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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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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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Scientific Conferences for Medical Students: Why do We Need more Spaces for Students to Enhance Research?

Amy Phelan,¹ Prakash Gupta,² Mihnea-Alexandru Găman,³ Juan C. Puyana,⁴ Francisco J. Bonilla-Escobar.⁵

The central role that clinical and translational research contributes to the advancement of medical treatment and enhancement of patient care places sustained research interests at the forefront of many physicians continued professional development.¹ Consequently, many medical students endeavour to begin their research careers in congruence with their studies at medical school. Early and active engagement in research can develop scientific writing technique, enhance skill such as data analysis, and provide mentorship opportunities, often fostering a life-long specialist research interest in medical students. Despite this, many barriers to involvement, publication and dissemination of medical student-led research remain, hindering access and participation.²

A previous editorial spoke to the barriers to conducting research at a student level and the consequences of such including lack of funding opportunities, lack of well-established research programmes, and a lack of mentorship available. In addition, the editorial posed many practical solutions to issues raised, such as the creation of dedicated platforms for medical students to share research activities such as symposiums, poster sessions and conferences.³ Furthermore, it is established in the literature that both certifications of participation and awards at conferences prove to be motivating factors for student participation and engagement in research. Thus, increased assurance to obtain such opportunities, in the form of student research-specific conferences, may act as an incentive.⁴

There are few research conferences dedicated entirely to medical student research. Prior to the inception of such events, some of which are listed in [Table 1](#), the only methods of research dissemination for medical students were speciality-specific national and international conferences, where medical students had to compete against highly qualified physician scientists, with illustrious careers in their specific field, for exposure of their work at such conferences. The disparity in research experience between

the two cohorts often leaves medical student research side-lined and shut out of such events.⁵

Academic conferences are essential to the growth of new scholars as medical students. Attending these events, according to research, is a learning process in which participants increase their knowledge, study skills, networking abilities, and professional connections.⁶⁻⁸ Particularly doctoral students utilize seminars to acquire new information.⁹ The process of socialization during conference attendance consists of four stages: introduction to new rules and roles, increased focus on tasks and comprehension of career objectives, growing confidence, and finally internalization of their roles as researchers, leading to the formation of a professional identity.¹⁰

Scientists usually rely on the published papers of their peers to gather knowledge; however, publishing delays frequently render this information outdated or obsolete. To keep current, researchers rely on "not yet published" knowledge and informal contacts, particularly during conferences.¹¹ These conferences allow for the exchange of not only scientific knowledge but also social issues, career news, and other topics.^{12,13} Unofficial encounters at conferences provide valuable resources to attendees' social networks. People benefit from partnerships that supply nonredundant knowledge, according to social network theory. The possibility of obtaining such data is contingent on scientists bridging gaps in diverse networks. Redundancy is caused by strong links within the same group or structural equivalence with similar contacts. The diversity of conference attendees influences the potential of collecting nonredundant information. International conferences draw a wider spectrum of groups than smaller, more homogeneous national conferences, increasing the chance of such access.^{14,15}

Researchers can benefit both personally and collectively from attending conferences. Personal growth, like a conference-

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inspired, single-authored work, is an example of an individual effect. Collective effects are the result of interactions between multiple people, which can lead to both formal and informal networks of cooperation and friendship. These sweeping impacts are consistent with the sociological idea of communal outcomes coming from people's individual choices. Researchers attend conferences to network and advance their careers, especially when jobs, funding, and connections are on the line.¹⁶⁻¹⁸ Collective effects happen because of the social interactions that these contacts create. These interactions can then lead to the creation of structures, organizations, and research partnerships. Lack of effective communication and strong ties, on the other hand, can hinder collaboration and the overall productivity of conferences. This is because conferences offer a social setting that is not usually found in academia. Because of this, conferences are likely to have effects on both individuals and groups.^{19,20}

A decline in the number of physicians actively participating in research has been widely reported in the literature, leading to many postulating the increased role of medical student research, including student-led research conferences, as a solution to safeguarding the future of academic medicine.²¹ It has been documented those students that are involved in, and published research as medical students are three times more likely to continue to publish after graduation when compared to their counterparts that did not participate in research while studying.²² With this in mind, it is evident that medical student-specific research conferences can, and will, play a vital role in ensuring the continued prosperity of the role of the physician scientist and academic medicine as a whole.

The success of the International Journal of Medical Students (IJMS) publications and subsequent research conference serves to highlight the vital role of student-led research and the need for increased avenues for its dissemination. It is evident that there is both a need and an appetite for an increase in opportunity for medical student-specific research conferences. Initiatives, such as the World Conference of Medical Student Research (WCMSR), have begun to dismantle barriers to these opportunities. An increase in both quantity and frequency of such events will continue to close the gap between medical students and access to such opportunities.

On 7th October 2023, the IJMS will host the 2023 WCMSR, a virtual research conference which will provide a platform for medical students and recent medical graduates (up to three-years post-graduation) to disseminate their own research on an international stage. This is the second such conference of its kind, following the success of the first WCMSR on 12th November 2022. The first conference featured 40 abstracts, including original research articles and case reports, from 30 different countries across the globe.²³ The audience can participate voting for their favorite presentation and raise their questions, opinions, and comments to improve discussions and create potential collaborations. The conference will be transmitted live on

YouTube® and you can register, attend or review it here: <https://www.youtube.com/watch?v=LqO3DfVdVxg>.

This issue of the IJMS underscores the vitality of medical student-led research through a range of articles. This includes four original articles, one short communication, two case reports, two reviews, one letter to the editor, two editorials and two experiences.

The IJMS had the honor of featuring another editorial written by editors of leading scientific journals from around the globe, putting their voice together to call for action on humanity issues. The fourth of its kind to feature in our journal, this article discusses the role of healthcare workers in reducing the risk of nuclear war, citing the International Physicians for the Prevention of Nuclear War, conceived in the 1980s, as a starting point for actionable change on such an issue by physicians.²⁴ This follows previous editorials by the group that addressed other humanitarian issues, namely climate change and its impact on health. They highlight the need to limit global temperatures and restore biodiversity and implored urgent change following the COP27 Climate Change Conference.²⁵⁻²⁷

In their short communication, Lin et al., explored potential lifestyle risk factors for burnout during medical school. Reporting that over half of medical students experience burnout, the study found lack of sleep and poor support system as dominant risk factors. Furthermore, it revealed that medical students suffering from burnout reported poorer mental health and reduced life satisfaction. In the context of medical student research as an extra-curricular commitment, this article highlights a need to ensure that appropriate resources are available to for medical students taking on additional research commitments to prevent burnout and facilitate sustained research participation while at medical school.²⁸

One case report featured in this edition focused on a rare neurological condition, Moersch-Woltman Syndrome and the establishment of anti-GAD antibodies to aid in its diagnosis.²⁹ In the second case report, Wilcox et al., describe the usefulness of early point of care ultrasound training in medical school in a student-run free clinic. The case reported in the article strongly supports their arguments for enhanced point of care ultrasound teaching to be incorporated in medical school curriculums.³⁰

One review in this edition presents a systematic review of pseudo-chilblains in confirmed cases of COVID-19.³¹ The second focuses on medical students' perspective of the operating theatre as a place of learning, exploring negative and demotivating experiences that discourage medical students from operating room attendance. In contrast, it shows that positive surgical experience serves as a motivating factor for a future surgical career. It could be postulated that a similar experience in medical student research could have the same impact on future research careers, emphasizing the importance of positive research involvement during medical school to ensure continued participation in research once a practicing physician.³²

Table 1. Medical Student Research Conferences.

Conference name	Organization	Location	Website
World Conference of Medical Student Research, WCMSR	International Journal of Medical Students	USA (global)	https://ijms.info/IJMS/Conference/welcome
Young European Scientist, YES Meeting*	Young European Scientist	Porto, Portugal	https://yesmeeting.org
Annual International Medical Students Meeting, AIMS*	University of Lisbon, Faculty of Medicine	Lisbon, Portugal	https://www.aimsmeeting.org
Colombian Student Congress of Medical Research, CECIM*	ASCEMCOL	Colombia	https://www.ascemcol.org
Congresso Médico-Academico Do Piauí, COMAPI *	Medical-Academic College, Federal University of Piauí,	Piauí, Brazil	www.comapi.org
International Student Medical Congress in Košice, ISMCK*	Association of Medical Students in Kosice - Spolok medikov mesta Košice (SMMK)	Kosice, Slovakia	www.ismck.com
National Medical Students' Conference, CNEM*	University Miguel Hernández	Spain	https://www.cnemcongress.com
International Medical Students' Research Congress, IMSRC*	Phramongkutklo College of Medicine (PCM)	Bangkok, Thailand	https://researchculturesociety.org/imsrc-2022
International Congress For Medical Students and Young Health Professionals, Medicalis*	Medicalis	Cluj-Napoc, Romania	www.medicalis.ro
International Student Psychiatry Conference Katowice, ISCP *	Students' Scientific Association at the Department of Psychiatry and Psychotherapy of Medical University of Silesia in Katowice	Katowice, Poland	-
International Medical-Academic Congress of Maranhao, COIMAMA	University Ceuma (UNICEUMA)	Maranhão, Brazil	www.coimama.com.br
Warsaw International Medical Congress for Young Scientists, WIMC*	Medical University of Warsaw	Warsaw, Poland	https://wimc.wum.edu.pl
Malaysian Medics International, MMI (MMSS)*	MAHSA University, Malaysia	Malaysia	www.malaysianmedics.org
Ainshams International Medical Student Congress, AIMSC*	AinShams University	Cairo, Egypt	www.aimscegypt.org
Student Research Unit Zazazig University, SRUZU*	Zazazig University	Zazazig, Egypt	-
International Medical Students Congress Sarajevo, SaMED*	Association of Students of the Medical Faculty in Sarajevo (ASMF Sarajevo), Bosnian and Herzegovinian Medical Students' Association (BoHeMSA), International Student Surgical Network (InciSioN BiH)	Sarajevo, Bosnia and Herzegovina	http://ojs.samed.ba
Brazilian International Congress of Medical Students, BRAINSCOMS*	Federal University of São Paulo, Brazil	São Paulo, Brazil	http://www.braincoms.com/2018/
Uzbekistan IFMSA*	Tashkent Medical Academy	Uzbekistan	www.tma.uz
International Congress of Medical Sciences, ICMS*	Association of Medical Students in Bulgaria	Sofia, Bulgaria	https://amsb-varna.com/en/
Yorkshire Imaging and Interventional Radiology Symposium International, YiiRs*	University of Leeds	Leeds, United Kingdom	-
Congresso Médico Universitário De Mogi Das Cruzes, COMUMC	University of Mogi das Cruzes	Mogi das Cruzes, Brazil	https://www.even3.com.br/comumc42/
Students Against SARS-CoV-2*	Students Against COVID	International	-
American Physician Scientist Association, APSA Pitt	University of Pittsburgh	USA	https://www.physicianscientists.org/events/EventDetails.aspx?id=1552860&group=
International Medical Students' Congress of Bucharest	Carol Davila University of Medicine and Pharmacy	Bucharest, Romania	https://imscbucharest.com

Lagos State University Medical Students Association Research Conference	Lagos State University	Nigeria	-
ISCI Annual Conference	International Society for Chronic Illnesses, ISCI*	International	https://www.isci.info/
Bangladesh International Medical Students' Scientific Congress, BIMSSCON	Bangladesh International Medical Students	Bangladesh	www.bimsscon.org
Atlantic Corridor Medical Student Research Conference	Atlantic Corridor	Cork, Ireland	https://www.ucc.ie/en/medical/research/atlanticcorsidor/
Student Neurosurgical and Neurological Research Conference, SNRC	Brown Neurosurgery	Rhode Island, USA	https://brownneurosurgery.com/education/aans-student-chapter/
International Conference for Healthcare and Medical Students, ICHAMS	Royal College of Surgeons	Dublin, Ireland	https://www.ichams.org
UQ Medical Student Research Conference	UQ Medical Student Research Conference	Queensland, Australia	https://medical-school.uq.edu.au/event/session/20597
Medical Student Orthopedic Society Research Conference, MSOS	Medical Student Orthopedic Society	Virtual	https://www.msosortho.com
Eastern-Atlantic Student Research Forum, ESRF	Eastern-Atlantic Student Research Forum	Miami, USA	https://med.miami.edu/research/esrf
Pediatric Research Forum for Medical Students	Florida Chapter of the American Academy of Pediatrics annual meeting	Florida, USA	https://research.pediatrics.med.ufl.edu/new-s-events/pediatric-medical-student-research-forum/
PODER Research Symposium	Latino Medical Student Association	Philadelphia, USA	https://national.lmsa.net/programming/nc2022/

Legend: *Abstract book(s) published by the International Journal of Medical Students (IJMS)

One of the experiences examines the impact of an electronic system at a student-run free clinic on maximizing efficiency of patient assistance program applications. This article further underscores the value that medical student-led programs can have in a clinical setting, as discussed in Wilcox et al.,’s case report.³³ The second experience explored bias among medical teams as experienced by Asian medical students in the United States and call for actions to tackle bias in the medical field.³⁴

In their letter to the editor, Zolo emphasized the role of medical students and surgical trainees in the advancement of global surgical research in low- and middle-income countries, once again supporting several points made both in this editorial and through other articles featured in this edition of the journal.³⁵

In their original research article, Thibaut et al., explore the opposing role of HLA-DQB1*0301 in bullous pemphigoid and pemphigus vulgaris through a meta-analysis.³⁶ Khuluf et al., report findings regarding the hepatotoxic effects of Doxorubicin on female rats.³⁷ Wei Wei Kong et al., describe a cross-sectional study looking at student perspectives on e-learning a year into the COVID-19 pandemic that forces most educational activities online. They report a negative impact on performance satisfaction and a perceived reduction in practical skills in medical students in Malaysia.³⁸ Finally, Osei-Hunor and Vorona’s article provides insight into the role and impact of dyslexia awareness workshops in medical school curriculum. They suggest that such workshops enhance medical student knowledge on the condition and provide students with the confidence to support peers with dyslexia.³⁹

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Reducing the Risks of Nuclear War—the Role of Health Professionals

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Introduction

In January, 2023, the Science and Security Board of the Bulletin of the Atomic Scientists moved the hands of the Doomsday Clock forward to 90 seconds before midnight, reflecting the growing risk of nuclear war.¹ In August, 2022, the UN Secretary-General António Guterres warned that the world is now in “a time of nuclear danger not seen since the height of the Cold War.”² The danger has been underlined by growing tensions between many nuclear armed states.^{1,3} As editors of health and medical journals worldwide, we call on health professionals to alert the public and our leaders to this major danger to public health and the essential life support systems of the planet—and urge action to prevent it.

