say?" The hidden curriculum at work in the medical school selection process: a qualitative study. BMC Med Educ. 2012;12(1):17.
17. Zheng DM, Yenawine P, Chisolm MS. Fostering wonder through the arts and humanities: using visual thinking strategies in medical education. Acad Med. 2024;99(3):256-260.
18. IsHak W, Nikravesh R, Lederer S, Perry R, Ogunyemi D, Bernstein C. Burnout in medical students: a systematic review. Clin Teach. 2013;10(4):242-245

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Author Contributions

Conceptualization: EC, MM, GG. Formal Analysis: EC. Methodology: EC, MM, GG. Writing - Original Draft: EC. Writing - Review Editing: MM, GG.

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Original Article

A Nationwide Evaluation of U.S. Geriatric Fellowship Websites: Assessing Program Information Availability

Emily C Courtois,[1] Jacob Lahti,[2] Thomas C Varkey,[3] Nimit Agarwal. [4]

Abstract

Introduction: Prospective students interested in any medical fellowship seek out program information in order to help them make application and attendance decisions. Additionally, the field of geriatric medicine is traditionally underserved in the United States, and attending geriatric fellowship programs can make a great impact in improving this population's care. The purpose of this study was to examine geriatric medicine fellowship program websites and assess their available information for prospective fellows. **Methods:** Using the Electronic Residency Application Services (ERAS), a list of websites was created of U.S. institutions offering Accreditation Council for Graduate Medical Education (ACGME)-accredited geriatric programs also participating in the National Residency Matching Program (NRMP, or "the Match"). Every website was evaluated for 8 items of application information such as application deadlines, program director/coordinator contact information, and a list of application requirements and 17 items of program information, such as compensation, locations of service, and rotation schedule. **Results:** In total, 103 programs were assessed in this study. Overall, the information most often listed on these fellowship websites were program affiliation (100%), training sites (88.3%), and program coordinator's contact (83.5%). In total, only 51% and 45% of all application and program information, respectively, was available according to the assessment criteria. There is a clear lack of information for prospective fellows to access. **Conclusion:** In order to help increase fellow attendance, adequate information must be available. With the increasing geriatric population, there will be an increased need for fellowship-trained physicians trained in geriatric medicine to serve them.

Introduction

By 2030, the geriatric population is expected to reach 73 million people in the United States.[1] To account for this exponential rise, and provide enough physicians trained in geriatric-centered care, there has been a substantial rise (64.6%) in geriatric medicine fellowship programs, from 2001 to 2018.[2] A survey study evaluating geriatric medicine scholarly concentration programs amongst nine different medical schools determined that curriculum and mentoring were two of the most important components which improved a physician's ability to care for older adults.[3] Unfortunately, despite this perspective and the resources being created to address this anticipated healthcare shortage, many of the geriatric medicine fellowship positions are consistently left unfilled. In 2022, only 177 of 411 positions, or 43% of geriatric medicine fellowships, were filled, which was the lowest rate among all 71 specialties.[4] Additionally, the current number of geriatricians has been falling in the United States to 7,300, which makes up less than 1% of all physicians.[5]

Many factors could be contributing to this, including lower compensation, minimal exposure to the field, and the complexities of managing multiple comorbidities; however, another potential cause for this diminished fill rate is a lack of knowledge of the application or program itself. A survey study by Oliver and Kelly noted that medical school applicants for family medicine residency programs received most or all of their program information from the internet and social media.[6] Due to the rise of accessible technology, providing information online is now the most effective avenue for making informed decisions. More specifically, online information has been known to act as a decision-aid for choosing career paths or programs.[7] It is hoped that the attention to lacking program information can be insightful and provide some means of addressing low U.S. fellowship attendance rates. In fact, some studies have sought to explore the availability of program information, from epilepsy fellowships, to orthopedic surgery residency programs, cardiothoracic surgery fellowship, and child and adolescent psychiatry fellowships.[8-11]To date, no study has yet to explore program information availability in geriatric fellowships across the United States. The purpose of this study was to investigate the available application and program information for geriatric medicine fellowships.

Methods

Study Overview

This is a cross-sectional website analysis, designed to examine the available application and program information for geriatric fellowships. Reporting followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

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Search Strategy

Using the Electronic Residency Application Services (ERAS), a list of websites from institutions offering Accreditation Council for Graduate Medical Education (ACGME)-accredited internal medicine-based geriatric medicine fellowship programs was created. All programs must also participate in the National Residency Matching Program (NRMP, or "the Match"). This list was acquired on July 23, 2023 and searched throughout September 2023 to January 2024.

For programs which had incorrect links or those that could not be accessed directly through ERAS, a simple Google search was conducted to try and locate an appropriate website for the program. Programs that could not be accessed either directly through ERAS or through this simple Google search were excluded from this study.

Evaluation Criteria

A list of evaluation criteria for both the application and the program itself were defined by the authors and tabulated in ***Supplementary Material.*** There were 8 items evaluated for the application information and 17 items evaluated for the program information.

Criteria Justification and Reasoning

All the application and program evaluation criteria were based on previously-established scientific literature evaluating website information for medical fellowship programs.[12,13] The current authors also incorporated some of their own criteria from personal experience of applying to varying educational programs. Much of the criteria were logistical and practical, such as program benefits and training sites, with additional factors they deemed important to consider for student life, such as faculty to fellow ratio and evaluation methods. While there is a chance some students may determine the selected criteria inapplicable to their personal needs, other students might disagree. To consider information based on many perspectives, an extensive list of criteria was developed beyond those used in previously published literature. Additionally, the expertise of a fellowship-trained geriatrician physician was obtained for this project and determined the selected criteria were sufficient for prospective fellows entering these programs.

Data Collection, Analysis, and Synthesis

To account for any potential biases in assessing each program, no team member assigned to evaluate program websites had entered or tried to enter any particular geriatric fellowship program, ensuring assessors were impartial. Additionally, all criteria for which the websites were evaluated relied on binary answers ('yes' or 'no'), for present or absent information, requiring objective judgement.

All geriatric medicine fellowship websites were equally divided and assigned to each of the reviewers (ECC, JL, TCV). All websites were screened for application and program evaluation criteria and compiled within a shared spreadsheet. If there was a dispute or inquiry into a certain criteria item, the other authors served as consultants to determine the information. All authors must come to a consensus before recording the final result.

All data were analyzed in Microsoft Excel.[14]The results were tabulated and then visually depicted by bar graphs and further analyzed by percentages of recorded versus missing data. All website data were kept separated between application and program criteria throughout the study.

Results

Search Results

Using ERAS, 111 programs were identified which offered geriatric medicine fellowships. Eight programs were excluded after they could not be located from the simple Google search. In total, 103 programs were included into this study.

Results of Available Application Information

There were 8 items for which each program application was assessed. As shown in ***Figure 1***, 86 programs listed their coordinator's contact information, 62 listed their director's contact information, 28 listed their program's opening date for applications, 33 listed their application's submission deadline, 70 listed their application's timeline, 79 listed their program's application requirements, only 1 listed their board score requirements, and 59 listed their program's visa sponsorship information for non-United States citizens interested in applying.

The information most often listed on program websites was the program coordinator's contact, however, this was only available for 86 of the 103 websites (83.5%). The second-most often available information was the list of application requirements, which was only listed for 79 of the 103 websites (76.7%).

The criteria found in less than 50% of the websites were opening date of application (27.2%), application submission deadline (32.0%), and board score requirements (1.0%)

Results of Available Program Information

There were 17 items for which each program was assessed. As seen in ***Figure 2***, 18 websites listed their program's call schedule, 85 listed their clinical schedule/rotation, 103 listed their program's affiliation, 34 listed their fellow alumni directory, 58 listed their current fellow directory, 49 offered a program video or virtual tour, 69 listed their program's didactic requirements, 14 listed their fellow's publications, 28 listed their fellow's demographics, 5 listed their fellow board pass rates, 73 listed their program's educational/academic activities, 7 listed their program's evaluation methods for fellow performance, 36 listed their diversity information, 41 displayed their compensation information, 42 provided program size information, 91 listed

Figure 1. Number of Fellowship Programs that Listed Information for the 8 Evaluated Items.

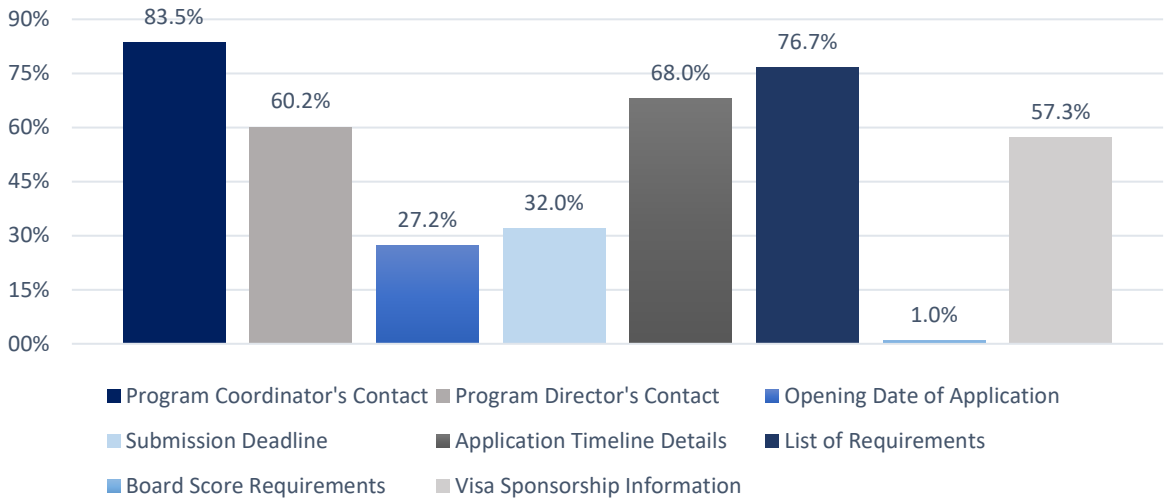
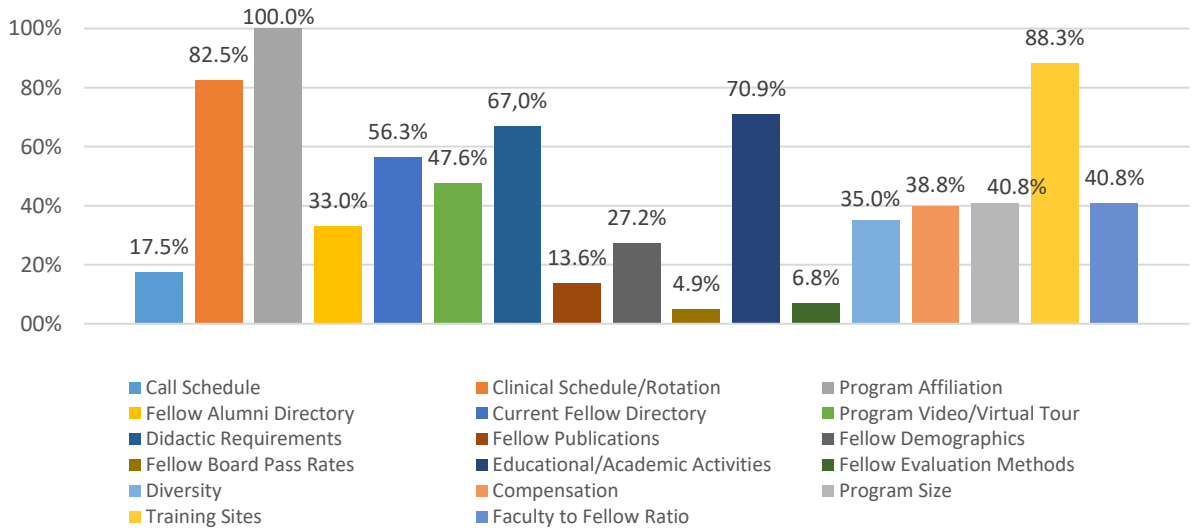


Figure 2. Number of Fellowship Programs that Listed Information for the 17 Evaluated Items.



training sites, and 42 provided sufficient information to calculate a faculty-to-fellow ration.

The information most often listed on these fellowship websites were program affiliation (100%) and training sites (88.3%), followed by the fellowship's clinical schedule (82.5%).

The criteria found in less than 50% of the websites were call schedule (17.5%), fellow alumni directory (33.0%), program video or virtual tour (47.6%), fellow publications (13.6%), fellow

demographics (27.2%), fellow board pass rates (4.9%), fellow. evaluation methods (6.8%), diversity (35.0%), compensation (39.8%), program size (40.8%), and faculty to fellow ratio (40.8%).

The results show that the majority of the program criteria (n = 11 of 17) was not found in 50% of the websites

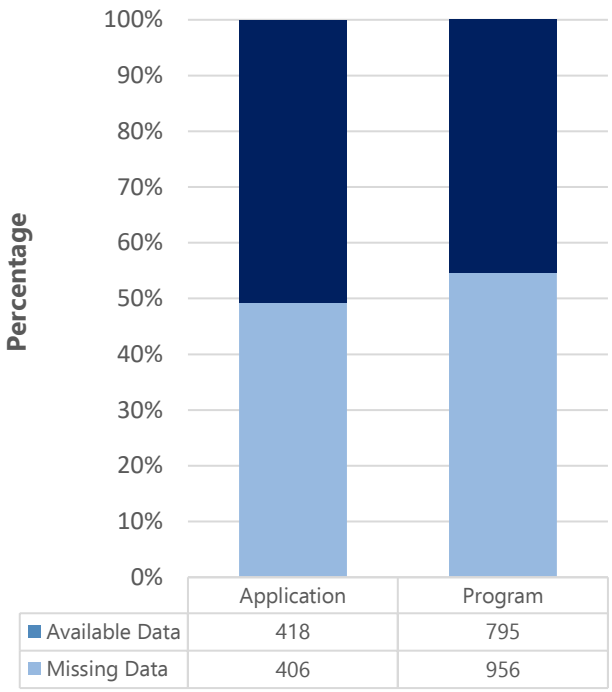
Results Overview

The application information that was the least available across the fellowship program was the board score requirement, followed by the opening date of the program application. For the program information, the least reported statistic was the fellow board pass rates for the program, followed by the program's evaluation methods for its fellows.

Out of the 8 application information assessment criteria that could have been recorded for all 103 websites (824 total), only 51% could be located, and similarly, for the 17 different program

information assessment criteria (1,751 total), only 45% could be located ***(Figure 3).***

Figure 3. Visual Representation of the Total Available Information Versus Missing Information for Both the Application and Program.



Discussion

Out of 103 geriatric medicine fellowship programs assessed, there was a significant lack of available information for both application and program criteria. This finding creates some cause for concern for prospective applicants. Notably, some trends exist across the programs. For example, all programs provided affiliation information, the majority also provided information for fellowship training sites, and most provided contact information for program coordinators. In contrast, almost all studies did not provide information for board score requirements, the fellow evaluation methods, or fellow board pass rates. From these results, we cannot infer the information's level of importance, however, it may be that these programs are required to provide affiliation information, while information on board scores may not be of their utmost concern, rather opting to highlight clinical experience and research opportunities.

There were two located studies which have examined geriatric medicine fellowship programs in previous years. One study found that there was difficulty pertaining to accessibility of program information, however, they analyzed 43 family medicine geriatric fellowship programs and utilized a less robust set of criteria in which they analyzed these programs.[15] Regardless, the same conclusion stands true—there is a need for improvement. The second study discovered, after reviewing these same 43 family medicine programs and an additional 107 internal medicine programs in 2019, that the websites listed inconsistent or absent information, similar to the findings in our current study.[16] Of note, there has been a decrease in the number of analyzed internal medicine geriatric fellowship programs, with the 2019 study analyzing 107 websites as compared to the current study, which could only evaluate 103 in 2024. Many reasons for this difference may exist, such as differing inclusion or exclusion criteria and a change in website access over time. In summary, the current study provides an updated assessment of the websites. Using this literature, a trend of insufficient geriatric fellowship program information can be established.

It is well-known in job recruitment that a clear job description and the candidate's self-assessment for a good fit strongly influences whether or not the candidate applies for the job. This real-world experience is the similar to, if not the same as, applying to a fellowship program. Thus, the current study's results may highlight a deterrent from fellowship enrollment, given that there is still an insufficient volume of geriatric medicine fellows.[17] For example, the prospective fellow may be more inclined to apply for a fellowship with available compensation information rather than applying to one that does not. The prospective fellow's assessment of the programs can only rely on the information readily available, before necessitating direct contact to program coordinators or faculty. Therefore, it is essential this information is available in order to prevent further dissuasion of potential applicants.

There are some limitations inherent with those of a retrospective review. None of the authors have recently begun or are currently pursuing a geriatric medicine fellowship and only one of the authors is a fellowship-trained geriatrician. These factors may lead to oversight regarding which criteria are more or less applicable to the pursuit of this type of fellowship.

The strengths of this review are the rigid methodology and concise definitions of the criteria for completion of this study, lending credible validity to the results. Also, the Google search for those fellowships not accessible via ERAS depicted the real-life experience of a prospective student trying to access program information.

Given both the decline of geriatricians and the quickly-rising geriatric population over the past 20 years, the demand for geriatric medicine specialists is only expected to increase.[4,18] Inadequate information for these programs may be an inadvertent deterrent for many applicants. Based on the findings of the current study, individual programs need to add, and if necessary, update their program information. It is recommended that programs assess their own websites using the evaluation criteria in the current study as a foundation. While we as an authorial team recognize that improving the presentation and amount of relevant information on program websites is in no way a perfect solution for the geriatrician shortage or perhaps even a primary factor expected to greatly increase geriatric medicine fellows, removing this barrier could alleviate some concerns around attendance and provide a potential avenue for increasing the number of fellowship-trained geriatricians in the future.

Conclusion

It is hoped that the findings of this study will bring light to areas needing improvement relating to the concerning scarcity of fellowship-trained geriatricians. Given the need for more geriatricians, it is important for these programs to update their websites to increase accessibility and provide more transparency to their prospective fellows. The evaluation criteria utilized for this investigation may serve as a checklist for programs self-assessing their own websites for adequate program information.

Summary – Accelerating Translation

A Nationwide Evaluation of U.S. Geriatric Fellowship Websites: Assessing Program Information Availability

Prospective students interested in any medical fellowship seek out program information in order to help them make application and attendance decisions. Additionally, the field of geriatric medicine is traditionally underserved in the United States, and attending geriatric fellowship programs can make a great impact in improving this population's care. To compensate for the growing need of geriatricians, more geriatric fellowship programs have been created; however, many of the fellowship positions are consistently left unfilled. One possible factor that could be limiting enrollment is the availability of program information for prospective fellows. The purpose of this study was to examine geriatric medicine fellowship program websites and assess their available information for prospective fellows.

This was a cross-sectional evaluation study. Using the Electronic Residency Application Services (ERAS), a list of websites was created of U.S. institutions offering Accreditation Council for Graduate Medical Education (ACGME)-accredited geriatric programs also participating in the National Residency Matching Program (NRMP, or "the Match"). Every website was evaluated for 8 items of application information such as application deadlines, program director/coordinator contact information, and a list of application requirements and 17 items of program information, such as compensation, locations of service, and rotation schedule.

In total, 103 programs were assessed in this study. Overall, the information most often listed on these fellowship websites were program affiliation (100%), training sites (88.3%), and program coordinator's contact (83.5%). In total, only 51% and 45% of all application and program information, respectively, was available according to the assessment criteria. There is a clear lack of information for prospective fellows to access.

In order to help increase fellow attendance, adequate information must be available. With the increasing geriatric population, there will be an increased need for fellowship-trained physicians trained in geriatric medicine to serve them

References

1. America Counts Staff. 2020 census will help policymakers prepare for the incoming wave of aging boomers. Available from: https://www.census.gov/library/stories/2019/12/by-2030-all-baby-boomers-will-be-age-65-or-older.html#:~:text=The%202020%20Census%20will%20provide,on%20America's%20population%20age%20structure.%E2%80%9D&text=Born%20after%20World%20War%20II,will%20turn%2074%20next%20year. Last updated October 3, 2024; cited Janurary 29, 2025.
2. Petriceks AH, Olivas JC, Srivastava S. Trends in geriatrics graduate medical education programs and positions, 2001 to 2018. Gerontol Geriatr Med. 2018;4:2333721418777659
3. Wilson L, Kelley C, Cheever CR, Harlow E, Buhr G. The impact of scholarly concentration programs on graduates' career choices and interest in the care of older patients. Cureus. 2024;16(1):e51697
4. Gurwitz JH. The Paradoxical Decline of Geriatric Medicine as a Profession. JAMA. 2023;330(8):693-94
5. Gleckman H. Why do so few doctors want to specialize in caring for older adults? Available from: https://www.forbes.com/sites/howardgleckman/2023/08/15/why-do-so-few-doctors-want-to-specialize-in-caring-for-older-adults/. Last updated August 16, 2023; cited January 29, 2025.
6. Oliver MG, Kelly K. Student perceptions and use of social media as residency program information. Fam Med. 2022;54(5):380-83
7. 7. Roscoe RD, Grebitus C, O'Brian J, Johnson AC, Kula I. Online information search and decision making: Effects of web search stance. Comput Hum Behav. 2015;56:103-118
8. Marsia S, Kamran A, Mahmood Shah SM, Merchant RA, Abbas SE. Exploring the content of epilepsy fellowship program websites: an analysis of information available to applicants. BMC Med Educ. 2024;24(1):699
9. Bernstein SL, Wei C, Gu A, Fufa D, Levine WN. Evaluating databases with orthopaedic surgery residency program information. J Am Acad Orthop Surg 2022;30(24):1177-83
10. Raza SS, Asban A, Donahue J, Wei B. Analysis of applicants' perspectives of cardiothoracic surgery fellowship program websites. Ann Thorac Surg 2022;114(6):2372-78
11. Bernstein SA, Gu A, Bernstein SL, Wei C, Vogel AC, Gold JA. Child and adolescent psychiatry fellowship program website content and accessibility. Acad Psychiatry 2021;45(4):425-28
12. Jafri FI, de Montfort Shepherd A, Raman P, Varkey TC, Hyman C, Agrawal D. Transplant hepatology fellowship websites: The good, the bad, and the unhelpful. Dig Dis Sci 2023;68(4):1091-95
13. Khan MS, Hayat J, Marsia S, et al. How well do we represent ourselves: an analysis of cardiology fellowships website content. Future Cardiol. 2020;16(4):281-87
14. Microsoft Excel. Microsoft Corporation 2018.
15. Chan M, Chan E, Wei C, et al. Geriatrics fellowship-family medicine: Evaluation of fellowship program accessibility and content for family medicine applicants. Cureus. 2020;12(9):e10388
16. Maybee C, Nguyen NT, Chan M, et al. Assessing the accessibility of content for geriatric fellowship programs. J Am Geriatr Soc. 2021;69(1):197-200
17. National Resident Matching Program, Results and Data: 2024 Main Resdiency Match. Washington, DC: National Resident Matching Program, 2024.
18. Caplan Z. U.S. older population grew from 2010 to 2020 at fastest rate since 1880 to 1890. Available from: https://www.census.gov/library/stories/2023/05/2020-census-united-states-older-population-grew.html. Last updated: May 25, 2023; cited January 29, 2025.

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Conflict of Interest Statement & Funding

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Author Contributions

Author A: preparation of manuscript, acquisition of data, data analysis; Author B: preparation of manuscript, acquisition of data; Author C: preparation of manuscript, acquisition of data; Author D: preparation of manuscript, project supervision.

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Supplementary Material

Appendix A. Tables 1 and 2 of Assessment Criteria

Table 1. List of the Criteria Used to Assess Each Included Geriatric Fellowship Program's Application Information.

Application Information Evaluation Criteria	
Item	**Definition**
Program Coordinator Contact	(other accepted titles include: Program Administrator or Program Manager) Program Coordinator first and last name AND phone number OR e-mail address. Contact information of an assistant to the Program Coordinator is acceptable.
Program Director Contact	Program Director first and last name AND phone number OR e-mail address. Any contact information must clearly not be for medical appointment scheduling. Webpage addresses related to the Director's medical practice does not satisfy this requirement.
Opening Date of Application	Any reference to the opening of the fellowship application cycle, which must include the month. A season or time of year (e.g. 'Fall' or 'Late Spring') does not satisfy the requirement. The timeframe for when a school begins reviewing applications does not satisfy the requirement.
Application Deadline	Any reference to the application cycle deadline, which must include the month. A season or time of year (e.g. 'Fall' or 'Late Spring') does not satisfy the requirement.
How to Apply	A simple statement that informs the reader that they must apply using the ERAS or similar service, with or without a link to such service is required. Additionally, the website must also include at least ONE of the following details: When application review begins; When interview invites are delivered; When interviews are held; When final decisions on acceptance will be delivered.
Application Requirements	At least ONE of the following must be listed: Completion of an internal medicine or family medicine residency program; An MD or DO degree; U.S. Citizenship, Permanent Residency, or Visa documentation; ERAS Application; Curriculum Vitae (CV); Personal Statement; Medical School Transcript/Medical School Performance Evaluation (MSPE); USMLE and/or COMLEX board exam scores; Letters of Recommendation (with or without required number of letters); Photograph
Board Score Requirements	The presence of a numerical, objective value, that defines the minimum required or recommended board exam score
Visa Sponsorship	The website must explicitly state that they either will or will not sponsor at least ONE of the following: H1-B; J-1; O-1; EB-1; EB-2.

Table 2. List of the Criteria Used to Assess Each Included Geriatric Fellowship Program's Available Information.

Program Information Evaluation Criteria	
Item	**Definition**
Current Call Schedule	Any information on the amount of time fellows will spend on call. This requirement can be satisfied if listing the required number of shifts or hours on call OR displaying the call rotation schedule. Mentioning that fellows will be required to take call with no reference to amount of time on call does not satisfy this requirement. Alternatively, consultations (this does not include being on a consultation rotation, such as being on a VA consult block or an ACE consult block) will satisfy this requirement.
Current Clinic/Rotation Schedule	Any information on fellow clinical rotations including rotation sites (note that the names of the physical facility do not need to be listed, but rotation name such as "inpatient palliative" or "ACE consults" are appropriate).
Program Affiliation	The name of the medical school or 3rd-party entity running the fellowship program.
Alumni Directory	A list of one or more fellowship alumni with their names.
Current Fellow Directory	A list of current fellows including at least the first and last name.
Videos or Virtual Tour	Any informational videos about the program. These can be linked to YouTube or another similar platform or embedded directly into the webpage. Generalized videos on the school running the fellowship do not meet this requirement.
Didactic Requirements	Any program information for fellows' expectations on at least ONE of the following: Grand Rounds; Case Presentations; Attendance of Mandatory Lectures.
Fellow Publications	Any information providing a list of publications authored in whole or in part by current and past fellows including at least ONE of the following: A link to a collection of these publications or links to external sources for them; DOI numbers; full citations for publications. Research that is affiliated with the department or institution but not explicitly linked to past or present fellows does not meet this requirement.
Fellow Demographics	Information about the current fellows, including Medical School OR Residency Location. Any school or program name clearly affiliated with the particular current fellow will be sufficient enough to meet this requirement.
Board Pass Rate	This requirement can only be met if a numerical, objective value, defining the average board exam pass rate must be listed.
Non-Didactic Educational/Academic Activities	Any information of fellows' expectations for at least ONE of the following: Conference presentations of research/quality improvement (QI) projects; Publication of research/QI projects; Other presentation of research/QI projects; Delivery of mandatory lectures or presentations to medical students and/or residents. Participation in a QI or research project, or a QI/Research rotation block, without further mention of presentation of work or results does not meet this requirement.
Fellow Evaluation Methods	Explicit statement of the ACGME competencies, skills, and/or metrics for which fellows will be evaluated at the end of their program OR alternative evaluation methods/techniques. • Statement that fellows will be evaluated without disclosure of (or access to a webpage displaying) the competencies, skills, and/or metrics does not meet this requirement. • Statement that fellows will be evaluated wholly or in part by their score on the mandatary practice board exam will meet this requirement.

	• If ACGME requirements are listed but not specified to be from the ACGME, this is sufficient to meet this requirement.
Diversity	This requirement can only be met either in the presence of a clear statement of diversity and/or inclusion practices OR a link to the webpage for the Office of Diversity. A statement solely stating that the program has an Office of Diversity and/or Inclusion does not meet this requirement unless the webpage is available on the website.
Compensation/Benefits	This requirement can only be met in the presence of a numerical, objective value, reflecting baseline financial compensation paid to fellows. The presence or absence of additional information such as time off, insurance, and other such pecuniary benefits does meet this requirement alone.
Program Size	This requirement can only be met in the presence of a numerical, objective value stating the open positions. This cannot be calculated based on the number of current fellows, as it will not necessarily reflect the number of positions.
Faculty to Fellow Ratio	This can be determined only if the ratio is explicitly stated OR the number of fellowship positions AND a faculty directory or number f total faculty members are available so the simple ratio can be calculated.
Training Sites/Locations of Service	A list of the names of different sites/locations where fellows may be practicing and training.

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Original Article

A Comparative Cross-Sectional Study on the Prevalence of Impostor Phenomenon in Medical and Non-Medical Students of Lahore City, Pakistan

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Abstract

Background: The Impostor Phenomenon (IP) is a psychological pattern characterized by feelings of inadequacy and self-doubt despite evident competence. This study aims to compare the prevalence of Impostor Phenomenon among medical and non-medical students in Lahore, Pakistan and to compare the distribution between genders. **Methods:** A cross-sectional study involving a total of 242 medical and non-medical students was conducted using the validated Clance Impostor Phenomenon (CIP) scale that ranges between 20 to 100 and includes scores categorised as ≤40 (mild), 41-60 (Moderate), 61-80 (Frequent), ≥81 (Severe). The data was collected between February 2023 to April 2023. It was analyzed using descriptive statistics and unpaired t-tests as well as multivariate linear regression model in SPSS version-26. **Results:** IP was prevalent among both medical and non-medical students, with significantly higher scores among non-medical students (mean CIP score: of 67.08 ±13.704) compared to medical students (mean CIP score: 58.36 ±11.413. It was noted that although IP is prevalent in both genders, it is much more significant in females as females exhibited higher IP scores than males (p-value <0.05). The multivariate linear regression model showed significant dependency of the total CIP scores on the variables, university and gender, with the p-value being less than 0.05. **Conclusion:** In conclusion, this study underscores the high prevalence of IP among medical and non-medical students and highlights the need for targeted interventions. It also explores the effect of both genders on having feelings of impostor-ism.

Introduction

The Impostor Phenomenon (IP), known as imposter syndrome commonly, is an intriguing psychological pattern affecting people across various ages, genders, and professions. It leads individuals to doubt their abilities and feel inadequate, despite clear evidence and recognition of their skills and achievements. This often happens to high achievers who believe they have misled others about their true capabilities.[1,2]

The term was first brought to attention in the 1970s by psychologists Pauline Rose Clance and Suzanne Imes, who observed it frequently in high-achieving women.[3] Over time, it has become evident that this experience is not limited by gender, impacting individuals of various backgrounds and professions.[4]

It can manifest as a nagging feeling of being a charlatan in one's field, a dread of inevitable failure, or an excessive tendency toward self-criticism. These feelings may cause individuals to minimize their achievements, shy away from taking risks, and feel out of place in their professional environment.[5] The impact of this phenomenon can be substantial, leading to reduced job satisfaction, burnout, and even career stagnation.[6] Nevertheless, there are strategies that both individuals and organizations can implement to address this and assist those affected by it.[7]

Since 1978, over twelve hundred studies have been published on the Impostor Phenomenon, with 80% of these emerging in recent years. Efforts have been made to educate the public on the topic, with articles from sources like Harvard Business Review shedding light on the psychological aspects of the phenomenon.[8] These wide variety of clinical research has led to the development of various scales of measurement. The first scale was introduced by Joan Carol Harvey in 1981, a fourteen-item scale.8 Following this, the Clance Impostor Phenomenon Scale (CIPS) was developed by Pauline Rose Clance in 1985, to improve the quality of detecting the impostor phenomenon.[8] It was made to clinically observe attributes or feelings not marked by the Harvey Impostor Scale. This scale consists of twenty questions, each rated on a 5-point Likert scale, resulting in a score ranging from 20 to 100. A higher score indicates stronger imposter feelings, while a score below 40 suggests a negative test. Hence this scale acknowledges the fear of evaluation and feeling of low self-esteem. It is the most commonly used measure by researchers.[9]

Medical students in general are noted to have a higher prevalence of cerebral distress than their peers in other departments. The feeling of detachment, peer pressure, academic stress, financial problems, time constraints and the insight of "implausible expectations" cause anxiety, depression and suicidal

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thoughts among the students.[10] This leads to the feeling of not being able to perform well as physicians while also affecting their mental health i.e. increasing anxiety, depression and low self-esteem eventually causing them to quit their profession.[11] This affects the patient's care negatively.

Many individuals working in non-medical fields also experience similar emotions. The belief that the Impostor Phenomenon (IP) is more prevalent in computer science than in other fields remains unvalidated. In Rosenstein's 2020 research, over half of the respondents met the diagnostic criteria for imposter phenomenon, with a higher occurrence among female computer science students compared to males.[12] Computer science students also showed significantly more imposter phenomenon feelings than students in other fields and even health professions.[12] Although it might be assumed that law students undergo an intense competition and stress, not much research has been performed. In a compelling survey, it was discovered that an impressive sixty-three percent of first-year law students exerted themselves beyond their limits to meet the high expectations set by their law professors.[13]

As the world gets competitive, the desire to ace every challenge put forward to the students by the institutes creates an inevitable pressure. Students of every field try to do better than the others yet not everyone succeeds. Feelings of being an outcast arise; not being able to do well as expected or having burnouts produces the phenomenon of 'imposter-ism' regardless of which field they are in.