Current nuclear arms control and non-proliferation efforts are inadequate to protect the world’s population against the threat of nuclear war by design, error, or miscalculation. The Treaty on the Non-Proliferation of Nuclear Weapons (NPT) commits each of the 190 participating nations “to pursue negotiations in good faith on effective measures relating to cessation of the nuclear arms race at an early date and to nuclear disarmament, and on a treaty on general and complete disarmament under strict and effective international control.”⁴ Progress has been disappointingly slow and the most recent NPT review conference in 2022 ended without an agreed statement.⁵ There are many examples of near disasters that have exposed the risks of depending on nuclear deterrence for the indefinite future.⁶ Modernization of nuclear arsenals could increase risks: for example, hypersonic missiles decrease the time available to distinguish between an attack and a false alarm, increasing the likelihood of rapid escalation.

Any use of nuclear weapons would be catastrophic for humanity. Even a “limited” nuclear war involving only 250 of the 13 000

nuclear weapons in the world could kill 120 million people outright and cause global climate disruption leading to a nuclear famine, putting 2 billion people at risk.^{7,8} A large-scale nuclear war between the USA and Russia could kill 200 million people or more in the near term, and potentially cause a global “nuclear winter” that could kill 5–6 billion people, threatening the survival of humanity.^{7,8} Once a nuclear weapon is detonated, escalation to all-out nuclear war could occur rapidly. The prevention of any use of nuclear weapons is therefore an urgent public health priority and fundamental steps must also be taken to address the root cause of the problem—by abolishing nuclear weapons.

The health community has had a crucial role in efforts to reduce the risk of nuclear war and must continue to do so in the future.⁹ In the 1980s the efforts of health professionals, led by the International Physicians for the Prevention of Nuclear War (IPPNW), helped to end the Cold War arms race by educating policy makers and the public on both sides of the Iron Curtain about the medical consequences of nuclear war. This was recognised when the 1985 Nobel Peace Prize was awarded to the IPPNW. (<http://www.ippnw.org>).¹⁰

In 2007, the IPPNW launched the International Campaign to Abolish Nuclear Weapons, which grew into a global civil society campaign with hundreds of partner organizations. A pathway to nuclear abolition was created with the adoption of the Treaty on the Prohibition of Nuclear Weapons in 2017, for which the International Campaign to Abolish Nuclear Weapons was awarded the 2017 Nobel Peace Prize. International medical organizations, including the International Committee of the Red Cross, the IPPNW, the World Medical Association, the World Federation of Public Health Associations, and the International Council of Nurses, had key roles in the process leading up to the

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negotiations, and in the negotiations themselves, presenting the scientific evidence about the catastrophic health and environmental consequences of nuclear weapons and nuclear war. They continued this important collaboration during the First Meeting of the States Parties to the Treaty on the Prohibition of Nuclear Weapons, which currently has 92 signatories, including 68 member states.¹¹

We now call on health professional associations to inform their members worldwide about the threat to human survival and to join with the IPPNW to support efforts to reduce the near-term risks of nuclear war, including 3 immediate steps on the part of nuclear-armed states and their allies: first, adopt a no first use policy;¹² second, take their nuclear weapons off hair-trigger alert; and, third, urge all states involved in current conflicts to pledge publicly and unequivocally that they will not use nuclear weapons in these conflicts. We further ask them to work for a definitive end

to the nuclear threat by supporting the urgent commencement of negotiations among the nuclear-armed states for a verifiable, timebound agreement to eliminate their nuclear weapons in accordance with commitments in the NPT, opening the way for all nations to join the Treaty on the Prohibition of Nuclear Weapons.

The danger is great and growing. The nuclear armed states must eliminate their nuclear arsenals before they eliminate us. The health community played a decisive part during the Cold War and more recently in the development of the Treaty on the Prohibition of Nuclear Weapons. We must take up this challenge again as an urgent priority, working with renewed energy to reduce the risks of nuclear war and to eliminate nuclear weapons.

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Journal Disclaimer

This Editorial is being published simultaneously in multiple journals. For the full list of journals see <https://www.bmj.com/content/full-list-authors-and-signatories-nuclear-risk-editorial-august-2023>.

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Student Perspectives on E-Learning in a Malaysian Medical College One Year into the COVID-19 Pandemic: A Cross-Sectional Study

Sylvia Wei Wei Kong,¹ Jade Lene Yong,² Sabrina Pei Yee Cheong,³ Edmund Liang Chai Ong.⁴

Abstract

Background: During the coronavirus disease 2019 (COVID-19) pandemic, most in-person classes in Newcastle University Medicine Malaysia (NUMed) were replaced with e-learning. Our study aims to explore students' e-learning experiences and its perceived benefits and challenges during the pandemic. **Methods:** 285 students recruited via convenience sampling participated in this cross-sectional study. Participants completed a self-administered online questionnaire on sociodemographic factors and experiences with e-learning. Descriptive statistics and Spearman's correlation tests were used to analyze the data. **Results:** Most students used laptops (n=275, 96.5%) for e-learning and owned at least two electronic devices (n=245, 86%). Over half our students (n=148, 51.9%) reported no change to theoretical knowledge, while about three-quarters (n=213, 74.7%) perceived practical skills to have worsened. Students preferred paper-based exams (n=170, 59.6%) and objectively formatted online exams (n=193, 67.7%). Since transitioning to e-learning, the majority of students (n=207, 72.6%) reported difficulties studying online and were unsatisfied with their academic performance (n=166, 58.2%). Students preferred e-learning due to the lower risk of contracting COVID-19 (n=256, 89.8%), the convenience of online classes (n=244, 85.6%) and flexible schedules (n=219, 76.8%). However, the lack of patient contact (n=236, 82.8%), lecturer and peer interaction (n=234, 82.1%), and unreliable internet (n=201, 70.5%) made e-learning challenging. Students' experiences were generally affected by multiple factors encompassing personal, lecturer, and environmental aspects. **Conclusion:** E-learning during the COVID-19 pandemic has negatively impacted students' practical skills and performance satisfaction. Therefore, the university should look towards addressing e-learning constraints and providing adequate support to improve students' educational experiences in the ongoing pandemic.

Introduction

When Malaysia's Movement Control Order (MCO) was announced in March 2020 as a measure to combat the spread of the coronavirus disease 2019 (COVID-19) pandemic, Newcastle University Medicine Malaysia (NUMed) immediately suspended in-person classes and adopted an online approach for teaching. The complete switch to e-learning was implemented across all teaching programmes in the institution, using a variety of platforms.

E-learning has been widely used as a digital web-based educational approach which aims to enhance students' learning through an interactive, personalized, and enjoyable learner-centred environment.¹ Despite being conducted in a completely different setting from traditional in-person education, studies have shown that e-learning can be as effective as classroom teaching.^{2,3} Current research has shown that e-learning is generally welcomed by students due to its flexibility and convenience, although many aspects make its implementation

challenging.^{2,4,5} For healthcare students, there is the added difficulty of replicating patient interaction and patient care in an online setting.^{6,7} These are crucial elements of training medical students' clinical skills, which form a core requirement of their education in terms of assessments, and will inevitably shape their careers as future healthcare workers.

With strict lockdowns and physical distancing measures in place, limited in-person sessions on campus, and disrupted hospital attachments in the last one and a half academic years, most of the teaching in NUMed is still being delivered online. As such, there is concern over the effectiveness and satisfaction with e-learning amongst our students, and how this affects their overall academic performance. Hence, this study aims to explore students' perceptions on the impact, benefits, and challenges of e-learning during the COVID-19 pandemic.

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Methods

Study Design and Participants

We conducted a cross-sectional study, using a convenience sampling technique via a self-administered online survey. The survey (attached as [Supplementary Material](#)) was designed with Google Forms and distributed via an embedded link in an invitation email to all students registered with NUMed for the 2020/2021 academic year. This comprised of students on the following programmes: Bachelor of Medicine, Bachelor of Surgery (MBBS) (Year 1 to 5), Biomedical Science (BMS) (Year 1 & 2), and Foundation in Biological and Biomedical Sciences course. The data was collected between July 12th, 2021 and August 12th, 2021 of which the link was accessible to students for submission of their responses during this period.

The questionnaire consisted of sections on sociodemographic factors and students' experiences with e-learning. This included items where students were asked to report their technology use, e-learning exposure, and perceptions of their experiences over the last academic year (2020/2021). These questionnaires were adapted and modified based on surveys used in previous empirical studies on university students' experiences with online learning during the COVID-19 pandemic.⁷⁻⁹ All the students who were studying at NUMed campus in the academic year 2020/2021 were eligible to participate as they were the first batch of students who have completed a full year of study with the e-learning adjustments undertaken by the university since the pandemic was first declared. Students who were taking a year off or had undergone an intercalation programme in another campus were not invited to the study. A total of 285 students responded to the questionnaire, amounting to a response rate of 40% of overall student population of 725 students.

Before dissemination, the survey was pretested with a sample of students, to ensure clarity in interpretation of the questionnaire.

Data Analysis

In this study, the data were analyzed using IBM SPSS Statistics Version 27, primarily through use of descriptive statistics for frequencies and percentages. Spearman's correlation test was used to identify correlation between students' e-learning experiences, the effects of e-learning, and academic performance. These variables were measured on a 5-point Likert scale from "1 = Strongly Disagree" through to "5 = Strongly Agree" and "1 = Never" to "5 = Always". A p-value of <0.05 was considered statistically significant.

Ethics

Ethical approval was granted by the NUMed Research Ethics Committee and the Newcastle Institutional Review Board (Ref: 13518/2020). Informed consent was gained from the students prior to their participation in this survey, and all responses collected were anonymized to maintain individual confidentiality.

Results

Our findings showed that from the total of 285 NUMed students who participated in the study, 81 (28.4%) were males and 204 (71.6%) females. The median age of the students was 22 ± 2 years. Most of the participants (n=239, 83.9%) were medical students, with two-thirds of the students being Malaysian (n=229, 66.7%). At the time of the survey, two-thirds of the students (n=190, 66.7%) were living in their hometowns, and the majority (n=258, 90.5%) were staying with family or friends. A total of 171 students (60%) had received at least one dose of the COVID-19 vaccine at the time of the survey.

The most popular electronic devices used for e-learning were laptops (n=275, 96.5%) More than half the students utilized tablets (n=159, 55.8%) and most students owned two or more electronic devices (n=245, 86%). A total of 263 respondents (92.2%) perceived their Information Technology (IT) proficiency level as good to proficient. For internet access, the majority of students (n=272, 95.4%) reported predominant use of broadband with 214 participants (96.1%) describing the quality of their internet service as ranging from acceptable to excellent ([Table 1](#)).

Table 1. NUMed Students' Technology Use in the 2020/2021 Academic Year (n=285).

Variables	Frequency (%)
Use of electronic devices	
Laptop	275 (96.5)
Smartphone	205 (71.9)
Tablet	159 (55.8)
Desktop	14 (4.9)
Number of electronic devices owned	
1	40 (14)
2	127 (44.6)
3	113 (39.6)
4	5 (1.8)
Perceived IT proficiency level	
Proficient	97 (34)
Very good	83 (29.1)
Good	83 (29.1)
Acceptable	22 (7.7)
Internet type	
Broadband	272 (95.4)
Mobile data	12 (4.2)
No personal internet access	1 (0.4)
Quality of internet service	
Excellent	25 (8.8)
Very good	82 (28.8)
Good	97 (34)
Acceptable	70 (24.6)
Bad	11 (3.9)

Legend: IT- Information technology

[Table 2](#) showed that almost two-thirds of students (n=188, 66%) had no prior experience with e-learning before the COVID-19 pandemic. Since transitioning to e-learning, almost three-quarters of students (n=207, 72.6%) reported difficulties studying online which include unreliable internet, technical problems, lack

of self-discipline, poor learning environment, etc (Table 3). As a result of e-learning, students generally perceived that their practical skills have worsened, whilst their theoretical knowledge remains unchanged. (Figure 1). Alongside these, more than half (n=166, 58.2%) of the students reported feeling unsatisfied with their overall academic performance after switching to e-learning. Most students still preferred paper-based exams (n=170, 59.6%) to online-based exams and two-thirds of the students preferred objectively formatted online exams (n=193, 67.7%) over a subjective format.

Table 2. NUMed Students' Academic Experiences with E-Learning in the 2020/2021 Academic Year (n=285).

Variables	n (%)
E-learning before COVID-19 pandemic	
Yes	97 (34.0)
No	188 (66.0)
Difficulties studying online	
Yes	207 (72.6)
No	78 (27.4)
Satisfaction with academic performance	
Satisfied	119 (41.8)
Not satisfied	166 (58.2)
Exam preferences	
<i>Type of exam preferences</i>	
Online based	60 (21.1)
Paper based	170 (59.6)
No preference	55 (19.3)
<i>Online exam preferences</i>	
Objective	193 (67.7)
Subjective	19 (6.7)
Both	73 (25.6)

Table 3. NUMed Students' Perceptions of E-Learning Benefits and Constraints in the 2020/2021 Academic Year (n = 285).

Variables	n (%)
Benefits of e-learning	
Lower risk of contracting COVID-19	256 (89.8)
Convenience	244 (85.6)
Flexible schedules	219 (76.8)
Access to online materials	193 (67.7)
Comfortable/conducive environment	143 (50.2)
Better focus	51 (17.9)
Improved communication	24 (8.4)
Constraints of e-learning	
Lack of patient interaction	236 (82.8)
Reduced interaction with lecturers/peers	234 (82.1)
Unreliable internet	201 (70.5)
Technical problems	195 (68.4)
Lack of self-discipline	191 (67.0)
Social isolation	190 (66.7)
Poor learning environment	142 (49.8)

The lower risk of contracting COVID-19 (n=256, 89.8%), the convenience of attending classes from home (n=244, 85.6%) and the flexible schedules (n=219, 76.8%) are benefits of e-learning during the pandemic that students have chosen (Table 4). The

majority of students also found the access to online materials (n=193, 67.7%) and the comfortable or conducive study environment (n=143, 50.2%) to be beneficial as well. Conversely, the most common constraints of e-learning according to students were the lack of patient interaction (n=236, 82.8%), as well as reduced interactions with lecturers and peers (n=234, 82.1%). Technological factors such as unreliable internet (n=201, 70.5%) and technical problems i.e., incompatible devices, power outage, etc. (n=195, 68.4%), in addition to personal factors like lack of self-discipline (n=191, 67%) and social isolation (n=190, 66.7%) were also reported by most students.

Multiple factors which were related to our students' e-learning experience are presented in Table 4. From the analysis using Spearman's correlation test, our study shows that students were facing difficulties with studying online and were unsatisfied with their academic performances due to various challenges faced during the COVID-19 pandemic. These included issues such as the inability to adjust to e-learning, feeling incapable of studying subjects online, as well as the lack of motivation and technical skills. Students who had difficulties studying online reported problems in terms of experiences with lecturers also. Particularly, this was when communication was poor, leading to a lack of clear direction from the lecturers ($r=-0.331$, $p<0.001$), when resources or skills for online teaching were lacking amongst them ($r=0.273$, $p<0.001$), and when they were not technology-friendly ($r=-0.137$, $p<0.021$). The results show that frequent fluctuations in lecture timings ($r=-0.238$, $p<0.000$) affected these students as well. Conversely, environmental factors such as non-conducive learning environments, technical issues, unreliable internet or power disruptions, lack of infrastructure, and resources to support online teaching also have an impact on online learning and academic performance satisfaction.

Figure 1. NUMed Students' Perceptions of Changes to Academic Performance after Transition to E-Learning during Academic Year 2020/2021.

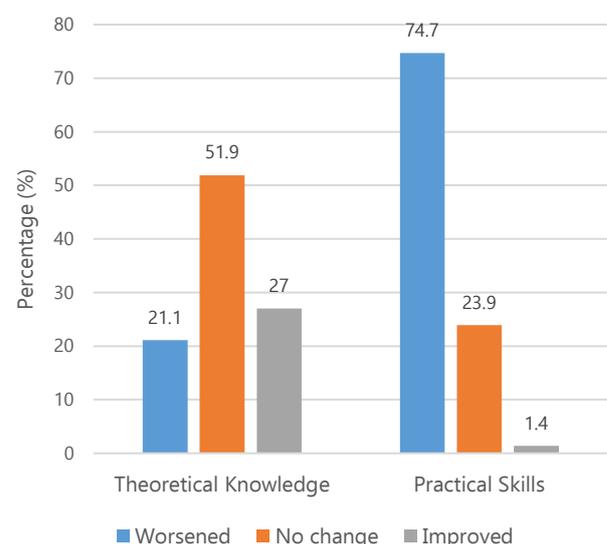


Table 4. Spearman Correlation Analysis: Student, Lecturer and Environmental Factors related to the E-Learning Experience (Difficulties Studying Online and Academic Performance) by NUMed Student during Academic Year 2020/2021.

	Difficulties studying online		Academic performance satisfaction	
	Correlation coefficient, r	p-value	Correlation coefficient, r	p-value
Student factors				
Inability to adjust to e-learning style	-0.314	<0.001*	0.288	<0.001*
Incapable of studying subjects online	0.409	<0.001*	-0.353	<.001*
Lack of motivation in online classes	-0.342	<0.000*	0.267	<0.000*
Lack of technical skills	-0.185	0.002*	0.136	0.022*
Academic grades negatively affected by the COVID-19 pandemic	-0.376	<0.000*	0.562	<0.000*
Lecturer factors				
Poor communication or lack of clear direction from lecturers	-0.331	<0.001*	0.196	0.001*
Lecturers' lack of resources or skills to teach courses online	0.273	<0.001*	-0.246	<0.001*
Lecturers not technology friendly in online teaching	-0.137	0.021*	0.340	0.568
Fluctuations in lecture timings	-0.238	<0.000*	0.057	0.340
Environmental factors				
Unconducive learning environment	-0.220	<0.001*	0.176	0.003*
Technical difficulties in online teaching	-0.259	<0.000*	0.087	0.142
Unreliable internet or power disruption	-0.263	<0.001*	0.150	0.011*
Lack of infrastructure and resources to support online teaching	0.269	<0.001*	-0.242	<0.001*

Discussion

In this study, we explored students' perceptions of e-learning during the COVID-19 pandemic. Across the world, the sudden and rapid shift of education from in-person teaching to an online setting has been met with mixed responses; varying degrees of students' acceptance of and adaptation to e-learning have been reported over the last two years.^{2,10,11} Previous studies have been undertaken addressing various issues amongst medical students during the pandemic, but there have been no detailed studies in

the Asia Pacific region.¹²⁻¹⁵ Our study included medical students across all years (Year 1 to 5) in Bachelor of Medicine, Bachelor of Surgery (MBBS), Biomedical Science (BMS) and Foundation programme, being the first study of its kind in the Asia Pacific region.

Despite almost three-quarters of our participants facing difficulties studying online and more than half feeling unsatisfied with their academic performance since switching to e-learning, interestingly, about half the students did not perceive any changes in their theoretical performance. Conversely, three-quarters of students reported their practical skills to have deteriorated. The perceived worsening in practical performance is worrying, although not unexpected due to the traditional hands-on training of medical and biomedical science students in the clinical and laboratory settings, respectively. According to Keržič et al., students' experiences and satisfaction with e-learning are main factors which contribute to perceive academic performance.¹⁶ Other studies amongst healthcare students have shown similar unchanged or negative trends in academic performance with the suspension of in-person teaching as well.^{7,17,18}

With the unprecedented shift to distance-learning in the COVID-19 pandemic, educational institutions have been forced to improvise on the delivery of assessments as well. The data we collected from our students shows that paper-based exams were still preferred over online-based exams. The possible reasons for this could be explained by results from a systematic review by Montenegro-Rueda et al. which summarized some of the challenges to online examinations, including e-proctoring or online invigilation of students; dishonest student behaviour with cheating and plagiarism; lack of training and technological issues, i.e. internet or power outage, privacy issues, etc.¹⁹ However, if exams were to be conducted online, about two-thirds of our students preferred them to be structured in an objective format over a subjective exam. Our study reported similar results with a study by Muthuprasad et al. amongst Indian graduates who preferred objective mode of examination.²⁰

According to our participants, the most popular chosen benefits of the transition to e-learning in this pandemic were being at a lower risk of contracting COVID-19, followed by the convenience of attending classes from home and the flexible schedules. This concurs with a study by Dhawan et al. on Strengths, Weaknesses, Opportunities and Challenges analysis of e-learning which reported that the "Anywhere-Anytime" flexibility in time and location is thought to be one of its main strengths.²¹ This is also in line with the findings from Muthuprasad et al. that preference for online education was due to the flexibility and convenience of its nature.²⁰

Our data has also shown that the main downside of the virtual setting is the lack of human connection, where the vast majority of students perceived their e-learning experiences to be lacking in interactions with patients, as well as with lecturers and peers. Besides this, issues like unreliable internet and technical problems

were widely perceived as limitations amongst our students. Additionally, Dhawan's work proposed weaknesses in the online learning approach to education, including lack of communication with others and technical difficulties.²¹ With previous research in Malaysia showing technological difficulties to be a barrier to e-learning amongst university students,²² moving forward, this should be an important consideration when planning for a transition of education to an online setting in the future.

Our results reflected that students who faced difficulties studying online also tended to report problems with their experiences with lecturers. Thus, we infer that educators play an important role in improving a student's transition to e-learning. Research conducted amongst other healthcare students in Jordan and Iran have shown similar opinions amongst their students,^{23, 24} where lecturers' readiness to engage in online learning and the effectiveness of their communication skills are thought to greatly influence the students' e-learning experiences. Hence, as proposed by Turnbull et al., there is a need to provide better training for university staff, allowing a higher level of online competence to be achieved,²⁵ and in turn, better outcomes for students.

Limitations & Recommendations

The limitations of this study include its cross-sectional design, resulting in only a brief snapshot of the respondents' perceptions towards e-learning. The study results are also limited in their broader interpretation as this is a single-centre study. Furthermore, data collection via a self-reported questionnaire, which was conducted during the students' summer breaks, likely could have led to reporting and recall biases. We also acknowledge that there may have been some element of selection bias in the recruitment of participants since this process was done on a voluntary basis through an email invitation disseminated to all students in NUMed. Thus, students interested in our research topic might have been more likely to respond to this study.

Understanding that our study population was relatively small at a total number of 285, and that students' perceptions of e-learning are subjective, diverse and can evolve over time, we believe that more research into this topic would be beneficial as the use of e-learning continues. While universities endeavour to improve their delivery of teaching with and beyond the 'new normal' of the COVID-19 pandemic, longitudinal research and qualitative studies on students' perceptions of e-learning over time could deepen general understanding on this topic for future use in education.

Conclusion

Overall, e-learning during the COVID-19 pandemic has impacted students negatively in terms of academics, particularly practical skills, and performance satisfaction. Nevertheless, students do perceive benefits of e-learning to include its convenience, flexibility, and safety, especially with the lower risk of contracting COVID-19. Constraints were predominantly focused on the lack of interactions, technological difficulties and personal factors. Generally, difficulties studying online and academic performance satisfaction are affected by personal, lecturer and environmental factors. With the likely incorporation of e-learning into educational systems, the university should strongly consider addressing students' concerns and providing academic support where appropriate to ensure the high quality of the student experience in the online setting as we continue to navigate this pandemic.

Summary – Accelerating Translation

Title: Student Perspectives on E-Learning in a Malaysian Medical College One Year into the COVID-19 Pandemic: A Cross-Sectional Study

Main Problems to Solve: The COVID-19 pandemic has affected students' education in Malaysia whereby in-person classes had to be converted into online learning. E-learning is a novel tool in the education, however, its effectiveness in replicating in-person classes still lacks evidence.

Aim of Study: This study would like to look at students' e-learning experiences and its perceived benefits and challenges during the pandemic. The outcomes might help future students learn more effectively online and rely less on traditional classroom sessions. Additionally, it will better equip the university to handle unforeseen situation such as the COVID-19 in the future.

Methodology: This study was conducted as a cross-sectional, self-administered online survey using a convenience sampling technique. The study included all students studying in NUMed in the academic year 2020/2021. The survey consists of sections on sociodemographic factors, students experience with e-learning which included items on technology use, e-learning exposure, and perceptions of their experiences over the last academic year.

Results: Overall, students find that their practical skills have been heavily affected due to the switch to online learning. The majority of students have contributed this to lack of interaction with patients, peers, and lecturers. However, students have also benefited from online learning as it gives students flexibility and convenience in learning whilst reducing the risk of contracting COVID-19.

Conclusions: This study has demonstrated that online education has both positives and negatives effects on students across the medical science programmes during the pandemic. Therefore, the institution should strive to address the drawbacks to enhance the overall educational experience.

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Author Contributions

Conceptualization: SWWK, ELCO. Supervision: ELCO. Data Curation, Investigation, Methodology, Project Administration, Resources, Software, Validation, Visualization, Writing – Review & Editing: SWWK, JLY, SPYC, ELCO. Writing – Original Draft Preparation, Formal Analysis: SWWK, JLY, SPYC.

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Supplementary Material

The impact of e-learning among students in Newcastle University Medicine Malaysia (NUMed) during COVID-19 pandemic: one year onwards

INFORMED CONSENT FORM

Dear Participant,

Thank you for taking part in this study which aims to understand the effects of online learning during the COVID-19 pandemic in NUMed. The information gathered through this survey will help to facilitate the integration of e-learning into the curriculum to improve the delivery of quality medical education in the future. Participation is open to all NUMed students. The questionnaire takes approximately 5 minutes to complete. You will not be asked to provide any personal data. Your data will remain completely anonymous, and it will not be possible to identify you individually from your answers. This study has received approval from the NUMed Research Ethics Review Committee. By taking part, you are agreeing that you have read and understood the information above about the study.

By ticking the box, you are agreeing that you have read the information about the study, and that you voluntarily agree to take part in it.

[] I agree to participate in this study.

SECTION A: DEMOGRAPHIC BACKGROUND

- Age: _____
- Gender: Male Female
- Ethnicity:
 Malay Chinese Indian Other, please specify: _____
- Programme and year of study in Academic Year 2020/2021:
 MBBS Year 1 MBBS Year 2 MBBS Year 3 MBBS Year 4
 MBBS Year 5 BMS Year 1 BMS Year 2
 Foundation Programme
- Nationality:
 Malaysian International, please specify: _____
- Where are you currently?
 Hometown
 University residences
 Rental room/house
 Friend's house
 Relative's house
 Others, please specify: _____
- Who are you living with currently?
 Alone
 With family/relatives
 With friends/coursemates

Others, please specify: _____

8. Do you suffer from any underlying medical illness? Check all that apply.

Physical health problems, please specify: _____

Psychological problems, please specify: _____

Physical or learning disability, please specify: _____

No

9. Are you vaccinated?

Completed 2 doses

Yes, first dose

Secured an appointment, waiting for vaccination

Registered, but no appointment yet

Considering but not registered yet

Considering to get vaccinated overseas

Not considering, please specify the reason: _____

SECTION B: E-LEARNING

B1. Experience with e-learning

B1.1 Which of the following devices do you own and utilize for your learning? Check all that apply.

Smartphone

Tablet or iPad

Personal laptop

Desktop computer

Others, please specify: _____

B1.2 What is your level of proficiency in using various electronic devices? (e.g. Computers, smartphones, tablet, etc)

Proficient

Very good

Good

Acceptable

Inadequate

B1.3 What type of internet service do you use primarily?

Broadband (Wi-Fi, LAN cable)

Mobile data

I don't have internet access and have to go elsewhere

Others, please specify: _____

B1.4 How would you describe your internet service?

Excellent

Very good

Good

Acceptable

Bad

B1.5 Have you ever participated in any type of e-learning before the pandemic?

- Yes
- No

B1.6 Do you face any difficulties studying online?

- Yes
- No

B1.7 How has your academic performance changed since you switched to e-learning?

B1.7.1 Theoretical knowledge

- Better
- No change
- Worse

B1.7.2 Practical skills

- Better
- No change
- Worse

B1.8 Are you satisfied with your overall academic performance?

- Yes
- No

B1.9 Which type of exam do you prefer?

- Online based
- Paper based
- No preference

B1.10 Which type of online exam do you prefer?

- Objective (SBA, MCQ, EMQ)
- Subjective (WRISKE, SAP, SAQ)
- Both

B2. Benefits and constraints of e-learning¹

B2.1 What are the benefits of e-learning during the COVID-19 pandemic? Check all that you consider true.

- Access to online materials
- Flexible schedules (e.g. learning at your own pace)
- Convenience (e.g. ability to stay at home, option to request for recording)
- Comfortable/conducive environment
- Better focus with less distractions
- Improved communication/interaction
- Lower risk of contracting COVID-19 infection
- Others, please specify: _____

B2.2 What are the constraints of e-learning during the COVID-19 pandemic? Check all that you consider true.