Until now, extensive research has been conducted, exploring the frequency of the Impostor Phenomenon amongst students and other professionals.[14-16] However, there has yet to be a study on a comparison between medical and non-medical fields. Hence, this research aims to give spotlight to the differences in both fields and how individuals from either might develop feelings of fraudulence. This reading may further explore the causes and consequences of impostor phenomenon, related to either field; helping in figuring out practical strategies for understanding and overcoming it.

Methods

This comparative cross-sectional study was conducted from February to April 2023 among medical students from CMH Lahore Medical and Dental College, and non-medical students from Lahore University of Management Sciences (LUMS) with the aim to compare the prevalence of imposter phenomenon between them.

This study involved a total of 242 students (121 medical students and 121 non-medical students). The inclusion criteria encompassed both medical and non-medical students from the two universities. Non-Medical includes courses primarily provided by the LUMS institute such as computer science, law, business, etc. Study participants included male and female students, aged 18-27 years, from all academic years, ranging from first to fifth year. Those who were willing to participate and provide informed consent were considered eligible, while who were not enrolled in either institute or were unwilling to give consent were excluded from the study.

The sample size was calculated by using the standard formulas for comparative studies which involve the comparison of two independent groups using unpaired t-test. With a confidence interval of 95%, the study power was set at 80% and the standard deviation was taken as 1.18 and then the critical Z-scores were added to the formula to calculate the sample size (n). Convenience sampling was employed due to the broad scope of the study involving two universities having near 1000 or more students enrolled, meaning participants were selected based on their availability and willingness to take part in the study. Despite this, efforts were made to address any bias by ensuring that all potential respondents had an equal chance to participate, clearly defining the inclusion criteria and by ensuring the adequacy of sample size for statistical analysis.

Approval for the study, Case #. 621 / ERC/ CMH / LMC was obtained from the Institutional Review Board of CMH LMC on 4th February 2023, ensuring compliance with all relevant ethical guidelines. Before participation, all participants were provided with information about the purpose and procedure of the study. Written informed consent was taken from all participants, ensuring voluntary participation. Participants were informed of their right to withdraw at any time. Data was collected using anonymous questionnaires to prevent any identifiable information and anonymized data were used for analysis.

The questionnaires were self-administered and distributed to the medical and non-medical students during their lectures' time. The students filled out the questionnaire in about ten minutes. The questionnaire comprised of sections on consent, socio-demographic characteristics and questions entailed in the Clance Impostor Phenomenon Scale (CIPS).

The Clance Impostor Phenomenon Scale (CIPS) is a validated survey, and it was used after proper permission and agreement.17 The questions encapsulate the different presentations of imposter phenomenon and the participants were to answer with the rate at which they had faced it themselves before the study was conducted, during their time in their respective courses. The reliability of the questionnaire was pretested again in the context of a comparative study using a pilot study for the duration of a week, on a sample size of twenty participants and it was found to be 88.9%. Based on the results of the pilot study, the scale was adapted as such without any modifications.
The responses from which the subjects could choose included: 'not at all true', 'rarely', sometimes', 'often' and 'very true'. A binary recording scheme was used to appraise the answers. According to this technique, a response of one is for not at all true and a five is for very true. The variable age was divided evenly

into three groups; 18-20, 21-23 and 24-27. The ranges were as such to incorporate maximum number of students.

Responses were scored on a Likert scale and the total score of each participant was obtained by adding their chosen options in each question. As there were twenty questions, therefore, a minimum of 20 and a maximum of 100 score was to be expected. Then the mean of the scores were calculated for each group; medical, non-medical as well for both males and females. Then these were categorized into four levels according to the Clance Impostor Phenomenon Scale (CIPS).

- ≤ 40 total score (Mild IP)
- 41-60 total score (Moderate IP)
- 61-80 total score (Frequent IP characteristics)
- ≥ 81 total score (Severe IP)

This classification helped determine the level of the impostor characteristics an individual, or individuals in a certain group felt

Data analysis was performed using SPSS version 26. Descriptive statistics, including means and standard deviations, were used to summarize demographic data. The mean score of total CIP unpaired t-test was performed to compare the mean of CIP scores between the two universities as well as between both genders. To further establish the dependency of the different total scores obtained on the aforementioned groups, a linear regression model was used. The significance level was set p-value <0.05. Prior to conducting the t-tests, assumptions of normality and homogeneity of variances were checked. The decision to use a t-test was based on satisfaction of these assumptions and if the assumptions had been violated, alternative tests such as non-parametric tests would have been considered.

Results

A total of 242 responses were collected, with 121 from each university. Maximum individuals were aged between the range 21-23 with around 47.1% of the total. Male respondents accounted for 57.4% of the] total, while females made up 42.6%. The highest response rates were from first-year (36.8%) and fourth-year students (34.7%), with only 2.1% of responses coming from fifth-year students. Table 1 provides detailed frequencies and percentages of the demographic data

Table 2 compares the mean total Clance Impostor Phenomenon Score (CIPS) of CMH and LUMS, calculated from the respondents' answers and analyzed using unpaired t-test. The total is the score achieved from the CIP scale calculated by adding all the answers to the twenty-questioned CIPS. Afterwards which a mean was calculated for each institute to aid in comparison. Later, the means were compared with the interpretation breakdown provided by the CIP scale itself; score less than equal to 40 has few imposter phenomenon characteristics, 41 to 60 has moderate IP experience, 61 to 80 means the respondent had experienced the phenomenon frequently, and a score higher than 80 means having intense impostor phenomenon. The total score shows significance when comparing both colleges at p-value <0.05 with LUMS having a higher mean value of 67.08 (±13.704), and CMH having 58.36 (±11.413). This suggests that the LUMS total score lies in the third category (61 to 80) of frequent imposter phenomenon characteristics and CMH lies in the moderate IP category (41 to 60). This classification helps distinguish the level of impostor characteristics in the two different institutes. CMH reflects the results of medical students, while LUMS shows how non-medical individuals feel.

Table 1. Demographic Characteristics of Medical and Non-Medical Study Participants by University and Gender.

Demographics	Frequency	Percentage
Age		
18-20	113	46.7
21-23	114	47.1
24-27	15	6.2
Gender		
Male	139	57.4
Female	103	42.6
University		
CMH	121	50.0
LUMS	121	50.0
Year of Study		
First	89	36.8
Second	23	9.5
Third	41	16.9
Fourth	84	34.7
Fifth	5	2.1

Legend: (CMH= CMH Medical College representing medical students, LUMS= LUMS University representing non-medical students).

Table 2 further goes on to compare the genders with their respective CIP score calculated, mean determined, as done for the universities, according to the questions chosen by the respondents, and unpaired t-test applied. The total CIP Score is significant, at p-value <0.05 and has a mean of 68.39 (± 13.737) for females and 58.52 (±11.345) for males. The total mean score for females suggests a higher value and indicates to be in the third category, where frequent impostor phenomenon characteristics are experienced. While the mean score for male lies in the second category with moderate IP characteristics.

Conclusively, non-medical students of LUMS and females are reported to fall in the frequent category, while medical students and males fall in the moderate category.

Figure 1, a clustered bar graph shows a comparison of the Total CIP score against the count, in both universities with confidence interval at 95%. Each bar represents a category from the Clance scale. Score less than 40 is depicted in blue, score between 40 and 60 is in orange, grey shows score between 61 and 80, while yellow

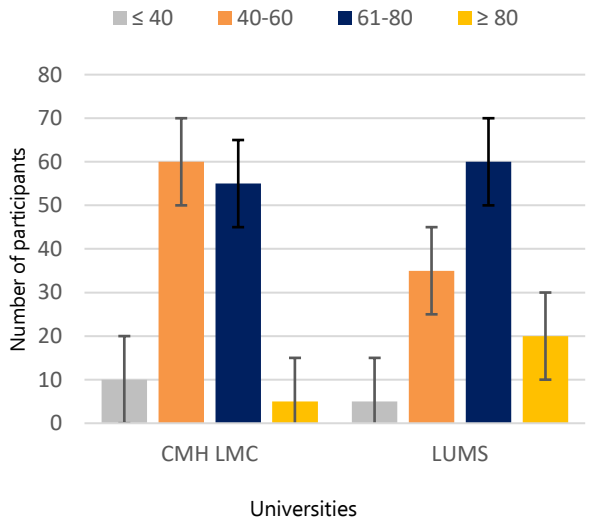
reflects the scores above 80. X-axis has both the universities with CMH showing result for medical students and LUMS for non-medical. Y-axis depicts the count or the number of participants in each institute having a certain CIP score. This graphical tally between the two groups is an easier portrayal of impostor characteristics. The figure shows that LUMS predominantly had a higher score in the range 61 to 80, as the grey bar is significantly taller, while CMH ranged maximum in the two ranges, 41 to 60, and 61 to 80, with the latter having a slightly higher frequency. This aligns with our previous tables and un-paired t-test analysis

Table 2. Comparison of Total CIP Scores by University and Gender using t-test.

Category	Group	Total CIP Score		p-value
		Mean	Standard Deviation	
University	CMH	58.36	11.413	<0.001
	LUMS	67.08	13.704	
Gender	Female	68.39	13.737	<0.001
	Male	58.52	11.345	

Legend: (CMH= CMH Medical College representing medical students, LUMS= LUMS University representing non-medical students).

Figure 1. Comparing Impostor Phenomenon Score with Universities.



Legend: (CMH= CMH Medical College representing medical students, LUMS= LUMS University representing non-medical students).

A multivariate linear regression model was used to further analyze the relationship of the various determining variables with the total CIP score. The results showed significant dependency of the total CIP scores on the variables, university and gender, with the regression p-value coming out to be less than 0.05. This highlighted the significance of these factors in influencing feelings of Impostor Phenomenon.

Discussion

Impostor Phenomenon is increasingly affecting aspiring individuals, leading capable professionals to doubt themselves amidst fears of falling short compared to their peers. This study aimed to examine its prevalence among both medical and non-medical students, while also exploring potential gender differences. Additionally, it sought to raise awareness among mentors and students to address and mitigate these challenges effectively.

The study accounted for the prevalence of Impostor Phenomenon (IP) among medical and non-medical students in the two universities CMH Lahore Medical College and Institute of Dentistry (CMH) and Lahore University of Management Sciences (LUMS) in Lahore, Pakistan. The results showed that both medical and non-medical students experience Imposter Phenomenon (IP) to a certain degree, with both of them having similar significance for each of the variables. However, the prevalence of IP was found to be slightly higher in LUMS students (non-medical) as compared to CMH students (medical) with the mean value of the total CIP scale to be 67.08 (±13.704) and 58.36 (±11.413) respectively. This showed the Impostor Phenomenon for LUMS to be in the range 61-80, the most frequent IP characteristic range. In contrast, in the medical students of CMH the distribution of the score was found to be 41-60, the moderate IP characteristics range. This finding is in accordance with previous studies that have reported a higher prevalence of IP in many different disciplines other than medicine. One such study done at a university of Southwest Arkansas on liberal arts students, showed a positive association was found between Impostor Phenomenon (IP) and depression (BDI-II) scores among college students, with women exhibiting higher IP scores than men.18 An article on chemical engineers and their feelings of imposter-ism quite interestingly describes how students in non-medical fields such as engineering feel this phenomenon.[19]

Over time, heightened competition among students has placed significant pressure on colleges to enhance curricula and integrate advanced information into already rigorous four-to-five-year educational programs. However, governmental alignment with these demands for educational changes has been lacking, resulting in increased stress and pressure on institutions, which subsequently impacts students' mental health negatively.[20]

The finding that medical students experience various levels of Impostor Phenomenon is understandable, given the competitive and demanding nature of medical education. Medical students face high levels of stress and pressure to excel, which can intensify feelings of inadequacy and self-doubt. This aligns with a previous study that highlighted impostor phenomenon among students in academically rigorous programs.[21]

Research comparing house officers and dental students has shown differences in how they experience intellectual disparity, particularly in clinical versus non-clinical aspects.[16] House officers, due to their greater exposure to diverse environments, tend to experience fewer impostor feelings over time, supporting the hypothesis that familiarity with one's surroundings reduces such thoughts.

Research consistently shows that Impostor Phenomenon (IP) affects both genders, but is more prevalent among females.22 This gender disparity is underscored by higher mean scores among females compared to males—68.39 (± 13.737) for males and 58.52 (± 11.345) for females—placing females in the frequent IP range (61 to 80) and males in the moderate IP range (41 to 60). These findings align with previous studies indicating that females are more likely to experience IP.[16,23]

Women often face more mental health challenges, including higher rates of depression, possibly influenced by hormonal fluctuations such as estrogen levels in disorders like premenstrual dysphoric disorder, postpartum depression, and postmenopausal depression.[24] Another such research on first-generation STEM majors concluded that women have higher phases of 'feeling like a fake'.15 They also have to face a lot of societal pressure and need to fight against many to achieve or accomplish goals that they have been dreaming about.[25] Frequently, female achievements are overlooked, potentially fueling self-doubt and exacerbating Impostor Phenomenon (IP).26 In another study comparing medical students, males scored significantly lower on the Clance Impostor Phenomenon scale (CIP) by 9.15 points.[27] A student from this research expressed feeling unworthy of pursuing a medical career when comparing herself to male colleagues. These instances underscore the impact of societal perceptions and gender dynamics on individuals' experiences of competence and self-worth in academic as well as professional settings.

There have been many such researches focusing primarily on the relation between mental health and impostor sickness such as the one done in Isfahan University Students that showed a positive correlation between the two.[17] There has been similar research exploring the idea of self-esteem and racial identity in relation to the Impostor Phenomenon, in an African American College.18 Both studies conclude the importance of support and confidence building by the mentors of the students.

Anna Parkman in her article about the incidence and impact of impostor phenomenon highlights the importance of mental health and compares it with Impostor Phenomenon.[28] Many articles have shown a positive correlation between stress, anxiety and depression with it.[22,28]

The drive for perfectionism, combined with the pressure to meet familial expectations, intensifies stress levels, as evidenced in a study comparing stress among medical, engineering, and nursing students.[29] A literature review exploring perfectionism, mental health, and Impostor Phenomenon in medical education underscores their interrelated negative impacts, aligning closely with our research objectives.[30]

The study identified several underlying causes of Impostor Phenomenon, including disparities related to program types, gender, and years of study, all of which negatively impact confidence and self-esteem. Educators across fields of education should recognize the prevalence of this phenomenon among students and implement interventions to enhance self-efficacy and confidence. These interventions could involve mentoring programs, stress-management training, and fostering supportive learning environments, particularly in medical education.

Despite aligning with previous research, the study encountered limitations. This included a relatively small sample size confined to two universities in Lahore, which may restrict the generalizability of findings. Future research should employ larger and more diverse samples, incorporate measures of depression, anxiety, and stress to assess correlations with Impostor Phenomenon, and explore variations among medical and non-medical specialties. Moreover, future studies could investigate whether the phenomenon is transient or permanently linked to mental health, and explore its association with academic performance more comprehensively. It is suggested to keep in view of the various socio-economic background as well as the level of maturity in the different year of studies that could also impact the results. Hence, further studies should be employed focusing on these confounders.

Conclusion

In conclusion, this study highlights the prevalence of the Impostor Phenomenon among medical and non-medical students, with non-medical students and females exhibiting higher CIP scores. These findings emphasize the need for targeted interventions to fostering a positive educational environment and to support students in managing imposter phenomenon through the implementation of programs aimed at promoting self-efficacy and self-confidence. Institutes should introduce compulsory monthly counseling sessions to monitor students' mental health. Parents should be involved as needed. Peer learning sessions, guided by mentors, should be encouraged to break down barriers and foster a supportive learning environment. Importantly, students should realize that each individual is unique, having their own strengths and weaknesses. Therefore, comparisons can be self-detrimental and should be avoided, focusing on one's own positive qualities, while being appreciative of all.

References

1. Clance, P. R. The impostor phenomenon: overcoming the fear that taunts your success. Atlanta: Peachtree Publishers; 1985.
2. Vergauwe J, Wille B, Feys M, De Fruyt F, Anseel F. Fear of being exposed: The trait-relatedness of the impostor phenomenon and its relevance in the work context. J Behav Psychol. 2015;30(3): 565-581
3. Clance PR, Imes S. The imposter phenomenon in high achieving women: dynamics and therapeutic intervention. Psychother Theory Res Pract. 1978;15(3): 241-7.
4. Sakulku J, Alexander J. The impostor phenomenon. J Behav Sci, 2011;6(1): 75–97.
5. Cokley, K. A critical review of the literature on imposter syndrome. J Couns Psychol. 2017;64(4): 369-386.

6. Gorsi H, Ali SA, Tariq S. A conceptual model of impostor phenomenon and job performance: role of vicarious learning, impression management, and self-reflection. J Prof Appl Psychol. 2023;4(3):460–77
7. Hutchins, H. M. Outing the imposter: A study exploring imposter phenomenon among higher education faculty. New Horiz Adult Educ Hum Resour Dev.2015; 27(2):3- 12
8. Mak KKL, Kleitman S, Abbott MJ. Impostor phenomenon measurement scales: a systematic review. Front Psychol. 2019 Apr 5;10.
9. Rosenthal S, Schlussel Y, Yaden MB, DeSantis J, Trayes K, Pohl C, et al. Persistent impostor phenomenon is associated with distress in medical students. Fam Med. 2021 Feb 3;53(2):118–22.
10. Levant B, Villwock JA, Manzardo AM. Impostorism in third-year medical students: an item analysis using the Clance impostor phenomenon scale. Perspect Med Educ. 2020;9(2):83-91.
11. Ikbaal MY, Salim Musa N 'Aqilah. Prevalence of impostor phenomenon among medical students in a malaysian private medical school. Int J Med Stud. 2018;6(2):66–70.
12. Rosenstein A, Raghu A, Porter L. Identifying the prevalence of the impostor phenomenon among computer science students. In: Proceedings of the 51st ACM Technical Symposium on Computer Science Education. New York, NY, USA: ACM; 2020.
13. Smith OG. Exploration of the impostor phenomenon in law school students [dissertation]. San Diego (CA): University of San Diego; 2011. Available from: https://digital.sandiego.edu/cgi/viewcontent.cgi?article=1834&context=dissertations
14. Peteet B.J, Montgomery L. Predictors of imposter phenomenon among talented ethnic minority undergraduate students. J Negro Educ. 2015 ;84(2): 175-186.
15. Trefts S. The imposter phenomenon in female, first-generation STEM majors [dissertation]. Thousand Oaks (CA): California Lutheran University; 2019.
16. Bhatti MUD, Ahmed I. Impostor phenomenon: a cross-sectional study of students and house officers from dental teaching institutes of Lahore. PODJ 2019; 39(3):262-6.
17. Şahin, E. E., & Uslu Gülşen, F. Clance impostor phenomenon scale (CIPS): adaptation and validation in turkish university students. Psychoeduc Res Rev. 2022;11(1): 270-282.
18. Neureiter, M., & Traut-Mattausch, E. Inspecting the mechanism: A longitudinal study of the relationships between impostor feelings, self-esteem and inauthenticity. J Vocat Behav. 2016;95-96:80-90.
19. Felder, R. Imposters everywhere. Chem Eng Educ, 1988; 22(4), 168-169.
20. Barnshaw J, Dunietz S. Busting the myths: The annual report on the economic status of the profession, 2014–15. Academe. 2015 Mar 1;101(2):4-19.
21. Coklar, A. N., Yuksel, E. G., & Calik, U. S Impostor phenomenon among medical students in a developing country: A multicenter study. Med Sci Monit. 2019;25:4546-53.
22. McGregor, L. N., Gee, D. E., & Posey, K. E. I feel like a fraud and it depresses me: The relation between the imposter phenomenon and depression. Social Behavior and Personality,2008; 36(1), 43-48.
23. Clance, P. R., & O'Toole, M. A. The imposter phenomenon: An internal barrier to empowerment and achievement. Wom Ther. 1987;6(3):51-64.
24. Albert PR. Why is depression more prevalent in women? J Psychiatry Neurosci. 2015 Jul; 40(4):219-21.
25. On pay gap, millennial women near parity-for now despite gains, many see roadblocks ahead [Internet: last updated. 2013;47-56.
26. Stamarski CS, Son Hing LS. Gender inequalities in the workplace: the effects of organizational structures, processes, practices, and decision makers' sexism. Front Psychol. 2015 Sep 16; 6:1400.
27. Franchi T, Russell-Sewell N. Medical students and the impostor phenomenon: a coexistence precipitated and perpetuated by the educational environment? Med Sci Educ. 2022 Dec 9;33(1):27-38.
28. Parkman A. The imposter phenomenon in higher education: Incidence and impact. J High Educ Theory Pract. 2016;16(1):1-9.
29. Cromwell B, Brown N, Adair FL. The impostor phenomenon and personality characteristics of high school honor students. J Soc Behav Pers. 1990 Nov 1;5(6):563.
30. Thomas M, Bigatti S. Perfectionism, impostor phenomenon, and mental health in medicine: a literature review. Int J Med Educ. 2020 Sep 28; 11:201-213.

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Author Contributions

Conceptualization: LR.,AL.,MN.,MT.,ZO. Methodology: LR..,AL.,MN.,MT.,ZO Software: LR., AL.,MN.,MT. Formal Analysis: LR .AL.,MN.,ZO Data Curation: LR., AL.,MN.,MT. Investigation: LR.AL.,MN.,MT. Writing – Original Draft: LR.,AL.,MN.,MT. Writing – Review & Editing: LR.,AL.,MN. Visualization:LR.,AL.,MN.,MT.,ZO Supervision: LR.,AL.,MN.,ZO Project Administration: LR., AL.,MN.

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Original Article

Pain Severity Ratings Among Patients with Comorbid Chronic Pain and PTSD: A Retrospective Cohort Study

Lily Charron,[1] Eduardo Espiridion.[2]

Abstract

Background: Posttraumatic stress disorder (PTSD) is a psychiatric disorder that may occur after experiencing or witnessing a traumatic event. PTSD is characterized by physiological symptoms such as sleep disturbances and hyperarousal. One understudied symptom in PTSD patients is chronic pain (CP). Acute pain can lead to CP when it persists beyond adaptation. The interconnection between stress and pain has been well-established in fields of neuroscience and psychology, though we still do not fully understand the nature of this clinical relationship. **Methods:** In the current retrospective cohort study, we use a sample of patients with PTSD and CP through a database of numerous healthcare organizations called TriNetX. We compare the reported pain severity rating between three groups: those with PTSD and no CP, those with CP and no PTSD, and those with comorbid PTSD and CP. The summary data was compared using a one-way analysis of variance with the Welch statistic. **Results:** The average reported pain severity was significantly different between all three groups ($F(2, 21288)=279.80$, $p < .001$). The patients with comorbid PTSD and CP reported the highest average pain severity, followed by patients with only CP and then patients with only PTSD. **Conclusion:** Our results demonstrate a need to further investigate the complex relationship between PTSD and CP. The higher average pain severity in patients with both disorders suggest that integrated pain management and mental health interventions must be prioritized in this population.

Introduction

Pain is defined as an unpleasant sensory and emotional experience often due to tissue damage. Often, pain is an adaptive experience to let the body know of this damage. However, pain can turn into chronic pain when it persists beyond adaptation. Chronic pain is frequently comorbid with other medical and psychiatric problems.

Posttraumatic stress disorder (PTSD) is a psychiatric disorder that may occur after experiencing or witnessing a traumatic event. Symptoms of PTSD include panic attacks, avoidance of triggers of the event, sleep disturbances, hyperarousal, and irritability. PTSD is often comorbid with other psychiatric disorders, mainly depression and substance use disorders, as reviewed by Morasco et al. (2013).[1]

A number of studies have documented the comorbidity and mutual maintenance between chronic pain and PTSD.[2-4] In several cohorts of veterans, those diagnosed with PTSD had higher pain severity, pain interference, and pain catastrophizing than those without PTSD.[5, 6] In a meta-analysis of studies from 1995 to 2016, PTSD prevalence was about 20% among patients with widespread chronic pain.[7] This appears to be a bidirectional relationship, where severity of initial pain of injury predicts development of PTSD, and the onset of PTSD is equally as predictive of development of chronic pain.[8] Further, there is a well-established correlation between pain symptom severity and PTSD-like symptoms.[9, 10] Though the frequency of the comorbidity is well-established, there are still questions about the nature of the relationship between the two disorders and whether the relationship is temporal.

There is also research demonstrating that having comorbid PTSD and chronic pain exacerbates symptoms of both disorders. In a systematic review of studies using traumatized refugees, those with chronic pain had more severe PTSD symptoms than those without chronic pain.[11] A similar result was found in a population of patients seeking chronic pain treatment in Sweden.[12] In 28.7% of the patients that met criteria for PTSD, patients exhibited higher severity of pain, fear of pain from movement, anxiety, and depression. These results and others, such as those reported by Reed et al. (2024), show that patients with comorbid PTSD and chronic pain are more likely to have additional psychiatric disorders and are more likely to commit suicide than those with PTSD or chronic pain alone.[13] Further, those with comorbid PTSD and chronic pain are more likely to heavily use opioids and benzodiazepines, which may escalate to dependence.[14, 15]

This comorbidity is unsurprising given the overlap of neural pathways for pain and traumatic memories.[2] Fearful and negative memories, including fear and memory of pain, have been long

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associated with the limbic system.[16] A number of neurological indicators have been observed in both PTSD and chronic pain, including significant elevations in neuropeptide Y, allopregnanolone, and pregnanolone. Other systems that appear to play roles in both disorders include GABAergic neuroactive steroids, opioids and endocannabinoids, immune factors, and several second messengers.

Despite evidence of this comorbidity, there is a lack of research on comorbid PTSD and chronic pain patients across these populations. In the current study, we seek to compare the severity of pain reported by patients with PTSD, chronic pain (CP), and comorbid PTSD and CP in a retrospective cohort of patients from the TriNetX database. Establishing a relationship in the pain severity of these populations will better allow providers to manage and treat these conditions together.

Methods

We gathered a retrospective cohort of patients across multiple healthcare organizations who were reported to be diagnosed with chronic pain only, PTSD only, and comorbid PTSD and chronic pain, respectively. The retrospective cohort was obtained through the TriNetX database. TriNetX is a research network providing researchers access to extensive deidentified patient information extracted from the electronic health records (EHRs) of over 250 million patients worldwide. Our study focused on a network of 61 HCOs, encompassing over 105 million patients exclusively from the United States.

We included patients between the ages of 18 and 90 years and records reported from 2000 to 2024. We identified our three cohorts using inclusion and exclusion criteria from the International Classification of Diseases, 10th Revision (ICD-10) codes, which were reported in the TriNetX database. Patients in the PTSD group were required to have ICD-10-CM F43.1 Post-traumatic stress disorder (PTSD) and were excluded if they met criteria for any of the following ICD-10-CM chronic pain diagnoses: R52 Pain, unspecified; F45.41 Pain disorder exclusively related to psychological factors; G89.2 Chronic pain, not elsewhere classified; G89.29 Other chronic pain; G89.4 Chronic pain syndrome. The CP (chronic pain) group met at least one of the five pain criteria and were excluded if they met criteria for PTSD. The PTSD/CP group met at least one of the five pain criteria and they met criteria for PTSD. There were no exclusions for other psychiatric and pain disorders.

Finally, all three cohorts were reduced to those with a self-reported pain severity value. The pain severity rating was on a scale from 1 to 10, with 1 being no pain and 10 being the most severe pain level. The means and standard deviations (SDs) of the reported pain severity was recorded for each of the three cohorts. Using the SPSS Statistics program, we performed a Welch one-way analysis of variance (ANOVA) to compare the means for these three groups. The Welch statistic was used since homogeneity of variance could not be assumed due to the lack of raw data provided by TriNetX. Finally, a post hoc Tukey Honest Significant Difference (HSD) test was performed to determine pairwise differences between groups. We did not adjust for confounders in this study.

Ethical Considerations: Given the use of de-identified patient records and the absence of any collection, use, or transmission of individually identifiable data in this retrospective cohort study, it was deemed exempt from institutional review board approval and informed consent as per the Health Insurance Portability and Accountability Act (HIPAA). Furthermore, we strictly adhered to the reporting guidelines outlined in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) framework throughout all phases of our investigation.

Results

The US collaborative Network TriNetX has 105,703,806 patients across 61 healthcare organizations (HCOs). We were able to identify 5,673 patients in the PTSD/CP group, 6,113 patients in the PTSD group, and 9,505 patients in the CP group ***(Figure 1, Table 1).*** The PTSD/CP group had M=5.07 and SD=2.94, the PTSD group had M=3.75 and SD=3.20, and the CP group had M=4.34 and SD=2.97.

A one-way ANOVA was run using the summary data provided by TriNetX. The test was significant between the three groups, Welch's F(2, 21288)=279.80, p<.001 ***(Table 2).*** A Tukey Honest Significant Difference (HSD) test was performed in order to compare each pair of groups. All three pairs of groups (PTSD/CP-PTSD only, PTSD/CP-CP only, PTSD only-CP only) were significantly different with p<.001 for each pairing. The eta-squared value of effect size was .026, indicating a small effect. Demographic data was not available for this cohort.

Table 1. Descriptive Statistics. SD = Standard Deviation; SE = Standard Error.

Group	N	Mean	SD	SE	95% Confidence Interval	
					Lower Bound	Upper Bound
PTSD	6113	3.75	3.20	.04	3.67	3.83
CP	9505	4.34	2.97	.03	4.28	4.40
PTSD+CP	5673	5.07	2.94	.04	4.99	5.15
Total	21291	4.37	3.07	.02	4.32	4.41

Discussion

In the current study, the pain severity experienced by those with chronic pain was exacerbated when the patients also had a PTSD diagnosis. Patients with both PTSD and chronic pain reported significantly higher pain severity than those with PTSD alone. This

was a small effect size. Expectedly, patients with only PTSD reported the lowest pain severity levels. These results add to the growing body of literature on comorbid PTSD and chronic pain.

Table 2. Welch One-Way ANOVA.

	Sum of Squares	df	Mean Square	F	Sig
Between Groups	5137.65	2	2568.83	279.83	<.001
Within Groups	195447.21	21288	9.18		
Total	200584.87	21290			

Figure 1. Study Flowchart.

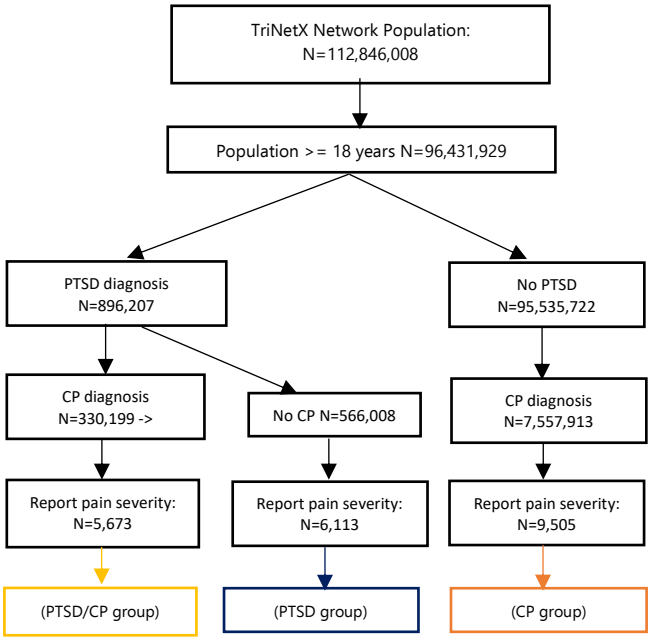
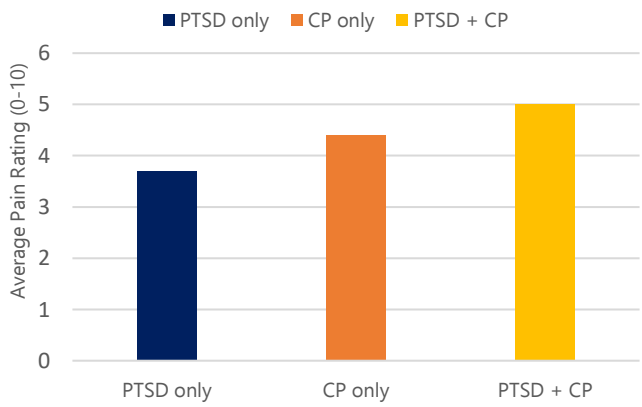


Figure 2. Average Pain Severity of Each Group. Pain Was on a Scale From 1-10 With 1 Being no Pain and 10 Being the Most Severe Pain. Error Bars Represent Standard Error (SE) for Each Group.



There are a number of theories explaining the frequent comorbidity of these disorders. Otis et al.[17] reviewed several of these. One hypothesis, known as the Shared Vulnerability Model, theorizes that patients with a predisposition for anxiety are more vulnerable to developing both chronic pain and PTSD. In this model, a person with high anxiety sensitivity is more likely to become fearful in response to physiological sensations, including pain. Anxiety sensitivity also increased people's fear and avoidance of pain, also known as pain catastrophizing, allowing chronic pain maintenance to persist.[18] The effect of pain catastrophizing on PTSD and chronic pain symptoms is seen in youth as well as adults.[19] Another proposed theory is the Triple Vulnerability Model, which postulates that three factors must be present for the comorbidity to occur: a general biological vulnerability, a general psychological vulnerability, and a more specific psychological vulnerability where one focuses their anxiety on a specific situation. This model is supported by research that demonstrates a lower pain threshold in those with PTSD in comparison to those with other anxiety disorders and a control group.[20, 21]

Further, the current literature also points to a mutual maintenance relationship between these two disorders.[22, 23] Cognition related to pain, meaning the interpretation of and excessive attention to pain, is associated with higher levels of distress and avoidance, which may exacerbate or precipitate PTSD symptoms. The shared aspect of fear-based avoidance in both PTSD and chronic pain seems to underpin this mutual maintenance model. Our findings support the theory of mutual maintenance as pain was exacerbated in patients with comorbid PTSD. Similar to the mutual maintenance model is the shared vulnerability model of PTSD-chronic pain comorbidity, as previously described.[18, 24, 25] These models are the basis of current evidence-based therapies for these disorders. These treatments primarily involve cognitive behavioral therapy (CBT) and interdisciplinary pain programs (IPPs).[25] By targeting anxiety as a common thread between the two disorders, CBT may be an effective way to reduce occurrence of both PTSD and chronic pain.[26] Since our current analysis did not look at temporality between PTSD and chronic pain, the possibility of shared vulnerability in this cohort is unclear. Prospective studies are needed to illustrate the causality between these two disorders.