- Reduced interaction with lecturers/colleagues
- Lack of interactions with patients
- Technical problems
- Unreliable internet connectivity/power interruption
- Poor learning environment at home
- Lack of self-discipline
- Social isolation
- Others, please specify: _____

B4. Challenges to e-learning²

How often have you encountered these problems during this COVID-19 pandemic		Never	Rarely	Sometimes	Often	Always
B4.1	Inability to adjust learning style (include poor time management, lack of discipline)	1	2	3	4	5
B4.2	Lack of technical skills	1	2	3	4	5
B4.3	Poor communication or lack of clear direction from educators	1	2	3	4	5
B4.4	Unreliable internet access or power interruption	1	2	3	4	5
B4.5	Limited physical space for conducive studying	1	2	3	4	5
		Strongly disagree	Disagree	Neutral	Agree	Strongly agree
B4.6	I am physically and mentally capable of studying all the subjects online	1	2	3	4	5
B4.7	The lecturers have the resources and skills necessary to teach our courses online	1	2	3	4	5
B4.8	The university has the infrastructure and resources to support online teaching	1	2	3	4	5

B5. Effect of online teaching³

		Strongly disagree	Disagree	Neutral	Agree	Strongly agree
B5.1	The COVID-19 pandemic affected my academic grades negatively	1	2	3	4	5
B5.2	Fluctuations in lecture timings are one of the downsides of online teaching	1	2	3	4	5
B5.3	The students lack motivation in online teaching	1	2	3	4	5
B5.4	Lecturers not being technology-friendly are one of main issues in online teaching	1	2	3	4	5
B5.5	Recorded lectures are better than live lectures as it enables the student to set their own learning time	1	2	3	4	5
B5.6	Technical issues (e.g. poor Wi-Fi connection, incompatible devices) makes online teaching difficult	1	2	3	4	5

Stereological Estimation and Zonal Distribution of the Hepatotoxic Effects of Doxorubicin on the Female Albino Rat (*Rattus Norvegicus*)

Khulud Nurani,¹ Anne Pulei,² Beda Olabu,³ Jeremiah Munguti,⁴ Talha Chaudhry,¹ Vincent Kipkorir.⁵

Abstract

Background: Doxorubicin is an anti-neoplastic agent widely indicated for a variety of cancers. One of its adverse effects is hepatotoxicity which presents with hepatocyte necrosis, sinusoidal dilation, and fibrosis. However, there remains a dearth in the quantification and zonal distribution of this damage. **Methods:** Twenty-three adult female Wister albino rats were placed into baseline, control, and experimental group receiving 2.5mg/kg bodyweight Doxorubicin intra-peritoneally thrice weekly for 3-weeks. Rats were sacrificed on days 0, 7, 14 and 21 and livers harvested for processing. Masson's Trichrome was used in staining 7 μ m thick sections. Images were taken and analyzed via STEPanizer, and data entered into SPSS for analysis. **Results:** Rats treated with Doxorubicin had increased liver to body weight ratios from 5.00% at baseline to 6.15%, 6.69% and 7.56% on days 7, 14 and 21 ($p=0.090$). There was a decrease in hepatocyte densities from 51.88/mm² to 48.61/mm², 46.65/mm² and 42.24/mm² on day 7, 14 and 21 ($p=0.779$). Collagen fiber deposition increased from 0.12 \pm 0.06 cm³ to 0.47 \pm 0.55 cm³, 1.64 \pm 0.11 cm³ and 1.88 \pm 0.24 cm³ on days 7, 14 and 21 ($p=0.009$). Deposition was greatest periportal and least pericentrally. Volume of sinusoidal spaces increased from 5.46 \pm 0.50 cm³ to 5.49 \pm 0.15 cm³, 5.53 \pm 0.24 cm³ and 5.50 \pm 0.17 cm³ on days 7, 14 and 21 respectively ($p=0.827$). Sinusoids were larger pericentrally than periportal. **Conclusion:** Doxorubicin administration is associated with an increase in volume density of fibrotic tissue and sinusoidal spaces but decrease in hepatocytes. The quantitative changes presented may facilitate histopathological grading of Doxorubicin-induced hepatotoxicity.

Introduction

Doxorubicin is a widely indicated anti-neoplastic agent for a variety of cancers including breast cancer, bladder cancer, thyroid cancer, Kaposi's sarcoma, lymphoma, soft tissue sarcoma, multiple myeloma, and acute lymphocytic leukemia. It is the first line agent for metastatic breast cancer as well as for metastatic and locally advanced un-resectable soft-tissue sarcoma.¹ It is administered intravenously in dosage regimens specific to the cancer type and progression.² With regards to its mechanism of action, Doxorubicin generates free radicals during its metabolism in the liver. These free radicals disrupt normal cellular physiology and subsequently may cause toxicity in multiple organs mainly in the heart, kidneys, and liver.³ Previous studies on Doxorubicin-induced hepatotoxicity have been descriptive and remain short of stereological and zonal data.^{4,5}

Stereology is a growingly applied quantitative method used for the estimation of 3D parameters.⁶ Because 2D profiles do not adequately depict object sizes and quantities, they are prone to inaccuracies when used in morphometric research.⁷ As a result,

significant mistakes might be made when interpreting quantitative data from 2D profiles. Stereology provides a solution to this by providing strong mathematical methods to eliminate bias and thus accurately make 3D estimations provided sampling, randomization, and isotropy are streamlined.⁸ Additionally, quantitative data that can show tiny variations in the volume or number of chosen parameters can be obtained using stereological procedures.⁷ This is of high significance in analysis of liver biopsies which continue to be the gold standard for classifying liver damage.⁹ Consequently, efforts have been made over the past few years to precisely quantify necrotic, fibrotic,¹⁰ steatotic¹¹ and cancerous tissue,¹² both in clinical and experimental studies.¹³ This study, therefore, sought to estimate and zonally determine the distribution of the toxic effects of Doxorubicin on the hepatic stroma and parenchyma of the female Albino rat over a 3-week period of Doxorubicin administration.

Methods

The study was of quasi-experimental design where female albino rats were used. These were obtained from the Department of

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Zoology and were kept and studied at the Department of Zoology Animal House. The harvested specimens were processed at the Department of Human Anatomy. These rodents were the preferred animal models for research due to their genetic, physiological, and anatomical similarity to humans, ease of maintenance, short life cycle and their small size.¹⁴

Sample size calculation was done using the formula by Charan & Biswas, 2013¹⁵ using a statistical significance of 0.05, a power of 80%, a smallest meaningful difference of 1.4% and the standard deviation of 0.87% for mean liver fibrosis derived from a study by Yi et al, 2012.¹⁶ A total of 23 rats were used of which two were baseline, six were controls and fifteen experimental.

Ethical approval for the study was sought from the Faculty of Veterinary Medicine (*Reference Number: FVM BAUEC/2021/286*). The study was conducted, and the animals were handled according to the guidelines provided by the committee.

Adult female albino rats of three months of age were used in the study upon selection by convenience sampling technique. Doxorubicin's commonest indication is for breast cancer, and breast cancer is more common in females than males, thus female rats were used to account for the protective effects of estrogen on the liver.¹⁷ Rats with any visible pathology or abdominal injuries were excluded. The sampling technique involved randomly assigning all the rats a number between 1 and 23 using non-repeating numbers generated by Intel® Digital Random Number Generator Software. The rats were labelled using picric acid on their fur and random selection applied to split them into 3 groups, where group A was the baseline group, Group B was the control group that was administered normal saline intra-peritoneally while group C was the experimental group that was administered Doxorubicin intra-peritoneally (IP). The rats were housed in standard cages floored with wooden shavings which were replaced every two days. The cages were placed in a room with a normal 12-hour light/dark diurnal cycle. The rats were kept in their cages for 3 days for acclimatization after which intervention was begun. They were provided with standard rat pellets and water ad libitum during the study period. No additional intervention was given to reduce chemotherapy-induced distress.

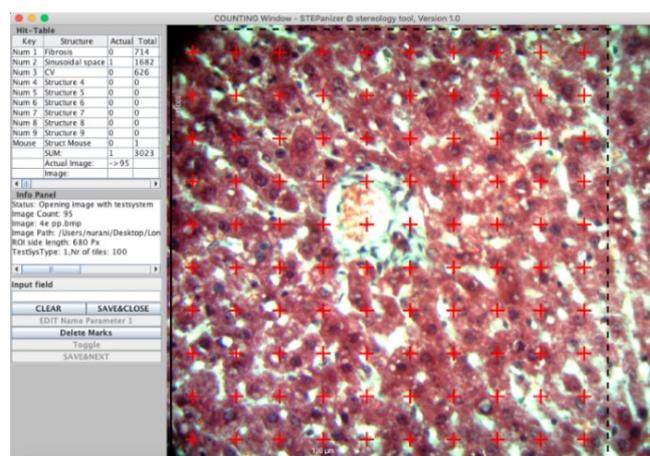
Each rat in the experimental group received 2.5 mg/kg body weight of Doxorubicin intra-peritoneally thrice weekly for three weeks (at an interval of 48 hours) to correspond with the intravenous route and timeline of administration of Doxorubicin in humans without posing toxicity to the rats. Animals in the control group received zero point five milliliters of normal saline intra-peritoneally thrice weekly as a sham. IP injections were done using a 31-gauge needle to prevent iatrogenic injury.

Tissue harvesting was done after weighing the rats using an electric measuring scale and euthanizing them by placing them in sealed containers with 1% halothane (1-3%) soaked in cotton

wool. Death was confirmed by the absence ocular reflexes. Then a longitudinal incision in the midline of the body was made and normal saline used to flush out all the blood. Thereafter, 10% formal saline was infused by the trans-cardiac method to start tissue fixation. The liver was harvested from each rat, absolute volumes calculated using Scherle's method and stored in formal saline. Systematic uniform random sampling method was used to get the liver segments. The liver was sliced across the lobes into 16 equal parts. The parts were rearranged into a diamond shape with smaller pieces arranged on either side of the largest piece of liver.⁹ Following this, the 2nd piece was selected and thereafter every 3rd piece. A total of 5 pieces per liver were picked for histological processing.

The liver pieces obtained were placed in specimen bottles containing 10% formalin for at least 24 hours to preserve the tissues. Following fixation, they were dehydrated in ascending concentrations of alcohol, then cleared in toluene then infiltrated with paraffin wax. The embedded tissues were blocked for sectioning. They were cut into 7 μ m thick sections. Every fourth section of the ribbon was selected and floated in a warm water bath to enhance spreading. The sections were fished from the water bath onto a gelatinized glass slide. They were dried at 38°C for 24 hours, then de-waxed, re-hydrated and stained using Masson's Trichrome.

Figure 1. STEPanizer Grid for Estimation of Volume Densities.



Out of the 10 stained sections, 5 even sections were chosen for histomorphometric analysis. Photomicrographs were taken at x400 magnification using a Richter Optica™ digital photomicroscope (Model UX1) connected to Motic Images Plus 3.0 for stereological analysis. Three images were taken per slide—one of the periportal region, one of the midzonal region and one of the pericentral region. The photomicrographs were analyzed using STEPanizer Stereology Tool Version 1.0. The estimation of volume densities and hepatocyte densities was done using Cavalieri's principle of point counting.⁸ The histological regions were analyzed using a superimposed 100-point grid over the photomicrographs (*Figure 1*). The volume densities of the histological components were calculated and averaged to reduce

bias. Absolute volumes were then calculated by multiplying the volume densities with the liver volumes.

Data obtained were keyed into the Statistical Package for Social Sciences software (version 28.0) for statistical analysis. Hepatocytes were expressed in numbers/mm² and fibrotic tissue and sinusoidal spaces were expressed as absolute volumes. The data were grouped into three groups: A, B and C. The Shapiro-Wilk test and a visual examination of the histograms and box plots produced from the data were used to determine whether the data were normal. Although the Shapiro Wilk test indicated a normal distribution, the histograms displayed skewed distributions. Thus, non-parametric tests were employed. Kruskal Wallis test was employed to check for statistically significant differences over time in both the control and experimental groups over the study period. A Dunn Bonferroni post-hoc test was carried out. Mann Whitney U tests were carried out to assess for significant differences between the control and experimental group on each of the perfusion days. A p value of 0.05 or lower was regarded as significant. Photomicrographs were used to demonstrate the histological findings.

Results

General health of Study Animals

Following Doxorubicin administration, the study animals developed diarrhea, roughness in their fur coat, mucosal inflammation and tremors. They exhibited hypoactivity and reduced food intake. No discernible gross changes in livers of the experimental rats were noted when compared to the control and the baseline groups.

Liver to Body Weight Ratio (LBWR)

The liver to body weight ratios of the control animals increased slightly over time ($p=0.180$) with those of the experimental animals increasing more rapidly ($p=0.090$). The difference in LBWR between controls and experimental groups was statistically significant ($p=0.029$).

Collagen fiber density

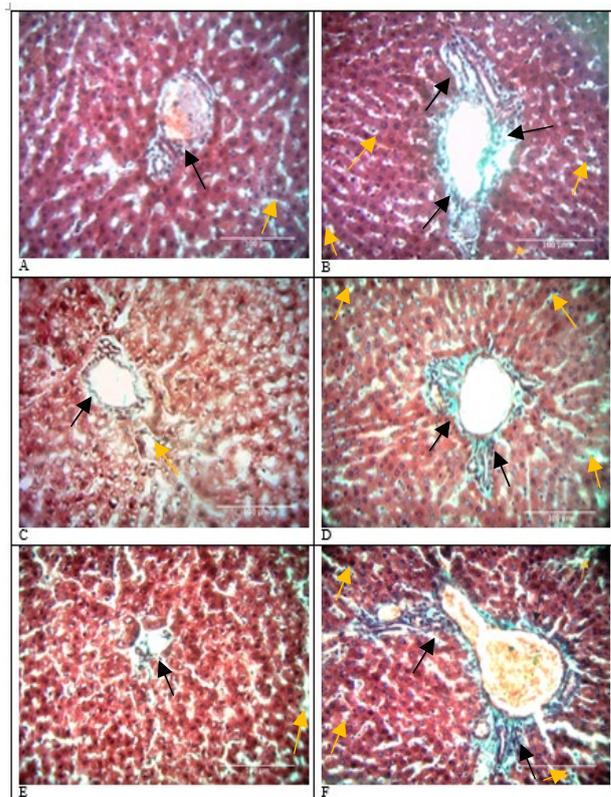
Doxorubicin administration resulted in deposition of collagen fibers in the periportal areas as well as within perisinusoidal spaces that increased with time ($p=0.009$). This is illustrated in [Figures 2](#) and [3](#) below. Bridging fibrosis also developed and was most defined on day 21. In contrast, the stroma of the control group hardly had any differences in collagen fiber volumes from baseline tissues. The experiment and control groups thus, had statistically significant differences in collagen fiber volumes ($p<0.001$). [Table 1](#) displays the means, standard deviations, medians, interquartile ranges and p values of the control and experimental groups over time.

Sinusoidal space density

Doxorubicin administration resulted in an increase in volumes of sinusoidal spaces over time ($p=0.827$). This is illustrated in [Figure 4](#) below. Sinusoids in the pericentral area were larger than those

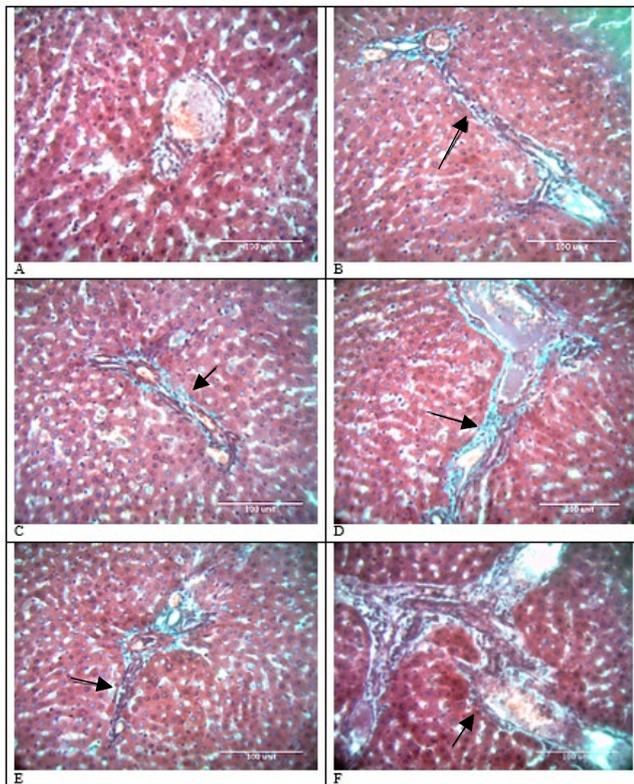
in periportal areas. In contrast, sinusoids in control tissue did not have distinct differences in sinusoidal densities from baseline tissue ($p=1.000$). The experimental and controls groups did not have statistically significant differences in sinusoidal volumes ($p=0.667$). [Table 2](#) displays the means, standard deviations, medians, interquartile ranges and p values of the control and experimental groups over time.

Figure 2. Collagen Fiber Profile in Rat Livers.



Legend: Figure 2A-F: Collagen Fiber Profile in the Rat Livers. Stain: Masson's Trichrome, Magnification: X 400. Figure 2A: Photomicrograph of the liver of a control rat on day 7 of the study. There are a few collagen fibers (yellow arrows) interspersed between the hepatocytes in the perisinusoidal spaces. The black arrows point at collagen fibers around the portal triad. Figure 2B: Photomicrograph of the liver of a rat treated with Doxorubicin on day 7 of the study. There are a few collagen fibers (yellow arrows) interspersed between the hepatocytes in the perisinusoidal spaces. The black arrows point at collagen fibers around the portal triad. Figure 2C: Photomicrograph of the liver of a control rat on day 14 of the study. There are a few collagen fibers (yellow arrows) interspersed between the hepatocytes in the perisinusoidal spaces. The black arrows point at collagen fibers around the portal triad. Figure 2D: Photomicrograph of the liver of a rat treated with Doxorubicin on day 14 of the study. There are collagen fibers (yellow arrows) interspersed between the hepatocytes in the perisinusoidal spaces. The black arrows point at collagen fibers around the portal triad. Figure 2E: Photomicrograph of the liver of a control rat on day 21 of the study. There are a few collagen fibers (yellow arrows) interspersed between the hepatocytes in the perisinusoidal spaces. The black arrows point at collagen fibers around the portal triad. Figure 2F: Photomicrograph of the liver of a rat treated with Doxorubicin on day 21 of the study. There are more collagen fibers (yellow arrows) interspersed between the hepatocytes in the perisinusoidal spaces. The black arrows point at collagen fibers around the portal triad.

Figure 3. Comparison of Bridging Fibrosis in Control and Experimental Rat Livers.



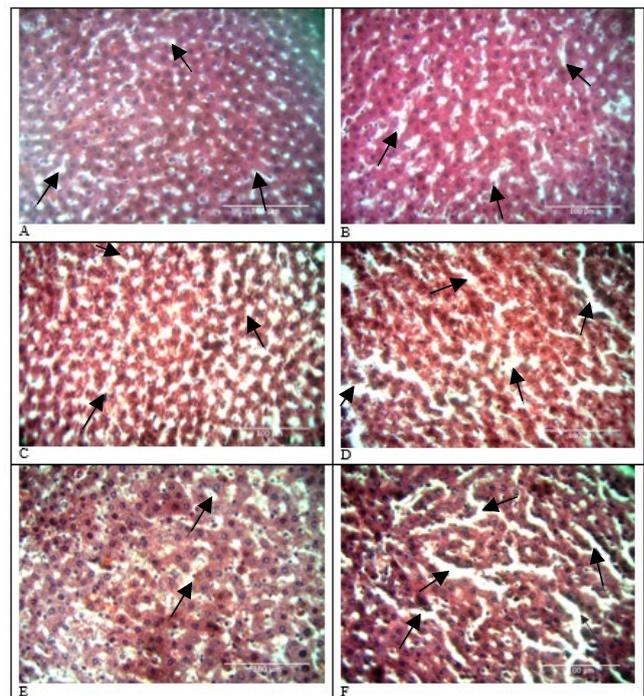
Legend: Figure 3A-F: Bridging Fibrosis in the Rat Livers. Stain: Masson's Trichrome, Magnification: X 400. Figure 3A: Photomicrograph of the liver of a control rat treated on day 7 of the study. There was no bridging fibrosis. Only some collagen fibers were present around the portal triad. Figure 3B: Photomicrograph of the liver of a rat treated with Doxorubicin on day 7 of the study demonstrating setting in of bridging fibrosis (black arrows). Figure 3C: Photomicrograph of the liver of a control rat on day 14 of the study demonstrating some bridging fibrosis (black arrows). Figure 3D: Photomicrograph of the liver of a rat treated with Doxorubicin on day 14 of the study demonstrating some bridging fibrosis (black arrows). Figure 3E: Photomicrograph of the liver of a control rat on day 21 of the study demonstrating some bridging fibrosis (black arrows). Figure 3F: Photomicrograph of the liver of a rat treated with Doxorubicin on day 21 of the study demonstrating the most extensive bridging fibrosis (black arrows).

Table 1. Volume of Fibrotic Tissue at Different Time Periods.

Day	Group	Volume of Fibrosis (cm ³)	
		Mean ± SD	Median (IQR)
0	Baseline	0.12 ± 0.08	0.12
7	Control	0.14 ± 0.03	0.14
	Experimental	0.47 ± 0.12	0.45 (0.36-0.59)
14	Control	0.13 ± 0.06	0.13
	Experimental	1.64 ± 0.24	1.54 (1.50-1.83)
21	Control	0.17 ± 0.11	0.17
	Experimental	1.88 ± 0.55	1.97 (1.37-2.35)

Legend: Sd, Standard deviation. IQR, Interquartile range.

Figure 4. Comparison of Sinusoidal Spaces in Control and Experimental Rat Livers.



Legend: Figure 4A-F: Sinusoidal Spaces in the Rat Livers. Stain: Masson's Trichrome, Magnification: X 400. Figure 4A: Photomicrograph of the liver of a control rat on day 7 of the study. The relatively small sinusoidal spaces are illustrated with black arrows. Figure 4B: Photomicrograph of the liver of a rat treated with Doxorubicin on day 7 of the study. There are relatively larger sinusoidal spaces (Black arrows). Figure 4C: Photomicrograph of the liver of a control rat on day 14 of the study. Sinusoidal spaces, pointed at by black arrows, are smaller than those in Figure 9D. Figure 4D: Photomicrograph of the liver of a rat treated with Doxorubicin on day 14 of the study. There are larger and more distorted sinusoidal spaces (Black arrows). Figure 4E: Photomicrograph of the liver of a control rat on day 21 of the study. Sinusoidal spaces, pointed at by black arrows, are smaller than those in Figure 9F. Figure 4F: Photomicrograph of the liver of a rat treated with Doxorubicin on day 21 of the study. Sinusoidal spaces, pointed at by black arrows, are the largest and most distorted.

Effects of Doxorubicin on the Hepatic Parenchyma

The control rats displayed normal liver histoarchitecture. However, the experimental rats had distortions in their parenchyma. There was marked degeneration with disruption of the cord-like arrangement of hepatocytes. There was also infiltration of deeply basophilic leukocytes in the periportal area and regions of focal necrosis in the pericentral area. The hepatocytes nearer the central veins were more vacuolated than those in the periportal areas.

Hepatocyte densities declined progressively with minimum numbers recorded in the 3rd week (p=0.779). This is illustrated in [Figure 5](#) below. The periportal areas had a higher concentration of hepatocytes relative to the pericentral areas. On the other hand, hepatocyte densities for the control rats remained similar in number to those in baseline tissue (p=0.867). The differences between control and experimental values were, however, not statistically significant (p=0.178). [Table 3](#) displays the means,

standard deviations, medians, interquartile ranges and p values of the control and experimental groups over time (Table 3).

Table 2. Volume of Sinusoidal Spaces at Different Time Periods.

Day	Group	Sinusoidal Spaces (cm ³)		p-value (vs control) Exact Sig. [2*(1-tailed Sig.)]
		Mean ± SD	Median (IQR)	
0	Baseline	5.46 ± 0.70	5.46	-
	Control	5.14 ± 0.56	5.44	
7	Experimental	5.49 ± 0.34	5.52 (5.15-5.80)	1.000
	Control	5.15 ± 0.21	5.45	
14	Experimental	5.50 ± 0.54	5.67 (5.04-5.95)	0.857
	Control	5.14 ± 0.45	5.44	
21	Experimental	5.50 ± 0.39	5.40 (5.18-5.88)	0.857

Legend: SD, Standard deviation. IQR, Interquartile range.

Figure 5. Change in hepatocyte densities over time.

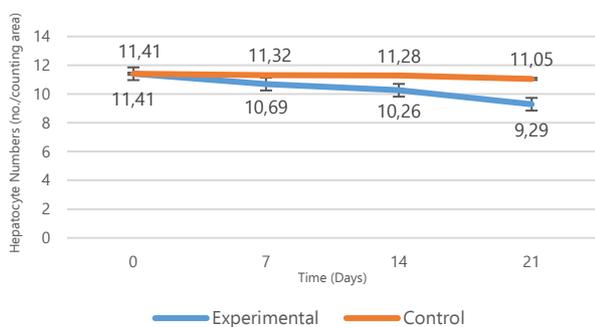


Table 3. Hepatocyte Area Densities at Different Time Periods.

Day	Group	Hepatocyte area densities (no./counting area)		p-value (vs control) Exact Sig. [2*(1-tailed Sig.)]
		Mean ± SD	Median (IQR)	
0	Baseline	11.41 ± 2.24	11.41	-
	Control	11.32 ± 1.09	11.32	
7	Experimental	10.69 ± 1.03	10.56 (9.74-11.71)	0.571
	Control	11.28 ± 0.16	11.27	
14	Experimental	10.26 ± 0.65	10.13 (9.71-10.88)	0.381
	Control	11.05 ± 0.72	11.05	
21	Experimental	9.29 ± 4.43	6.52 (5.85-14.12)	0.857

Discussion

The findings in this study are suggestive of a temporal increase in the deposition of collagen fibers and in sinusoidal dilatation but decrease in hepatocyte densities as discussed below. These structural changes may be helpful in grading of toxicity via liver biopsies, provide clarity on the zonal distribution of structural changes, and pave way for studies to determine strategies to reduce the severity of Doxorubicin induced hepatotoxicity.

General health of Study Animals

The experimental rats in this study developed diarrhea, roughness in their fur coat, mucosal inflammation and tremors. These effects may be due to an inhibition of multiplication of otherwise rapidly proliferating cells of the gastrointestinal tract, skin and bone marrow by Doxorubicin.¹⁸

Liver to Body Weight Ratio

Doxorubicin treatment resulted in an increase in the LBWR compared to that of the control rats. The increase in liver weight observed in this study following Doxorubicin is similar to the findings by Salouge et al., (2014) which found an increase in organ to body weight ratios of the heart, liver, spleen and kidneys following Doxorubicin administration in rats. The increase in liver weights corresponds to augmentative hepatomegaly which is a compensatory regenerative process following hepatocyte necrosis.²⁰ The initial phase of hepatomegaly is hypertrophy of the existing hepatocytes then later hyperplasia if regeneration is still incomplete. In this study, hypertrophy of hepatocytes could explain the increase in LBWR since a reduction in hepatocyte densities precluding regenerative hyperplasia of hepatocytes was observed. Hepatomegaly is a common adverse effect of chemotherapy and may culminate in severe liver injury and even liver failure if not controlled.²¹

Collagen Fiber Density

Doxorubicin administration resulted in an increase in collagen fiber deposition in the perisinusoidal and periportal areas over time. Perisinusoidal fibrosis is postulated as being a result of hepatocyte stellate cell (HSC) activation by the reactive oxygen species (ROS) released during Doxorubicin metabolism. The activated HSC transform into highly proliferative myofibroblast-like cells with a greatly enhanced capacity to synthesize ECM components including type I and III fibrillary collagen, laminins and fibronectin.²² The periportal and bridging fibrosis may be due to the activation of portal fibroblasts to form portal myofibroblasts which are pronounced for their matrix deposition and contractility.²³ Placement of groups of contractile cells in collagen type I matrices leads to compaction and alignment of the collagen between them, creating the appearance of bridging fibrosis. This may explain the realignment of connective tissue fibers seen in bridging fibrosis. Advancing of liver fibrosis may result in nodular regeneration, cirrhosis, and portal hypertension and often requires liver transplantation.²²

Sinusoidal Space Dilatation

Doxorubicin administration resulted in an increase in the sinusoidal space density. Injury to sinusoidal endothelial cells by ROS leads to embolization of endothelial cells and blood cells in sinusoidal spaces. This blocks venous outflow, resulting in hepatic congestion and subsequent sinusoidal dilatation. This is followed by sinusoidal obstruction syndrome characterized by fiber deposition in the sinusoids by activated HSC and obliteration of central venules.²⁴ The result is the loss of fenestrations and development of basement membranes by sinusoidal endothelial

cells in a process of capillarization, forming channels with larger calibers.²⁵ Sinusoidal obstruction syndrome can progress into regenerative nodular hyperplasia or may normalize with time after cessation of chemotherapy.²¹ Sinusoidal obstruction causes congestion, hepatomegaly, fluid retention, jaundice and ascites, and becomes fatal in 20-50% of patients on high dose chemotherapy.²⁶

Effects of Doxorubicin on the Hepatic Parenchyma

Periportal leukocyte infiltration following Doxorubicin administration as observed in this study may be due to an increase in recruitment of immune cells via chemotaxis following hepatocyte injury and death.²⁷ Hepatocyte vacuolation following Doxorubicin administration, as observed in this study, was associated with larger nuclei, and is postulated as being a marker of senescence. It is present in a variety of acute and chronic liver diseases. However, the exact pathophysiology behind the vacuolation is unclear and is suggested as being the result of hydropic change.²⁸ Focal necrosis, in association with lymphocytes, as observed in this study, describes a continuum of lobular injury.²⁹

Decrease in hepatocytes following doxorubicin administration, as observed in this study, may be a result of hepatocyte necrosis and apoptosis. The FR released during Doxorubicin metabolism reacts with hepatocyte lipids, proteins and nuclei acids causing mitochondrial dysfunction and lipid peroxidation which induces apoptosis. Following cell death, regeneration of hepatocytes is also impaired as Doxorubicin inhibits topoisomerase II activity and thus inhibiting cell division.³⁰ The result is a decline in hepatocyte numbers and distortion in the radial organization of cords. Severe hepatocyte apoptosis and necrosis may culminate into liver failure.