Interestingly, studies have shown that previous trauma does not have to be physical or pain-related to see this association with chronic pain. Kascakova et al.[27] found that childhood emotional abuse and emotional neglect, in addition to physical neglect, were associated with higher odds of chronic pain and anxiety conditions later in life. Results such as these point to the significant role of emotional trauma, rather than physical trauma, in the relationship between PTSD and chronic pain.

For the same reasons it is associated with PTSD, chronic pain is frequently comorbid with several other psychiatric disorders. As described in the aforementioned models, anxiety disorders play a large role in the relationship between chronic pain and PTSD.[9, 10] Similarly, depression has been demonstrated to be associated with PTSD and pain severity.[8] Depression is often comorbid with

PTSD and has been found to be a mediator of PTSD and higher pain severity and interference.[1]

One systematic review found different rates of PTSD among patients with different types of chronic pain.[28] For example, the prevalence of both PTSD and chronic pain were highest in the veteran population. This result may be because veterans are more likely to experience traumatic events and physical injuries resulting in pain and does not necessarily illustrate the association between the two disorders. Since the majority of PTSD literature focuses on veterans, this point indicates that PTSD research on non-veterans should be further explored. Another aspect of this relationship that must be further explored is that of patients with complex PTSD (CPTSD), usually driven by childhood trauma and/or recurrent traumatic events.[29] Some studies have shown that patients with CPTSD have even higher rates of chronic pain than those with PTSD. This result may be due to the more severe avoidance and anxiety symptoms observed in those with CPTSD. Further research of this population is needed to explore the association with different presentations and sources of PTSD. Future investigations are also needed to assess integrated treatment of these disorders and screen for this comorbidity.

Limitations: There are several limitations to our analysis. First, we were only able to run our analysis using the summary data provided by TriNetX, as the raw data on pain severity ratings was not provided. Due to the lack of raw data, we were unable to run the homogeneity of variances test needed to ensure the ANOVA assumptions were not violated, and needed to rely on the Welch statistic which does not share this assumption. This is important given the large difference in sample sizes for each of our groups and may affect the validity of our results. Because a limited number of HCOs provided pain severity ratings, the TriNetX platform was also unable to provide demographic information for our three study groups. This information could have been valuable to understanding the characteristics of our patient population and for comparison to other study populations with PTSD and chronic pain and limits the generalizability of these results. Further, we were not able to verify the validity of the ICD-10 codes reported by TriNetX, leading to potential misclassification. We also cannot necessarily attribute the significant increase in pain severity of the PTSD+CP group to the presence of PTSD. As previously noted, patients with PTSD are likely to have other comorbid disorders such as depression which may serve as a mediator to exacerbate the chronic pain severity.

Conclusion

The relationship between PTSD and chronic pain is complex, and still requires examination. In this current study we illustrated the effect of comorbid PTSD and chronic pain on reported pain severity using a retrospective cohort of patients from around the United States between 2000 and 2024. That this comorbidity had significantly higher ratings of pain severity compared the patients with only PTSD or chronic pain indicates a need to focus on this population for pain management and psychiatric care. Our findings emphasize the needed for integrative approaches to treatment of these comorbid conditions to best improve patient outcomes.

References

1. Morasco BJ, Lovejoy TI, Lu M, Turk DC, Lewis L, Dobscha SK. The relationship between PTSD and chronic pain: Mediating role of coping strategies and depression. Pain. 2013;154(4).
2. Kind S, Otis JD. The interaction between chronic pain and PTSD. Curr Pain Headache Rep. 2019;23(12):91.
3. Siqveland J, Hussain A, Lindstrøm JC, Ruud T, Hauff E. Prevalence of posttraumatic stress disorder in persons with chronic pain: A meta-analysis. Front Psychiatry. 2017;8.
4. Sharp TJ. The prevalence of post-traumatic stress disorder in chronic pain patients. Curr Pain Headache Rep. 2004;8(2):111–115.
5. Benedict TM, Keenan PG, Nitz AJ, Moeller-Bertram T. Post-traumatic stress disorder symptoms contribute to worse pain and health outcomes in veterans with PTSD compared to those without: A systematic review with meta-analysis. Mil Med. 2020;185(9–10):e1481–e1491.
6. Bair MJ, Outcalt SD, Ang D, Wu J, Yu Z. Pain and psychological outcomes among Iraq and Afghanistan veterans with chronic pain and PTSD: ESCAPE trial longitudinal results. Pain Med. 2020;21(7):1369–1376.
7. Siqveland J, Ruud T, Hauff E. Post-traumatic stress disorder moderates the relationship between trauma exposure and chronic pain. Eur J Psychotraumatol. 2017;8(1):1375337.
8. Brennstuhl MJ, Tarquinio C, Montel S. Chronic pain and PTSD: Evolving views on their comorbidity. Perspect Psychiatr Care. 2015;51(4):295–304.
9. Gasperi M, Afari N, Goldberg J, Suri P, Panizzon MS. Pain and trauma: The role of criterion A trauma and stressful life events in the pain and PTSD relationship. J Pain. 2021;22(11):1506–1517.
10. Asmundson GJG, Katz J. Understanding the co-occurrence of anxiety disorders and chronic pain: State-of-the-art. Depress Anxiety. 2009;26(10):888–901.
11. Rometsch-Ogioun El Sount C, Windthorst P, Denkinger J, Ziser K, Nikendei C, Kindermann D, et al. Chronic pain in refugees with posttraumatic stress disorder (PTSD): A systematic review on patients' characteristics and specific interventions. J Psychosom Res. 2019;118:83–97
12. Åkerblom S, Perrin S, Rivano Fischer M, McCracken LM. The impact of PTSD on functioning in patients seeking treatment for chronic pain and validation of the Posttraumatic Diagnostic Scale. Int J Behav Med. 2017;24(2):249–259.
13. Reed DE, Fischer IC, Williams RM, Na PJ, Pietrzak RH. Co-occurring chronic pain and PTSD among US military veterans: Prevalence, correlates, and functioning. J Gen Intern Med. 2024;39(11):2009–2016.
14. Sullivan M. Dangerously numb: Opioids, benzodiazepines, chronic pain, and posttraumatic stress disorder. Pain. 2018;159(3).
15. Phifer J, Skelton K, Weiss T, Schwartz AC, Wingo A, Gillespie CF, et al. Pain symptomatology and pain medication use in civilian PTSD. Pain. 2011;152(10):2233–2240.
16. Scioli-Salter ER, Forman DE, Otis JD, Gregor K, Valovski I, Rasmusson AM. The shared neuroanatomy and neurobiology of comorbid chronic pain and PTSD: Therapeutic implications. Clin J Pain. 2015;31(4).
17. Otis JD, Keane TM, Kerns RD. An examination of the relationship between chronic pain and post-traumatic stress disorder. J Rehabil Res Dev. 2003;40(5):397–405.

18. Gilliam WP, Craner JR, Schumann ME, Gascho K. The mediating effect of pain catastrophizing on PTSD symptoms and pain outcome. Clin J Pain. 2019;35(7).
19. Janssen J, Abou-Assaly E, Rasic N, Noel M, Miller JV. Trauma and pain sensitization in youth with chronic pain. Pain Rep. 2022;7(2).
20. Defrin R, Ginzburg K, Solomon Z, Polad E, Bloch M, Govezensky M, et al. Quantitative testing of pain perception in subjects with PTSD: Implications for the mechanism of the coexistence between PTSD and chronic pain. Pain. 2008;138(2).
21. Gasperi M, Panizzon M, Goldberg J, Buchwald D, Afari N. Posttraumatic stress disorder and chronic pain conditions in men: A twin study. Psychosom Med. 2021;83(2).
22. Sharp TJ, Harvey AG. Chronic pain and posttraumatic stress disorder: Mutual maintenance? Clin Psychol Rev. 2001;21(6):857–877.
23. Jenewein J, Wittmann L, Moergeli H, Creutzig J, Schnyder U. Mutual influence of posttraumatic stress disorder symptoms and chronic pain among injured accident survivors: A longitudinal study. J Trauma Stress. 2009;22(6):540–548.
24. Asmundson GJ, Coons MJ, Taylor S, Katz J. PTSD and the experience of pain: Research and clinical implications of shared vulnerability and mutual maintenance models. Can J Psychiatry. 2002;47(10):930–937.
25. Bosco MA, Gallinati JL, Clark ME. Conceptualizing and treating comorbid chronic pain and PTSD. Pain Res Treat. 2013;2013(1):174728.
26. Asmundson GJG, Hadjistavropoulos HD. Addressing shared vulnerability for comorbid PTSD and chronic pain: A cognitive-behavioral perspective. Cogn Behav Pract. 2006;13(1):8–16.
27. Kascakova N, Furstova J, Hasto J, Madarasova Geckova A, Tavel P. The unholy trinity: Childhood trauma, adulthood anxiety, and long-term pain. Int J Environ Res Public Health. 2020;17(2).
28. Fishbain DA, Pulikal A, Lewis JE, Gao J. Chronic pain types differ in their reported prevalence of post-traumatic stress disorder (PTSD) and there is consistent evidence that chronic pain is associated with PTSD: An evidence-based structured systematic review. Pain Med. 2017;18(4):711–735.
29. Karimov-Zwienenberg M, Symphor W, Peraud W, Décamps G. Childhood trauma, PTSD/CPTSD and chronic pain: A systematic review. PLoS One. 2024;19(8):e0309332..

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Conflict of Interest Statement & Funding

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Author Contributions

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Original Article

Comparison of serum PSA and IMPDH-2 in Predicting Aggressive Prostate Cancer: A Cross-sectional Study

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Abstract

Background: Prostate cancer is a cause of morbidity and mortality among men globally. This study compared serum Prostate-Specific Antigen (PSA) and Inosine Monophosphate Dehydrogenase-2 (IMPDH-2) in predicting aggressive prostate cancer. **Methods**: Sixty-three prostate adenocarcinoma patients were recruited for this quantitative descriptive cross-sectional study. Their serum was assayed for IMPDH-2 and PSA. Serum IMPDH-2 and PSA correlations with Gleason score and ISUP Grade Groups were determined using Spearman's rho and Kendall tau correlation coefficients, respectively. The magnitude of the correlation was assessed by calculating the coefficient of determination for the respective analysis (R2). Similarly, regression analysis and receiver operating characteristic (ROC) curve were used to assess the ability of the biomarkers to predict aggressive prostate cancer. Levels of statistical significance were set as $p < 0.05$. **Results:** The mean age was 68.6 years. The mean serum IMPDH-2 and PSA were 76.2pg/ml and 65.9ng/ml respectively. Serum IMPDH-2 did not predict aggressive prostate cancer; ($r = 0.08$, $p = 0.55$ Spearman rho), ($\tau = 0.03$, $p = 0.79$ Kendal tau). Serum PSA weakly predicted aggressive prostate cancer; ($r = 0.30$, $p = 0.02$ Spearman rho), ($\tau = 0.21$, $p = 0.04$ Kendal tau). It was responsible for 10.1 and 8.8% of Gleason score and ISUP grade group variances respectively. However, it did not significantly outperform IMPDH-2 in predicting the Gleason score ($p = 0.53$). **Conclusion:** PSA weakly predicted aggressive prostate cancer but did not statistically significantly outperform IMPDH-2. As such, none is sufficiently accurate in predicting aggressive prostate cancer when used in isolation.

Introduction

Prostate cancer is the second most common cancer among men globally and is only superseded by lung cancer.[1] In Africa, It is the most common cancer among men with an estimated 104,050 new cases based on 2022 records.[1] The true burden of prostate cancer in Nigeria is unknown due to underreporting and poor statistics.[2] However, it is reported to be the most common male cancer in Nigeria, constituting 37.5% of all newly diagnosed male cancers.[1] Furthermore, It is the most common cause of cancer deaths in Nigerian men.[1] African ethnicity is a significant risk factor for PCa and the disease tends to appear at an earlier age and is often more aggressive. Other risk factors are advanced age, family history of PCa, red meat, diet rich in fat, and dairy products.[3] Most of our patients present with locally advanced or metastatic disease. This makes prostate cancer an important public health concern in Nigeria. Prostate cancer is the fifth leading cause of mortality among men and the highest death rates have been reported among African descent.[4] The global burden of the disease is on the rise due to widespread prostate specific antigen (PSA) testing and the use of transrectal ultrasound-guided prostate biopsy.[5–7]

The use of serum prostate specific antigen has led to earlier detection of prostate cancer at the expense of overdiagnosis.[8] The greatest limitation of PSA is its poor specificity and low ability to distinguish aggressive from non-aggressive prostate cancer.[8] Identifying patients with aggressive prostate cancer is indispensable as over 80% of them will develop skeletal complications with its attendant negative effect on their quality of life.[8] The correct grading of prostate cancer is vital for management decision-making. At present, Gleason grading is used to predict the aggressive nature of prostate cancer with higher Gleason scores corresponding to more aggressive disease.[8] Hence, the Gleason score is one of the most powerful prognostic predictors of prostate cancer.[9] The Gleason grading system has undergone revisions over the years to improve on its limitations. One such revision is assigning a score of 6 as the lowest grade on prostate needle biopsy and developing a new grading system.[9] This new grading system proposed in 2013 by a group from Johns Hopkins Hospital has five grade groups. These grade groups are more accurate in predicting disease progression than the traditional Gleason grading system.9 The system was validated and proposed by the International Society

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of Urological Pathologists (ISUP) consensus. It was later adopted by the 2016 World Health Organization (WHO) classification of prostate tumors.[9,10]

Even though the Gleason score and ISUP grade group are more reliable than PSA in predicting aggressive prostate cancer, they can miss some patients with aggressive disease. This is because high-grade foci of prostate cancer can be missed during trucut needle biopsy. Furthermore, prostate biopsy is an invasive procedure with some complications. Because of these limitations, a reliable, accessible, non-invasive, and affordable screening modality for aggressive prostate cancer is required to improve diagnosis and management. This desirable biomarker will reduce the need for repeated biopsies to identify patients with aggressive disease. It will also help identify disease upgrades in patients undergoing active surveillance or watchful waiting

Serum inosine monophosphate dehydrogenase (IMPDH) may assume this role. It is a rate-limiting enzyme involved in a crucial step in the de novo pathway of purine nucleotide biosynthesis, which is essential for DNA synthesis.[11] IMPDH catalyzes the oxidation of inosine 5′—monophosphate to xanthosine 5′—monophosphate.[12] It is associated with cell growth, malignant transformation, and differentiation.[13] The enzyme exists in two isoforms, and Isoenzyme 2 is preferentially upregulated in malignant cells, including prostate, bladder, and renal cancers.[11] This enzyme was chosen in this study because high-grade aggressive cancers have higher cell replication and, hence, higher DNA requirements, which may translate to higher expression of the enzyme. Furthermore, previous reports have also found high expression of IMPDH-2 to be associated with aggressive human nasopharyngeal carcinoma.[11,13] Similarly, overexpression of IMPDH-2 in hepatocellular carcinoma (HCC) tissues was reported to be closely related to aggressive disease.[11] Likewise, a study in Poland found that serum IMPDH-2 had some usefulness in predicting aggressive prostate cancer.[14] Given the fact that the previous study was in a European population, this study aims to compare serum PSA and IMPDH-2 in predicting aggressive prostate cancer in our predominantly black population. We hypothesize that serum IMPDH-2 was better than PSA in predicting aggressive prostate cancer.

Methods

This hospital-based quantitative, descriptive cross-sectional study was conducted at the Institute of Urology and Nephrology of Usmanu Danfodiyo University/Teaching Hospital, Sokoto, Nigeria from January to December 2020. A non-randomized sampling technique was used whereby consecutive patients with adenocarcinoma of the prostate were recruited into the study. A minimum estimated sample size of 54 subjects was calculated using the formula for calculating sample size for a cross-sectional study with a quantitative outcome variable.15 Details of the calculation are contained in the supplementary file.

The inclusion criteria were all newly diagnosed patients with a histologically confirmed adenocarcinoma of the prostate who presented to the urology clinic of Usmanu Danfodiyo University Teaching Hospital, Sokoto, Nigeria. The exclusion criteria were patients on any form of treatment for prostatic diseases such as 5-alpha reductase inhibitors, androgen deprivation therapy, and radiation therapy. Patients who had any form of prostatectomy, those with any histological type of cancer other than adenocarcinoma, and those who refused to consent to be enrolled in the study were similarly excluded.

All enrolled participants were clinically evaluated through detailed history taking and physical examinations. Similarly, the participants had their routine laboratory tests that included full blood count (FBC), serum electrolytes, urea, creatinine (EUCr), urinalysis and urine microscopy, culture, and sensitivity (M/C/S). Additionally, all participants had their serum assayed for IMPDH-2 and PSA by a competent laboratory scientist at the chemical pathology department of Usmanu Danfodiyo University Teaching Hospital, Sokoto, Nigeria using the Sunlong® Biotech IMPDH-2 enzyme-linked immunosorbent assay (ELISA) kit (REF SL3371Hu) and PSA AccuBind® ELISA kit (REF 2125-300A) based on the manufacturers' instruction as contained in the instruction manual.[16,17]

For the assay of the biomarkers, the collected blood samples were allowed to clot for 30 minutes. The samples were then centrifuged at 2000 rpm for 20 minutes. The supernatant serum was collected and stored at -20oC. Any haemolyzed blood sample was discarded and a fresh blood sample was collected because it could interfere with the result. The details of the procedure are contained in the supplementary file. The diagnosis of PCa was made through a systematic prostate needle biopsy obtained via transrectal ultrasound guidance using Mindray® Diagnostic Ultrasound System DC-30. Additional targeted biopsies were obtained in subjects with suspicious nodules using a Bard® Magnum spring-loaded biopsy gun. The histopathologists at the histopathology department of Usmanu Danfodiyo University Teaching Hospital, Sokoto, Nigeria made the histological diagnosis and Gleason grading.

The patients were grouped into the five ISUP Grade groups of increasing aggressiveness of the tumor. These grade groups are 1 (Gleason score ≤ 6), 2 (Gleason score 3+4), 3 (Gleason score 4+3), 4 (Gleason score 8), and 5 (Gleason score 9 – 10). The research data were collected using structured pro-forma. At the end of the study, the data were entered into and analyzed using IBM® SPSS® statistics for Windows, version 23.0. Multiple statistical analysis was performed to assess the ability of the biomarkers to predict aggressive prostate cancer. The first was to determine the correlation of serum IMPDH-2 and PSA with the Gleason score using Spearman's rho correlation coefficient as the data were not normally distributed. The correlation with the ISUP grade group was determined using the Kendall tau correlation coefficient. The correlation was graded as very weak if r (< 0.3), weak (0.3 – 0.4), moderate (0.5 – 0.6), or strong (≥ 0.7). The magnitude of the correlation was determined by calculating the coefficient of determination for the respective analysis = (R2).[18]

The second statistical analysis was the linear regression analysis to establish a relationship between the biomarkers and the Gleason score/ISUP grade groups. Then the receiver operating characteristic (ROC) was also used to test the ability of the biomarkers to predict aggressive prostate cancer (ISUP grade group 4 and 5). A biomarker with an area under the ROC curve (AUROC) of 0.5 – 0.6 was considered to have failed, while 0.6 – 0.7 was a poor predictor of aggressive prostate cancer. A biomarker with an AUROC of 0.7 – 0.8 was considered a fair predictor, 0.8 – 0.9 as a good predictor, and 0.9 – 1.0 was considered to be a very good predictor. All levels of statistical significance were set as $p < 0.05$. The health research and ethics committee of Usmanu Danfodiyo University Teaching Hospital approved the study with reference number UDUTH/HREC/2019/No. 852

Results

The study involved sixty-three participants, whose ages ranged from 43 to 102 years, with a mean age of 68.6 years ± 8.9 and a median age of 70 years (IQR 13). Of the participants, twenty-two (34.9%) were under 65 years old, 41 (65.1%) were over 65, and just one (1.6%) was under 50. The histogram in ***Figure 1*** shows the age distribution of the participants. Every participant had symptoms; 62 (98.4%) reported lower urinary tract symptoms (LUTS), and 15 (24.2%) of them had an indwelling urethral catheter as a result of obstructive nephropathy or urine retention. In ***Table 1,*** additional typical presenting symptoms are displayed. The mean duration of symptoms before presentation was 20.4 months ±18.4. Twenty-nine (46%) participants had comorbidity as listed in ***Table 2.*** Out of the 63 participants, 5 (7.9%) exhibited benign digital rectal examination (DRE) findings and 58 (92.1%) had DRE findings suggesting prostate cancer.

In 20 (31.7%) of the participants, the urine culture yielded microorganisms as displayed in ***Table 3.*** Seven (11.1%) subjects had elevated creatinine ±urea, whereas 53 (84.1%) had normal renal function test results. The mean packed cell volume (PCV) was 31.7% ±4.7. The mean serum PSA was 65.9ng/ml ±38.6, ranging from 1.2ng/ml to 100ng/ml. Fifty-six (88.9%) participants had serum PSA above 10ng/ml while 4 (6.3%) participants had serum PSA levels in the gray zone between 4 and 10ng/ml. Interestingly, 3 (4.8%) participants had normal serum PSA <4ng/ml. Serum IMPDH-2 levels ranged from 0.25 pg/ml to 176.4 pg/ml, with a mean of 76.2 pg/ml ±55.1. The boxplot in ***Figure 2*** displays the serum biomarkers' distribution.

The prostate ranged from 14.8 to 196 ml in size, with a mean of 67.9 ml ±36.2. Of the participants, 42 (66.7%) had a breach of the prostate capsule, and 49 (78.8%) had prostatic nodules. Of those with prostatic nodules, 22 (44.9%) had hypoechoic nodules, 6 (12.2%) had isoechoic nodules, and 21 (42.9%) had mixed echoic nodules. Twenty-seven (42.9 percent) of the participants had tumor invasion of the seminal vesicles. Of the 63 participants, forty-seven (74.6%) had a Gleason score of ≥8. ***Table 4*** displays the distribution of the ISUP grade group and Gleason score.

Table 1. The Presenting Symptoms of the Study Population with Prostate Cancer.

Presenting SymptomS	Frequency	Percentage
Voiding LUTS[a]	62	98.4
Storage LUTS[a]	61	96.8
Low Back Pain	36	57.1
Lower limb Paraesthesia	28	44.4
Paraparesis/Paraplegia	14	22.2
Weight Loss	16	25.4
Body Weakness	14	22.2
Anorexia	14	22.2
Urinary Incontinence	3	4.8
Faecal Incontinence	2	3.2
Pressure Ulcer	2	3.2
Hematuria	1	1.6

Legend: [a] Lower Urinary Tract Symptoms.

Table 2. List of Comorbidities Among the Study Population with Prostate Cancer.

Co-morbidity	Frequency	Percentage
Nil	34	53.9
hypertension	21	33.3
Diabetes Mellitus	3	4.8
Hypertension & Diabetes Mellitus	2	3.2
Hypertension & CKD[a]	1	1.6
Cerebrovascular Disease	1	1.6
Cardiac Failure	1	1.6
TOTAL	**63**	**100**

Legend: [a] Chronic Kidney Disease

Table 3. List of Microorganisms Cultured in the Urine of the Study Population with Prostate Cancer.

Microorganism	Frequency	Percentage
Escherichia coli	7	11.1
Staphylococcus aureus	5	7.9
Klebsiella	3	4.8
Proteus mirabilis	2	3.2
Candida albicans	2	3.2
Pseudomona specie	1	1.6
Negative Culture	43	68.2
Total	**63**	**100**

No significant correlation was seen between serum IMPDH-2 and ISUP grade group (τ = 0.03, p = 0.79, Kendall tau) or between serum IMPDH-2 and Gleason score (r = 0.08, Spearman's rho, p = 0.55). Similarly, using linear regression analysis, serum IMPDH-2 had no relationship with the Gleason score (B=0.001, P=0.56) and ISUP grade group (B = 0.001, p = 0.78). The scatter plot in ***Figure 3*** shows the lack of a linear relationship between serum IMPDH-2 and the Gleason score. Furthermore, serum IMPDH-2 was only responsible for 0.6% (R2 = 0.006) of the Gleason score variance and 0.1% (R2=0.001) of the ISUP grade group variance.

Nonetheless, there was a positive correlation (r = 0.30, Spearman's rho, p = 0.02) between the serum PSA level and the Gleason score. However, the correlation was weak. Serum PSA also had a very weak correlation (τ = 0.21, p = 0.04, Kendall tau) with the ISUP grade group. Using linear regression analysis, PSA had a positive relationship with the Gleason score (B= 0.009, p = 0.01) and the ISUP grade group (B = 0.009, p = 0.02). It determined 10.1% (R2 = 0.101) and 8.8% (R2 = 0.088) of the Gleason score and ISUP grade group variances respectively. The weak linear relationship of the PSA and Gleason score is displayed in ***Figure 4***. Using the ROC curve, the overall ability of serum PSA in predicting aggressive PCa (ISUP grade group 4 and 5) was fair with an area under the curve of 0.74 (95% CI; 0.61 – 0.88) as shown in ***Figure 5***. However, serum IMPDH-2 failed to predict aggressive prostate cancer with an area under the curve of 0.52 (95% CI; 0.34 – 0.69) as shown in ***Figure 6.*** However, when compared, the serum PSA did not considerably outperform IMPDH-2 (p = 0.53) in predicting the Gleason score. Consequently, neither serum PSA nor IMPDH-2 can be used in isolation to predict aggressive prostate cancer.

Table 4. The Gleason Score and ISUP Grade Groups of the Study Population with Prostate Cancer.

Variable		Frequency	Percentage
Gleason Score	6	3	4.8
	7	13	20.6
	8	17	27
	9	22	34.9
	10	8	12.7
Total		**63**	**100**
ISUP[a] Grade Group	1 (GS[b] ≤6)	3	4.8
	2 (GS 3 + 4)	6	9.5
	3 (GS 4 + 3)	7	11.1
	4 (GS 8)	17	27
	5 (GS 9 & 10)	30	47.6
Total		**63**	**100**

Legend: [a] International Society of Urologic Pathologists, [b] Gleason score

Figure 1. A Histogram Showing the Age Distribution of the Study Subjects.

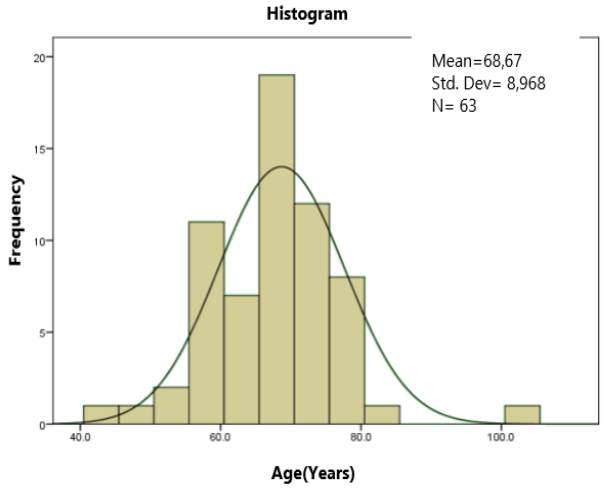


Figure 2. Boxplot Showing the Maximum, Minimum, Median, and Interquartile Range of Serum PSA and IMPDH-2.

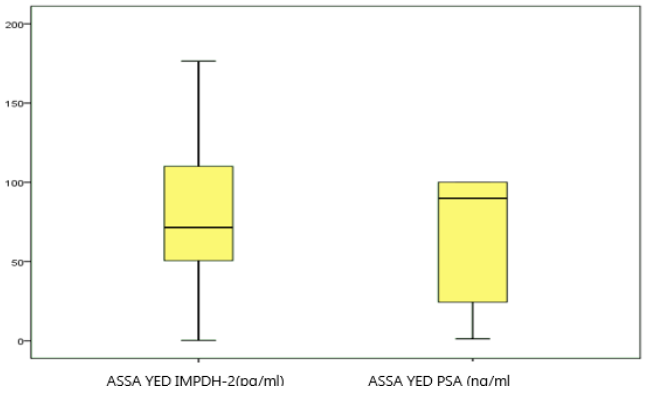


Figure 3. A Scatter Plot Showing the Absence of a Linear Relationship Between IMPDH-2 and Gleason Score.

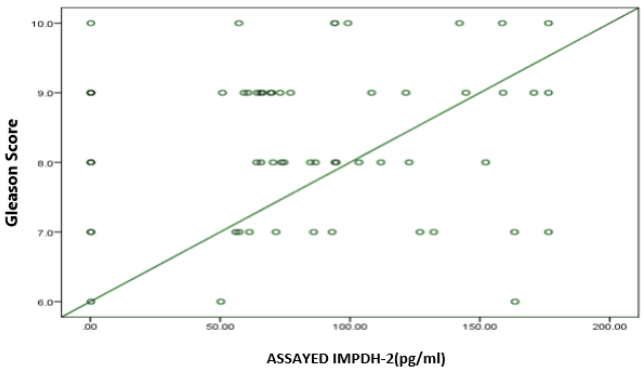
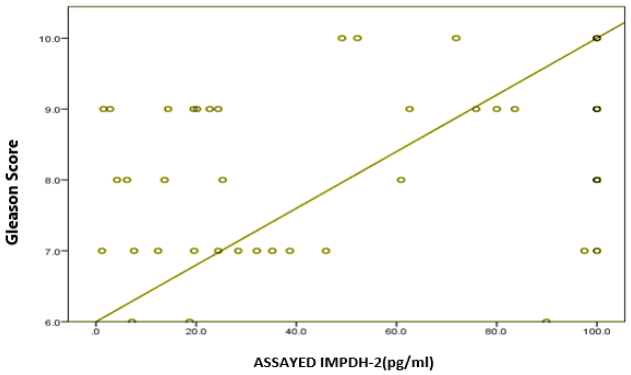


Figure 4. A Scatterplot Showing the Weak Linear Relationship Between PSA and Gleason Score.



Discussion

It is worrisome that our patients still present late with locally advanced and occasionally metastatic prostate cancer, even with the availability of PSA testing facilities. Furthermore, we frequently see patients with advanced illnesses that progress to skeletal metastasis. To make informed management decisions and lower the morbidity and death rate related to the condition,

it is essential to identify individuals with high-grade, aggressive PCa who are at risk of disease progression.

Age is a significant risk factor for prostate cancer and the majority of cases are diagnosed at 65 years or older with the risk rising after the age of 50.19 This study obtained comparable results, with a mean age of 68.6 years and most participants being older than 65. The findings by Wieczorek et al.14 in Poland and Odubanjo et al.20 in Nigeria were similar to ours reporting a mean age of 68.2 years and 68.5 years respectively. Similarly, Elabbady et al.21 in Egypt reported a mean age of 67 which is also not significantly different from ours. In Ghana, however, Egote et al.22 reported a higher mean age of 71.7 years. This may be either because their patients present late or they may have less aggressive disease and hence late onset of symptoms..

Figure 5. The ROC Curve for Serum PSA Showing some Usefulness of PSA in Diagnosing Aggressive Prostate Cancer.

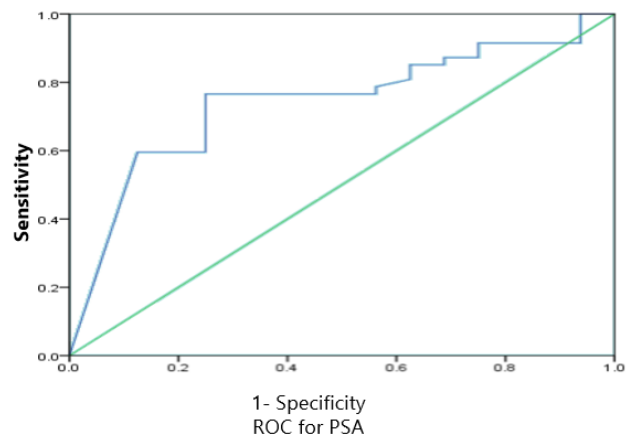
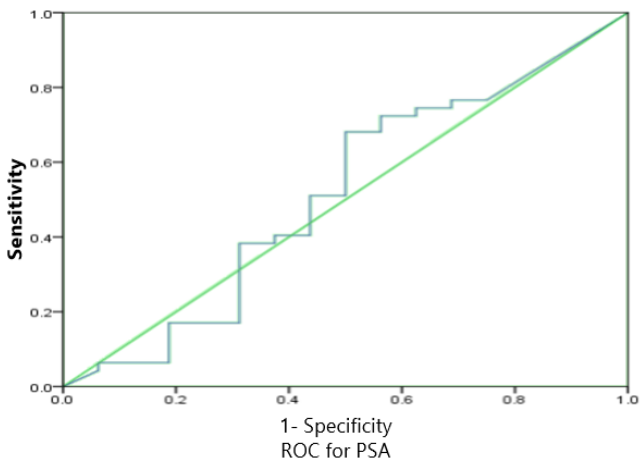


Figure 6. The ROC Curve for Serum IMPDH-2 Showing its Poor Usefulness in Diagnosing Aggressive Prostate Cancer.



Almost all our study participants had lower urinary tract symptoms (LUTS), indicating at least a locally advanced illness. This indicated inadequate PCa screening practices, which can be linked to several factors including low awareness, poverty, anxiety and fear of developing cancer, lack of urologists in primary and secondary healthcare facilities, and a dearth of PSA testing facilities in rural areas. Yahaya et al.[23] also reported LUTS as the most common form of presentation of their PCa patients. In contrast, Adewumi et al.[24] reported LUTS as the second most common complaint after bone pain. In another study, Oyibo et al.4 reported LUTS in three-quarters of their study participants. However, Elabbady et al.[21] in Egypt, reported that a quarter of their PCa patients were asymptomatic at diagnosis due to improved practice of PSA screening. In Lagos, Odubanjo et al.[20] also reported 20% of their patients being asymptomatic at diagnosis possibly due to better PCa screening awareness. According to their report, LUTS was still the most often reported form of presentation in 68.6% of their patients. Based on the aforementioned studies, LUTS is a major form of presentation of PCa patients. This may be attributed to locally advanced disease or coexisting benign prostatic hyperplasia.

Medical comorbidity affected over half of our participants; the majority had hypertension, and a small number had diabetes mellitus. The presence of a medical co-morbidity in prostate cancer patients may constitute a competing cause of mortality. This was buttressed by Stikbakke et al.[25] who reported that a systolic blood pressure of >150 mmHg among PCa patients is associated with a 49% increase in overall mortality. Also, a threefold increase in overall mortality risk was observed among prostate cancer patients with diastolic blood pressure > 90mmHg treated with curative intent.[25] The small number of diabetics among our study participants is in keeping with the findings by Kasper et al.[26] that diabetes has an inverse relationship with PCa. Ofoha et al.[19] also reported that about half of their PCa patients had comorbidity with hypertension being the commonest. The majority of participants' DRE was suspicious of PCa, supporting how late our patients presented. Oyibo et al.[4] also reported similar findings as 90% of the patients in their study had suspicious DRE. In contrast, Elabbady et al.[21] and Wieczorek et al.[14] reported less than a quarter of their study subjects with suspicious DRE which reflects an earlier diagnosis of prostate cancer in their regions. The majority of individuals with positive urine cultures were asymptomatic and had indwelling urethral catheters. According to studies, the duration of the indwelling catheter is the main determining factor of catheter-associated bacteriuria. Catheter-associated bacteriuria affects patients with an indwelling urethral catheter at a daily rate of 3 – 8%.[27]

The mean serum PSA level of our participants was 65.9ng/ml which is lower than 207.9ng/ml reported by Okolo et al.[28], 82.9ng/ml reported by Oyibo et al.[4], and 73.4ng/ml reported by Ofoha et al.[19] but higher than 37.1ng/ml reported by Egote et al.22 These variations can be a result of the biology of the cancer cells or variations in the ELISA kits used in the various studies. Even though the majority of participants had PSA levels above 10ng/ml, a few had PSA levels below 4ng/ml. This suggests that certain patients with prostate cancer may not be detected by the PSA threshold of 4ng/ml, which is why additional clinical and radiological parameters are necessary. This was also corroborated by Odubanbjo et al.[20] who reported that 3% of their PCa patients had PSA <4ng/ml. The mean serum level of IMPDH-2 in our study

was higher than the 60.[5] that Wieczorek et al.[14] The difference observed in both studies may be due to different ELISA kits, tumor biology, population characteristics, or sample size. This is because our sample size is larger than theirs and our study population is black compared to the white study population in Poland.

The mean size of the prostate was 67.9ml which is similar to 67.2ml reported by Oyibo et al.[4] also in Nigeria, but slightly higher than the 63ml reported by Elabbady et al.[21] The majority of research participants had a breached prostatic capsule, and nearly half of them had tumor invasion of one or both seminal vesicles, indicating at least a locally advanced disease. Oyibo et al.[4] likewise stated that 85% of their patients had a capsular breach. Prostatic nodules on TRUS were present in most of our research participants. These nodules were primarily hypoechoic or mixed echoic. The study by Manseck et al.[29] also reported hypoechoic lesions in 34.5% of all biopsy cores making it the most common lesion associated with PCa. The majority of the research participants had Gleason scores of 8 or above (ISUP grade group 4 and 5) which emphasizes the aggressiveness of prostate cancer in these individuals. Prior research has revealed that black and Asian individuals had germline mutations linked to high-risk prostate cancer.[30] Oyibo et al.4 reported that 52% of their study participants had Gleason scores of 8-10 which is lower than ours. Ngwu et al. 31 reported less than a quarter of their patients, 18.2% with a Gleason score of 8 – 10. Only 4.8% of our study participants had a Gleason score of 6 which is lower than the 32.5% that was reported by Oyibo et al.4 In contrast to our study Elabbady et al.[21] and Wieczorek et al.[14] reported Gleason scores of ≤7 as the most common Gleason scores in their respective studies. This shows that Arabs and Caucasians are more likely to have less aggressive prostate cancer compared to blacks.

Our research revealed that the Gleason score and ISUP Grade groups could not be predicted by serum IMPDH-2. This is in contrast to the finding of Wieczorek et al.[14] who reported a weak positive correlation between serum IMPDH-2 and ISUP grade group (τ = 0.4, p = 0.005, Kendall tau). Variances in the ELISA kits used in the two research, differences in sample size, or even variations in tumor biology related to race or ethnicity could be responsible for the disparities observed between the two studies. Serum PSA did, however, showed a very weak positive correlation with ISUP Grade groups and a weak positive correlation with the Gleason score. This further affirms PSA as a weak predictor of aggressive prostate cancer. Additionally, 10.1% of the variance in the Gleason score was dictated by serum PSA. Thus, about 80% of the Gleason score variance can be attributed to other causes. Okolo et al.[28] and Oyibo et al.[4] both in Nigeria, also reported a weak positive correlation of 0.4 between serum PSA and Gleason score. Likewise, Ngwu et al.31 reported a positive association between serum PSA and Gleason score (r = 0.6) with a moderate strength. Ngowi et al.[3] in Tanzania also reported weak ability of serum PSA in predicting aggressive PCa with an AUC of 0.71 which is not different from ours. However, in a study by Mohammed et al.[32] there was no correlation between PSA and Gleason score (p = 0.175). Most of the aforementioned studies showed that serum PSA could predict aggressive PCa. However, it is not an accurate biomarker, and therefore, at most, it should be used in combination with other markers and parameters such as Gleason score, number, and percentage of prostate biopsy core involvement among others to predict aggressive prostate cancer. Serum IMPDH-2 did not predict aggressive prostate cancer. There is a need to intensify further research into other biomarkers and advanced imaging techniques including functional imaging that may predict aggressive prostate cancer with high accuracy.

Conclusion

Serum PSA is a weak predictor of aggressive prostate cancer. It was responsible for 10.1 and 8.8% of the Gleason score and ISUP grade group variances. However, serum IMPDH-2 could not predict aggressive prostate cancer. Even though serum PSA weakly predicted aggressive prostate cancer, it was not statistically better than serum IMPDH-2. Therefore, neither of the two biomarkers can reliably predict aggressive prostate cancer, especially when used in isolation. Hence, further studies need to be done to search for better predictors of aggressive prostate cancer.

Summary – Accelerating Translation

Comparison of Serum PSA and IMPDH-2 as Predictors of Aggressive Prostate Cancer: A Cross-sectional Study

Main Problem to Solve: Prostate cancer is a major cause of morbidity and mortality globally. It is the most common male cancer among Nigerian men. Most of our patients present with locally advanced and metastatic disease. Serum PSA is not accurate in discriminating aggressive from indolent prostate cancer. Even though the Gleason score and ISUP grade group are more accurate than PSA in that regard, they require a biopsy. Prostate biopsy is an invasive procedure and foci of high-grade disease can be missed. Therefore, some patients with aggressive prostate cancer can be missed using the Gleason score and ISUP grade. Therefore, a reliable, accessible, and affordable screening modality is required to improve the diagnosis of aggressive prostate cancer.

Aim of the Study: This article aims to compare serum prostate-specific antigen and Inosine Monophosphate Dehydrogenase 2 in predicting aggressive prostate cancer.

Methodology: Sixty-three prostate adenocarcinoma patients were recruited for this quantitative descriptive cross-sectional study. Their serum was assayed for IMPDH-2 and PSA. Serum IMPDH-2 and PSA correlations with Gleason score and ISUP Grade Groups were determined using Spearman's rho and Kendall tau correlation coefficients, respectively. The magnitude of the correlation was assessed by calculating the coefficient of determination for the respective analysis (R^2). Similarly, regression analysis and receiver operating characteristic (ROC) curve were used to assess the ability of the biomarkers to predict aggressive prostate cancer. Levels of statistical significance were set as $p < 0.05$.

Results: The mean age was 68.6 years. All the recruited participants were symptomatic. The mean serum IMPDH-2 and PSA were 76.2pg/ml and 65.9ng/ml respectively. Serum IMPDH-2 did not correlate with the Gleason score (r = 0.08, p = 0.55 Spearman rho) and ISUP grade group (τ = 0.03, p = 0.79 Kendal tau). Similarly, using linear regression analysis, serum IMPDH-2 had no relationship with the Gleason score (B=0.001, P=0.56) and ISUP grade group (B = 0.001, p = 0.78). It also failed to predict aggressive prostate cancer (ISUP grade group 4 and 5) using the ROC curve with an area under the curve of 0.52 (95% CI; 0.34 – 0.69). Therefore,

IMPDH-2 is not a good predictor of aggressive prostate cancer. However, serum PSA weakly correlated with Gleason score (r = 0.30, p = 0.02 Spearman rho) and ISUP grade group (τ = 0.21, p = 0.04 Kendal tau). It was responsible for 10.1 and 8.8% of Gleason score and ISUP grade group variances respectively. Similarly, using regression analysis, there was a weak linear relationship between PSA and both the Gleason score (B= 0.009, p = 0.01) and the ISUP grade group (B = 0.009, p = 0.02). The overall ability of serum PSA in predicting aggressive PCa (ISUP grade group 4 and 5) was fair with an area under the curve of 0.74 (95% CI; 0.61 – 0.88). However, when compared, serum PSA did not significantly outperform IMPDH-2 in predicting the Gleason score (p = 0.53).

Conclusion: Serum PSA weakly predicted aggressive prostate cancer but did not statistically significantly outperform IMPDH-2. It was responsible for 10.1 and 8.8% of Gleason score and ISUP grade group variances. Therefore, neither PSA nor IMPDH-2 is sufficiently accurate in predicting aggressive prostate cancer when used in isolation.

References

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022 GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74(3):229-263.
2. Popoola AO. Prevalence and pattern of cancers among adults attending a tertiary health institution in Lagos, Nigeria. IOSR J Dent Med Sci. 2013;6(3):68-73.
3. Ngowi BN, Mremi A, Seif MJ, Kyara YS, Mteta VK, Bright F, et al. Prostate cancer: burden and correlation with prostate specific antigen among screened African men in Tanzania. Res Rep Urol. 2024;16:315-325.
4. Oyibo EU, Umar MA, Abdullahi K, Muhammad SA, Agwu PN. Clinicopathological correlates of patients with prostate cancer in a tertiary hospital in northwestern Nigeria. Orient Journal of Medicine. 2023;35(1-2):1-10.
5. Ojewola RW, Tijani KH, Jeje EA, Ogunjimi MA, Anunobi CC, Adesanya AO. An evaluation of usefulness of prostate specific antigen and digital rectal examination in the diagnosis of prostate cancer in an unscreened population: experience in a Nigerian teaching hospital. West Afr J Med. 2013;32(1):8-13.
6. Oluwole OP, Rafindadi AH, Shehu MS, Samaila MOA. A ten-year study of prostate cancer specimens at Ahmadu Bello University Teaching Hospital Zaria, Nigeria. Afr J Urol. 2015;21(1):15-18.
7. Ogunbiyi JO, Shittu OB. Increased incidence of prostate cancer in Nigerians. J Natl Med Assoc. 1999;91(3):159-164.
8. Wang C, Höti N, Lih TSM, Sokoll LJ, Zhang R, Zhang Z, et al. Development of a glycoproteomic strategy to detect more aggressive prostate cancer using lectin-immunoassays for serum fucosylated PSA. Clin Proteomics. 2019;16:13.
9. Gordetsky J, Epstein J. Grading of prostatic adenocarcinoma: current state and prognostic implications. Diagn Pathol. 2016;11:25.
10. Chen N, Zhou Q. The evolving Gleason grading system. Chin J Cancer Res. 2016;28(1):58.
11. He Y, Zheng Z, Xu Y, Weng H, Gao Y, Qin K, et al. Over-expression of IMPDH2 is associated with tumor progression and poor prognosis in hepatocellular carcinoma. Am J Cancer Res. 2018;8(8):1604.
12. Hedstrom L. IMP dehydrogenase: structure, mechanism, and inhibition. Chem Rev. 2009;109(7):2903-2928.
13. Xu Y, Zheng Z, Gao Y, Duan S, Chen C, Rong J, et al. High expression of IMPDH2 is associated with aggressive features and poor prognosis of primary nasopharyngeal carcinoma. Sci Rep. 2017;7:745. doi:10.1038/s41598-017-00887-1
14. Wieczorek P, Bałut-Wieczorek M, Jasinski M, Szabłoński W, Antczak A. Inosine monophosphate dehydrogenase 2 as a marker of aggressive and advanced prostate cancer. Cent European J Urol. 2018;71(4):399-403.
15. Awosan KJ. Student friendly statistics for health, life, and social sciences. Lagos: Somerest Ventures; 2020
16. Monobind. PSA AccuBind Elisa kit (product code 2125-300). Available from: https://www.monobind.com/immunoassays-cancer-markers-psa. Cited January 7, 2021.
17. Sunlong Biotech. Human inosine monophosphate dehydrogenase 2 (IMPDH2) ELISA kit Instruction manual. Available from: https://www.sunlongbiotech.com. Cited January 7, 2021
18. Moore DS, Notz WI, Flinger MA. The basic practice of statistics. 6th ed. New York. W H Freeman; 2013.
19. Ofoha CG, Magnus FE. Presentation, characteristics and co-morbidities of men with prostate cancer in Nigeria. J Adv Med Res. 2019;31(5):1-7.
20. Odubanjo MO, Banjo AA, Ayoola S, Abdulkareem FB, Anunobi CC, Olayinka AA. The clinicopathologic pattern of prostatic carcinoma in Lagos, Nigeria. N A J Med Sci. 2013;6(2). 71-75.
21. Elabbady A, Eid A, Fahmy A, Kotb AF. Pattern of prostate cancer presentation among the Egyptian population: A study in a single tertiary care center. Cent European J Urol. 2014;67(4):351-356.
22. Egote AK, Ossei PPS, Agyeman-Duah E, Taylor J, Quarshie E. Patterns and presentation of prostate cancer in the Brong Ahafo region of Ghana: a 6-year single center retrospective study. Health. 2019;11(4):351-360.
23. Yahaya JJ. Clinical and histopathological profile of patients with prostate cancer in Kampala, Uganda. Med J Zamb. 2019;46(1):19-27.
24. Adewumi AO, Anthonia SC, Alabi AS, Amina FO, Kingsley KK. Pattern of prostate cancer among a Nigerian population: a study in a single tertiary care centre. Niger J Med. 2016;25(1):70-76.
25. Stikbakke E, Schirmer H, Knutsen T, Støyten, M, Wilsgaard T, Giovannucci EL, et al. Systolic and diastolic blood pressure, prostate cancer risk, treatment, and survival. The PROCA-life study. Cancer Med. 2022;11(4):1005-1015.
26. Kasper JS, Giovannucci E. A meta-analysis of diabetes mellitus and the risk of prostate cancer. Cancer Epidemiol Biomarkers Prev. 2006;15(11):2056-2062
27. Hooton TM, Bradley SF, Cardenas DD, Colgan R, Geerlings SE, Rice JC, et al. Diagnosis, prevention, and treatment of catheter-associated urinary tract infection in adults. Clin Infect Dis. 2010;50(5):625-663.
28. Okolo CA, Akinosun OM, Shittu OB, et al. Correlation of serum PSA and Gleason score in Nigerian men with prostate cancer. Afr J Urol. 2008;14(1):15-22.
29. Manseck A, Guhr K, Hakenberg O, Rossa K, Wirth MP. Clinical significance of the echogenicity in prostatic ultrasound findings in the detection of prostatic carcinoma. Onkologie. 2000; 23(2):151-156.
30. Okoye JO. High mortality risk of prostate cancer patients in Asia and West Africa: A systematic review. Avicenna J Med. 2020;10(3):93-101.
31. Ngwu PE, Achor GO, Eziefule VU, Orji JI, Alozie FT. Correlation between Prostate Specific Antigen and Prostate Biopsy Gleason Score. Annals of Health Research. 2019;5(2):243-248.
32. Mohammed U, Rasheed MW, Adegboye AT, Abdullahi K, Sahabi SM, Mohammed TO, et al. Correlation of serum PSA with Gleason score and Gleason group grade in patients with prostate adenocarcinoma at Sokoto north-western Nigeria. Intl J Recent Innov Med Clin Res. 2024;2(2):6-13.

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Conflict of Interest Statement & Funding

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Author Contributions

Conceptualization: AMU, IAM, NPA, AAA. Data Curation: AMU, EUO. Formal Analysis: AMU. Funding Acquisition: AMU. Methodology: AMU, ASM, AK. Project Administration: IAM. Resources: AMU, EUO. Software: AMU. Supervision: IAM, NPA, AAA, ASM. Validation: AMU, NPA, ASM. Visualization: AMU. Writing - Original Draft: AMU, AK, EUO. Writing - Review Editing: AMU, IAM, NPA, AAA, ASM, AK.

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Short Communication

Evaluating Hypoglossal Nerve Stimulation Outcomes in Obstructive Sleep Apnea: Impact of Predisposing Conditions in a Retrospective Cohort

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Abstract

Background: This retrospective study aimed to analyze treatment outcomes for patients receiving a hypoglossal nerve stimulation (HNS) device for obstructive sleep apnea (OSA). **Methods:** Chart reviews were conducted for HNS patients who underwent a post-implantation polysomnography (PSG) (typically performed approximately 2 months after device activation) to assess therapeutic response and optimize stimulation settings. Patients were categorized into "green (GP)" (optimal response: AHI <15, ≥4 hours/night device use, and subjective benefit) and "yellow (YP)" (suboptimal response: failure to meet one or more of these criteria) response pathways. **Results:** Out of 111 patients assessed, 27 patients met pathway categorization criteria. 12 of those were classified in green and 15 in yellow. Median age and BMI were 63.9 years and 28.7 kg/m^2, respectively, with a balanced sex assigned at birth distribution. HNS treatment reduced median AHI by 85.6% (from 34.7 to 5.0) for the green pathway (GP), and by 87.4% (from 39.6 to 5.0) for the yellow pathway (YP). Patients who had at least one sleep-related comorbidity were more likely to be in the yellow pathway ($p < .001$). Comorbidities such as depression and insomnia were significantly associated with suboptimal treatment response (yellow pathway) ($p = .003$ and $p = .02$, respectively). **Conclusions**: This study emphasizes the significance of sleep-related comorbidities as a strong predictor of patient outcomes. More efficient utilization of resources may be achieved by considering comorbid conditions prior to HNS implantation. Given the small sample size and retrospective single-institution design, these findings should be interpreted with caution and may not be generalizable to broader populations.

Introduction

Obstructive sleep apnea (OSA) affects approximately 35.9% of older adults and is associated with obesity, age, cardiovascular disease, diabetes, and excessive daytime sleepiness.[1] Although continuous positive airway pressure (CPAP) devices are effective for OSA management, adherence rates remain low, with only 30-60% of patients consistently using them as prescribed.[2] CPAP intolerance is prevalent, affecting patients due to discomfort, claustrophobia, and lifestyle incompatibility.[3] This leaves a significant portion of patients untreated or inadequately managed, highlighting the need for alternative OSA therapies. Recent studies demonstrate that targeted hypoglossal nerve stimulation (HNS) has emerged as a promising therapy for CPAP intolerant patients. It significantly improves apnea severity, quality of life, and sleepiness in patients with moderate to severe OSA. The therapy benefits a diverse range of patients across varying body mass index (BMI) and Apnea-Hypopnea Index (AHI) levels, with clinically meaningful responses observed in randomized clinical trials.[4]

OSA is a potentially life-threatening disorder characterized by episodes of upper-airway collapse that recur during sleep. It presents during sleep as loud snoring and breathing interruptions that can lead to the low partial pressure of oxygen, high partial pressure of carbon dioxide, and excessive daytime sleepiness.[5] The most common treatment for OSA is the use of CPAP devices. However, lack of adherence continues to be a significant issue for using such devices. Studies show that only 40-60% of patients adhere to using the CPAP device as prescribed by their physician.[6] In addition, many OSA patients do not seek medical attention for the disorder and therefore do not use any method to manage it.[7] The lack of patient knowledge regarding their sleep apnea and the available treatment options has led to OSA being overlooked by many clinicians.[8] Untreated OSA is associated with diminished quality of life and increased risk of cardiovascular, neurologic, and psychiatric complications.[9, 10] These risks underscore the need for effective, tolerable alternatives such as hypoglossal nerve stimulation for patients who cannot adhere to CPAP therapy.

Recently, HNS has emerged as an alternative treatment for patients. HNS is a second line of therapy for treating sleep apnea, particularly in patients who cannot tolerate CPAP and meet other eligibility criteria.[11] After implantation of HNS, the device is activated at the clinic, and settings are fine-tuned during a

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specialized titration night. Annual sleep medicine follow-ups ensure sustained efficacy and necessary adjustments. Treatment outcomes are documented by categorizing patients in two response pathways that are established by the HNS device maker: "green" and "yellow." Prior studies on HNS has demonstrated its benefits for patients with moderate to severe OSA, but there is limited knowledge regarding which comorbidities predict treatment outcomes.[12] Given the diverse nature of OSA manifestations and its associated comorbidities, understanding factors that may contribute to patient outcomes facilitates individualized approaches which can increase treatment efficacy. This study aimed to investigate whether sleep-related comorbidities and other patient characteristics predict categorization into these pathways among OSA patients undergoing HNS.

While HNS has shown promise, the factors influencing patient response to this treatment remain unclear. Prior studies lack comprehensive analyses of co-morbidities and other patient characteristics that might predict positive outcomes.[12] Therefore, the purpose of this retrospective study was to investigate the predictive factors for patient placement in "green" and "yellow" response pathways post-HNS implantation. By clarifying these factors, this study aims to contribute to more individualized and effective OSA management strategies. We hypothesized that patients with sleep-related comorbidities (such as insomnia, depression, or anxiety) would be more likely to experience suboptimal outcomes following HNS implantation, as reflected by yellow pathway classification.

Methods

A retrospective chart review was conducted on all patients diagnosed with OSA and CPAP intolerance who presented for HNS consult between 2019 and 2023. Chart reviews were conducted for 111 patients who underwent HNS implantation at our institution. All patients received the Inspire® Upper Airway Stimulation system (Inspire Medical Systems, Inc., Golden Valley, MN).

Inclusion criteria for HNS implantation included patients diagnosed with moderate to severe OSA, defined by an AHI of 15 or more, who demonstrated intolerance to CPAP therapy or inadequate response to CPAP. Additional criteria required patients to have a BMI of 35 or less, no complete concentric collapse observed on drug-induced sleep endoscopy (DISE), and no significant comorbid conditions that could interfere with HNS outcomes. Exclusion criteria involved patients with significant neuromuscular disease, central sleep apnea, or those with anatomical abnormalities that contraindicated HNS.

Health behaviors, comorbid conditions, and treatment outcomes, including data from a titration polysomnography (PSG), were documented. Device activation typically occurred four weeks post-surgery, followed by a titration PSG approximately two months later to assess therapeutic response and adjust stimulation settings. Patients were classified in the 'green' pathway if AHI was below 15, the device was used more than 4 hours/day, and the patient reported improvement in symptoms (reduced daytime sleepiness and enhanced sleep quality). Patients were classified as "yellow" pathway if any of the criteria were not met. Those clinical pathways are part of the clinical framework established by the HNS device maker based on the criteria mentioned above. Symptom improvement was determined based on clinician-documented patient reports during follow-up visits. No standardized survey instrument (ESS) was used. Comorbid conditions, including depression, insomnia, and anxiety, were identified through clinician documentation in

Table 1. Comparison of Yellow & Green Pathway Demographics and Treatment Results for Patients Receiving a Hypoglossal Nerve Stimulation Device.

	Green Pathway (*n* = 12)	**Yellow Pathway** (*n* = 15)	***p*-value**
Median Age at Initial Visit (IQR)	64.6 (57.8, 73.6)	63.4 (55.6, 69.4)	.48†
Sex Assigned at Birth n (%)			1.00
Male	5 (45.5%)	6 (54.5%)	
Female	7 (43.8%)	9 (56.3%)	
Median BMI at Initial Visit (IQR)	28.5 (26.0, 31.0)	28.9 (27.0, 31.0)	0.54†
Smoking Status n (%)			.08††
Active or Former Smoker	4 (28.6%)	10 (71.4%)	
Never Smoker	8 (61.5%)	5 (38.5%)	
Comorbid Conditions n (%)			
Depression			.003††
No	10 (71.4%)	4 (28.6%)	
Yes	2 (15.4%)	11 (84.6%)	
Insomnia			.02
No	12 (57.1%)	9 (42.9%)	
Yes	0 (0.0%)	6 (100.0%)	
Anxiety			.11
No	10 (58.8%)	7 (41.2%)	
Yes	2 (20.0%)	8 (80.0%)	
Restless Leg Syndrome			.49
No	12 (48.0%)	13 (52.0%)	
Yes	0 (0.0%)	2 (100.0%)	
Narcolepsy			-
No	12 (44.4%)	15 (55.6%)	
Sleepwalking/Eating/Talking			.49
No	12 (48.0%)	13 (52.0%)	
Yes	0 (0.0%)	2 (100.0%)	
Nightmares or Night Terrors			1.00
No	12 (46.2%)	14 (53.8%)	
Yes	0 (0.0%)	1 (100.0%)	
Bruxism			-
No	12 (44.4%)	15 (55.6%)	
At least One Or More Comorbidity			< .001
No	10 (90.9%)	1 (9.1%)	
Yes	2 (12.5%)	14 (87.5%)	
Median AHI (IQR)			
Pre-Implantation	34.7 (24.7, 52.1)	39.6 (23.0, 54.1)	.94†
Post-Implantation	5.0 (3.6, 8.5)	5.0 (3.8, 10.4)	.48†

Legend: P-values from Fisher's exact tests unless otherwise specified. †P-value from Wilcoxon rank-sum test. ††P-value from Chi-Square test.

the electronic medical record, based on entries in problem lists or clinical notes prior to HNS implantation. No structured diagnostic instruments or ICD-10 codes were used.

All data extraction and chart review were conducted by a single investigator using a standardized data abstraction template to ensure consistency across variables. Medians and interquartile ranges (IQRs) were used to summarize continuous data. Differences between the two pathway groups were analyzed using Chi-square and Fisher's exact tests for categorical variables, and Wilcoxon Rank Sum tests for continuous variables. All statistical analyses were conducted using SAS software version 9.4 (SAS Institute Inc., Cary, NC).

Results

Of the 111 patients who proceeded with the HNS implantation post-implantation treatment, outcomes were available for 27 patients. The remaining 84 patients were excluded from analysis due to not yet reaching the required follow-up for pathway classification (e.g., pending titration PSG or clinical reassessment) or being lost to follow-up. Statistical analyses were completed for 12 in the green pathway (GP) and 15 in the yellow pathway (YP). Demographic characteristics are in ***Table 1***. Patient age at initial visit, sex assigned at birth, and median BMI at the initial visit were not significantly different between groups. The median AHI pre-implantation was 34.7 in the GP and 39.6 in the YP (p=.94). Post-implantation, the median AHI was reduced to 5.0 in both the GP and YP groups (p=.48).

Significant differences in pathway categorization were noted in certain comorbid conditions. YP categorization was significantly more common in patients with depression (84.6%) compared to those without depression (28.6%) (absolute difference: 56%, p = .003). YP was more prevalent in patients with insomnia (100.0%) versus those without insomnia (42.9%) (absolute difference: 57.1%, p = .02). While more patients with anxiety were in the YP (80.0%) than those without anxiety (41.2%), this difference was not statistically significant, p = .11. Restless leg syndrome, sleepwalking/eating/talking, and nightmares or night terrors did not significantly differ between the pathway groups. Overall, patients who had at least one comorbidity of all the above-mentioned conditions were more likely to be in the YP (87.5%) than patients who did not have a comorbidity (9.1%), p < .001.

Discussion

This study summarized the outcomes for 27 patients following HNS implantation who met pathway classification criteria, revealing key insights into treatment efficacy and comorbidity impacts. It identified key comorbid predictors and factors associated with treatment outcomes following HNS implantation that were consistent with prior studies.[13] Our findings reveal that comorbidities significantly influenced pathway categorization, with patients having at least one comorbidity, such as depression or insomnia, more likely to be in the yellow pathway. These conditions may influence HNS outcomes through several well-recognized pathways. Insomnia can reduce the restorative quality of sleep and interfere with perceived benefit, even when respiratory parameters improve. Depression may impair treatment adherence or amplify symptom perception, limiting subjective improvement. Both conditions are also associated with disrupted circadian regulation and altered sleep-wake dynamics, which may blunt the perceived efficacy of HNS. One of the most striking outcomes is the marked reduction in the average AHI post-Inspire implantation, dropping from 34.7 to 5.0 for the green pathway and from 39.6 to 5.0 for the yellow pathway. Recognizing that an AHI below 5.0 represents effective OSA control, this result underscores the potential efficacy of Inspire HNS.

Clinical outcomes may be improved by understanding comorbid predictive factors that impact the effectiveness of HNS treatment. A recently published study examined the impact of comorbid insomnia on patient-reported outcomes and objective measures in OSA patients. Results reported that OSA patients with insomnia (COMISA) experienced reduced improvement and were less satisfied compared to those without insomnia.[14] A similar study observed a significant drop in patient-reported insomnia three months after HNS activation. Although these results were encouraging, a strong inverse correlation between pre-op subjective assessments and post-op respiratory metrics suggests that patients with more severe pre-op insomnia may have less favorable clinical outcomes.[15] These findings have important clinical implications. Awareness of yellow pathway predictors, particularly insomnia and depression, may help clinicians identify patients at risk for suboptimal outcomes prior to HNS implantation. This could guide more informed shared decision-making, prompt early behavioral health referral, and tailor follow-up intensity. Incorporating pathway categorization into post-implantation workflows may also help flag patients who are not responding optimally and benefit from earlier intervention or re-titration, improving long-term device efficacy and patient satisfaction. These findings may also inform the design of future prospective studies aimed at validating predictive models for HNS response. Stratifying patients based on pre-existing comorbidities, particularly psychiatric and sleep-related, could support development of clinical decision-making tools to guide candidate selection, counseling, and personalized follow-up strategies. Prospective studies incorporating standardized outcome metrics and multivariable models could enhance the precision of HNS treatment pathways.

Overall, patients in our study with comorbidities of insomnia, depression, or anxiety, were more likely to be in the suboptimal YP post-treatment. This insight provides an opportunity for more personalized HNS approaches, as patients with these comorbidities may benefit from tailored pre-and post-implantation interventions, such as mental health support, targeted behavioral therapies, or enhanced follow-up protocols, to mitigate the effects of these comorbidities on treatment adherence and effectiveness. Recognizing this predisposition

allows for the tailoring of interventions, potentially enhancing treatment outcomes. For instance, implementing structured pre-treatment counseling sessions could help set realistic expectations and address concerns specific to patients at higher risk for yellow pathway outcomes. Integrating mental health or sleep specialists into the care team may also support optimal outcomes for these patients. A closer look at the treatment response pathways revealed that while the GP patients showed significant clinical benefits, a substantial portion of patients were classified in the YP. This categorization highlights the importance of a personalized approach to OSA management. Tailoring treatment strategies could enhance efficacy and adherence, addressing the critical problem of under-management of OSA.

Limitations of this study include the retrospective design, which may introduce certain biases. Selection bias is possible, as only patients who completed post-implantation follow-up and pathway classification were included in the analysis. This may disproportionately exclude patients with barriers to care, lower adherence, or worse outcomes, potentially skewing the representativeness of our sample. Moreover, certain potential confounding variables were not controlled for, including medication use, cognitive status, and socioeconomic factors such as insurance status or access to care, all of which could influence both treatment adherence and perceived clinical benefit. Additionally, the reliance on patient-reported outcomes, especially for subjective measures such as sleep quality and daytime sleepiness, introduces the potential for recall bias. Furthermore, the relatively small sample size of patients who underwent Inspire implantation and had available post-treatment data, combined with the single-institution setting, limits external validity. Furthermore, the relatively small sample size of patients who underwent Inspire implantation and had available post-treatment data, combined with the single-institution setting, limits external validity. Moreover, due to the limited sample size, we did not perform multivariable regression and thus cannot rule out residual confounding by factors such as age, sex assigned at birth, BMI, and baseline AHI. Practice patterns, patient populations, and follow-up protocols may differ across institutions, which could affect generalizability, although ongoing data collection will expand this sample size in future analysis. Additionally, a large proportion of patients (84/111) could not be included in pathway analysis due to incomplete follow-up, which may reflect real-world barriers to care, such as access limitations, delayed titration PSG scheduling, or patient attrition. This restricts the generalizability of our findings and underscores the importance of implementation research in HNS therapy. Due to the retrospective design, continued follow-up data collection will expand the sample in the future.

In conclusion, this study sheds light on the potential benefits and challenges of utilizing HNS in managing OSA. It underscores the need for personalized and equitable approaches in treating this common yet often overlooked disorder. By proactively identifying patients who may fall into the yellow pathway, clinicians can modify treatment plans and potentially improve long-term outcomes for a broader patient population. Further research is warranted to validate these findings and to delve deeper into understanding how to optimize treatment pathways for all OSA patients with comorbid conditions.