Limitations and Delimitations

This study may have had some possible confounders such as inter-animal differences in the absorption and metabolism of Doxorubicin. This was, however, minimized by the use of in-bred rats which are genetically similar. Also, stress due to intraperitoneal injections may have affected the hepatic histoarchitecture. This was standardized by the administration of normal saline intraperitoneal injections in the control group. In addition, tissue shrinkage during tissue processing may have altered the normal parameters. However, errors due to tissue processing were carried through all measurements.

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1. Paridaens R, Biganzoli L, Bruning P, Klijn JGM, Gamucci T, Houston S, et al. Paclitaxel Versus Doxorubicin as First-Line Single-Agent Chemotherapy for Metastatic Breast Cancer: A European Organization for Research and Treatment of Cancer Randomized Study With Cross-Over. *J Clin Oncol.* 2000;18(4):724.

Strengths of the Study

1. The histoarchitecture of the Albino rat liver very closely resembles that of humans.
2. Intermittent dosage forms administered make it analogous to Doxorubicin therapy in humans.
3. Sacrifice at the end of each week enabled establishment of temporal effects.

Conclusion

Doxorubicin administration is associated with an increase in the volume densities of fibrotic tissue and sinusoidal spaces and decrease in hepatocyte densities. The quantitative structural changes further corroborate Doxorubicin-induced hepatotoxicity and may facilitate histopathological diagnosis of hepatotoxicity.

Summary – Accelerating Translation

Title: Stereological Estimation and Zonal Distribution of the Hepatotoxic Effects of Doxorubicin on the Female Albino Rat (*Rattus Norvegicus*)

Main Problem: Doxorubicin is a chemotherapeutic agent widely indicated for a variety of cancers. One of its side effects is liver toxicity which presents with cellular death, vascular dilation, and fibrosis. However, there has remained a dearth in the quantification and zonal distribution of this liver damage.

Aim: To quantify and zonally determine the distribution of the hepatotoxic effects of Doxorubicin on the female Albino rat.

Methodology: Twenty-three adult female Wistar albino rats were placed into 3 groups: baseline, control and experimental. The experimental group received 2.5mg/kg bodyweight of Doxorubicin intra-peritoneally thrice weekly for 3 weeks. The control group received 0.5 ml normal saline intra-peritoneally thrice weekly as a sham. Rats were then sacrificed on days 0, 7, 14 and 21 and their livers harvested for processing and analysis.

Results: Rats treated with Doxorubicin had increased liver to body weight ratios from 5.00% at baseline to 6.15%, 6.69% and 7.56% on days 7, 14 and 21 ($p=0.090$). There was a decrease in hepatocyte densities from 51.88/mm² to 48.61/mm², 46.65/mm² and 42.24/mm² on day 7, 14 and 21 ($p=0.779$). Collagen fiber deposition increased from 0.12±0.06 cm³ to 0.47±0.55 cm³, 1.64±0.11 cm³ and 1.88±0.24 cm³ on days 7, 14 and 21 ($p=0.009$). Deposition was greatest periportal and least pericentrally. Volume of sinusoidal spaces increased from 5.46±0.50 cm³ to 5.49±0.15 cm³, 5.53±0.24 cm³ and 5.50±0.17 cm³ on days 7, 14 and 21 respectively ($p=0.827$). Sinusoids were larger pericentrally than periportal.

Conclusion: Doxorubicin administration is associated with an increase in volume density of fibrotic tissue and sinusoidal spaces but decrease in hepatocyte densities. The quantitative changes presented may facilitate histopathological grading of doxorubicin-induced hepatotoxicity.

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The Role and Impact of Dyslexia Awareness Workshops in the Medical Curriculum

Mitchell Osei-Junior,^{1,2}  Mayya Vorona,^{1,2} 

Abstract

Background: To increase recognition of the number of students who study medicine with dyslexia and the support available, it is important to cultivate a culture in which peers can support fellow peers with dyslexia academically and pastorally. This study aims to understand medical students' perceptions of dyslexia and confidence with supporting fellow peers with dyslexia before and after a workshop on dyslexia. **Method:** Pre-Post Intervention Evaluation form of 36 1st year medical students before the start of a small group dyslexia awareness session and one month after using a standardized 36 True/False/Don't know questionnaire to elicit any significant change in knowledge about dyslexia. A standardized 6-item Likert Scale questionnaire was also administered in the same time frame to measure confidence in supporting peers with dyslexia. **Results:** Pre-dyslexia awareness workshop, the mean score on the knowledge and beliefs about dyslexia questionnaire was 15.22, post-intervention this improved to 24.03 ($p < 0.001$). Additionally, pre-intervention greater than 70% of participants reported feeling not confident in items in the confidence questionnaire associated with supporting dyslexia peers academically or signposting to reasonable adjustments and further support. This changed post-intervention with greater than 88% agreeing or strongly agreeing with these items. **Conclusion:** At a baseline level, medical students have less precise accuracy in knowledge and beliefs about dyslexia and are not confident in supporting dyslexia peers academically. The findings suggest that dyslexia awareness workshops in the medical curriculum have benefits in increasing knowledge about dyslexia and providing students with confidence in supporting their fellow peers with dyslexia.

Introduction

According to statistics from the British Medical Association (BMA), the estimated prevalence of medical students with dyslexia was 1.7% in 2009 and is believed to have increased since then.¹ Dyslexia is a common "learning difficulty" present in approximately 10% of the UK population.² According to the 10th edition of the International Classification of Disorders (ICD-10), dyslexia is classified as difficulties with reading despite normal intelligence.³ Although the severity of different aspects of dyslexia varies amongst individuals, common traits include difficulties with spelling, reading speed, comprehension, and pronunciation of words.³ Dyslexia is formally diagnosed by either an educational psychologist who specializes in specific learning difficulties or a specialist teacher/assessor with an assessment practicing certificate.⁴ This is done through a series of cognitive tests which measure the individual's strengths and weaknesses. This cognitive profile can influence significantly how medical students diagnosed with dyslexia are impacted in university.

Common challenges faced by students with dyslexia in higher education include notetaking in lectures, writing essays for assignments, and processing large information of text in their independent reading and revision.⁵ In medicine specifically, a review conducted by Shaw et al. (2017) found that students with

dyslexia experienced more difficulties with essay-based assessments in the degree and were slow to adapt to the study format required for medical school. This often made the first year of medical school difficult for students with dyslexia. However, it was found that after first-year students with dyslexia were able to perform on a similar level with their non-dyslexic counterparts through the rest of the degree if reasonable adjustments were in place.⁶ Common reasonable adjustments available to students with dyslexia include access to dictaphones and spell checkers, as well as 25% extra time for exams.⁷ The 25% extra time adjustment has been seen to be useful in closing the gap in scores between medical students with and without dyslexia.⁸

Not only can dyslexia affect students academically but psychologically as well. A study by Ghishi et al. (2016), who compared 28 university students who had dyslexia with a control group, found that the students with dyslexia reported higher rates of depression and lower self-esteem.⁹ In the field of healthcare specifically, this could be attributable to stigma and confidence in disclosing their dyslexia to fellow peers. Although research on this has not been carried out specifically with medical students, a study by Shaw and Anderson (2017) which interviewed 8 junior doctors found that the junior doctors reported common themes of feeling uncomfortable with disclosing their dyslexia and struggling emotionally at work.¹⁰

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These feelings were also echoed by nursing students with dyslexia on placement who have felt unwanted.^{11,12} As such, it is important to assess knowledge and stigma in healthcare degrees, to facilitate the development of supportive peers in these healthcare programmes. It is also interesting to see what role near-peer mentoring could have on addressing both the academic challenges associated with the first year of medical school and the psychological aspects.

Near-peer mentoring involves medical students in more senior years helping junior students with accessing the medical curriculum.¹³ Generally, junior students report feeling more prepared and supported in medical school and the senior medic mentors find this role beneficial for when they will be in similar roles as doctors in teaching hospitals.¹³ In terms of emotional wellbeing, a review conducted by Akinola et al. (2018) found that not only do studies show an academic benefit for first-year medical mentees, but also psychological benefits in terms of reducing stress levels, facilitating the transition into university and inter-personal development.¹⁴ No study so far has investigated the role of peer mentoring specifically on students with dyslexia. However, before a study investigating this can be conducted, it is important that a study is done to measure medical students' baseline knowledge of what dyslexia is and the academic challenges which students with dyslexia can experience.

Currently, no research has been done to see medical students' current knowledge and beliefs on dyslexia, as well as how confident they feel with supporting their peers with dyslexia. This is important as older medical students play a significant role academically, socially, and emotionally to their younger peers, and as such, it is important medical students are trained in how to support their peers with dyslexia. For this change to be facilitated, a study needs to be done which assesses the baseline of what medical students already know about dyslexia and their views about how confident they are in supporting their peers with dyslexia. A training session then needs to be delivered which aims to increase the medical students' knowledge of dyslexia and provide them with an interactive simulated activity of supporting their peers with dyslexia. This must be followed up one month later to observe if longitudinally this session improved the students' knowledge and confidence in supporting peers with dyslexia.

Once these questions have been researched, these findings could be used to firstly address if there is any need or benefit for dyslexia awareness workshops in the medical degree programme. If there is a need, then the study could illustrate what can be learnt in terms of replicating or amending the workshop provided to medical students in this study to integrate into the medical curriculum across medical schools.

This study aims to achieve these objectives by:

- (i) Administering a pre-intervention evaluation questionnaire that quantitatively assesses the baseline of the following:
 - (a) How accurate are medical students' pre-existing knowledge of dyslexia?
 - (b) How confident are medical students in supporting their peers with dyslexia?
- (ii) One month after the delivery of a small group seminar which aims to inform students about dyslexia and offer a simulated activity to practice supporting a peer with dyslexia, administer a post-intervention evaluation which quantitatively assesses if there was any change in the accuracy of the knowledge of dyslexia and confidence in supporting peers with dyslexia.

Methods

The study was completed with the support and collaboration of the lead for the steering committee for Diversity and Cultural Competency in Medical Education at King's College London Medical School. The study was ethically approved by King's College London Research Council (MRSU-20/21-21889) and the data was handled in accordance with the policies outlined in the General data protection regulation Act (2018).

Design

This study was a pre-post intervention evaluation study which was both cross-sectional and longitudinal. This study aimed to primarily test medical students' knowledge of dyslexia before and after attending a taught session on dyslexia. The independent variable was attending the small group seminar on dyslexia awareness. The dependent variable was the score on a standardized dyslexia knowledge test. Their responses were scored correctly or incorrectly according to the statement. A confounding variable this study controlled for was the influence of revision of the content in the session on the validity of the answers provided in the post-intervention questionnaire. Consequently, to control for this, students were not sent a copy of the slides during the research period. Students were also informed at the end of their workshop not to revise facts about dyslexia from the internet or books during the month interval.

Sample

The sample consisted of medical students currently in their 1st year of the degree programme at King's College London. They were invited to take part in the study by a participant information letter being placed on their 1st-year medical students Facebook and WhatsApp Groups via the Medical Student Association. Initially, 46 students were recruited into the study. Between the 2 phases of the study, there was an attrition rate of 21.7%, and as such 36 participants' data were included in the final analysis with the sample including 94.4% being females and 5.6% being males. This is illustrated below in [Figure 1](#).

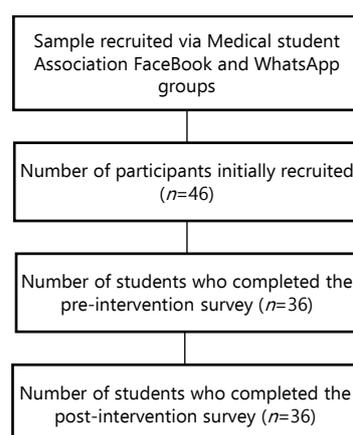
Survey questionnaire

A scale of knowledge and beliefs about developmental dyslexia (Soriano-Ferrer & Echegaray-Benoga, 2014)

The scale of knowledge and beliefs about developmental dyslexia contains 36 items measuring knowledge of dyslexia.¹⁵ The item format included "true" "false" and "don't know" questions. Items

assessed 3 main aspects of knowledge of dyslexia: general information, diagnostic traits, and management.¹⁵ The items were scored positively for any correct answers which matched up with the guidance provided by Soriano-Ferrer & Echegary-Benoga (2014). A cumulative total score was acquired by adding up the number of correct responses to the items. Higher total scores demonstrated that the student had more knowledge and awareness of dyslexia. It has been found in the very same study in which the questionnaire was created that the test is psychometrically reliable with a Cronbach's alpha of 0.76.¹⁵

Figure 1. Flow Diagram of Sample Size During the Recruitment and Pre-post Intervention Phases of the Study.



Prevalence estimate

This segment of the questionnaire asked the participants the following two questions on prevalence:

Question 1: In the UK, according to data provided by GOV.UK 2017 statistics, what percentage of the population have been diagnosed with dyslexia?

Question 2: According to the data provided by the British Medical Association in 2009, what percentage of medical students in higher education in the UK have been diagnosed with dyslexia?

Participants provided responses in the form of a percentage and the accuracy of their guess was analysed by how significantly their responses deviate from the actual statistics provided by GOV.UK and British medical Association.^{1,2} A significant difference in the estimate will be deemed as being an 'underestimate' if significantly lower and an 'overestimate' if significantly higher.

Confidence in supporting peers with dyslexia questionnaire

This questionnaire contained the following 6 items which measure the participant's confidence in supporting their peers with dyslexia:

Question 1: I am confident that I am aware of how to adapt my way of giving information to my fellow peers with dyslexia.

Question 2: I am confident in my abilities to adapt my teaching style to be "dyslexic friendly".

Question 3: I am confident in my ability to provide emotional support to my fellow peers with dyslexia.

Question 4: I am confident in my abilities to empower my peers with dyslexia with strengths they may have.

Question 5: I am confident in my abilities to inform peers with dyslexia what reasonable adjustments they are entitled to in my medical school?

Question 6: I am confident in my abilities to sign-post my peers with dyslexia where they could find out more information addressing their needs at my medical school.

These items used a 5-point Likert scale measuring how much the participants agree with each statement. The answers ranged from 'Strongly disagree' to 'Strongly agree'. Items were grouped according to the following categories: Items 1 and 2 assessed the students' confidence in supporting their peers with dyslexia academically, items 3 and 4 assessed the students' confidence in supporting psychologically and items 5 and 6 assessed the student's confidence in their abilities in giving and signposting information for reasonable adjustments that may help their peers with dyslexia.