References

1. Ghavami T, Kazeminia M, Ahmadi N, Rajati F. Global Prevalence of Obstructive Sleep Apnea in the Elderly and Related Factors: A Systematic Review and Meta-Analysis Study. J Perianesth Nurs. 2023;38(6):865-875.
2. Lin HS, Prasad AS, Pan CJ, Rowley JA. Factors associated with noncompliance to treatment with positive airway pressure. Arch Otolaryngol Head Neck Surg. 2007;133(1):69-72.
3. Qiao M, Xie Y, Wolff A, Kwon J. Long term adherence to continuous positive Airway pressure in mild obstructive sleep apnea. BMC Pulm Med. 2023;23(1):320.
4. Schwartz AR, Jacobowitz O, Eisele DW, et al. Targeted Hypoglossal Nerve Stimulation for Patients with Obstructive Sleep Apnea: A Randomized Clinical Trial [published correction appears in JAMA Otolaryngol Head Neck Surg. 2024 Jun 1;150(6):530. JAMA Otolaryngol Head Neck Surg. 2023;149(6):512-520.
5. Strollo PJ Jr, Rogers RM. Obstructive sleep apnea. N Engl J Med. 1996;334(2):99-104.
6. Sawyer AM, Gooneratne NS, Marcus CL, Ofer D, Richards KC, Weaver TE. A systematic review of CPAP adherence across age groups: clinical and empiric insights for developing CPAP adherence interventions. Sleep Med Rev. 2011;15(6):343-356.
7. Baillieul S, Dekkers M, Brill AK, et al. Sleep apnoea and ischaemic stroke: current knowledge and future directions. Lancet Neurol. 2022;21(1):78-88.
8. Kirsch DB. Obstructive Sleep Apnea. Continuum (Minneap Minn). 2020;26(4):908-928.
9. Bouzerda A. Risque cardiovasculaire et syndrome d'apnées obstructives du sommeil [Cardiovascular risk and obstructive sleep apnea]. Pan Afr Med J. 2018;29:47.
10. Hobzova M, Prasko J, Vanek J, et al. Depression and obstructive sleep apnea. Neuro Endocrinol Lett. 2017;38(5):343-352.
11. Malhotra A. Hypoglossal-nerve stimulation for obstructive sleep apnea. N Engl J Med. 2014;370(2):170-171.
12. Tukanov E, Van Loo D, Dieltjens M, Verbraecken J, Vanderveken OM, Op de Beeck S. Baseline Characteristics Associated with Hypoglossal Nerve Stimulation Treatment Outcomes in Patients with Obstructive Sleep Apnea: A Systematic Review. Life (Basel). 2024;14(9):1129. Published 2024 Sep 7.
13. Soose, RJ, Faber, K, Greenberg H, Boon M, Woodson T, Strollo P. (2021). Post-implant care pathway: lessons learned and recommendations after 5 years of clinical implementation of hypoglossal nerve stimulation therapy. Sleep, 44(Suppl 1): S4–S10.
14. Steffen A, Baptista P, Ebner EM, Jeschke S, König IR, Bruchhage KL. Insomnia affects patient-reported outcome in sleep apnea treated with hypoglossal nerve stimulation. Laryngoscope Investigative Otolaryngology. 2022;7(3):877–884.
15. Pordzik J, Ludwig K, Seifen C, Huppertz T, Bahr-Hamm K, Matthias C, Gouveris H. Insomnia in Patients Undergoing Hypoglossal Nerve Stimulation Therapy for Obstructive Sleep Apnea. Biology. 2023;12(1):98.

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Conflict of Interest Statement & Funding

This study received approval from the Institutional Review Board (IRB) at our institution. Given its retrospective design, all data were de-identified, and patient confidentiality was maintained in accordance with ethical standards. This research was funded by University of Nebraska Medical Center. No conflicts of interest are declared by any of the authors.

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Review

Diagnostic Performance of Western Blot for Congenital Toxoplasmosis: A Systematic Review and Meta-Analysis

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Abstract

Background: Congenital toxoplasmosis results from infection with the parasite Toxoplasma gondii, which is transmitted from mother to child during pregnancy. Although Western blot is considered the most sensitive diagnostic tool for congenital toxoplasmosis, its diagnostic performance has not been subjected to meta-analysis. **Methods:** We conducted a systematic review and meta-analysis by performing literature searches across PubMed, Scopus, and Web of Science. The search strategy included the terms "western blot OR immunoblot" AND "congenital toxoplasmosis." The selected studies were required to meet specific inclusion criteria, which involved comparing the performance of the western blot test against the gold standard criteria for permanence of IgG after 10 months of age. These studies had to be case and control studies. The data obtained from the studies were then organized into an evidence synthesis table and the sensitivity, specificity, and Diagnostic Odds Ratio (DOR) index were calculated. This meta-analysis was performed in compliance with the recommendations of PRISMA guidelines. **Results:** After evaluating the selection criteria, we identified 44 articles; however, only 10 were selected for the meta-analysis. Western blot assay demonstrated a pooled sensitivity of 93.8% (95% CI: 79.2-98.4) and a pooled specificity of 96.6% (95% CI: 89.8-98.9) for the diagnosis of congenital toxoplasmosis. Six of the 10 studies had a DOR higher than 300, whereas the in-house method yielded a lower DOR of 1.2. **Conclusions:** This meta-analysis confirmed the utility of well-standardized western blot tests as a dependable diagnostic approach for congenital toxoplasmosis in terms of both sensitivity and specificity.

Introduction

Toxoplasmosis is a disease caused by the parasite Toxoplasma gondii, which has a distinct reproductive cycle. The extraintestinal asexual cycle occurs in intermediate hosts, such as humans, whereas the intraintestinal sexual cycle occurs in definitive hosts, such as felines. The parasite has different stages, including tachyzoites that replicate during acute infection, bradyzoites that multiply slowly during latent tissue infections, and oocysts that are excreted in cat feces.[1] Infection can occur through the consumption of contaminated food, water, and other materials that contain the resistant form of the parasite, oocysts.[1] There is also a possibility of transmission through blood transfusions or organ transplants.[1] The human host is where the parasite forms cysts in tissues, particularly in the muscles, heart, brain, and eyes. The transmission of the parasite to the fetus can occur, causing severe damage if the mother is infected for the first time during pregnancy.[1]

The symptoms of toxoplasmosis in immunocompetent adults vary and can be mild or flu-like in the presence of cervical lymphadenopathy.[1] Complications of the central nervous system, such as hemiplegia, may occur in immunocompromised individuals.[1] Infected newborns can develop permanent sequelae such as hydrocephalus, intracranial calcifications, seizures and chorioretinitis.[1] Its diagnosis is particularly difficult because as many as 40% of children infected with T. gondii do not exhibit the traditional diagnostic markers, such as the presence of IgM or IgA anti-Toxoplasma antibodies. Additionally, a significant number of cases are asymptomatic at birth, but may develop retinal lesions later in life.[2] The western blot technique has become a key support for making an early diagnosis, allowing, according to some authors, the identification of up to 90% of cases before the first month of life.[2] In newborns, the diagnosis can be challenging, especially if the mother receives prenatal treatment and the newborn is asymptomatic.[1] It is recommended to combine tests for diagnosis in newborns, such as IgA anti-Toxoplasma and PCR in cerebrospinal fluid.[3] It is important to note that a definitive diagnosis of congenital toxoplasmosis is achieved if IgG anti-Toxoplasma antibodies are still present in the newborn at ten months of age, indicating that these are not IgG transmitted by the mother and confirm newborn production. This is particularly important in asymptomatic newborns, where treatment is difficult to justify if no congenital infection is demonstrated, which can

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delay the early diagnosis and initiation of treatment.[2] It should be noted that early diagnosis will help children receive timely treatment and thus reduce the possible consequences of congenital toxoplasmosis in the future.[3]

Currently, no meta-analysis of congenital toxoplasmosis related to Western Blot diagnostic test performance has been found in the databases consulted, compared to other diagnostic methods such as PCR and serology, of which meta-analyses were found. This highlights the need to evaluate diagnostic performance through a critical and systematic analysis of the studies that evaluated this diagnostic test. Therefore, the present meta-analysis aimed to evaluate the western blot test's performance in diagnosing congenital toxoplasmosis and assess its reliability as a tool for the early detection of the disease.

Methods

A literature search was conducted in April 2023 on digital platforms, such as PubMed, Scopus, and Web of Science. This research was carried out on the usefulness of the western blot test in diagnosing congenital toxoplasmosis, with the search terms "western blot", "Immunoblot" and "Congenital toxoplasmosis". It is important to clarify that there was no contact with the authors to seek additional information. The articles selected were original case-control studies evaluating the diagnostic properties of western blot assays presenting primary data.

Selection: When the search was completed, articles that contained cases and controls and compared the western blot test with the Gold Standard (follow-up of children with anti-Toxoplasma IgG after 10 months of life) were independently selected by two researchers. Only studies with follow-up of children with negativization of specific IgG after 10 months of life for non-infected newborns (true negative) and persistence of specific IgG positivity after 10 months of life (true positive) were included. Only articles published in English were included in this study.

Initially, 172 articles were found in PubMed, Scopus, and the Web of Science. Of these 172, 55 were excluded because they were duplicates in the databases for a total of 117 unique articles. The titles and abstracts of the 117 articles were reviewed, seeking to evaluate the western blot test, and they were case-control studies. Consequently, 104 articles were excluded because only 13 met this criterion, which was later reviewed in the full text. Of the remaining 13 articles, 3 did not report data that would allow the evaluation of sensitivity, specificity, and DOR. Therefore, 10 articles published between 2001 and 2016 were included in the meta-analysis.

Organization: The data from the articles were organized into a matrix of evidence tables or comparative property tables, which were arranged in the following fields:

- Platform and date of consultation.
- Study population and definitions of the cases and controls.
- Criteria used to determine the negativity or positivity of cases and controls by WB.
- True positives (patients infected with congenital toxoplasmosis who were correctly identified as positive for persistent IgG beyond 12 months).
- False positives (uninfected newborns who were incorrectly identified as positive by the positive IgG test at birth but disappeared before 12 months).
- True negatives (uninfected newborns who are correctly identified as IgM-negative and IgG-positive at birth but disappear before 6–12 months).
- False negative (newborns infected with congenital toxoplasmosis who were incorrectly identified as negative).

This matrix of evidence allowed all researchers to analyze the data objectively at any time, without allowing for the detection of observational bias. In addition, we organized the search dates for the information, authors, and citations of the selected works. The main objective was established and analyzed in the evidence matrix using the information available in the reference bibliographic databases. In this way, the population of each study (infants exposed and not exposed to seroconversion during pregnancy), the diagnostic criteria stipulated in each study (different bands between mother and child, increased number of bands or persistent IgG in the baby, IgM in the baby's serum, positive PCR in amniotic fluid, and parasitological detection by inoculation in mice), and the use of the western blot test in each study were identified.

The statistical analyses were performed as follows:

A. The sensitivity was calculated using the following formula: $\frac{POSITIVE\ CASES\ WITH\ WB}{POSITIVE\ CASES\ (CHILDREN\ WITH\ CONFIRMED\ CONGENITAL\ TOXOPLASMOSIS)}$

B. Specificity was calculated using the following formula: $\frac{NEGATIVE\ CASES\ WITH\ WB}{NEGATIVE\ CASES\ DUE\ TO\ THE\ CRITERIA\ ESTABLISHED\ BY\ THE\ STUDY}$

C. The Diagnostic Odds Ratio was calculated using the following formula: $\frac{\#\ TRUE\ POSITIVES}{\#\ FALSE\ POSITIVES} / \frac{\#FALSE\ POSITIVES}{\#TRUE\ NEGATIVES}$ (#True positives/# false positives/# false positives/# true negatives). When the number was zero, it was replaced with one to avoid infinite values.

D. Confidence intervals of 95% (95% CI) were estimated for sensitivity, specificity, and DOR by applying the formula $p \pm z\sqrt{\frac{\hat{d}p(1-\hat{}p)/}{n}}$, where p= percentage, n=sample size, and z=1.96.

Data were examined for normality using the Kolmogorov-Smirnov test, correlation with Pearson's test, and means comparison by ANOVA using SPSS (IBM Corp. Released 2021. IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Corp). Calculation of pooled sensitivity and poled specificity were made on the software Open Meta [Analyst] downloaded at: http://www.cebm.brown.edu/openmeta/index.html.

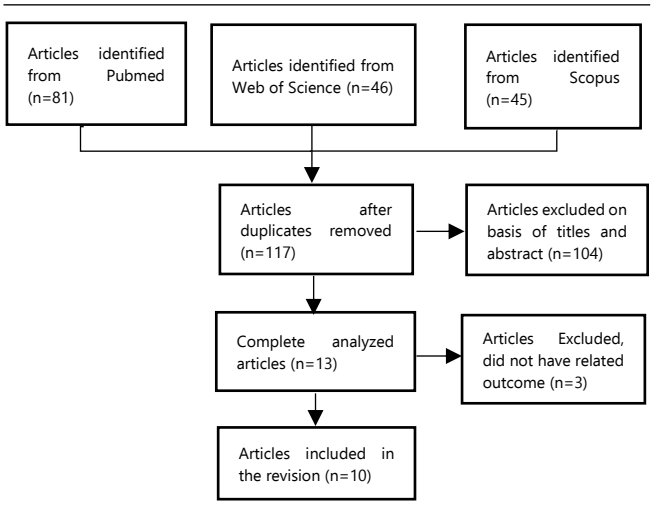
Search and Treatment of Heterogeneity

Heterogeneity was calculated by calculating I2, which provides an estimate of the proportion of variability in a meta-analysis due to heterogeneity rather than sampling error (chance) using the following formula: $I^2 = ((Q - df) / Q) \times 100\%$. Where Q is the result of the X2 test and df is the number of degrees of freedom. The interpretation was as follows: 0% to 40%, might not be important; 30% to 60%, may represent moderate heterogeneity*; 50% to 90%, may represent substantial heterogeneity*; and 75% to 100%, considerable heterogeneity*.

Results

Ten articles met the inclusion criteria (Figure 1). The pooled sensitivity (Figure 2) was 93.8 (95% CI: 79.2-98.4) and the pooled specificity (Figure 3) was 96.6% (95% CI: 89.8-98.9) for the diagnosis of congenital toxoplasmosis. A notable heterogeneity in the results was observed (Figures 2 and 3), with 83.7% sensitivity and 77.5% specificity, both of which were statistically significant (p<0.001). The DOR was higher than 300 in six studies (Figure 4). An average of 3.8 years of follow-up was found in six of the 10 articles.

Figure 1. Flowchart and Results of Article Selection Used in the Meta-analysis.

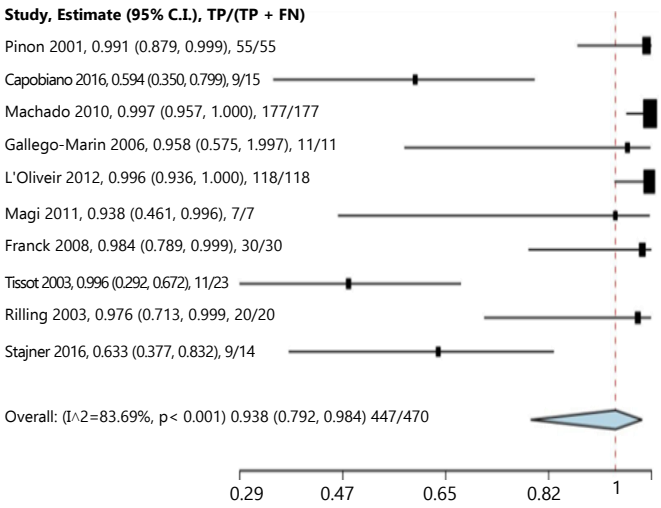


We examined whether there is a correlation between sample size and DOR values. The data showed normality in distribution according to the Kolmogorov Smirnov test (p=0.14 for DOR values and p=0.81 for sample size values). In consequence. We obtained a correlation coefficient of 0.66 with a p-value of 0.005 after the Pearson test, indicating a strong correlation between the DOR value and sample size. In contrast, when DOR mean values were compared between commercial and in-house tests (DOR in-house methods = 2380; DOR with commercial test= 2588), no significant differences were found (F Snedecor 0.004, p= 0.94).

Discussion

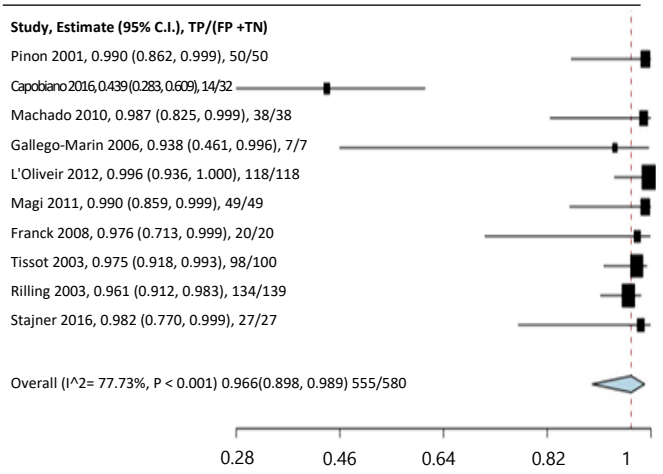
Out of the ten articles examined, seven displayed a sensitivity of 100%, while only three showed a sensitivity of less than 70%.[5,11,13] Additionally, 60% of the evaluated articles exhibited a sensitivity

Figure 2. Sensitivities and Confidence Intervals (CI 95%) and Pooled Sensitivity (Diamond) of Western Blot.



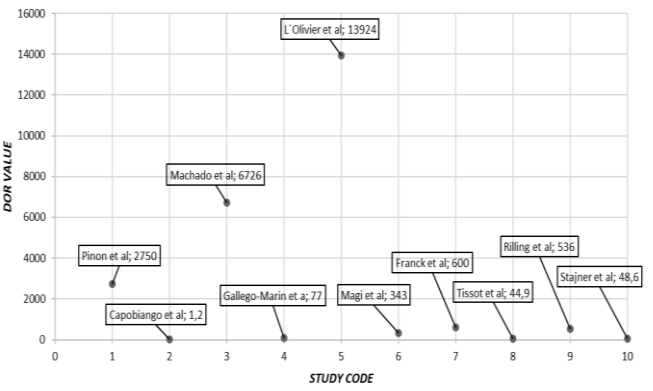
Legend: Techniques for the diagnosis of congenital toxoplasmosis. TP: True positive. FN: False negative.

Figure 3. Specificity and Confidence Intervals (CI 95%) and Pooled Specificity (Diamond) of the Western Blot Technique for the Diagnosis of Congenital Toxoplasmosis.



Legend: TN: True Negative. FP: False Positive.

Figure 4. Diagnostic Odds Ratios (DOR) of Western Blot Technique for the Diagnosis of Congenital Toxoplasmosis.



and specificity of 100%.[11,13] The specificity of the articles was 100% with the exception of Capobiango5 (43.7%), which had the lowest specificity.[11,13] These findings corroborate the superior performance of most western blot assays in congenital toxoplasmosis and the low variability among the studies.[5,11,13] The lower performance of Capobiango5 can be attributed to the usage of an in-house test, which is not extensively standardized but only validated within the laboratory where it was developed.[14] The use of in-house tests is often necessary when there are no commercially available tests, as is the case in Latin-American countries where the cost of importing such tests can be prohibitive.[15] The utilization of in-house tests likely leads to an increase in false negatives.[14] Overall, these results emphasize the importance of employing well-standardized western blot assays to ensure diagnostic accuracy and in this way implement early treatment and avoid long-term sequelae such as chorioretinitis, brain calcifications

Heterogeneity within the studies can be attributed to differences in sample size. Upon examining the DOR values, we observed that most studies had a comparable DOR (> 300), whereas those with a DOR < 100 had smaller sample sizes. Despite these discrepancies, our meta-analysis demonstrated that western blotting provided consistent results in studies conducted in various geographic locations, with differences in population characteristics and local prevalence rates. Similarly, the use of various manufacturing methods, including commercial or in-house approaches, could have influenced the diagnostic performance of the test; however, our analyses suggest minimal impact considering these variations. Notably, only one of the ten studies had a low DOR. The present meta-analysis demonstrates that western blotting is a highly effective diagnostic tool for detecting congenital toxoplasmosis at an early stage and should be incorporated as a confirmatory test within evidence-based clinical practice guidelines.[3,16] Despite this, a significant obstacle to its widespread use is the high cost and limited availability of the western blot assay of the western blot assay and its limited availability. However, despite its relatively high cost, the use of western blotting was cost-effective for all different willingness-to-pay options according to a cost-benefit economic analysis considering the high cost of the sequela of congenital toxoplasmosis.[10] We believe that this issue could be addressed by expanding the market and reducing marginal use by pediatricians, which could ultimately lead to a decline in the prices of commercial western blot tests and easing its inclusion within the diagnostic protocols.[16]

The primary limitation of the current meta-analysis was the scarcity of studies that provided a comprehensive description of test performance, case-confirmation methods, and well-defined criteria for cases. Furthermore, it is essential to conduct long-term postnatal monitoring to detect new retinal lesions as they emerge. It is worth mentioning that this meta-analysis represents an initial endeavor to evaluate the diagnostic efficacy of western blot assays for congenital toxoplasmosis. Notably, the in-house methods yielded a lower DOR than the commercial tests. However, this difference was not statistically significant (F = 0.004, p = 0.94). These findings highlight the need to investigate the standardization and validation of in-house assays.

Summary – Accelerating Translation

El diagnóstico de toxoplasmosis congénita puede retrasarse si no hay IgM o IgA en el recién nacido. La técnica de Western Blot puede contribuir a un diagnóstico más temprano. El principal objetivo de este estudio fue analizar el rendimiento de la prueba Western blot para el diagnóstico precoz de la enfermedad. Para la recopilación de la información se recuperaron los artículos de las bases de datos de referencia bibliográfica de Internet (PubMed, Scopus y Web of Science) utilizando términos de búsqueda relacionados con nuestro objetivo (western blot, Immunoblot). Se continuó seleccionando artículos que cumplieran con los términos de elección e incluyeran los requisitos de criterios diagnósticos para casos y controles mediante el seguimiento serológico de niños después de los 10 meses de vida. Luego, cada estudio fue organizado en una matriz de Excel con las características relevantes para nuestra investigación, como la población estudiada, definición de casos y controles, criterios para determinar la positividad o negatividad de los casos (verdaderos positivos) y controles (verdaderos negativos), quienes fueron positivos en la prueba pero no estaban enfermos (falsos positivos), y aquellos que dieron negativo pero estaban enfermos (falso negativo). Luego se realizó un análisis estadístico calculando la sensibilidad, la especificidad y el índice de probabilidad de diagnóstico (DOR, por sus siglas en inglés) que establece las probabilidades de positividad en sujetos con enfermedad en relación con las probabilidades en sujetos sin enfermedad. Además, se examinó la heterogeneidad entre los estudios. Se identificaron y filtraron cuarenta y cuatro artículos relacionados con los términos de búsqueda utilizando los criterios de inclusión y exclusión y se seleccionaron diez artículos. La sensibilidad promedio de los estudios fue 93,8 (IC 95: 79,2-98,4) y la especificidad fue 96,6% (IC 95: 89,8-98,9). Los resultados mostraron que la prueba de Western blot es confiable para el diagnóstico seguro y oportuno de la toxoplasmosis congénita. Además, es importante considerar las diferencias entre unos estudios y otros en cuanto a su sensibilidad y especificidad cuando se usaron pruebas caseras las cuales no por definición faltan de mayor estandarización.

References

1. Mandelbrot L, Gomez-Marin J. Protozoan diseases: Toxoplasmosis. Reference Module in Biomedical Sciences. 2024.
2. Pinon JM, Dumon H, Chemla C, Franck J, Petersen E, Lebech M, et al. Strategy for diagnosis of congenital toxoplasmosis: evaluation of methods comparing mothers and newborns and standard methods for postnatal detection of immunoglobulin G, M, and A antibodies. J Clin Microbiol. 2001;39(6):2267-71.
3. Cortés J, Gómez-Marin J, Silva P, Arévalo L, Arévalo Rodríguez I, Alvarez MI, et al. Clinical practice guideline. Integral Care Guidelines for the prevention, early detection and treatment of pregnancy, childbirth and puerperium complications: Section on toxoplasmosis in pregnancy. Infectio. 2012;16(3):166-77.
4. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. PLoS Med. 2021;18(3):e1003583.
5. Capobiango JD, Monica TC, Ferreira FP, Mitsuka-Breganó R, Navarro IT, Garcia JL, et al. Evaluation of the western blotting method for the

diagnosis of congenital toxoplasmosis. J Pediatr (Rio J). 2016;92(6):616-23.

6. Tissot Dupont D, Fricker-Hidalgo H, Brenier-Pinchart MP, Bost-Bru C, Ambroise-Thomas P, Pelloux H. Usefulness of western blot in serological follow-up of newborns suspected of congenital toxoplasmosis. Eur J Clin Microbiol Infect Dis. 2003;22(2):122-5.
7. Stajner T, Bobic B, Klun I, Nikolic A, Srbljanovic J, Uzelac A, et al. Prenatal and early postnatal diagnosis of congenital toxoplasmosis in a setting with no systematic screening in pregnancy. Medicine (Baltimore). 2016;95(9):e2979.
8. Public Health England. Commercial and In-House Diagnostic Tests: Evaluations, Verifications and Validations. UK Standards for Microbiology Investigations [Internet]. London: Public Health England; 2015 [cited 2025 May 8]. Available from: https://www.gov.uk/uk-standards-for-microbiology-investigations-smi-quality-and-consistency-in-clinical-laboratories
9. Lemos Luengas EV. Selección de la opción costo-efectiva para Colombia en la detección de toxoplasmosis congénita en el recién nacido. Infectio. 2013;17(2):51-2. Spanish.
10. Chicaíza-Becerra L, García-Molina M, Oviedo-Ariza S, Gómez-Marín JE, Gómez-Sánchez P. Costo efectividad de diferentes estrategias diagnósticas para detección de toxoplasmosis congénita en el recién nacido. Infectio. 2013;17(2):53-60. Spanish.
11. Machado AS, Andrade GM, Januário JN, Fernandes MD, Carneiro AC, Carneiro M, et al. IgG and IgM western blot assay for diagnosis of congenital toxoplasmosis. Mem Inst Oswaldo Cruz. 2010;105(6):757-61.
12. Gallego-Marín C, Henao AC, Gómez-Marín JE. Clinical validation of a western blot assay for congenital toxoplasmosis and newborn screening in a hospital in Armenia (Quindío), Colombia. J Trop Pediatr. 2005;52(2):107-12.
13. L'Ollivier C, Wallon M, Faucher B, Piarroux R, Peyron F, Franck J. Comparison of mother and child antibodies that target high-molecular-mass Toxoplasma gondii antigens by immunoblotting improves neonatal diagnosis of congenital toxoplasmosis. Clin Vaccine Immunol. 2012;19(8):1326-8.
14. Magi B, Migliorini L. Western blotting for the diagnosis of congenital toxoplasmosis. New Microbiol. 2011;34(1):93-5.
15. Franck J, Garin YJ, Dumon H. LDBio-Toxo II immunoglobulin G western blot confirmatory test for anti-toxoplasma antibody detection. J Clin Microbiol. 2008;46(7):2334-8.
16. Rilling V, Dietz K, Krczal D, Knotek F, Enders G. Evaluation of a commercial IgG/IgM western blot assay for early postnatal diagnosis of congenital toxoplasmosis. Eur J Clin Microbiol Infect Dis. 2003;22(3):174-80.

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Conflict of Interest Statement & Funding

There is not any conflict of interest in the development of this work, financial Universidad del Quindio.

Author Contributions

Conceptualization: SSR, JEGM; Data Curation: SSR, MARD, JAAT, JDFL, LFMS; Formal Analysis: SSR, MARD, JAAT, JDFL, LFMS; Investigation: SSR, MARD, JAAT, JDFL, LFMS; Project Administration: JEGM; Supervision: JEGM; Visualization: JEGM; Writing – Original Draft: SSR, MARD, JAAT, JDFL, LFMS; Writing – Review & Editing: JEGM..

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Review

Effects of Blood Pressure Variability and Its Association With Dementia and Cognitive Impairment: A Systematic Review

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Abstract

Background: This systematic review aimed to assess the relationship between blood pressure variability, cognitive function, and the potential for dementia in individuals with hypertension. Hypertension has been increasingly associated with cognitive impairment, with studies suggesting it may lead to structural and functional changes in the brain. This association involves damage to the blood-brain barrier, white matter lesions, and microvascular abnormalities, highlighting the importance of managing blood pressure to preserve cognitive health." **Methods:** The review adhered strictly to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. A comprehensive search was conducted in databases, including PubMed, Research Gate, Google Scholar, and Science Direct. The inclusion criteria required studies that examined the association between blood pressure variability and the occurrence or progression of dementia and cognitive impairment. Two independent reviewers evaluated each study's quality and potential bias using study-specific tools before inclusion. **Results:** There were 17 studies, including four systematic reviews and meta-analyses, four randomized controlled trials, and nine observational studies, with 16,985,492 participants. The findings indicated that late-life blood pressure had a stronger association with cognitive function than midlife blood pressure. Hypertension was linked to an increased risk of all-cause dementia, Alzheimer's disease, and vascular dementia. Anti-hypertensive medications could reduce the risk of dementia or cognitive impairment, although the specific type of medication did not significantly affect overall cognitive performance. A significant limitation of this review was the heterogeneity in diagnostic criteria, cognitive assessment tools, and imaging techniques used among the studies, which limited direct comparisons and conclusive findings. **Conclusion:** Blood pressure variability emerged as a potential predictor for cognitive impairment. Implementing strategies to reduce blood pressure variability may help mitigate the risk of dementia and improve cognitive outcomes in vulnerable populations.

Introduction

The number of older people with dementia is rising. Worldwide, dementia affects around 50 million people and this number is projected to increase thrice by 2050. Dementia affects the economy with global costs estimated at United State $1 trillion annually. According to the 2017 Lancet Commission on dementia prevention, intervention, and care, the nine potentially modifiable risk factors for dementia include less education, hypertension, hearing impairment, smoking, obesity, depression, physical inactivity, diabetes, and low social contact. The 2020 report of the Lancet Commission included three more risk factors for dementia: excessive alcohol consumption, traumatic brain injury, and air pollution. Together the 12 modifiable risk factors account for around 40% of worldwide dementias, which consequently could theoretically be prevented or delayed.[1]

Hypertension is a leading cause of age-related cognitive impairment. Hypertension was previously associated primarily with vascular dementia but has recently been linked to Alzheimer's disease as well.[2] It is well-established that midlife (40-65years age) hypertension is a modifiable risk factor for late-life dementia (>65 years if age).[3] One meta-analysis found that blood pressure lowering with antihypertensive agents was significantly associated with a lower risk of dementia or cognitive impairment.[4] Another study concluded that visit-to-visit blood pressure variability (BPV) independent of average blood pressure is associated with higher cardiovascular risk in older adults and that older subjects with higher levels of blood pressure variability have worse cognitive function.[5] Mechanisms by which high Systolic Blood Pressure (SBP) and BPV are thought to contribute to cognitive impairment include endothelial dysfunction, microemboli, and oxidative stress, promoting cerebral atherosclerosis.[6] Another study found that a large variation in blood pressure, rather than the direction of the variation,

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increases the risk of dementia.[7] Another study added that having both higher Systolic Blood Pressure Variability (SBPV) and Diastolic Blood Pressure Variability (DBPV) additively increased the risk of dementia and its subtypes in a general population.

Multiple studies have been carried out to find the exact association between hypertension, BPV, and cognitive impairment. However, we still don't know the exact mechanisms through which hypertension and BPV lead to cognitive impairment and ultimately to dementia. If we do find the mechanisms responsible, it would help us further to prevent dementia in later stages of life. Moreover, the role of anti-hypertensives in the prevention of dementia is unclear. This review aims to further explore the correlation between high blood pressure, blood pressure variability, and cognitive impairment, and to examine the role of antihypertensives in preventing cognitive impairment.

This systematic review addresses several key questions regarding the association between hypertension, dementia and cognitive impairment. Firstly, the age and gender composition of participants in these studies contribute to our understanding of the relationships between blood pressure, cognitive function, and the risk of dementia. Secondly, the findings regarding the association between blood pressure variability and the occurrence or progression of dementia and cognitive impairment. Thirdly, the diverse diagnostic and testing methods employed in these studies contribute to our understanding of the impact of blood pressure on cognitive function and the risk of dementia. Furthermore, the effects of anti-hypertensive medications on the development and progression of dementia and cognitive impairment. Additionally, the prognostic value of SBPV or DBPV for cognitive impairment and the risk of dementia. Lastly, long-term SBPVs and mean heart rate levels affect cognitive function in high-risk individuals. This systematic review assesses the correlation between BPV and dementia, particularly the role of hypertension in cognitive impairment, stratified by age and gender, while examining the effects of anti-hypertensive treatment. Despite existing research, the precise mechanisms connecting BPV to cognitive decline remain underexplored, necessitating a systematic review to better elucidate these associations and potential therapeutic implications.

Methods

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.[9]

Search Strategy

A comprehensive literature search was performed using PubMed, ResearchGate, Google Scholar, and ScienceDirect databases. The following filters were applied while considering the studies for the identification process for the review: Studies in the English language, free full-text, and Human studies. Keywords and Medical Subject Headings (MeSH) terms were used to identify 12 studies about our discussion. The search was generated using keywords such as "anti-hypertensives," "dementia," "hypertension," "Alzheimer's disease," "cerebrovascular disease/stroke," "neurovascular dysfunction," and combining them using the BOOLEANs "AND" and "OR." *Table 1* summarizes the search strategy used for the identification process in this systematic review. The search strategy for this review concluded in November 2023.

Eligibility criteria for considering studies under this review

Inclusion criteria

The studies were chosen for inclusion based on the following participant, intervention, and outcome characteristics. Population: Adults without specific medical conditions, diagnosed with or at risk for hypertension, Intervention: Blood pressure variability, Comparison: Consistent blood pressure levels or low blood pressure variability, Outcome: Association between blood pressure variability and the occurrence or progression of dementia and cognitive impairment.

The following study characteristics were considered for inclusion: studies written and published in the English language, focusing on a population age over 50 years, involving only human participants, available as free full text, published within the last 30 years (1993-2023). The studies were required to investigate the association between blood pressure variability and the occurrence or progression of dementia and cognitive impairment. Diagnostic and testing methods for dementia and cognitive impairment needed to be clearly described and appropriate cognitive assessment tools with standardized outcome measures were required. The studies were required to have an adequate sample size and report the duration of blood pressure follow-up for cognitive performance. Study designs including systematic reviews, meta-analyses, randomized controlled trials, and observational studies were considered for inclusion.

Exclusion criteria

To ensure the relevance and quality of the included studies, certain exclusion criteria were applied: Animal participants, studies published before 1993, patients aged less than 50 years, Non-English language studies, paid articles, Gray literature, Studies with incomplete or insufficient data, Case reports, editorials, reviews, and conference abstracts, Studies without specific mention of blood pressure variability, Studies lacking relevant outcomes related to dementia and cognitive impairment, Studies using cognitive assessment tools that are not standardized, Studies without clear diagnostic and testing methods for dementia and cognitive impairment.

By applying the above inclusion and exclusion criteria, the systematic review aims to include relevant studies that provide valuable insights into the association between blood pressure variability and the occurrence or progression of dementia and

cognitive impairment in adults with hypertension or at risk for hypertension.

Selection of studies for inclusion in the review

The screening of the articles was carried out by AJ and VB, who independently reviewed the titles and abstracts of the identified studies. Any disagreements were resolved through discussion and consensus between the two reviewers. In cases where a consensus could not be reached, a third reviewer, AP, was involved in providing a final decision. This ensured a thorough evaluation of all potentially relevant records and minimized bias. Throughout the screening process, detailed notes were taken to record the specific reasons for excluding research studies from the review.

Assessment of the Methodological Quality and Risk of Bias

The remaining studies were individually evaluated for quality by two independent authors using study-specific techniques. Each assessment tool has its scoring system, and studies with a score of more than 70% were accepted for inclusion in this study. The quality assessment of the studies, as well as the tools utilized, are summarized in ***Tables 2 and 3***.[10-12]

Results

A systematic search yielded a total of 11,690 records from various sources, including PubMed (n=3,112), Research Gate (n=100), Science Direct (n=8,310), and Google Scholar (n=168). After removing duplicates (n=8,096) and conducting an initial screening based on titles and abstracts leaving 125 studies for full-text screening. Among these, 106 studies were excluded during full-text screening, resulting in 19 studies that underwent quality assessment. Ultimately, two studies were excluded, leaving 17 studies with a total of 16,985,492 participants for inclusion in the systematic review.[3-8, 13-23]Based on the assessment tools employed, the studies' quality scores exceeded 70%. Data collection concluded on December 3, 2023. For a visual representation of the selection process, refer to ***Figure 1,*** which presents the PRISMA flow chart detailing the identification and screening process used to select the final articles for review.

The studies on hypertension and late-life dementia involved participants aged 54 to 84.4 years, with some studies having a majority of male participants and others with more balanced gender distribution. The duration of blood pressure follow-up for cognitive performance and the mean blood pressure values varied across the studies, providing valuable insights into the relationship between blood pressure and cognitive outcomes in different contexts. Each of these studies contributed to our understanding of the relationship between blood pressure and cognitive function by considering different follow-up durations and mean blood pressure values in their respective populations.

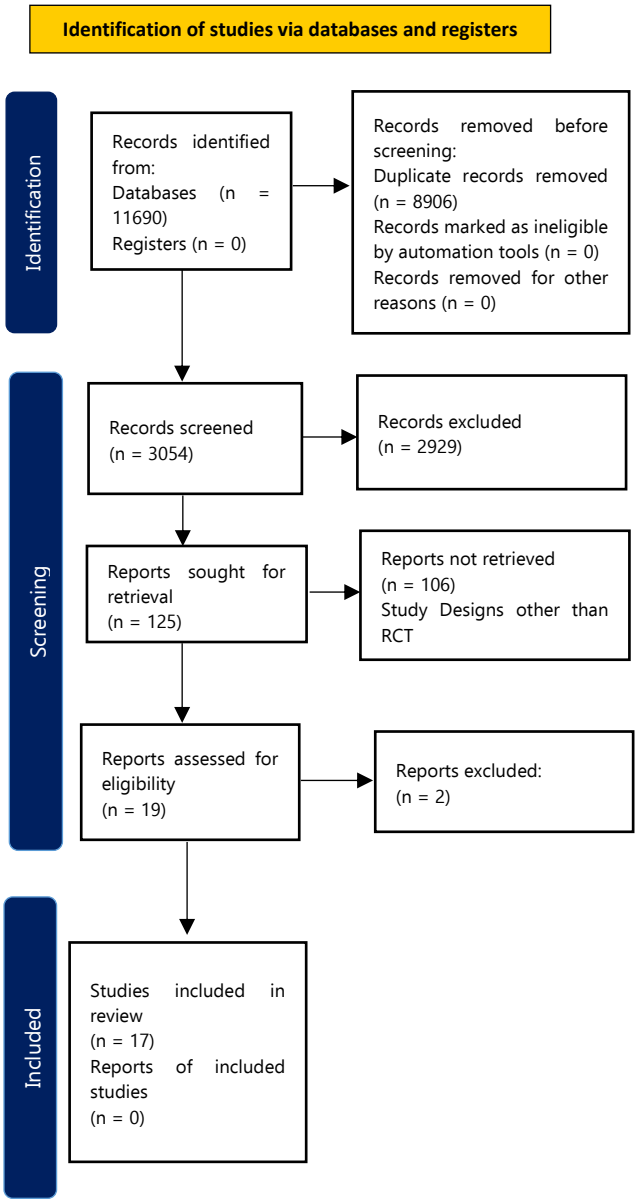
The diagnosis and testing methods employed in the studies varied, reflecting the diverse approaches to assessing cognitive function and dementia. Several studies relied on comprehensive neuropsychological assessments to evaluate cognitive performance. Hughes et al, in their meta-analysis, utilized various cognitive tests, including the Mini-Mental State Examination (MMSE), to assess cognitive impairment.[4] Similarly, Yano et al employed cognitive function tests, including the Digit Symbol Substitution Test and the Word Recall Test, to evaluate cognitive function.[18]Other studies, such as Chiu et al, focused on the diagnosis of dementia as an outcome.[20]These studies incorporated clinical diagnostic criteria, such as the Diagnostic and Statistical Manual of Mental Disorders (DSM) or the International Classification of Diseases (ICD), to identify cases of dementia. Additionally, imaging techniques, such as magnetic resonance imaging (MRI), were used to assess structural brain changes associated with cognitive impairment.[19]Therefore, a comprehensive understanding of the diagnostic and testing methodologies used is essential for accurately evaluating the

Table 1. Details of the Search Strategy Used in This Systematic Review.

Serial No.	Database	MeSH terms	Filters applied	Results
1.	PubMed	((((("Blood Pressure"[Mesh] OR "Hypotension"[Mesh] OR "Hypertension"[Mesh]) OR "Blood Pressure Monitoring, Ambulatory"[Mesh]) AND "Dementia"[Mesh]) OR (“Frontotemporal Dementia"[Mesh] OR "Dementia, Multi-Infarct"[Mesh] OR "Dementia, Vascular"[Mesh] OR "Alzheimer Disease"[Mesh] OR "Mixed Dementias"[Mesh])) OR "cognitive impairment"[Mesh]	Free full text, published within the last 30 years (1993-2023), systematic reviews, meta-analyses, randomized controlled trials	3112
2.	Research Gate	("Blood pressure" OR "Hypertension") AND ("Dementia" OR "Alzheimers")	-	100
3.	Science Direct	Keywords: Dementia, Anti-hypertensives, Hypertension, Blood pressure	1993- 2023; Open access and Open archive	8,310
4.	Google Scholar	Keywords: Hypertension, Dementia, cognitive impairment, Anti-hypertensives, cerebrovascular disease/stroke	Full text	168

impact of blood pressure on cognitive function and dementia risk.

Figure 1. The PRISMA Flow Chart Detailing the Identification and Screening Process Used to Select the Articles.



Legend: PRISMA 2020 flow diagram for new systematic which included searches of databases and registers only

Data extraction and management

Table 3 includes a summary of the included studies. The data was extracted in a Microsoft Excel spreadsheet by MK, SSV, and Ad.P to include authors, year of publication, mean age and % sex of the patients, sample size, type of study, duration of blood pressure follow-up for cognitive performance, mean BP, outcomes, diagnosis and testing, and conclusions. The data extraction concluded on Nov 2023. We did not use any statistical analysis to interpret results because of the heterogeneity of data and qualitatively analyzed the included studies.

Table 2. Quality Assessment of the Included Studies (Except RCTs).

Author	Publication year	Report type	Quality assessment tool used	Score
De Heus, RAA et al.[3]	2021	Systematic review and Meta Analysis	AMSTAR	10
Hughes, D et al.[4]	2020	Systematic review and Meta Analysis	AMSTAR	9
Ya-Nan Ou et al.[19]	2020	Systematic review and Meta Analysis	AMSTAR	9
Tzu-Jung Chiu et al.[20]	2015	Systematic review and Meta Analysis	AMSTAR	8
Ozioma C. Okonkwo et al.[13]	2011	Non-randomised controlled trial	Newcastle Ottawa scale	8
Laure Rouch et al.[14]	2020	Cohort study	Newcastle Ottawa scale	8
Bo Qin et al.[17]	2016	Cohort study	Newcastle Ottawa scale	7
Yuan Ma et al.[7]	2019	Cohort study	Newcastle Ottawa scale	8
Jung Eun Yoo et al.[8]	2020	Cohort study	Newcastle Ottawa scale	8
Xu Liu et al.[22]	2016	Observational study	Newcastle Ottawa scale	7
Yuichiro Yano et al.[18]	2018	Cohort study	Newcastle Ottawa scale	8
Luxinyi Xu et al.[21]	2022	Cohort study	Newcastle Ottawa scale	6
Isabel J. Sible et al.[23]	2022	Cross sectional Study	Newcastle Ottawa scale	9

Legend: Newcastle Ottawa scale accepted score (>=70%): Minimum score 6 out of 9;[10] AMSTAR checklist accepted score (>=70%): Minimum score 8 out of 11.[11]

Discussion

Hypertension and Late-life Dementia and cognitive impairment

Midlife hypertension is significantly associated with a 1.19- to 1.55-fold excess risk of cognitive disorders, with potential benefits of a 21% reduction in dementia risk through antihypertensive medications.[19] Chiu et al indicated a higher dementia risk among the elderly subgroup, suggesting a potential association between hypertension and late-life dementia.[20] Similarly, the study conducted by Ya Nan and colleagues suggests a potential association between BPV, specifically SBPV or DBPV, and the risk of developing all-cause dementia in later life.[24] The research findings indicate that

Table 3. Cochrane Risk of Bias Assessment for Randomized Controlled Trials.[12]

Author	Publication year	Overall risk of bias	Random Sequence Generation	Allocation Concealment	Selective Reporting	Other sources of Bias	Blinding	Blinding Outcome assessment	Incomplete outcome data
Wijsman et al.[5]	2015	Low-risk	Moderate risk	Low-risk	Low- risk	Low- ris	Low- risk	Low-risk	Low-risk
Böhm et al.[6]	2015	Moderate risk	Low-risk	Low-risk	Moderate risk	Moderate risk	Low- risk	Low-risk	Low-risk
Williamson et al.[15]	2019	Low-risk	Low-risk	Moderate risk	Low- risk	Low- risk	Low- risk	Low-risk	Low-risk
Prince et al.[16]	1996	Moderate risk	Moderate risk	Low-risk	Low- risk	Low- risk	Moderate risk	Low-risk	Low-risk

fluctuations in blood pressure may be linked to an increased likelihood of developing dementia.[13]Xu et al found that late-life blood pressure had stronger associations with cognitive function than mid-life blood pressure.[21]Furthermore, among late-life blood pressure control groups, those with controlled hypertension had higher cognitive scores. However, no significant correlation was found between midlife blood pressure control, late-life visit-to-visit DBPV, visit-to-visit pulse pressure (PP) variability, and cognitive scores. These results suggest that late-life blood pressure control and variability may have a more significant impact on cognitive function than midlife blood pressure.[21]The findings are in agreement with the results reported by Rouch et al. And Dregan et al.[14, 25]

Yano et al showed that higher midlife SBP levels were associated with lower cognitive function in later life.[18] Consistent research findings indicate that individuals with higher SBP levels during midlife tend to experience lower cognitive function as they age. These studies have consistently demonstrated an association between elevated SBP in middle age and subsequent cognitive impairment or impairment in later life. The link between midlife SBP and cognitive function suggests that maintaining optimal blood pressure levels during midlife may play a crucial role in preserving cognitive abilities and reducing the risk of cognitive impairment as individuals grow older.[26-28] This suggests that elevated blood pressure during midlife may have long-term implications for cognitive health.

Association of Blood pressure variability with Dementia and cognitive impairment

Elevated SBPV and DBPV independently associated with a higher risk of dementia and cognitive impairment, surpassing the impact of mean blood pressure.[3] Chiu et al observed insignificant results regarding the incidence of cognitive impairment and no significant association between all-cause dementia risk and SBP.[20] In contrast, Ma et al. indicated that a large variation in both SBP and diastolic blood pressure (DBP) was associated with an increased risk of dementia.[7] This association became more pronounced with longer intervals between the assessment of blood pressure variation and the diagnosis of dementia. Similarly, Yoo et al focused on the relationship between hypertension and the risk of all-cause dementia, AD, and VaD. The findings demonstrated that hypertension increased the risk of all-cause dementia, AD, and VaD. Furthermore, there was an incrementally higher risk of these outcomes with SBPV and DBPV.[8]

Rouch et al. examined the association between blood pressure variability and cognition and found that higher systolic and DBPV were independently associated with poorer cognition, even when controlling for baseline SBP and DBP, respectively. In line with previous research, this study found that while SBPV was associated with poorer cognitive performance and an increased risk of developing dementia, the strongest associations were observed for DBP and mean arterial pressure (MAP).[17,22,23,29-31] This suggests that blood pressure variability, regardless of baseline blood pressure levels, may contribute to cognitive impairment.

Effects of Anti-hypertensives on Dementia and cognitive impairment

Hughes et al performed a meta-analysis and demonstrated that blood pressure lowering with anti-hypertensive agents compared to control was significantly associated with a reduction in dementia or cognitive impairment.[4]Additionally, they found a significant association between blood pressure lowering and a reduction in cognitive impairment. However, no significant correlation was observed between blood pressure lowering and the standardized mean cognitive score.[4]These findings suggest that anti-hypertensive treatment may benefit dementia and cognitive impairment, but it may not directly affect overall cognitive performance. Similarly, Wijsman et al's trial focused on the association between blood pressure-lowering medication (BPLM) and cognitive function/decline. Interestingly, they found no significant association between BPLM and cognitive function or decline, despite investigating different combinations of blood pressure-lowering medication.[5]This suggests that the specific medications used for blood pressure control may not have a direct impact on cognitive outcomes. Prince et al compared the effects of different treatments (diuretics, beta-blockers, and placebo) on cognitive function. The study found no significant difference in the mean learning test coefficients and trail-making coefficients between the three treatment groups.[16]These results suggest that the specific type of anti-hypertensive medication may not significantly impact cognitive function.

Table 4. Characteristics of Included Studies in this Systematic Review.

ID	Author name and year	Mean age and % sex of patients	Sample size	Type of Study	Duration of Blood pressure (BP)follow-up for cognitive performance	Mean BP	Outcomes	Diagnosis and testing	Conclusion
1	Tzu-Jung Chiu et al. (August 2021) [20]	54.3–84.4 years; 52.4% male, 47.6% female	7924168 (20 cohort studies)	Systematic review and meta-analysis	3 months to 22 years	-	Higher dementia risk among the elderly subgroup.No significance was found between the risk of all-cause dementia and SBP.	MMSE, MoCA, CAMCOG, non-global cognitive test (eg, Trail Making Test (parts A and B, TMT- A&B), Letter Cancellation test, Stroop test, COWA test, Telephone Interview for Cognitive Status-modified, global composite cognitive score, Letter-Digit Coding test, non-global cognitive test (eg, DWRT, DSST, WFT), ICD, ADAS-COG, CDR, MSE, DSM-III-R, NINCDS-ADRDA, NINDS-AIREN	Higher SBPV was significantly associated with higher all-cause dementia risk but was not specifically associated with the dementia sub-types.]
2	Diarmaid Hughes et al (May 2020) [4]	69 (5.4) years,57.8% male, 42.2% female	92135 (16 randomzied controlled trials)	Meta analysis	4.1 years	SBP: 154 (14.9) mmHg; DBP: 83.3 (9.9) mmHg	The primary outcome was blood pressure lowering with anti-hypertensive agents compared with control was significantly associated with a reduction in dementia or cognitive impairment. The secondary outcome was Blood pressure lowering with anti-hypertensive agents compared with control was significantly associated with a reduction in cognitive impairment and was not significantly associated with a difference in the standardized mean cognitive score.	Short-care instrument, MMSE, MoCA, DSCT, LMF II, DSST, TMT Part B, CASI z score, PALT	Lowering blood pressure may be associated with a lower risk of dementia or cognitive impairment.
3	Liselotte W. Wijsman et al (March 2016) [5]	70–82 years	5,606	Randomized, double blind, placebo-controlled trial (PROSPER)	Every 3 months for 3.2 years	-	There was no significant association of BPLM and cognitive function.	MMSE	The association between BP variability and cognitive impairment was not mediated by BPLM.

4	Michael Böhm Et al (Jan 2015) [6]	>55 years	24593	RCT	56 months	SBP: 130-240 mmHg DBP: 80-90 mmHg	cognitive impairment was observed in 1857 patients (7.6%) and cognitive impairment in 1176 patients (4.8%) and incident cognitive impairment in high-risk cardiovascular patients.	MMSE	Long-term SBP variations and mean HR levels are associated with the development of cognitive impairment, decline, and deterioration in high-risk patients.
5	Ozioma C. Okonkwo et al (Sept 2012) [13]	55-85 years	172	Prospective multi center cohort study	Baseline, 12 and 36 months	-	Reduced variability in systolic BP was associated with a faster rate of decline in Attention-Executive-Psychomotor function and vice versa.	MMSE, DRS-2, DSST, TMT Part A and B, COWA, Letter Cancellation Test, the Stroop test. WAIS-III	Decline in frontal-subcortical cognitive functions is mediated by variability in blood pressure.
6	Laure Rouch et al (August 2020) [14]	76.9 (7.8) years old; 43% male, 57% female	3319	Cohort study	Every 6 months for 3 years.	SBP: 133.7 (11.8) mmHg, DBP: 76.9	Higher systolic and diastolic BPV was associated with poorer cognition independently.	MMSE, DSM-III-R. NINCDS-ADRDA, NINDS-AIREN	BPV is a major clinical predictor of cognitive impairment and dementia.
7	Luxinyi Xu et al. (August 2022) [21]	61.5 years	3511	Prospective study	four waves for 7-year follow-up	-	Late-life BP showed stronger associations with cognitive function than midlife BP.		
8	Yuan Ma et al. (Nov 2019) [7]	67.6 years; 58.1% women, 21.9% male	5273	Prospective cohort study	14.6 years	-	A large SBP and DBP variation was associated with an increased dementia risk, which became more pronounced with longer intervals between the assessment of SBP variation and the diagnosis of dementia.		
9	Jung En Yo et al. (March 2020) [8]	55.5 years; 52.5% male, 47.5% female	7844814	Retrospective cohort study	6.2 years	SBP: 127 (15.2) mmHg; DBP: 78 (10) mmHg	There were 200 574 new cases of all-cause dementia (2.8%), 165 112 cases of AD (2.1%), and 27 443 cases of VaD (0.3%). Hypertension increases the risk of all-cause dementia, AD, and VaD.	-	BPV is an independent predictor for developing dementia and its sub types.
10	Yuichiro Yano et al. (July 2018) [18]	54 years; 56% female, 44% male	11408	Retrospective cohort study	25 years	SBP: 123 (11) mmHg; DBP 72 (7) mmHg	Lower cognitive performance in later life has been consistently associated to higher midlife SBP levels.	Global cognitive z score	From midlife on, SBP or DBP variability is mildly associated with lower cognitive function, whereas higher mean SBP and lower DBP levels from midlife to later life are modestly associated with cognitive impairment in later life.

11	Jeff Williamson et al. (January 2019) [15]	67.9 years; 64.4% male, 35.6% female	9361	Randomized controlled trial	11 years	SBP: 139.7 (15.6) mmHg, DBP: 80 mmHg	The primary outcome in the intensive treatment group, 149 participants dementic compared with 176 participants (8.6 per 1000 person-years) in the standard treatment group.	MoCA, Wechsler Memory scale, Wechsler Adult Intelligence scale	Treatment to a systolic blood pressure goal of fewer than 120 mm Hg versus a goal of less than 140 mm Hg did not result in a meaningful reduction in the incidence of probable dementia in ambulatory persons with hypertension.
12	MJ Prince et al. (March 1996) [16]	3 years; 58% female, 42% male	4396	Randomized placebo controlled single blinded trial	54 months	SBP: 160-209 mmHg, DBP: <115 mmHg	The mean learning test coefficients (rate of change of score over time) and trail-making coefficients of the three treatments, diuretics, beta-blockers, and placebo, did not vary.	PALT, TMT Part A	It's doubtful that treating moderate hypertension in elderly persons will have an impact on their subsequent cognitive function, either favorably or unfavorably.
13	De Heus, RAA et al. (November 2021) [3]	73±7 years; 58±13% women	7915 946	Systematic review and Meta-analysis	-	-	Elevated systolic and DBPV were independently associated with a higher risk of dementia and cognitive impairment not mean BP	MMSE, MoCA, CDR	Both an elevated average blood pressure and increased blood pressure variability were correlated with higher odds of experiencing dementia or cognitive impairment.
14	Ya-Nan Ou et al. (May 2020) [19]	35.3 to 93.2 years, 46% women	221481 4	Systematic review and meta analysis	1 month to 5years	-	The analysis revealed stronger associations in midlife compared to late-life. The findings emphasized midlife hypertension's significant association with a 1.19- to 1.55-fold excess risk of cognitive disorders and the potential benefits of antihypertensive medications, which demonstrated a 21% reduction in dementia risk.	Variable	The associations between blood pressure (BP) factors and cognitive disorders vary based on age and the type of blood pressure. The use of antihypertensive medications was linked to a lowered risk of dementia.
15	Bo Qin et al. (July 2016) [17]	63.1 (6.9); 52% female	976	Cohort study	5.3 years	SBP: 122mmHg; DBP: 78mmHg	Higher visit-to-visit variability in diastolic BP was associated with a faster decline of cognitive function, independent of mean diastolic BP amongst elderly.	MMSE, Telephone Interview for Cognitive Status – modified (TICS-m)	Higher long-term BP visit-to-visit variability is associated with a faster rate of cognitive impairment among older adults.

16	Zhendong Liu et al. (July 2016) [27]	74.5% female	232	Cohort study	2.3 years	-	In the oldest old, higher variability in self-measured systolic high blood pressure, as indicated by tertiles of the coefficient of variation at baseline, was significantly associated with greater declines in MMSEscores and increased progression of periventricular and deep white matter hyperintensities.	MMSE	Excessive variability in self-measured systolic HBP exacerbates the progression of cognitive impairment and brain white matter lesions in the oldest old.
17	Isabel J. Sible et al. (October 2022) [23]	69.9 (8.2); 37% female and 63% male	54	Cross-sectional study	-	SBP: 131 mmHg; DBP: 74 mmHg	Elevated blood pressure variability over a 5-minute period was associated with lower levels of plasma Aβ1–42 and Aβ1–42: Aβ1–40 ratio, as well as higher levels of total tau and Ptau181:Aβ1–42 ratio in the study population.		Increased variability in blood pressure is correlated with elevated plasma biomarkers indicative of heightened Alzheimer's disease pathophysiology.

Legend: MMSE: Mini-Mental State Examination, MoCA: Montreal Cognitive Assessment, CAMCOG: Cambridge Cognition Examination, ADAS-COG: Alzheimer's Disease Assessment Scale-Cognitive Subscale, CDR: Clinical Dementia Rating Scale, MSE: Modified Mini-Mental State Examination, DSM: The Diagnostic and Statistical Manual of Mental Disorders, NINCDS-ADRDA: National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association, NINDS-AIREN: International Workshop of the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences, COWA: Controlled Oral Word Association, DWRT: delayed Word Recall Test, DSCT: Digital Symbol Coding Test, DSST: Digit Symbol Substitution Test, WFT: Word Fluency Test, ICD: International Classification of Disease, ADAS-COG: Alzheimer's Disease Assessment Scale–Cognitive Subscale, LMF: Logical Memory form, TMT: Trail making test, CASI: Cognitive Ability Screening Instrument, PALT: Paired Associate Learning Test, BP: Blood pressure, SBP: Systolic Blood pressure, DBP: Diastolic Blood pressure, BPLM: Blood pressure lowering medication, RCT: Randomized controlled trial, DRS-2: Dementia Rating Scale-2,WAIS: Wechsler Adult Intelligence Scale, CVD: Cardiovascular disease, BPV: Blood Pressure Variability, GMS: Geriatric Mental Schedule, SBPV: Systolic Blood pressure Variability, DBPV: Diastolic Blood pressure Variability, TICS-m: Telephone Interview for Cognitive Status –modified.

Prognostic value of SBPV or DBPV for cognitive impairment

The prognostic value of BPV with cognitive impairment and dementia has been a subject of interest in various studies. Several researchers have explored the association between BPV and cognitive outcomes, shedding light on its potential as an independent predictor and its implications for dementia prevention.

Yoo et al. conducted a study emphasizing that BPV is an independent predictor for developing dementia and its subtypes.[8] Their findings suggest that reducing BPV could be a target for preventing dementia in the general population. Recent research has demonstrated a correlation between the occurrence of dementia and elevated day-to-day or visit-to-visit BPV, as measured by the CV index.[28,31]This highlights the importance of considering BPV as a potential risk factor and the need to control blood pressure fluctuations to mitigate cognitive impairment. Chiu et al examined the association between SBPV and dementia risk and revealed that higher SBPV was significantly associated with an increased risk of all-cause dementia.[20]The significant association between higher SBPV and increased risk of all-cause dementia underscores the potential prognostic significance of SBPV as a predictor for dementia development

Böhm et al conducted a study focusing on the long-term effects of SBP variations and mean heart rate (HR) levels on cognitive function in high-risk patients and demonstrated that these fluctuations were associated with the development of cognitive impairment, decline, and deterioration in these individuals.[6] These findings highlight the prognostic significance of long-term SBP variations and mean HR levels as potential indicators for identifying high-risk patients prone to cognitive impairment and decline.[22]In contrast, one study revealed the prognostic significance of excessive BPV for the progression of cognitive impairment.[32]

Collectively, these studies contribute to our understanding of the prognostic value of BPV for cognitive impairment. While there is evidence suggesting that BPV is an independent predictor of dementia and its subtypes, further research is needed to elucidate the specific associations and underlying mechanisms. Reducing BPV and maintaining stable blood pressure levels may hold promise as potential preventive strategies for cognitive impairment and dementia. Continued investigation into the role of BPV in cognitive health will be crucial for developing targeted interventions and improving overall cognitive outcomes.

Strengths

The systematic review has notable strengths that enhance the reliability and comprehensiveness of our findings. By including studies with different durations of blood pressure follow-up, we could better understand how blood pressure affects cognitive performance over time. These studies ranged from a few months to several years, allowing us to examine short-term and long-term effects. As a result, our review offers significant insights into how blood pressure fluctuations may impact cognitive abilities.

Limitations

The main limitation of our review is the differences in diagnostic criteria, cognitive assessment tools, and imaging techniques employed across the studies that may contribute to variations in the reported results. These discrepancies may have contributed to heterogeneity in the reported results and limited the ability to make direct comparisons and draw generalizable conclusions. The use of different diagnostic criteria for dementia introduces variability in case identification and classification, potentially impacting the synthesis of findings. Additionally, the inclusion of specific populations, such as older adults or individuals with cardiovascular diseases, may restrict the generalizability of the observed associations between blood pressure variability and cognitive outcomes. Furthermore, despite our comprehensive search strategies to minimize publication bias, its potential influence on the results cannot be completely ruled out.

Conclusion

In conclusion, the systematic review explored the effects of BPV and its association with dementia and cognitive impairment. After an in-depth analysis, we were able to derive significant findings. In addition to using cognitive tests like the MMSE, Digit Symbol Substitution Test, and the Word Recall Test to assess cognitive changes, we also measure the diagnosis of dementia in the patient set.

Firstly, the studies indicate a high risk in the elderly subgroup, a stronger association of late-life blood pressure with cognitive impairment, and long-term implications of midlife blood pressure. Secondly, we emphasize the association between blood pressure variability and poor cognition suggesting the need for early intervention and continuous monitoring of blood pressure fluctuations. We share the impact of anti-hypertensive treatment on cognitive performance. Lastly, we cover the potential of using BPV as a predictor for dementia and its implications for preventing cognitive impairment.

In terms of future research recommendations, we propose investigating the specific mechanisms underlying this relationship to better understand the pathophysiology and develop targeted interventions. Conducting longitudinal studies to establish a causal relationship between BPV and cognitive impairment and exploring the potential moderating factors, such as age, gender, and comorbidities, could provide a more comprehensive understanding of the relationship. Implementing strategies to reduce BPV may help mitigate the risk and improve cognitive outcomes in susceptible populations. By emphasizing the need for further research and highlighting potential interventions, we hope to provide valuable insights for healthcare professionals, policymakers, and individuals seeking to maintain cognitive health.

Summary – Accelerating Translation

Introduction: Dementia's global prevalence is surging, affecting about 50 million people, with projections indicating a threefold increase by 2050.

Beyond the significant public health impact, the economic burden is substantial, with annual global costs estimated at $1 trillion. Hypertension, once primarily linked to vascular dementia, is now associated with Alzheimer's disease. Midlife hypertension is identified as a modifiable risk factor for late-life dementia. However, the precise mechanisms connecting hypertension, blood pressure variability (BPV), and cognitive impairment leading to dementia remain unclear.
Aim of Study: This systematic review aims to investigate the correlation between high blood pressure, BPV, and cognitive impairment, along with exploring the potential preventive role of anti-hypertensives. Key questions include the age and gender composition of study participants, the impact of BPV on dementia risk, diagnostic methods used, and the effects of anti-hypertensive medications.

Methodology: Following the PRISMA 2020 guidelines, a thorough literature search identified 12 relevant studies from sources like PubMed, Research Gate, Google Scholar, and ScienceDirect. Inclusion criteria focused on English language studies, human participants over 50 years, and a clear investigation into the association between BPV and dementia. After screening, 17 studies, involving 16,985,492 participants, were included in the review.

Results: Midlife hypertension consistently showed an increased risk of cognitive disorders. The duration of blood pressure follow-up and mean blood pressure values varied across studies, providing insights into the relationship between blood pressure and cognitive outcomes. Elevated SBPV and DBPV were independently linked to a higher risk of dementia and cognitive impairment, surpassing the impact of mean blood pressure. Anti-hypertensive medications were associated with a reduction in dementia risk, although the impact on overall cognitive performance was inconclusive. Different types of medications did not show significant differences in cognitive function outcomes. Studies highlighted the prognostic significance of BPV for cognitive impairment. Elevated day-to-day or visit-to-visit BPV was identified as an independent predictor for developing dementia, emphasizing the need to control blood pressure fluctuations. Long-term SBP variations and mean heart rate levels were associated with cognitive decline, indicating their potential as indicators for identifying high-risk patients prone to cognitive impairment.

Conclusion: In summary, the intricate connection between high blood pressure, BPV, and cognitive impairment leading to dementia is a global health challenge. Evidence suggests that midlife hypertension poses a significant risk, and controlling blood pressure in later life may help reduce the likelihood of cognitive decline. Anti-hypertensive medications show promise in lowering dementia risk, but their impact on overall cognitive function requires further investigation.

The findings reveals the importance of managing blood pressure variability, maintaining stable blood pressure levels, and considering personalized interventions for individuals at risk. This research provides valuable insights into the global concern of dementia, laying the groundwork for targeted preventive strategies and improved cognitive outcomes. Continued research in this field is crucial to unravel the specific mechanisms and optimize interventions for a healthier aging population worldwide.