Each item's response will be compared proportionally using a divergent stacked bar chart. Confident responses were counted as 'agree' and 'strongly agree' to the items. A higher proportion of participants who gave 'strongly agree' or 'agree' to an item suggests higher levels of confidence towards the domain of interventional peer support the item was testing.

Demographics questionnaire

The questionnaire recorded the participant's sex.

Procedure

Two weeks before the session, participants who were recruited were provided with a reminder of the participation information sheet and were informed of their rights to consent and withdraw from the study at any time.

Participants were asked via a confidential mailing list to fill in an online pre-intervention questionnaire on Google Forms which contained a scale of knowledge and beliefs about developmental dyslexia, prevalence estimate, confidence in supporting peers with dyslexia questionnaire, and demographics questionnaires.

The participants then attended a one-hour semi-structured small group hour-long session which is delivered by a medical student in their advanced years of the training through Microsoft Teams, who was provided a presentation provided by the researchers of the study. The instructor was trained by the researchers through a detailed run-through of the slides, to give the presentation which covered the following:

1. What is dyslexia (diagnostic criteria) and how can it impact the medical education experience both positively and negatively. [Knowledge and Awareness component]
2. Discussion activity: How could dyslexia impact learning preclinical medicine and how can we navigate this? [Doctor as Teacher component]
3. What reasonable adjustments and services are available in medical school for students with dyslexia? [Knowledge and Awareness/Pastoral Support components]
4. A simulated practical component linking Communication Skills taught in their first-year workshops with providing advice and addressing concerns of a fellow medical peer with dyslexia. [Pastoral Support components]

Each session consisted of a seminar group consisting of group sizes ranging between 3 to 5 students. The name of the attendees was recorded into a confidential mailing list for the post-intervention evaluation forms. Participants who attended the workshop were then reminded that one month later they will be sent a Google Form link to the post-intervention questionnaire which will be provided in a confidential e-mail sent to them. The questionnaire was the same as the one used for the pre-intervention questionnaire.

Statistical analysis

Data were analysed using the SPS Version IBM 27.0 software package. Statistical significance was measured at a 5% level ($p \leq 0.05$). For interpretation of the results, the accuracy of knowledge and the estimate of dyslexia in the population and medicine was provided as a mean percentage before and after the programme. Any significant difference before and after the taught programme was analyzed using a two-tailed dependent t-test. Additionally, any significant difference between the estimates and actual prevalence was measured too using a two-tailed dependent t-test.

Participants' confidence in supporting peers with dyslexia pre-and post-session was analyzed descriptively using a stacked bar chart to show the proportions associated with each point of the Likert scale per item.

Results

Baseline demographics

Demographically, over nine-tenths of the sample were female (94.4%).

Questionnaires- Accuracy of knowledge about dyslexia

The mean number of items correct in the A scale of knowledge and beliefs about developmental dyslexia questionnaire, as well as the mean estimate in the prevalence estimate questionnaire before and after the workshop are summarized in the table below ([Table 1](#)).

A scale of knowledge and beliefs about developmental dyslexia

To determine whether there was any significant change in the number of items scored correct in the questionnaire post-

intervention, a two-tailed dependent t-test was conducted. The number of items scored correctly from the pre-intervention (Mean= 15.22, SD= 4.81) and post-intervention (Mean=24.03, SD= 3.19) indicates that the dyslexia awareness workshop resulted in an improvement in the number of items scored correctly in the knowledge and beliefs questionnaire, $t(35) = 9.2$, $p < 0.001$.

Table 1. Mean Scores and Standard Deviation (SD) for Questionnaires "A Scale of Knowledge and Beliefs about Developmental Dyslexia" and "Prevalence Estimate".

Variable	Pre-intervention (n=36)		Post-intervention (n=36)	
	Mean	SD	Mean	SD
Number of items correct in the "a scale of knowledge and beliefs about developmental dyslexia"	15.22	4.81	24.03*	3.19
Estimate for percentage prevalence of dyslexia in the UK (in %)	14.65	11.24	11.28	6.23
Estimate for percentage prevalence of dyslexia in UK medical schools. (in %)	8.51	9.60	2.73*	2.08

Legend: [*] – to indicate any significant difference made pre-and post programme ($p < 0.05$).

Prevalence estimate

To determine if there was any significant difference between the estimates for the percentage prevalence of the people in the UK with dyslexia and medical students in the UK with dyslexia and the participants' estimations pre-intervention ([Table 1](#)), a one-sample t-test was conducted. For the percentage prevalence of dyslexia in the UK, the test value was 10.0 and for the percentage prevalence of dyslexia in medical schools the test value was 1.7. Pre-intervention, participants overestimated both the percentage prevalence of dyslexia in the UK, $t(35) = 2.8$, $p = 0.008$ and the percentage prevalence of dyslexia in UK medical schools, $t(35) = 4.8$, $p < 0.001$.

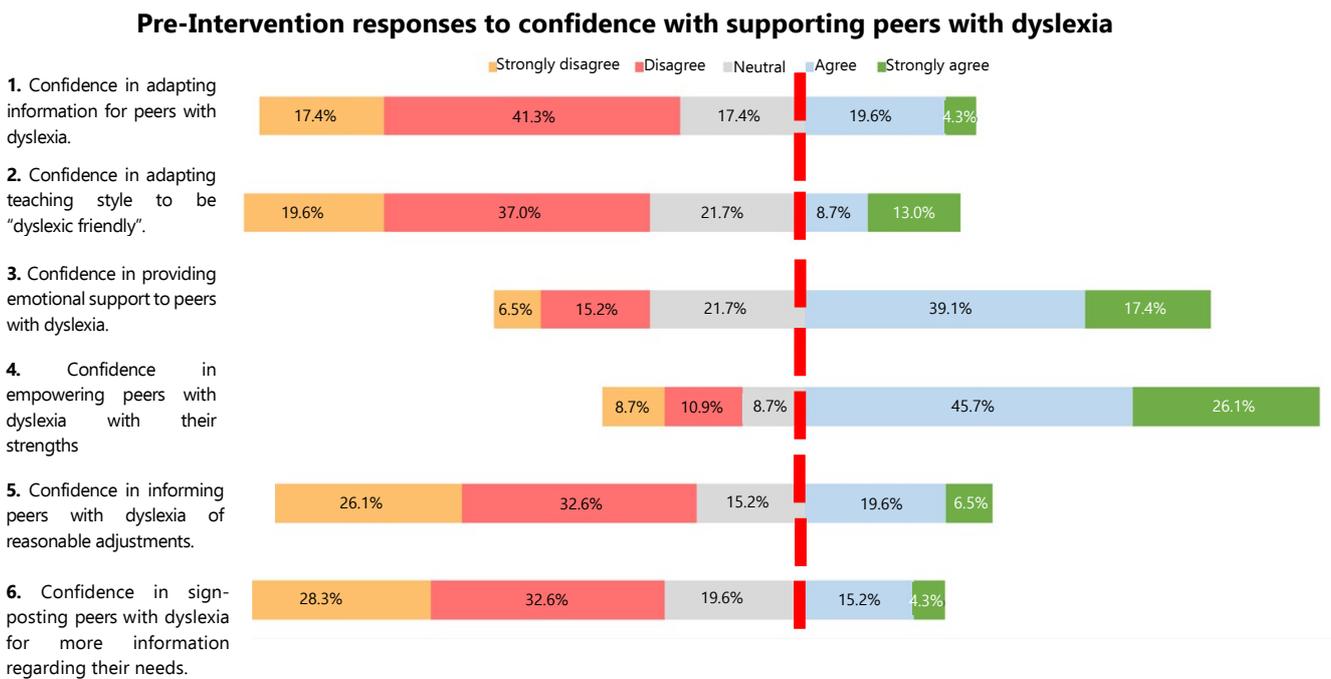
To investigate if there was any significant change in the estimates provided by participants pre-and post-workshop, a two-tailed dependent t-test was conducted. The estimated percentage prevalence of dyslexia in UK pre-intervention and post-intervention showed the dyslexia awareness workshop did not make any significant difference on the participant's estimate of the percentage prevalence of dyslexia in the UK, $t(35) = 2.1$, $p = 0.12$. However, the estimated prevalence of dyslexia in UK medical schools pre-and post-intervention showed that the dyslexia awareness workshop made a significant improvement to the

participant’s estimate of the percentage prevalence of dyslexia in UK medical schools, $t(35)= 3.5, p < 0.001$. Despite this improvement, a one-sample t-test conducted on the post-intervention estimate of the percentage prevalence of dyslexia in UK medical schools showed that the participants still overestimated the percentage prevalence, $t(35)= 3.0, p = 0.005$.

Questionnaires- Level of confidence in supporting peers with dyslexia

The proportional distribution of the responses to the different items of the Likert scale “Confidence in supporting peers with dyslexia questionnaire” pre-and post-intervention are graphically summarized in [Figure 2](#) and [Figure 3](#) below.

Figure 2. Divergent Stacked Bar Chart of Responses to Confidence in Supporting Peers with Dyslexia Questionnaire Pre-Dyslexia Awareness Workshop. The red dotted vertical line separates the proportion of non-confident responses to the statements (left hand side) from the proportion of confident responses (right hand side).



Proportionally, [Figure 2](#) shows that before attending the dyslexia awareness workshop, the majority of the participants reported feeling not confident in the items involving adapting the way they teach and deliver information to their peers with dyslexia (76.1% for Item 1 and 78.3% for Item 2) and items involving giving and signposting information for reasonable adjustments that may help their peers with dyslexia (73.9% for Item 5 and 80.9% for Item 6). However, for items based on providing support for the emotional aspects of dyslexia there just over a half of the participants reported feeling confident in providing emotional support to peers with dyslexia (56.5% for Item 3) and almost three-quarters (71.8% for Item 4) reported feeling confident in empowering peers with dyslexia with strengths they may have.

[Figure 3](#) shows proportionally how levels of confidence for each item of the “confidence in supporting peers with dyslexia” questionnaire have become after the dyslexia awareness workshop. For all items, no participants strongly disagreed or disagreed with any of the statements. For all items except Item 6, more than 90% of participants agreed or strongly agreed with the statements. The results suggest an improvement overall for participants in the study in the level of confidence in supporting peers with dyslexia.

Discussion

The data gathered for this study represents the first study to measure medical students’ baseline knowledge of dyslexia as well as their level of confidence in supporting their peers with dyslexia. It is also the first study to measure the influence of an interventional dyslexia awareness workshop on impacting the student’s level of knowledge of dyslexia as well as their confidence in their role of supporting other medical students with dyslexia.

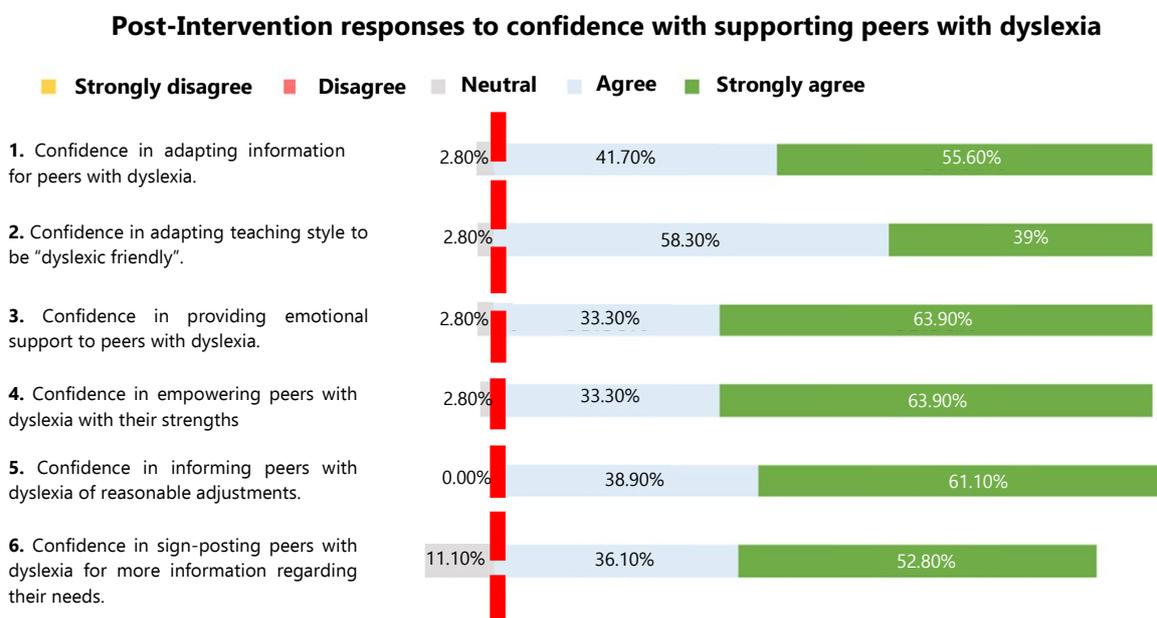
At a baseline level, the study found that the first-year medical students had less than 50% accuracy in the 36-item questionnaire on knowledge and beliefs about dyslexia before attending the interventional workshop. The study also found at a baseline level, that medical students overestimate not only the prevalence of dyslexia the UK but also in the UK medical student population. Additionally, before the intervention almost over three-quarters of the first-year medical students self-reported lower levels of confidence in supporting fellow medical student peers with dyslexia academically through altering their teaching and information delivery approach and signposting them to where they can get more information on reasonable adjustments and

support for their academic needs. However, most of the same students self-reported feeling able to provide emotional support and empowerment to their peers with dyslexia in medicine.

Observing findings from similar studies assessing knowledge of individuals in roles that involve supporting students with dyslexia such as teaching and lecturing, it is not unexpected to see such findings in terms of a lower level of accuracy in knowledge in terms of dyslexia and thus providing support to the dyslexic student community. Soriano-Ferrer et al. (2016), who used the same knowledge and beliefs questionnaire in this study, found that in a sample of 246 pre-service teachers and 267 in-service teachers in Peru and Spain scored similar means to those found in this study (M=16.38 for pre-service teachers and M=19.55 for in-service teachers).¹⁶ This study did explain that experience and

exposure to students with dyslexia can improve knowledge and beliefs, as shown by the higher score in the in-service teachers. However, experience alone without the training in dyslexia awareness, cannot positively improve knowledge about dyslexia. A similar study to this investigating both knowledge and level of confidence in supporting students with dyslexia was conducted with 260 primary school teachers in Turkey, which also found that primary school teachers demonstrated a low level of knowledge about dyslexia and additionally reported feeling not ready to teach students with dyslexia.¹⁷ This study suggests a relationship between knowledge about dyslexia and confidence in facilitating education to individuals with dyslexia. These findings are also similarly reported in the higher education sector.

Figure 3. Divergent Stacked Bar Chart of Responses to Confidence in Supporting Peers with Dyslexia Questionnaire Post-Dyslexia Awareness Workshop. The red dotted vertical line separates the proportion of non-confident responses to the statements (left hand side) from the proportion of confident responses (right hand side).