References

1. Livingston G, Huntley J, Sommerlad A, Costafreda SG, Huntley J, Ames D, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet. 2020;396:413-446.
2. Iadecola C, Gottesman RF. Neurovascular and cognitive impairment in Hypertension. Circ Res. 2019;124:1025-1044.
3. De Heus RAA, Tzourio C, Lee EJL, Opozda M, Vincent AD, Anstey KJ, Hofman A, et al. Association Between Blood Pressure Variability With Dementia and Cognitive Impairment: A Systematic Review and Meta-Analysis. Hypertension. 2021;78:1478-1489.
4. Hughes D, Judge C, Murphy R, , Loughlin E, Costello M, Whiteley W, Bosch J, et al. Association of Blood Pressure Lowering With Incident Dementia or Cognitive Impairment: A Systematic Review and Meta-analysis. JAMA. 2020;323:1934-1944.
5. Wijsman LW, de Craen AJ, Muller M, Sabayan B, Stott D, Ford I, Trompet S, et al. Visit-to-Visit Blood Pressure Variability, and Cognitive Function in Old Age. Am J Hypertens. 2016;29:311-8.
6. Böhm M, Schumacher H, Leong D, Mancia G, Unger T, Schmieder R, et al. Systolic blood pressure variation and mean heart rate is associated with cognitive impairment in patients with high cardiovascular risk. Hypertension. 2015;65:651-61.
7. Ma Y, Wolters FJ, Chibnik LB, Licher S, Ikram MA, Hofman A, et al. Variation in blood pressure and long-term risk of dementia: A population-based cohort study. PLoS Med. 2019;16.
8. Yoo JE, Shin DW, Han K, Kim D, Lee SP, Jeong SM, et Al. Blood Pressure Variability and the Risk of Dementia: A Nationwide Cohort Study. Hypertension. 2020;75:982-990.
9. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6:e1000097.
10. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017;358:j4008.
11. Hartling L, Hamm M, Milne A, Vandermeer B, Santaguida PL, Ansari M, et al. Validity and Inter-Rater Reliability Testing of Quality Assessment Instruments. In Agency for Healthcare Research and Quality (US); 2012
12. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.
13. Okonkwo OC, Cohen RA, Gunstad J, Poppas A. Cardiac output, blood pressure variability, and cognitive impairment in geriatric cardiac patients. J Cardiopulm Rehabil Prev. 2011;31:290-297.
14. Rouch L, Cestac P, Sallerin B, Piccoli M, Benattar-Zibi L, Bertin P, et al. Visit-to-Visit Blood Pressure Variability Is Associated With cognitive impairment and Incident Dementia: The S.AGES Cohort. Hypertension. 2020;76:1280-1288.
15. Williamson JD, Pajewski NM, Auchus AP, Bryan RN, Chelune G, Cheung AK, Cleveland ML, et al. Effect of Intensive vs Standard Blood Pressure Control on Probable Dementia: A Randomized Clinical Trial. JAMA. 2019;321:553-561.
16. Prince MJ, Bird AS, Blizard RA, Mann AH. Is the cognitive function of older patients affected by antihypertensive treatment? Results from 54 months of the Medical Research Council's trial of hypertension in older adults. BMJ. 1996;312:801-805.
17. Qin B, Viera AJ, Muntner P, Plassman BL, Edwards LJ, Adair LS, et al. Visit-to-Visit Variability in Blood Pressure Is Related to Late-Life cognitive impairment. Hypertension. 2016;68:106-113.
18. Yano Y, Griswold M, Wang W, Greenland P, Lloyd-Jones DM, Heiss G, et al. Long-Term Blood Pressure Level and Variability From Midlife to Later Life and Subsequent Cognitive Change: The ARIC Neurocognitive Study. J Am Heart Assoc. 2018;7.
19. Ou YN, Tan CC, Shen XN, Xu W, Hou XH, Dong Q, et al. Blood Pressure and Risks of Cognitive Impairment and Dementia: A Systematic Review and Meta-Analysis of 209 Prospective Studies. Hypertension. 2020;76:217-225.
20. Chiu TJ, Yeh JT, Huang CJ, Chiang CE, Sung SH, Chen CH, et al. Blood pressure variability and cognitive impairment: A systematic review and meta-analysis of longitudinal cohort studies. J Clin Hypertens (Greenwich). 2021;23:1463-1482.
21. Xu L, Yang Y, Cui D. Association between blood pressure control status, visit-to-visit blood pressure variability, and cognitive function in elderly Chinese: A nationwide study. Front Public Health. 2022;10:877192.
22. Liu Z, Zhao Y, Zhang H, Chai Q, Cui Y, Diao Y, et al. Excessive variability in systolic blood pressure that is self-measured at home exacerbates the progression of brain white matter lesions and cognitive impairment in the oldest old. Hypertens Res. 2016;39:245-253.
23. Sible IJ, Yew B, Jang JY, Alitin JPM, Li Y, Gaubert A, et al. Blood pressure variability and plasma Alzheimer's disease biomarkers in older adults. Sci Rep. 2022;12:17197.
24. Duron E, Hanon O. Vascular risk factors, cognitive impairment, and dementia. Vasc Health Risk Manag. 2008;4:363-81.
25. Dregan A, Stewart R, Gulliford MC. Cardiovascular risk factors and cognitive impairment in adults aged 50 and over: a population-based cohort study. Age Ageing. 2013;42:338–345.
26. Singh-Manoux A, Marmot M. High blood pressure was associated with cognitive function in middle-age in the Whitehall II study. J Clin Epidemiol. 2005;58:1308–1315.
27. Waldstein SR, Giggey PP, Thayer JF, Zonderman AB. Nonlinear relations of blood pressure to cognitive function: the Baltimore Longitudinal Study of Aging. Hypertension. 2005;45:374–379.
28. Oishi E, Ohara T, Sakata S, Fukuhara M, Hata J, Yoshida D, Shibata M, et al. Day-to-Day blood pressure variability and risk of dementia in a general Japanese elderly population: the Hisayama Study. Circulation. 2017; 136:516–525.
29. Gottesman RF, Schneider AL, Albert M, Alonso A, Bandeen-Roche K, Coker L, et al. Midlife hypertension and 20-year cognitive change: the Atherosclerosis Risk in Communities Neurocognitive Study. JAMA Neurol. 2014;71:1218–1227.
30. Tsivgoulis G, Alexandrov AV, Wadley VG, Unverzagt FW, Go RC, Moy CS, et al. Association of higher diastolic blood pressure levels with cognitive impairment. Neurology. 2009; 73:589–595.
31. Den Heijer T, Launer LJ, Prins ND, van Dijk EJ, Vermeer SE, Hofman A, Koudstaal PJ, et al. Association between blood pressure, white matter lesions, and atrophy of the medial temporal lobe. Neurology. 2005; 64:263–267.
32. Chen KH, Henderson VW, Stolwyk RJ, Dennerstein L, Szoeke C. Prehypertension in midlife is associated with worse cognition a decade later in middle-aged and older women. Age Ageing. 2015;44:439–445.

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Case Report

A Case of Successful Surgical Resection of Locally Advanced (T4) Lung Cancer Utilizing a Multi-Disciplinary Approach Involving Previously Unresectable Structures

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Abstract

Background: Lung cancer is the leading cause of cancer-related deaths worldwide and the second most prevalent cancer. Tumor-node-metastasis (TNM) staging remains the primary prognostic factor, with T4 disease traditionally deemed unresectable due to tumor invasion into critical structures. We report a case of a T4 non-small cell lung cancer that was initially deemed unresectable but successfully treated with radical surgical resection. **The Case:** A 66-year-old asymptomatic male underwent a routine pre-operative chest X-ray, revealing an incidental lung nodule. Imaging identified a 6.1 cm mass with local extension to the stomach (excluded from TNM classification), diaphragm, and pericardium, rendering it initially unresectable. A multidisciplinary team pursued an aggressive surgical approach. The patient underwent a low left thoracoabdominal incision, left lower lobectomy, wedge liver resection, lymph node dissection, en bloc diaphragmatic resection, and omentum resection. Partial gastrectomy was unnecessary. Histopathology confirmed non-small cell lung cancer, pT4 N0, M0, R0, stage IIIA, with omental and diaphragmatic involvement. At six months postoperatively, the patient remained well. **Conclusion:** T4 disease exhibits heterogeneity, and although it is typically deemed unresectable, recent developments in surgery are challenging this conventional belief particularly where a radical dissection is anticipated.

Introduction

Lung cancer is the most commonly diagnosed cancer worldwide and the leading cause of cancer-related deaths, with approximately 2 million new cases and 1.8 million fatalities annually.[1] In the United States, the 5-year survival rate for lung cancer patients diagnosed with localized disease (Stage I-II) is 59.0%. This declines to 31.7% for those with regional spread (Stage III) and further drops to 5.8% for metastatic disease (Stage IV). Additionally, 57% of lung cancer cases in the U.S. are diagnosed after metastasis.[1]

The tumor node metastasis (TNM) classification (9th edition) characterizes Tumor (T) 4 disease as a tumor exceeding 7 cm in its largest dimension or one that invades the mediastinum, diaphragm, heart, great vessels, recurrent laryngeal nerve, carina, trachea, oesophagus, or spine, or represents a separate tumor in a different lobe of the ipsilateral lung.2, 3 Typically, T3 and T4 tumors are locally advanced and associated with poor prognosis. T3 disease describes tumors that remain amenable to surgical resection, whereas T4 disease describes local invasion that traditionally precludes safe resection. Consequently, T4 disease is classified as stage IIIB and is deemed unresectable in most cases.

Highlights:

- The importance of multi-disciplinary surgical planning before surgery.
- Surgical options for locally advanced lung cancer.
- The exclusion of organs such as the stomach and liver in the current T4 classification of lung cancer

However, recent advancements in surgical techniques and perioperative management have expanded treatment options for select patients with T4 lung cancer. Technologies such as cardiopulmonary bypass (CPB) and extracorporeal membrane oxygenation (ECMO) now enable the safe resection of tumors involving critical anatomy. Superior vena cava (SVC) invasion can be managed with SVC replacement, and right carinal pneumonectomy offers treatment for carinal invasion.[4]

Achieving a curative resection requires meticulous preoperative planning to assess the feasibility of removing all of the tumor remnants, including lymph node involvement. This planning often necessitates a multidisciplinary approach to optimize outcomes.

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We present a case of T4 disease with local invasion of the diaphragm, pericardium, and omentum, which was successfully resected through a collaborative surgical approach. This case challenges the conventional perception of unresectability and highlights the potential for curative treatment in select patients with advanced lung cancer.

The Case

An asymptomatic 66-year-old gentleman was referred to the lung cancer team with an incidental lung nodule found on a pre-operative chest x-ray before elective aortic Endovascular Aneurysm Repair (EVAR) ***(Figure. 1: A).***

The patient had a history of laryngeal squamous cell carcinoma treated with chemoradiation, previous EVAR, ischemic heart disease, hypertension, previous stroke with residual left eye blindness and chronic renal function impairment. He is an ex-smoker of 20 years with a 40-pack-year smoking history and has a European Cooperative Oncology Group (ECOG) score of 1-2.

The lesion was initially assessed as radiologically benign. However, a subsequent CT Thorax demonstrated considerable enlargement of the nodule with diaphragmatic invasion ***(Figure 1: B).*** A PET-CT was then conducted. This revealed a 6.1cm intensely fluorodeoxyglucose (FDG) avid mass (standardized uptake value (SUV) max of 21) in the left lower lobe of the lung. ***(Figure 1: C-D).*** Additionally, an enlarged left hilum near the origin of the lingular bronchi showed mild FDG avidity (SUV max of 7) ***(Figure 1: E).*** Diffuse FDG uptake was seen throughout the stomach which was considered most likely benign. This was further investigated with an esophagogastroduodenoscopy which was normal. A diagnosis of presumed primary lung cancer was made. The tumor was radiologically staged as T4, primarily due to the possibility of invading the stomach and mesentery, and as N1 due to the presence of an ipsilateral hilar node

Mediastinal staging with endobronchial ultrasound confirmed squamous cell carcinoma and staged as cT4 N0/1 M0. The case was discussed at the lung cancer tumor board. Due to the size and central location of the lesion radiotherapy ablation was not feasible. Immunotherapy was not a treatment option due to the exceedingly low levels of targets such as Programmed Death Ligand 1 (PD-L1). Hence, despite its T4 classification, surgery was considered. Thus, this case represents the first reported resection involving local invasion into the diaphragm, pericardium, omentum and onto the liver surface.

The patient was brought to theatre by both the cardiothoracic and the upper GI teams. Intra-operatively, a low left thoracoabdominal incision was used following induction of general anaesthesia, with double lumen intubation, central line monitoring and epidural catheter insertion.

Initial hilar dissection was performed to isolate the left lobe hilar structure. The pericardium was opened sparing the phrenic nerve and a margin was obtained. Then, the left lower lobe hilar structures were divided. Once the left lower lobe was freed from the hilum and mediastinum, the diaphragm and mediastinum were divided taking care to leave a margin and a cuff of the remaining diaphragm. Tumor extension was found through the diaphragm and involving the pericardium (***Figure 2:*** A shows the invasion of the tumor through the diaphragm). Where it was possible, large portions of the left hemidiaphragm were resected medially up to the arcuate ligament. This revealed no invasion into the stomach. However, there were suspicious adhesions of the lesion to the omentum and liver. These structures were resected (***Figure 2***: B demonstrates the total specimen sent to pathology).

Following the completion of resection, a full lymphadenectomy was performed. The diaphragmatic defect was then reconstructed with permacol bioprosthesis and the pericardial defect was reconstructed with bovine pericardium (***Figure 2:*** C depicts the repaired pericardial defect). The thoracoabdominal incision was then closed in layers.

Post-operatively, the patient developed acute limb ischemia of the right lower limb. This was managed conservatively. There were no other post-operative complications. The patient was discharged on day 10 post-operation.

Histology confirmed non-small cell lung cancer (NSCLC) of squamous cell carcinoma subtype. Clear margins were obtained, and no lymph nodes were involved. The tumor was pathologically staged as T4 N0 M0, stage IIIA. The omentum, abdominal diaphragm and pericardium were also involved. The tumor was abutting the liver but the liver tissue itself was not involved.

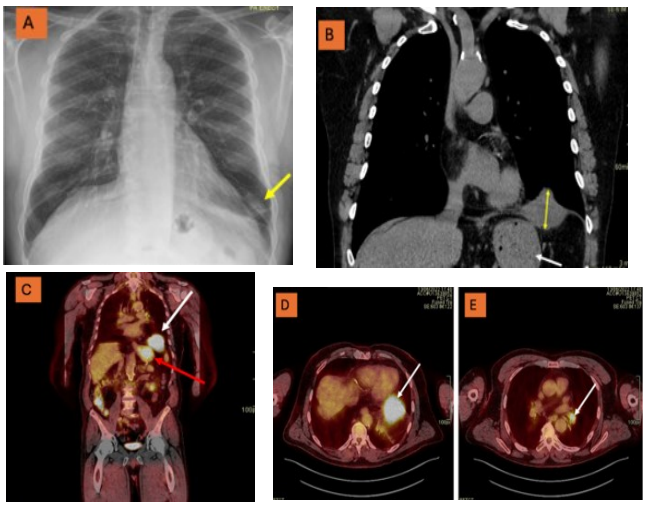
Following discussion at the lung multi-disciplinary meeting, adjuvant chemotherapy was recommended as the tumor was larger than 4 cm. However, the patient declined adjuvant chemotherapy due to previous intolerance experienced during treatment for laryngeal squamous cell carcinoma. At post-operative follow-up, the patient demonstrated satisfactory clinical recovery with no reported complications.

Discussion

Lung cancer is the leading cause of cancer death worldwide and the second most prevalent cancer in the world.[5] Tumor Node Metastasis (TNM) staging continues to serve as the primary prognostic factor for survival in lung cancer. Tumor (T) 3 and 4 disease describes locally advanced tumors which are associated with poor prognosis. T3 staging refers to invasion of anatomy which is amenable to resection whereas, T4 disease describes local invasion into anatomical structures which cannot be safely surgically resected. Consequently, T4 disease is classified as stage IIIB.[6] To pursue a curative resection, it is essential to pre-operatively assess the feasibility of eliminating all remnants of disease, including lymph node involvement.

T4 lung cancer is heterogenous.[7] For example, T4N0 cancers with multifocality often exhibit survival rates more akin to those of Stage IB or II non-small cell lung cancer (NSCLC). Although technically challenging, surgical resection of tumors involving the superior vena cava, carina, or thoracic inlet is considered feasible. Post-operative mortality rates vary across studies, with one study reporting rates between 4% and 13%.[4] Dartevelle et al. presented a 30-year review of extended surgical resections for T4 NSCLC focusing on resection techniques involving the superior vena cava and thoracic inlet.[4] They reported that 5-year survival rates for patients with N0–N1 disease exceeded 40%, demonstrating that surgery, in carefully selected cases, can provide significant survival benefits for locally advanced T4 NSCLC.[4]

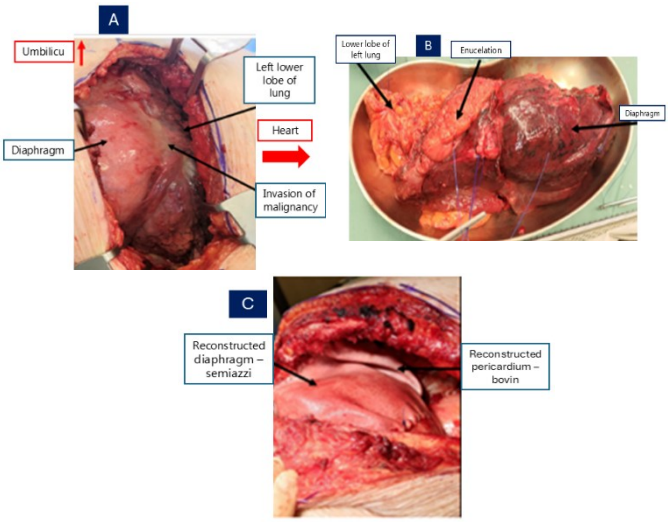
Figure 1. Diagnostic Imaging.



Legend: **A:** Chest x-ray showing an approximately 2cm lesion in the left lower lobe (yellow arrow). **B:** Computed Tomography image demonstrating the left lower lobe lung mass (yellow arrow) extending beyond the diaphragm and potentially abutting the stomach (white arrow). **C:** PET CT scan showing 6.1cm intensely fluorodeoxyglucose (FDG) avid mass (standardized uptake value (SUV) max of 21) in the left lower lobe of the lung (white arrow) along with an approximately 1cm mildly FDG avid lymph node in the left intrahilar region adjacent to the origin of the lingular bronchi (SUV max of 7) (red arrow). There was diffuse FDG uptake seen throughout the stomach which was considered most likely benign. This was confirmed using esophagogastroduodenoscopy. **D:** PET CT demonstrating on the left an approximately 6.1cm intensely FDG avid pulmonary mass at the left lung base (SUV max 21). **E:** PET CT demonstrating an approximately 1cm mildly FDG avid lymph node in the left intrahilar region adjacent to the origin of lingular bronchi (SUV max 7). This was found to be benign on endobronchial node biopsy.

This variability in prognosis within T4 disease has become increasingly evident, particularly with the change in T4 classification criteria between the 7th and 8th editions of the American Joint Committee on Cancer (AJCC) guidelines. In the 8th edition guidelines, tumors larger than 7cm are categorized as pT4 in the absence of invasion into adjacent organs.8 Under the 7th edition, only tumors with extrapulmonary invasion were considered T4. This updated classification now encompasses a broader range of disease presentations, leading to a significant disparity in overall survival rates: rising from 35.5% under the 7th edition to 49.6% with the 8th edition.[9]

Figure 2. Intra-operative Imaging



Legend: **A:** An intra-operative image showing invasion of the malignancy into the diaphragm. Local invasion of the central tendon extended both medially and posteriorly. The diaphragm was resected en bloc with a small sleeve of greater omentum. **B:** This image depicts the specimen sent for histopathology. It included the left lower lobe lung, aspect of the left hemidiaphragm, peritoneum and left lobe of the liver. **C:** This intra-operative image demonstrates the diaphragm reconstructed with Permacol prosthesis and the pericardium reconstructed with bovine pericardium.

Tankel et al's study compared outcomes in patients with pT4 NSCLC classified under the AJCC 8th edition, with those classified as T4 under the 7th edition. Patients with extrapulmonary invasion exhibited higher disease burden, increased likelihood of requiring pneumonectomy, greater 90-day mortality, and a trend towards shorter overall survival.[10] The authors suggest that the expanded pT4 criteria in the 8th edition encompass a diverse patient population, necessitating a more tailored approach. However, The 9th edition of the TNM classification for lung cancer, which took effect in 2024, introduces some refinements, although the T (tumor) descriptors remain unchanged from the 8th edition.[3]

A study published in 2019 highlighted that the most significant prognostic factors for post-operative survival in T4 disease were achieving clear resection margins and nodal status.[11] To pursue a curative resection, it is essential to pre-operatively assess the feasibility of eliminating all remnants of the disease, including lymph node involvement. An international series involving 388 cases of surgery for T4 non-small cell lung cancer estimated a postoperative mortality rate of 4%.[4] An anticipated 5-year survival rate of 28% was expected in the R0 and N0-1 groups respectively.[12] However, notably for our case no studies have included patients with invasion into the stomach due to its exclusion from the T4 classification.

Rates of surgery in lung cancer are generally low, this is for a myriad of reasons. The 2008 National Lung Cancer audit revealed that lung cancer resection rates stand at just 11% with notable disparities among different medical centers, ranging from less than 5% to as high as 25%.[13] The patient's initial health status

often serves as a common factor contributing to low rates of surgical intervention. Patients undergoing extensive surgical resection have an increased risk of morbidity and mortality.[6] These patients require assessment and optimization of their co-morbidities pre-operatively. Enhanced Recovery After Surgery (ERAS) plays a key role in patient optimization. Our patient had multiple co-morbidities which posed a significant surgical risk. ERAS is a multimodal and evidence-based approach to perioperative care that aims to optimize management and outcomes for patients.[14] ERAS protocols incorporate a wide range of preoperative, intraoperative, and postoperative strategies, all geared toward improving surgical outcomes and accelerating the recovery process.[14] By adhering to these principles, pain can be minimized, hospital stays reduced with a quicker return to patient's daily lives.[14]

To optimize the patient pre-operatively, a multidisciplinary approach was employed. Cardiovascular function was reviewed with an up-to-date pre-operative echocardiogram and electrocardiogram given the patient's history of ischemic heart disease. Hypertension management was optimized. Renal function was managed with maintenance intravenous hydration while fasting due to chronic renal impairment. The patient's history of smoking was addressed with pre-operative pulmonary rehabilitation. ERAS protocols were followed to improve postoperative recovery, focusing on nutrition, multimodal analgesia, and minimizing fasting to enhance outcomes.

Chemotherapy wasn't a viable option in this case due to patient preference. However, neoadjuvant therapy could potentially enhance the feasibility of surgical intervention for T4 cancer. A 1994 study involving twenty-three patients with stage IIB (T4) NSLCC, of which twelve also underwent radiation prior to surgery, found that complete eradication was observed in 13% of patients.[15] However, major post-operative complications occurred more commonly in those patients who received chemotherapy as well as radiotherapy compared to chemotherapy alone. This study did not include any patients with invasion through the diaphragm. The three-year survival was determined to be 54%.[15]

A study published in 2022 assessed the outcomes of extended resections in patients with stage III T3/T4 NSCLC following induction therapy.[16] Of 197 patients, 80% achieved R0 resection, including 36 extended resections, with no significant difference in mortality compared to standard resections. Extended resections showed promising survival rates, with 61% at 3 years and 29.5% at 10 years. R0 resection was associated with improved survival, but pretreatment N2 status had no significant impact. This highlights the potential for surgery post-induction therapy in selected patients with advanced T4 NSCLC.[16]

The LACE trial demonstrated that postoperative cisplatin-based chemotherapy significantly improves overall survival (OS) in patients with resected NSCLC. In a pooled analysis of five major trials with 4,584 patients, the median follow-up was 5.2 years, showing a 5-year absolute survival benefit of 5.4%. The benefit was more pronounced in stage II and III patients, with hazard ratios of 0.83 for both stages, compared to no benefit in stage IA. Chemotherapy was most effective in patients with better performance status, regardless of the associated drugs used.[17]

In summary, T4 disease exhibits heterogeneity, and although it is typically deemed unresectable, recent developments in surgery are challenging this conventional belief and demonstrating the potential benefits of surgical resection, particularly where a radical dissection is anticipated. Our case represents the first reported resection involving local invasion into the diaphragm, pericardium, omentum, and onto the liver surface. This case underscores the critical role of multidisciplinary collaboration and the need for consulting specialties not traditionally involved in lung cancer tumor boards when managing complex, challenging cases

Summary – Accelerating Translation

We present a case where a multidisciplinary approach enabled the complete surgical resection of locally advanced lung cancer that had invaded the diaphragm, pericardium, omentum and onto the liver surface.

References

1. Thandra KC, Barsouk A, Saginala K, Aluru JS, Barsouk A. Epidemiology of lung cancer. Contemp Oncol (Pozn). 2021;25(1):45–52.
2. Lababede O, Meziane MA. The eighth edition of TNM staging of lung cancer: Reference chart and diagrams. Oncologist. 2018;23(7):844–848.
3. Erasmus LT, Strange CD, Ahuja J, Agrawal R, Shroff GS, Marom EM, et al. Imaging of lung cancer staging: TNM 9 updates. Semin Ultrasound CT MR. 2024.
4. Dartevelle P, Mitilian D, Fadel E. Extended surgery for T4 lung cancer: A 30 years' experience. Gen Thorac Cardiovasc Surg. 2017;65:321–328.
5. Aldarouish M, Wang C. Trends and advances in tumor immunology and lung cancer immunotherapy. J Exp Clin Cancer Res. 2016;35(1):1–13.
6. DiPerna CA, Wood DE. Surgical management of T3 and T4 lung cancer. Clin Cancer Res. 2005;11(13):5038s–5044s.
7. Port JL, Korst RJ, Lee PC, Kansler AL, Kerem Y, Altorki NK. Surgical resection for multifocal (T4) non-small cell lung cancer: Is the T4 designation valid? Ann Thorac Surg. 2007;83(2):397–400.
8. Rami-Porta R, Bolejack V, Crowley J, Ball D, Kim J, Lyons G, et al. The IASLC lung cancer staging project: Proposals for the revisions of the T descriptors in the forthcoming eighth edition of the TNM classification for lung cancer. J Thorac Oncol. 2015;10(7):990–1003.
9. Jung HS, Lee JG, Lee CY, Kim DJ, Chung KY. Validation of the T descriptor in the new 8th TNM classification for non-small cell lung cancer. J Thorac Dis. 2018;10(1):162.
10. Tankel J, Mouhanna J, Katz A, Fiset P-O, Rayes R, Siblini A, et al. The 8th edition TNM stage reclassification of T4 non-small cell lung cancer: A granular examination of short and long-term outcomes. Clin Lung Cancer. 2023.
11. Yamanashi K, Menju T, Hamaji M, Tanaka S, Yutaka Y, Yamada Y, et al. Prognostic factors related to postoperative survival in the newly classified clinical T4 lung cancer. Eur J Cardiothorac Surg. 2020;57(4):754–761.

12. Grunenwald DH, André F, Le Péchoux C, Girard P, Lamer C, Laplanche A, et al. Benefit of surgery after chemoradiotherapy in stage IIIB (T4 and/or N3) non–small cell lung cancer. J Thorac Cardiovasc Surg. 2001;122(4):796–802.
13. Verdecchia A, Francisci S, Brenner H, Gatta G, Micheli A, Mangone L, et al. Recent cancer survival in Europe: A 2000–02 period analysis of EUROCARE-4 data. Lancet Oncol. 2007;8(9):784–796.
14. Brown JK, Singh K, Dumitru R, Chan E, Kim MP. The benefits of enhanced recovery after surgery programs and their application in cardiothoracic surgery. Methodist Debakey Cardiovasc J. 2018;14(2):77.
15. Macchiarini P, Chapelier AR, Monnet I, Vannetzel J-M, Rebischung J-L, Cerrina J, et al. Extended operations after induction therapy for stage IIIb (T4) non-small cell lung cancer. Ann Thorac Surg. 1994;57(4):966–973.
16. Furrer K, Weder W, Eboulet EI, Betticher D, Pless M, Stupp R, et al. Extended resection for potentially operable patients with stage III non-small cell lung cancer after induction treatment. J Thorac Cardiovasc Surg. 2022;164(6):1587–1602.e5.
17. Pignon J-P, Tribodet H, Scagliotti GV, Douillard J-Y, Shepherd FA, Stephens RJ, et al. Lung adjuvant cisplatin evaluation: A pooled analysis by the LACE Collaborative Group. J Clin Oncol. 2008;26(21):3552–3559.

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Case Report

To Test or Not to Test? How a Positive Rapid Strep Test May Perplex the Diagnosis of Serum Sickness-Like Reaction in a Case Report

Christodoulos Chatzigrigoriadis,[1] George Eleftherakis,[2] Kostis Gyftopoulos,[3] Stelios F. Assimakopoulos.[4]

Abstract

Background: Serum sickness-like reaction (SSLR) is a rare cause of drug eruption. The clinical presentation includes fever, rash, and arthralgia which typically occurs 1-2 weeks after the administration of common antibiotics such as amoxicillin or cefaclor. It is a challenging diagnosis because it mimics sepsis and other exanthematous diseases. Rapid Strep Test (RST) is a useful diagnostic test for detecting Streptococcus pyogenes in patients with pharyngitis and Centor score of 3 or more guiding the administration of antibiotics. **The Case:** We report a case of a 63-year-old female patient seen in the emergency department (ED) with high-grade fever, diffuse rash, musculoskeletal pain, and a positive RST without clinical evidence of pharyngitis. The primary care physician ordered the RST before the referral to the ED to investigate the febrile rash without a clear indication, misleading to the diagnosis of streptococcal sepsis. She was eventually diagnosed with SSLR and she was treated with corticosteroids, leading to rapid symptomatic relief. **Conclusion:** SSLR is an interesting clinical entity, and its pathogenesis is poorly understood. This case emphasizes that SSLR is a clinical diagnosis of exclusion after ruling out other similar disorders. Physicians should be familiar with this benign condition to avoid unnecessary diagnostic testing such as RST which may misguide diagnosis and treatment. Simple diagnostic tests should be used with caution under certain indications; misuse of RST can cause false-positive results, complicating the management of these cases.

Introduction

Adverse cutaneous drug reaction is a common cause of Emergency Department (ED) visits or hospital admissions.1 Serum sickness-like reaction (SSLR) is a rare cause of this common diagnostic problem.[2-5] It is usually triggered by beta-lactam antibiotics (especially amoxicillin and cefaclor).[2-8,12] Other drugs such as analgesics, vaccinations, and infectious diseases trigger SSLR less often.[2,4,7,8,9,12] SSLR usually occurs 1-2 weeks after the exposure, but this is variable (0-21 days).2,5-7 The classic triad is fever, diffuse arthralgia and rash, although renal involvement and lymphadenopathy may also occur.[2,-5,7,8,12] The rash is diffusely located over the trunk and extremities with maculopapular or urticarial morphology and may be occasionally pruritic.[2,4,5,9]

Streptococcus pyogenes is the most common cause of bacterial pharyngitis, although viral pharyngitis is generally more common.[10] Rapid strep test (RST) is useful for the diagnosis of pharyngitis caused by S. pyogenes, with a specificity of over 90%. RST should be ordered in patients who present with pharyngitis and Centor score of 3 or more.[10] However, simple carriage of S. pyogenes may give a positive RST result in patients without pharyngitis, hence misguiding their management.[10,11]

Highlights:

- Serum sickness-like reaction (SSLR) is a rare immunologic disorder with unclear pathogenesis related to serum sickness, a type III hypersensitivity reaction.
- The clinical presentation of SSLR includes fever, arthralgia, and maculopapular or urticarial rash mimicking sepsis.
- Rapid Strep Test (RST) must be used cautiously, mainly in patients with clinical suspicion of pharyngitis and Centor score of 3 or more.
- SSLR is a clinical diagnosis and a false-positive RST may misguide the management of these patients.
- The prognosis of SSLR is excellent and the treatment is symptomatic, but severe cases may lead to unnecessary hospitalization, antibiotic treatment and diagnostic testing.

Overdiagnosis of streptococcal infections and overuse of antibiotics are possible consequences of false-positive RST, especially when the clinical presentation is unclear and the previously outlined requirements do not apply.

In this report, we present an unusual case of SSLR without clinical evidence of pharyngitis and a positive RST, following treatment of respiratory tract infection with amoxicillin/clavulanate and analgesics.

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The Case

A 63-year-old woman presented to the Emergency Department with diffuse rash, high-grade fever, chills, diffuse musculoskeletal pain, and a positive RST performed by her physician despite the absence of throat pain. Past medical and epidemiological history was unremarkable except for a respiratory tract infection (RTI) 12 days ago treated with amoxicillin/clavulanate (7-day course), acetaminophen, and ibuprofen. Ibuprofen was administered for the last 3 days only. No recent travel or exposure to other infectious agents was reported. The rash was neither painful nor pruritic and was diffusely spread, sparing the face, the palms, and the soles, with a maculopapular pattern and occasional urticarial-like plaques ***(Figure 1).*** The rest of the physical examination, including the head and neck examination, was unremarkable. She developed the aforementioned symptoms the day before the ED visit. Laboratory tests revealed normochromic normocytic anemia (Hb 11.2 g/dl), normal white blood cells (WBCs) with a neutrophilic predominance (9.94 K/ μ l with 94.1 % neutrophils), elevated C-reactive protein (CRP) (44.7 mg/dL), elevated erythrocyte sedimentation rate (ESR) (75 mm/h) and elevated ferritin (1546 ng/ml). Renal function (urea 24 mg/dl and creatinine 0.7 mg/dl) and urinalysis were normal. Cardiac evaluation with an electrocardiogram and echocardiogram was unremarkable. Liver function tests, C3, and C4 levels were normal. Antistreptolysin O titer (ASTO), rapid plasma reagin test (RPR), blood cultures, and serological tests for antibodies against viruses and rickettsiae were negative. Clindamycin was administered for coverage of S. pyogenes, based on the positive RST and the clinical suspicion of sepsis, but was discontinued due to diarrhea. The lack of response to clindamycin and the negative microbiological work-up reduced the suspicion of streptococcal infection. Hence, additional antibiotics were not considered.

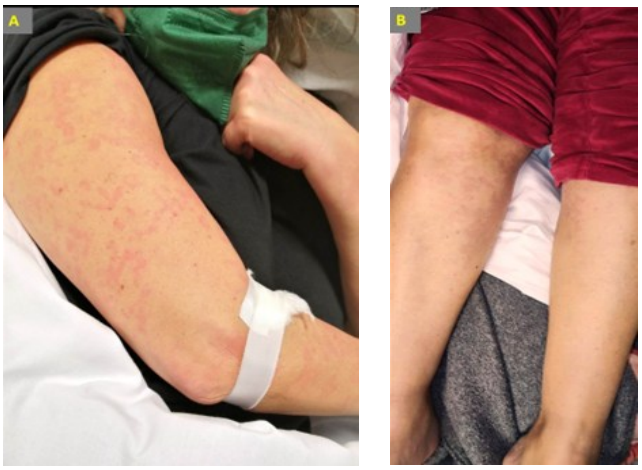
The clinical findings and the negative diagnostic work-up raised suspicion of adverse drug reactions. The patient was eventually diagnosed as suffering from a serum-sickness like reaction (SSLR) caused by the treatment of RTI 1-2 weeks before the development of her symptoms. The most likely trigger was amoxicillin, although clavulanate and ibuprofen cannot be excluded.[2] Methylprednisolone 0.5 mg/kg per os was administered, resulting in the resolution of symptoms after 2 days, while the dose was gradually tapered over one week.

Table 1. The Parameters of the Centor Score**.**

Fever (more than 38 °C)	+1
Anterior cervical lymphadenopathy	+1
Tonsillar exudate	+1
Lack of cough	+1
Age 3-14 years	+1
Age 15-44 years	0
Age >44 years	-1

Legend: The calculation of the Centor score is the first step in the clinical evaluation of pharyngitis. Patients with a Centor score of 3 or more should be tested with a RST. A positive result is an indication for antibiotic treatment, but a negative result should be investigated with a throat culture

Figure 1. The Diffuse Maculopapular Rash of the Patient.



Legend: The diffuse maculopapular pattern of the developed rash; note the occasional urticarial-like plaques in the area of arms (A) and legs (B).

Discussion

SSLR is an immunologic disorder that usually occurs 1 to 2 weeks after the administration of a drug. The most common triggers are amoxicillin and cefaclor.[2-8] The pathogenesis is not fully understood, although factors related to the immune system, age, drug metabolism, and infectious agents are considered essential for the development of SSLR.[2-3] Re-exposure to cefaclor increases the risk of developing SSLR, which does not apply to amoxicillin.[3,5] However, SSLR is not associated with atopy, hence, it is not considered a part of the type I hypersensitivity reactions spectrum.[5] SSLR is more common in pediatric patients, but this observation might be explained by the fact that children are more likely to be diagnosed with respiratory tract infections and treated with antibiotics than adults.[2,3,6,12] Infectious agents such as viruses and bacteria can precipitate the development of drug-induced rash.[2] This theory may explain the close relationship between SSLR and antibiotics.[2] In our case, amoxicillin/clavulanate was more likely the trigger of SSLR, because SSLR usually develops 1-2 weeks after the administration of the responsible drug. Amoxicillin/clavulanate was administered 11 days before the development of SSLR, but ibuprofen was administered 2 days before SSLR. However, the clinical presentation of the patient and the positive RST initially misled the diagnosis and urged the attending physician to (unnecessarily) administer clindamycin.

The original version of this hypersensitivity reaction is serum sickness (SS) which occurs after the administration of heterologous antitoxins such as antitetanus or antirabies serum.[4-8,12] True serum sickness is a type III hypersensitivity reaction that commonly involves the lymph nodes and the internal organs such as the kidneys, in contrast to the SSLR.2-7,12 The pathogenesis of SS explains the vasculitis and the low levels of complement which are typically normal in SSLR, like in our case.[2,3,4,6,9,12]
The diagnosis of SSLR is mainly clinical. Key points include a diffuse maculopapular or urticarial rash, fever, and arthralgia, although the classic triad is not always present.[2-4,6,8,9,12] Laboratory

studies commonly reveal elevated inflammatory markers (ESR, CRP), elevated WBCs with neutrophilic predominance, thrombocytosis, and anemia.[6,9,12] Renal involvement may be present with hematuria and proteinuria.9 However, these findings are neither sensitive nor specific to this condition. More severe cases are misdiagnosed as sepsis, leading to unnecessary empiric antibiotic treatment7. The rash of SSLR mimics other common skin disorders such as urticaria, erythema multiforme, and viral exanthems.[2,3]

The course of SSLR is generally benign, hence the treatment is mostly symptomatic.[2,3,8,9,12] The most important step is to discontinue the responsible medication.[4,7,12] Although the treatment remains controversial, there is limited evidence that supports the administration of acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), antihistamines, and fluids.[2,4,7,12] It must be noted that analgesics are responsible for a minority of SSLR cases, so they must be used with caution.[2,6,8] Corticosteroids are reserved for severe cases such as in our patient.[2,7,12] Although there is a small risk of beta-lactam cross-reactivity in patients with SSLR, there is limited evidence to suggest avoidance of other beta-lactam antibiotics.[3]

Viruses usually cause pharyngitis, but S. pyogenes is the most common bacterial pathogen.[10] The initial step is the calculation of the Centor score ***(Table 1),*** which is correlated with the pre-test probability of streptococcal pharyngitis.[10,11] RST is a first-line test for the differentiation between viral and bacterial pharyngitis; current guidelines suggest testing with RST in patients with a Centor score of 3 or more.[10] However, this guideline does not apply to individuals without pharyngitis, as a positive test result is likely to be false due to the asymptomatic carriage of S. pyogenes. The positive RST in this patient with the febrile rash raised the suspicion of streptococcal complications.

The differential diagnosis in a febrile patient with rash, arthralgia, and positive RST is broad and challenging. The lack of facial rash, strawberry tongue, sandpaper texture, and Pastia lines make the diagnosis of scarlet fever unlikely.[13] The absence of cardiac involvement, arthritis, and other criteria of acute rheumatic fever, including the serpiginous morphology of erythema marginatum, make this diagnosis unlikely in a patient above the age of 40 years.[14] Urticaria causes pruritus while the fever and malaise are absent.[2,3,9] The rash of erythema multiforme is associated with pain, pruritus, palmoplantar distribution, targetoid lesions, and blistering which are not present in this case.[2,3,9] Absence of eosinophilia, elevated transaminases, lymphadenopathy, and facial rash or edema in conjunction with the presence of generalized arthralgias and short latency period (less than 2-6 weeks), make the diagnosis of drug reaction with eosinophilia and systemic symptoms (DRESS) unlikely.[8] Adult-onset Still's disease which is associated with spiking fever, hyperferritinemia, neutrophilia, and episodic salmon-like colored rash with fever spikes, may be ruled out by the constant presence of the rash.[15] Infectious diseases - associated rash may be ruled out by serological tests and similarly, acute interstitial nephritis is excluded by the absence of renal involvement, when renal function and urine analysis appear normal.

Physicians should be aware of the SSLR as a clinical entity and should maintain a high clinical suspicion index in patients presenting with fever and rash after a recent exposure to antibiotics. This case report emphasizes the importance of clinical diagnosis and reasonable use of even simple diagnostic tests like RST, which may be misleading when performed without a clear clinical indication, to avoid unnecessary diagnostic testing, hospitalization, and antibiotic treatment.[4,7] The restricted use of antibiotics in patients with immunologic disorders is essential to avoid delayed diagnosis and treatment.[4,7]

Summary – Accelerating Translation

Να Κάνουμε Τεστ ή να Μην Κάνουμε; Πώς ένα θετικό Rapid Strep Test Μπορεί να Περιπλέξει τη Διάγνωση της Αντίδρασης Δίκην Ορονοσίας ς

Η αντίδραση δίκην ορονοσίας αποτελείνα σπάνιο αίτιο εμπύρετου εξανθήματος. Η κλινική εικόνα ποικίλει και περιλαμβάνει εξάνθημα, πυρετό και αρθραλγία/αρθρίτιδα, τα οποία παρατηρούνται 1-2 εβδομάδες μετά την έκθεση σε φαρμακευτικούς ή/και λοιμογόνους παράγοντες. Θεωρείται δύσκολη διάγνωση, επειδή πρόκειται για σπάνια οντότητα και μιμείται τη σήψη και άλλες εξανθηματικές νόσους. Η διάγνωση είναι κλινική και τίθεται μετά από τον αποκλεισμό λοιμωδών και ανοσολογικών παθήσεων με παρόμοια κλινική εικόνα. Η φαρυγγίτιδα συνήθως είναι ιογενούς αιτιολογίας και δε χρήζει αντιβιοτικής αγωγής, αλλά ο Streptococcus pyogenes είναι το πιο κοινό αίτιο βακτηριακής φαρυγγίτιδας. Η στρεπτοκοκκική φαρυγγίτιδα πρέπει να καταπολεμάται με αντιβιοτικά για την αποφυγή σοβαρών επιπλοκών. Το rapid strep test (RST) αποτελεί μία χρήσιμη διαγνωστική εξέταση για την ανίχνευση του Streptococcus pyogenes σε ασθενείς με φαρυγγίτιδα και Centor score 3 ή παραπάνω καθοδηγώντας τη χορήγηση αντιβιοτικών. Ωστόσο, η κατάχρηση του μπορεί να οδηγήσει σε ψευδώς θετικά περιστατικά περιπλέκοντας την κλινική διαχείριση, όπως συνέβη στο περιστατικό μας.

Παρουσιάζουμε το ενδιαφέρον περιστατικό μίας ασθενούς 63 ετών, η οποία προσήλθε στο Τμήμα Επειγόντων Περιστατικών με διάχυτο εξάνθημα, υψηλό εμπύρετο και διάχυτο μυοσκελετικό άλγος. Αξίζει να σημειωθεί ότι είχε προηγηθεί παραπομπή της ασθενούς από το γενικό ιατρό, ο οποίος πραγματοποίησε RST με θετικό αποτέλεσμα. Το εξάνθημα παρουσίασε κνιδωτική και ηλιοβλατιδώδη μορφολογία, ήταν ανώδυνο, χωρίς κνησμό και δεν εμφανιζόταν

στην περιοχή του προσώπου, των παλαμών και των πελμάτων. Η φυσική εξέταση δεν ανέδειξε άλλα ευρήματα. Το ατομικό αναμνηστικό και το επιδημιολογικό ιστορικό της ασθενούς ήταν ελεύθερα, ωστόσο το ιστορικό της ήταν θετικό για προσφάτη απνευστική λοίμωξη, η οποία θεραπεύτηκε με αμοξικιλλίνη/κλαβουλανικό οξύ, ιβουπροφαίνη και ακεταμινοφαίνη. Η κλινική εικόνα σε συνδυασμό με τους αυξημένους δείκτες φλεγμονής έθεσαν ισχυρή υποψία σοβαρής στρεπτοκοκκικής νόσου οδηγώντας στην εισαγωγή της ασθενούς και στη χορήγηση κλινδαμυκίνης. Κατά τη διάρκεια της νοσηλείας έγινε πλήρης έλεγχος για λοιμώδη και ρευματικά νοσήματα, ενώ η κλινδαμυκίνη διακόπηκε λόγω διάρροιας. Στο σημείο αυτό, ο αρνητικός διαγνωστικός έλεγχος σε συνδυασμό με την έλλειψη ανταπόκρισης στην εμπειρική αντιβιοτική αγωγή με κλινδαμυκίνη έθεσαν την υποψία ανοσολογικής αντίδρασης. Τελικά, η ασθενής διαγνώστηκε με αντίδραση δίκην ορονοσίας και θεραπεύτηκε επιτυχώς με κορτικοστεροειδή.

Η αντίδραση δίκην ορονοσίας πρέπει να λαμβάνεται υπόψιν σε ασθενείς με εμπύρετο εξάνθημα στα πλαίσια πρόσφατης λοίμωξης/και λήψης αντιβιοτικής αγωγής. Το περιστατικό αυτό τονίζει τη σημασία της κλινικής διάγνωσης σε ασθενείς με αντίδραση δίκην ορονοσίας. Επιπλέον, αναδεικνύεται η αναγκαιότητα εκλογικευμένης χρήσης απλών διαγνωστικών εξετάσεων, όπως το RST. Η κατάχρηση τους μπορεί να οδηγήσει σε ψευδώς θετικά αποτελέσματα περιπλέκοντας την διαχείριση των περιστατικών με περιττές αντιβιοτικές αγωγές και νοσηλείες..

References

1. Montané E, Santesmases J. Adverse drug reactions. Med Clin (Barc). 2020;154(5):178-84.
2. Del Pozzo-Magaña BR, Abuzgaia A, Murray B, Rieder MJ, Lazo-Langner A. Paediatric serum sickness-like reaction: A 10-year retrospective cohort study. Paediatr Child Health. 2021;26(7):428-35.
3. Knowles S, Shapiro L, Shear NH. Serious dermatologic reactions in children. Curr Opin Pediatr. 1997;9(4):388-95.
4. Galvão Dos Santos de Araujo AC, Moura de Almeida L, Moura de Almeida AP, Fontenelle de Oliveira E, Carrijo Rochael M, Aires de Morais R, et al. Serum sickness-like reaction: drug-induced cutaneous disease in a child. Dermatol Pract Concept. 2021;11(3):e2021029.
5. Isaacs D. Serum sickness-like reaction to cefaclor. J Paediatr Child Health. 2001;37(3):298-9.
6. Mohsenzadeh A, Movahedi M, Saatchi M, Parvaneh N, Shariat M, Aghamohammadi A, et al. Serum sickness-like reactions in Iranian children: a registry-based study in a referral center. Allergol Immunopathol (Madr). 2020;48(5):424-9.
7. Güngörer V, Ertan K, Arslan Ş. Diagnosis that clinicians don't think of, serum sickness-like reaction. Pediatr Int. 2022;64(1):e14740.
8. Wolf R, Orion E, Marcos B, Matz H. Life-threatening acute adverse cutaneous drug reactions. Clin Dermatol. 2005;23(2):171-81.
9. Arnold KA, Gao J, Stein SL. A review of cutaneous hypersensitivity reactions in infants: From common to concerning. Pediatr Dermatol. 2019;36(3):274-82.
10. ESCMID Sore Throat Guideline Group; Pelucchi C, Grigoryan L, Galeone C, Esposito S, Huovinen P, Little P, et al. Guideline for the management of acute sore throat. Clin Microbiol Infect. 2012;18Suppl 1:1-28.
11. Hoffmann S. The throat carrier rate of group A and other beta hemolytic streptococci among patients in general practice. Acta Pathol Microbiol Immunol Scand B. 1985;93(5):347-51.
12. Patel D, Fernung LP, Davis LS. Bruising, hives, and joint pain in a 3-year-old boy. JAAD Case Rep. 2024;55:83-5.
13. Alotaibi A, Binsaqr MA, Mutlaq MR, Khojah AA, Khojah SA, Mohamed HA. Atypical presentation of scarlet fever. Cureus. 2022;14(12):e33142.
14. Batta S, Pederson H, Brust KB, Fiala KH. Acute rheumatic fever and erythema marginatum in an adult patient. Proc (Bayl Univ Med Cent). 2022;35(4):550-1.
15. Fautrel B, Mitrovic S, De Matteis A, Bindoli S, Antón J, Belot A, et al. EULAR/PReS recommendations for the diagnosis and management of Still's disease, comprising systemic juvenile idiopathic arthritis and adult-onset Still's disease. Ann Rheum Dis. 2024;83(12):1614-27.

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The authors certify that patient consent was obtained for publication of clinical details and images. The patient understands that the name and initials would not be published, and all standard protocols will be followed to conceal their identity.

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Experience

Challenges and Gender Disparities Faced by Women in Surgery in Pakistan

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Abstract

Medicine continues to face significant challenges in gender imbalance. The issue of gender discrepancy in the field of surgery has become more pronounced in low or middle-income countries like Pakistan due to the growing trend of women leaving the healthcare profession after completing education. Even fewer graduates go on to become surgeons. Female surgeons face clinical biases, excessive workloads and lack of recognition. Cultural norms and patriarchal mindsets impose additional challenges, making it difficult for female surgeons to balance professional and personal responsibilities, particularly motherhood. Gender biases in hiring, salary disparities, and a lack of institutional support further exacerbate the issue. Deeply ingrained preferences for male surgeons, with workplace harassment, reinforce the gender gap in operating theaters. This leads to stress, burnout, and lower job satisfaction causing fewer females to opt for surgical fields, creating gender disparity. In recent years, a newer trend has emerged with more females following their passion, but there is an increased need for support groups, proper mentorship programs, and implementation of equal opportunities for both males and females. It requires mentorship, institutional reforms promoting inclusive hiring, flexible work policies, and cultural shifts to challenge gender norms. Encouraging representation in surgical networks and advocacy groups fosters an inclusive and diverse surgical workforce.

The Experience

As a final-year medical student with a strong inclination towards surgery, stepping into the OR felt like stepping into another world. The familiar scent of disinfectant tingled in the air, a sharp yet oddly comforting reminder that I was exactly where I wanted to be. The floors gleamed under the bright overhead lights, reflecting the careful sterility of the space. Instruments were laid out meticulously on the mayo stand, their metallic edges glinting in anticipation. The steady murmur of the morning handoff between the night and day teams hummed in the background, blending seamlessly with the rhythmic beeping of monitors. Perhaps, I had found my passion.

The scrub gowns and gloves were tailored for larger hands and broader shoulders, leaving me adjusting and rolling up sleeves that were always too long. The step stools, meant to offer better visibility over the drapes, were a quiet reminder that the space had not accounted for a surgeon who wasn't built like her male colleagues. But it wasn't just the physical space, it was the culture.

Comments, sometimes subtle and sometimes overt, reminded me of my place. "Are you sure you want to do surgery? It's tough for women." A senior chuckled when I struggled to retract during a long case, "See, this is why women don't last in surgery." Even the unspoken rules were clear—show no weakness, take no breaks, and never, ever complain.

It was disappointing to see how easily the scalpel was handed over to male surgeons while females were asked to observe. The gender discrepancy and bias were conspicuous. Even patients, well-meaning but influenced by the same biases, sometimes looked past female surgeons, addressing questions to the nearest man in scrubs.

Despite this, even though a minority, the aura of female surgeons was absolutely awe-inspiring. Their resilience was proof that change, though slow, was happening. And as I stood there in the OR, watching one of them take charge of a complex case with unwavering confidence, I realized that if they could do it, so could. ***Figure 1***

Introduction

Surgery has been a male-dominated field, with significant barriers preventing women from entering and excelling in the specialty. In the United States, women represent less than 25% of professionals across ten surgical specialties, with particularly low representation in fields like orthopedic surgery (5.3%).[1] Similar pattern can be seen in Pakistan as well. As of December 2017, the Pakistan Medical and Dental Council reported a total of 168,842 registered MBBS doctors, with females comprising approximately 48.2% (81,456). In terms of specialists, there were 40,328 registered MBBS specialists, of which only 31.4% (12,652) were female.[2]

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Our perspective of gender discrimination in surgical fields, made it evident that female surgeons in Pakistan face significant bias throughout their careers in multiple ways. These biases are particularly noticeable in leadership opportunities, respectful boundaries, salary parity, and overall job satisfaction, which have had adverse effects on the professional experiences of Pakistani female surgeons. Although, a number of women in Pakistan pursue a medical career there remains severe under-representation of females in surgery residency programs. Underrepresentation of women in surgery raises concerns about unequal opportunities and its impact on healthcare quality. Traditional gender norms with undue pressure on female surgeons, hindering their professional growth which deteriorates the overall system leading to poor healthcare services.[3]

A previous study from Janjua et al.[4] highlights significant gender disparity in surgical specialties, with male dominance in vascular (100%), orthopedic (92%), otolaryngology (89%), urology (86%), and neurosurgery (81%). While cardio-thoracic (77%), plastic (75%), and general surgery (62%) also show male predominance, ophthalmology (60%) and pediatric surgery (55%) are more balanced. Notably, breast surgery is the only specialty with 100% female representation, emphasizing stark gender divisions in surgery.

Challenges faced by female surgeons

The field of surgery demands immense dedication and unwavering resilience. In developing countries, female surgeons encounter a myriad of challenges that hinder their career progression. A study done on female surgeons revealed that 18% of participants felt they experienced gender discrimination in medical school, 36% in residency, 12% in fellowship, and 41% as staff surgeons. More than half felt that their gender had played a role in the career challenges they faced.[5] These formidable obstacles encompass inadequate mentorship, pervasive gender discrimination, prolonged working hours, and the lack of equipment tailored to meet the needs of female surgeons. Motherhood plays a pivotal role in shaping the career decisions of female medical students. Balancing motherhood with a rigorous surgical career can prove to be exceptionally challenging. Furthermore, societal attitudes in Pakistan perpetuate the preference for male surgeons over their equally competent female counterparts, which reinforces gender superiority in this field.[6] Distressing instances of harassment against female surgeons with deep rooted cultural barriers act as formidable hindrances for aspiring female medical students who dare to pursue surgery as their professional calling. Together, we can create an environment where female medical students are emboldened to pursue surgery without the burden of undue obstacles and discrimination, leading to a more inclusive and diverse surgical workforce that thrives on excellence.

Changing trends in surgical fields

We have come a long way from a time when women such as Dr. Miranda Stewart impersonated men to practice medicine and surgery. Multiple female surgical residents have suggested that trends are changing, and the historical disparity is slowly declining. This claim can be supported by a recent study that revealed a ratio of 1.3:1 male-to-female attending plastic and reconstructive surgeons' compared to 4.8:1 in 2019.7 In Pakistan, the increase in female progression in surgical programs has been credited initially to their drive towards surgery and then to a more conducive work environment. A study by Cochrane et al.8 found that in the U.S., the proportion of women in general surgery residency programs increased from 17.3% in 2000 to 41.1% in 2020.

While women now constitute nearly half of medical school graduates in many countries, their representation in some surgical fields still lags. A 2023 study showed minimal representation of women in the surgical faculty at Pakistani medical colleges at only 10.3%.9 A globally it is seen that despite increasing female enrollment in general surgery, gender disparities persist in highly specialized fields such as cardiothoracic, neurosurgery, and orthopedic surgery. Women now make up approximately 40–45% of general surgery trainees in developed countries. However, despite progress, women represent only 5–10% of practicing orthopedic and cardiothoracic surgeons, indicating significant gaps in these high-intensity fields.[10]

All of the literature suggests that the issue is deeper than a linear curve. Over the last two decades, discrimination has taken on a subtler form but is still certainly present.

Figure 1: Women Shaping the Surgical Field: A Medical Student's Experience Assisting in Coronary Artery Bypass Grafting. Yumna Shariff (MBBS), Medical Student

Conclusion

Gender disparity is a deep-rooted problem in Pakistan's healthcare system, especially in surgical fields, and aspirants like

ourselves believe that we need to address this issue through awareness and education to shift the mindsets of patients, colleagues, and female medical students who give up their dreams due to fear of discrimination. Introduction of mentorship programs, zero-tolerance policies towards microaggression, and harassment, anti-discrimination policies, and gender equity initiatives in medical education could lead ways to decrease the gender-gap in surgical specialties.

References

1. Association of American Medical Colleges (AAMC). (n.d.). Where are all the women in surgery? https://www.aamc.org/news/where-are-all-women-surgery
2. Pakistan Council for Science and Technology (PCST). Women in higher education and academia in Pakistan. https://www.pcst.org.pk/wst/wst_whea.php
3. Iqbal Y, Khan W, Mooghal M. Impediment to Leadership Opportunities for Female Doctors–Gender Disparity in Pakistani Healthcare System–SHORT REPORT. Adv Med Educ Pract. 2022;213–5.
4. Janjua MB, Inam H, Martins RS, Zahid N, Sattar AK, Khan SM, et al. Gender discrimination against female surgeons: a cross-sectional study in a lower-middle-income country. Ann Med Surg. 2020;57:157–62.
5. Seemann NM, Webster F, Holden HA, Carol-anne EM, Baxter N, Desjardins C, Cil T. Women in academic surgery: why is the playing field still not level?. The American Journal of Surgery. 2016 Feb 1;211(2):343-9.
6. Mavedatnia D, Ardestani S, Zahabi S, Neocleous P, Madou E, Dzioba A, et al. The Experiences of Motherhood in Female Surgeons: A Scoping Review. Ann Surg. 2023;277(2):214–22.
7. Wood DE. How can men be good allies for women in surgery?# HeForShe. J Thorac Dis. 2021;13(1):492.
8. Cochran A, Hauschild T, Elder WB. Gender equity in surgery is much more than numbers. MedPage Today; 2022. Available from: https://www.medpagetoday.com/opinion/second-opinions/99566
9. Rauf H, Martins RS, Arif HE, Ahmed A, Nawaz A, Malik MA. Sex-based Disparities Among Surgical Faculty Positions Across Medical Colleges in Pakistan. World J Surg. 2023 Apr 1;47(4):870–6.
10. Association of Women Surgeons. Gender disparities in surgical subspecialties: a CMS data analysis [Internet]. Chicago, IL: AWS; 2022.

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Experience

Integrating Health and Education: A Medical Student's Teaching Experience in a Government School

Annem Haritha.[1]

The Experience

In today's dynamic world, the concept of social responsibility has become deeply rooted in communities. One powerful way this impact is felt is through education. This story reflects my journey as a part-time teacher in a government school, in collaboration with Teach For Change - an NGO that is dedicated to addressing disparities in education.

My commitment to social responsibility in education has shaped my professional aspirations. While I was motivated to make a positive difference, the challenge was finding the right platform to channel my passion. This journey as a part-time government school teacher, began with a chance encounter on Instagram, where an advertisement conveyed a powerful message about closing educational gaps in government schools and helping underserved communities. I strongly believe teaching offers hands-on experience that complements my medical education by giving me invaluable insights into the socio-economic factors that impact both health and education. A study conducted in Spiti valley, India on integrating health education into the curricula showed that the community valued the curricula content and it also considered health literacy as a mediator in maternal and infant health outcomes.[1]

Thus, drawn by the compelling message and deeply believing in the transformative power of education, I eagerly signed up, hoping to contribute to a brighter future for the students and communities I would soon serve. What began as a spontaneous decision evolved into a fulfilling chapter of my life - one that allowed me to make a genuine difference.

Balancing the intense demands of medical school with the responsibilities of a part-time teaching role in a government school required careful planning, commitment and dedication. In medical studies, where learning is intense and time-consuming, finding a balance became a crucial part of my journey. A mixture of excitement and nervousness accompanied me as I stepped into the classroom for the first time. Standing before a group of young learners, I felt the weight of the responsibility to positively influence their development, which motivated me to design a learning experience that was both inspiring and engaging.The challenge lay in building rapport with the students and capturing their attention. To overcome this, I focused on creating a supportive and interactive environment which kept them actively involved in the lessons. As I continue my journey as a teacher in a government school, I have found deep fulfillment in expanding educational initiatives beyond the traditional classroom. Recognizing the transformative power of extracurricular activities, with initiative from Teach for Change, I have organized art and music competitions for the children. ***Figure 1*** illustrates children enthusiastically displaying their artistic talents.

Over time, having observed the common patterns of illness and behavioral practices of my students, I gradually stepped into my role as a healthcare provider alongside my duties as their teacher. Integrating health and education serves as a strong tool to improve health literacy. Public health pioneer Lemuel Shattuck wrote that " every child should be taught early in life, that to preserve his own life and his own health and the lives of others, is one of the most important and abiding duties".[2] Recognizing that young minds are quick to learn and share knowledge with their peers and families, I saw an ideal opportunity to introduce essential health practices. To effectively integrate health education into their existing curriculum, I collaborated with my colleagues and gained their support. After obtaining the necessary institutional approvals, I organized focused sessions on hand hygiene education. Teaching students handwashing techniques and the importance of personal hygiene not only supports their immediate well-being but also instills lifelong habits that help prevent the spread of diseases.

Building on my initial efforts, my enthusiasm for enhancing the students' health and lifestyle practices grew stronger each day. With volunteer support, including from my mother, I organized a health study aimed at benefiting the children titled **"***Study on nutritional status, prevalence of vitamin deficiencies and morbidity pattern among school children in Mandal Parishad Primary School, Miyapur, Hyderabad.",* after obtaining appropriate consent from the headmaster of the school and guardians of the study subjects. This cross-sectional study was

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subsequently published, marking a significant milestone in our efforts to improve student well-being. A total of 100 children in the age group of 9-12 years were studied by a convenient sampling method, using a pre-tested questionnaire and thorough clinical examination was done. Chi-square test was used to analyze the statistical significance. The study significantly showed that 34% of them were suffering from anemia out of which 21% of them were girls. 60% of the students had a healthy BMI while 35% were underweight, 4% were at a risk of developing overweight, 1% were overweight.[3] Other morbidities including parasitic and worm infestations were also studied.

Reviewing the results of the study, I felt a strong desire to apply my medical knowledge to improve the children's health. At this point social and preventive medicine took center stage, leading me to implement health education and preventive measures to improve their well-being. Providing foundational education on health, nutrition, basic sanitation, and hygiene became the first step in this journey. With the children's enthusiasm for learning, I was able to make learning engaging and effective by encouraging them to grow their own food. The next milestone involved collaborating with the school principal to inspect the school's surroundings, kitchen, and ration storage room for hygiene standards and take corrective actions wherever needed. Additionally, I highlighted the importance of regular health camps and hygiene inspections to ensure a safe, healthy environment for the students. Literature review showed that 80% of all cases of heart diseases, strokes, type 2 diabetes and one third of all cancers can be prevented through health education with schools being the ideal setting of action.[4] Thus by providing children and parents with proper nutrition and knowledge of healthy practices, one can enhance their physical and mental well-being, boost academic performance, and improve their quality of life.

Being both a teacher and a healthcare provider for my students was deeply rewarding, enabling me to integrate theoretical knowledge with practical application while pursuing my passion for education. By encouraging creativity, teaching essential life skills, and promoting health and hygiene, I strive to create an educational environment that extends far beyond textbooks, empowering students to lead healthier lives. Although balancing medical training with my extensive school activities was often exhausting, the gratitude and appreciation my students showed on my final day were immeasurable. I left the school with satisfaction and confidence that I had made a positive difference and grown into a more responsible and compassionate individual.

Conclusion

This experience has taught me invaluable lessons in time management, task prioritization, and resource optimization. As a medical student, I gained insight into the practical challenges faced in implementing preventive care and the strategies needed to overcome them. As a future physician, it deepened my understanding of the critical role preventive medicine plays beyond curative approaches in hospital settings. To enhance impact, collaboration between educators and health care professionals is recommended to design practical and age appropriate and culturally acceptable health programs. Also, including community based health education projects in medical training further enhances understanding of social and preventive medicine. In conclusion, including preventive health education in both school and medical training curricula is crucial to advance public health goals.

Figure 1. Extracurricular Activities for the Children.

Summary – Accelerating Translation

This experience highlights my dual role as a medical student and a part-time teacher in a government school through the NGO Teach For Change — a journey that began with a chance encounter on Instagram. One of the initial challenges was balancing the demands of medical school with my teaching responsibilities, as well as building rapport with the students. I overcame these by following a structured schedule and using interactive teaching methods to keep students engaged.

While teaching, I began noticing common health issues among the children, which inspired me to include health education in my lessons. With appropriate permissions and support, I first conducted a hand hygiene session and later organized a health study involving 100 students aged 9–12. We assessed their nutritional status and common illnesses using simple questionnaires and physical check-ups. The study revealed that 34% of the children had anemia, with a higher proportion among girls. While 60% had a healthy BMI, 35% were underweight, and a few were at risk of becoming overweight and 1% were overweight. Other morbidities including parasitic and worm infestations were also studied. In response, I held sessions on hygiene, nutrition, and basic sanitation, encouraged home gardening, and helped inspect the school kitchen and surroundings for cleanliness.

This experience benefited the students and taught me valuable life skills like communication, leadership, and the real-world importance of preventive medicine. It also reinforced the idea that schools are ideal settings for health education. Including such initiatives in school and medical curricula can promote healthier communities and shape socially responsible future healthcare professionals.

References

1. Cheung B, Browne S, Shih K, Smith B, Smith M, Raff D, et al. Integration of health education into a school curriculum in rural India: an evaluation of challenges faced. Ann Glob Health. 2016;82(3):375–396.
2. Auld, M. E., Allen, M. P., Hampton, C., Montes, J. H., Sherry, C., Mickalide, A. D., et al. (2020). Health literacy and health education in schools: Collaboration for action. NAM Perspectives, 2020(Jul 20).
3. Haritha A, Harikrishna. Study on nutritional status, prevalence of vitamin deficiencies and morbidity pattern among school children in Mandal Parishad Primary School, Miyapur, Hyderabad. Indian J Basic Appl Med Res. 2024;13(2):4–12.
4. Pulimeno, M., Piscitelli, P., Colazzo, S., Colao, A., Miani, A., Miraglia Del Giudice, E., et al. (2020). School as ideal setting to promote health and wellbeing among young people. Health Promotion Perspectives, 10(4), 316–324.

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Conflict of Interest Statement & Funding

Appropriate consent was obtained for the use and display of photographs. Verbal consent was secured from study participants and guardians of the participants for organizing the health study and institutional consent obtained. The data collected was non-invasive, non-identifiable and posed minimal risk to the participants.The guardians were fully informed that the data collected would be used solely for educational and research purposes. Financing: None

Author Contributions

Conceptualization: AH. Data Curation: AH. Formal Analysis: AH. Investigation: AH. Methodology: AH. Project Administration: AH. Resources: AH. Visualization: AH. Writing - Original Draft: AH. Writing - Review Editing: AH.

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