Findings from a study conducted by Schabmann et al. (2018), which assessed the knowledge of 234 university lecturers in Germany, found that the majority of lecturers lacked knowledge especially in the areas of how dyslexia is diagnosed and measures that can be implemented for students with dyslexia.¹⁸ One third of the participants also reported only offering exam adjustments support and advice and were unsure of what other advice to give. Similar levels of confidence were reported in a UK university-based study by Ryder and Norwich (2018) which included lecturers from 12 different universities.¹⁹ The lecturers felt not only were they unaware of how best to support their students with dyslexia but also unaware of current research knowledge into dyslexia pedagogically.¹⁹ These studies implicate the relationship between knowledge and the ability to confidentially support students academically and be aware of signposting to address academic needs. Similar findings highlighted in both

those responsible for teaching and peers who could provide support show the need for training in dyslexia awareness.

Post-intervention, this study has found that there was an improvement in the medical students' knowledge and beliefs about dyslexia with an average of 66% accuracy in the items of the same questionnaire. In addition, post programme the study found a large improvement with almost all participants self-reported feeling confident with supporting their peers with dyslexia academically, psychologically and being more confident in knowing where to signpost their peers to obtain reasonable adjustments and advice for their needs. These findings suggest an applicational benefit in the role of providing dyslexia workshops in the medical curriculum especially for older medical students who are involved in near peer mentoring. There are implications that dyslexia awareness trained near-peer mentors

will be more confident in providing academic and psychological support to potential mentees who may have dyslexia. Despite these improvements, the medical students still overestimated the prevalence of dyslexia in both the UK and UK medical schools.

So far there are currently no findings that explore the public's perceptions of the prevalence of dyslexia. This empathises that there is not only a gap in understanding how those who play role in medical education estimate how common dyslexia is but in society in general. Without understanding, if the trend to overestimate the prevalence of dyslexia is also found in the general population, it will make it difficult to find the best solution to reduce this overestimate in the medical education sector. Therefore, this study highly recommends future research conducted which investigates the public's perception of the prevalence of dyslexia.

In terms of the post-interventional improvements found in this study, similar findings were found in a larger scale study which is the only of its kind to investigate the role of dyslexia awareness on perceptions. Knight's 2018 study involved a sample of 2,600 teachers in England and Wales.²⁰ In this study, teachers completed an online survey that assessed their knowledge of dyslexia, confidence with working with students with dyslexia, and if they had much training with dyslexia. Less than 30% of the participants had dyslexia awareness training as part of their teacher training programme.²⁰ The teachers who had dyslexia awareness training demonstrated more knowledge of the cognitive aspects of dyslexia as well as reported feeling more confident with assisting students with dyslexia.²⁰ Given the reliability and statistical power of the large-scale study presenting similar findings to our study for medical students, it is important to have dyslexia awareness embedded into the medical curriculum and have more research done on larger cohorts to see if similar results are found. However, this does raise the question for future studies, if a different method of delivery of the dyslexia awareness intervention such as in a lecture-based format could yield a similar impact on the benefits gained from this intervention.

Limitations

This study was limited by its small, predominately female-based sample (94.4% female to 5.6% male). Future studies replicating the methods of this study should use a larger sample that is representative of the general male-to-female ratio present within medical schools. Additionally, the study was limited to only longitudinally measuring change in behaviours regarding knowledge, beliefs, and confidence in helping peers with dyslexia in pre-clinical medicine and the more theoretical academic side of medicine. It will be interesting for future programmes and research aiming to shape neurodiversity awareness and support in medicine by identifying the challenges most persistently present in students with dyslexia during clinical years in terms of clinical skills acquisition and how student peers and mentors can play a significant role in supporting their counterparts with dyslexia.

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Summary – Accelerating Translation

Title: The Role and Impact of Dyslexia Awareness Workshops in the Medical Curriculum

Main problem to solve: According to statistics from the British Medical Association (BMA), the estimated prevalence of medical students with dyslexia is 1.7% during 2009 and is believed to have increased since then. Dyslexia is classified as difficulties with reading despite normal intelligence. Other common difficulty traits shared amongst individuals with dyslexia include spelling, reading speed, comprehension, and pronunciation with words. Previous research has shown that medical students (especially firstyear students) with dyslexia experienced more difficulties with adjusting to the study format required for medical school. Psychological difficulties were also found with members of healthcare professionals with dyslexia exhibiting lower self-esteem and struggling emotionally.

Research has shown a benefit generally of the role of near-peer mentoring in supporting younger medical students both academically and emotionally. Currently no research exists that understands what medical students know about dyslexia. Therefore, it is essential to understand what current medical students know about dyslexia and their level of confidence in supporting their peers with dyslexia. Additionally, it is crucial to teach them the knowledge required to help their near-peer mentees with dyslexia in the medical program both academically and emotionally.

Aims of the study: The primary aim of the research is to administer a questionnaire to measure a baseline of the following: (a) How accurate are medical students' pre-existing knowledge of dyslexia? And (b) How confident are medical students in supporting their peers with dyslexia? The study also wanted to measure if an hour workshop would have an effect on their knowledge of dyslexia and their confidence in supporting their peers with dyslexia one month later.

Methodology: 36 1st year medical students were included in the study. Prior to the workshop the participants were given a standardized 36-item "scale of knowledge and beliefs about developmental dyslexia" questionnaire to assess their baseline knowledge as well a questionnaire in confidence in supporting peers with dyslexia to assess their baseline confidence. A one-hour small group workshop was then delivered to participants which covered the following components about dyslexia: knowledge and awareness, teaching, and pastoral support. One month later, the same questionnaires were administered to the participants to measure any changes in knowledge and confidence.

Results: In terms of knowledge about dyslexia, at a baseline level the participants scored an average of 15.22 out of the 36 points available. This average increased significantly to 24.03 one month after the workshops. In terms of confidence, pre-workshop greater than 70% of participants reported feeling not confident in items in the confidence questionnaire associated with supporting dyslexic peers academically or signposting to reasonable adjustments and further support. This changed post-workshop with greater than 88% agreeing or strongly agreeing with these items.

Conclusion: At a baseline level, medical students have less precise accuracy in knowledge and beliefs about dyslexia and are not confident in supporting their peers with dyslexia academically. The findings suggest

that dyslexia awareness workshops in the medical curriculum have benefits in increasing knowledge about dyslexia and providing students with confidence in supporting their fellow peers with dyslexia.

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HLA-DQB1*0301 in Bullous Pemphigoid and Pemphigus Vulgaris: A Meta-Analysis

Dylan Thibaut,¹ Ryan Witcher,¹ Breana Barnes,¹ Kersten T. Schroeder.²

Abstract

Background: The linkage of HLA-DQB1*0301 to autoimmune disorders is becoming more common in literature. Despite bullous pemphigoid (BP) and pemphigus vulgaris (PV) both having similar symptoms, such as blistering skin conditions, research has shown different relationships with HLAs. **Methods:** In this systematic review, HLA-DQB1*0301 and the odds of developing BP and PV were explored. Google Scholar and Pubmed were consulted, and articles were included if living subjects were used, odds ratio was available or could be ascertained from the study, and if it was not a meta-analysis of other researcher's works. MetaXL software was used to generate data for analysis and a forest plot was generated for each. Nine studies conducted between 1996 and 2021 met study selection criteria for the BP HLA-DQB1*0301 meta-analysis (1,340 patients and 6,673 controls) and five studies (247 patients and 2,435 controls) for PV. **Results:** HLA-DQB1*0301 increased the odds of developing BP (OR= 1.64, 95% CI [1.44, 1.87], I²= 0%) yet decreased odds of PV (OR= 0.60, 95% CI [0.40, 0.89], I²= 34%). **Conclusion:** Results suggest HLA-DQB1*0301 may serve opposite roles in BP and PV despite similarity in symptoms, finding higher odds for developing BP versus lower odds for developing PV. Understanding this HLA's function in each requires further exploration. Limitations of the analysis included minor asymmetry in the PV Doi plot, suggesting publication bias. No funding was used; study protocol was not registered.

Introduction

Autoimmune blistering diseases are conditions in which autoantibodies form against the dermal or subdermal layers of skin, causing damage to the skin. The most common of these conditions include bullous pemphigoid (BP) and pemphigus vulgaris (PV), with each having a different target by which autoantibodies attack despite having a similar immunologic mechanism. Both conditions occur through a T2 hypersensitivity reaction.¹ This reaction occurs through a series of steps: human antigens are taken up by major histocompatibility complexes (MHCs) and are incorrectly seen as foreign, antibodies are formed against normal human substances, the antibodies attach to the human antigens they recognize, and the autoantibodies attached to human antigen cause immune cells to attack the human tissue. This process revolves around human leukocyte antigens (HLA), which are variable genes encoding MHCs. With a vast variance in HLAs across populations and with humans inheriting multiple from each parent, immunity across different individuals differs greatly.

In BP, a T2 hypersensitivity reaction occurs where IgG anti-hemidesmosome antibodies are directed towards the hemidesmosomal proteins BPAg1 and BpAg2.² Hemidesmosomes connect cells to the basement membrane below. The result of autoantibody attack of hemidesmosomes in BP is the formation of large and rigid subepidermal blisters which

rarely rupture that primarily affect palms, soles, groin, and axillae.³ BP is the most common of the blistering skin conditions, with a peak incidence of >60 years of age. PV instead uses IgG anti-desmosomal antibodies which target desmoglein 3 and desmoglein 1.⁴ Desmosomes are responsible for connecting cells in the epithelium to one another, unlike hemidesmosomes, which connect the cells to the basement membrane below. The result of the autoantibody attack in PV is the formation of smaller and fragile intraepidermal blisters that frequently rupture and crust.³ These blisters primarily affect intertriginous areas, with a unique perioral involvement.

Understanding the specific HLAs that lead to this autoimmune process is essential to understanding BP and PV development, progression, and treatment. Presently, the combined prevalence of HLA research on BP and PV has been centered on HLA-DQB1 allele variances. HLA-DQB1 has been associated with several pathologies including susceptibility to Type 1 Diabetes Mellitus (T1DM), as well as superimposed BP when T1DM patients are treated with DPP4i.⁵⁻⁶ In association with other alleles in linkage disequilibrium, it has shown to be related to rheumatoid arthritis as well as multiple sclerosis.⁷ Research specific to HLA alleles has shown that each allele, even if similar, can have a different effect on autoimmune development and bodily response.

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HLA-DQB1*0301 is one specific allele with implications to care, as it is connected to prognosis, treatment response, and even symptom profile in dermatologic conditions.⁸⁻¹⁰ This is apparent with BP and PV, which are also seemingly connected to the allele.¹⁰⁻¹¹ With this allele being mentioned in both skin conditions as showing opposing effects of protecting versus predisposing patients to PV and BP, a meta-analysis is necessary. Through a better understanding of the effects of this specific allele, the connection between it and these conditions can further be understood and potential medical applications for immunologic methods can be deduced. This systematic review hopes to find the connection between HLA-DQB1*0301 alleles and the odds of BP and PV to better highlight the alleles and their role in disease pathophysiology.

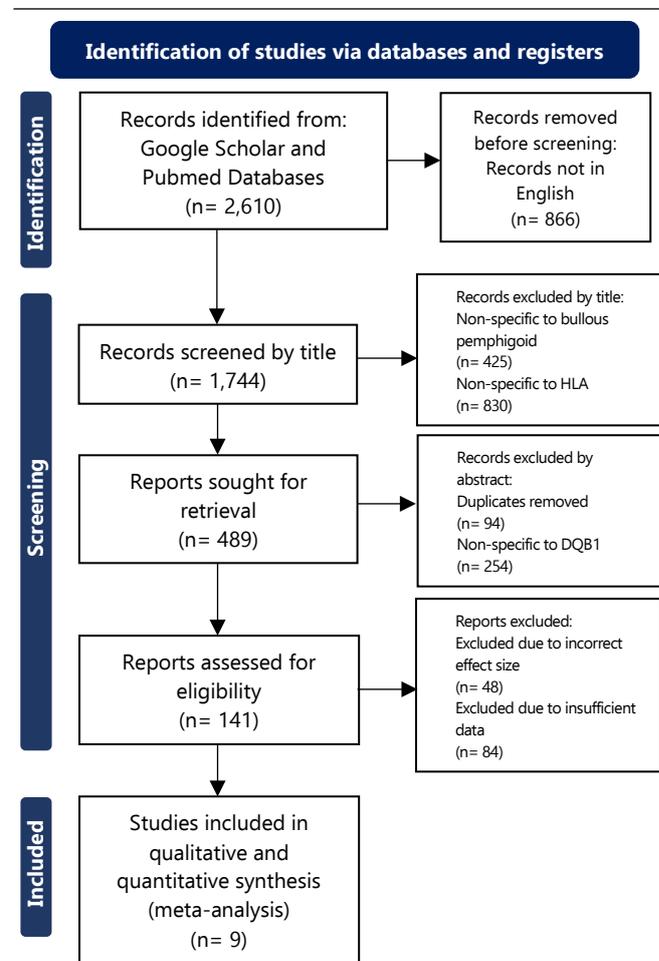
Methods

Systemic reviews were conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.¹² Eligibility criteria for this study included a requirement that all subjects to be living and all studies to be in the English language. All included studies were required to be case-control studies. Each included study required control samples and case samples to be from the same population. Case samples were required to either be diagnosed patients with BP or PV to be compared. Exclusions for this study include the use of subjects that are classified as deceased, animal, or cell subjects or samples. No meta-analyses were included in this study as part of the analysis. The databases used for this meta-analysis were Google Scholar and PubMed. The search for each meta-analysis used the following exact terms: "HLA-DQB1*0301", "HLA-DQB1*0301 bullous pemphigoid", "HLA-DQB1*0301 pemphigus vulgaris." The protocol was agreed upon prior to beginning the analysis consistent with the methods described here.

The search for articles began May 2021. The selection process was conducted through two researchers independently searching for and finding studies with the oversight of a PhD principal investigator. The search strategy was designed by the principal investigator in which two researchers collected data and sifted through search results. First, the search terms were used on the databases, followed by removal of all studies using a language other than English through search tools that are part of the databases. This was followed by compiling search results on a shared document based on the title. After this, results were filtered out if they did not meet inclusion criteria. No specific filter software was used. The variables gathered for assessment were the odds ratio, lower and upper range for confidence intervals (CI), number of patients, control group, as well as the demographic groups within the publication. If an odds ratio was not provided, but sufficient data was present, this data was used to calculate the odds ratio. All data was compiled on a shared document where either another researcher would agree to including a study or disagree with its inclusion. If disagreement occurred, the final decision was made by the principal

investigator. Database search results and study evaluation for inclusion criteria are indicated in [Figure 1](#) and [Figure 2](#).

Figure 1. PRISMA Flow Diagram for HLA-DQB1*0301 in Bullous Pemphigoid

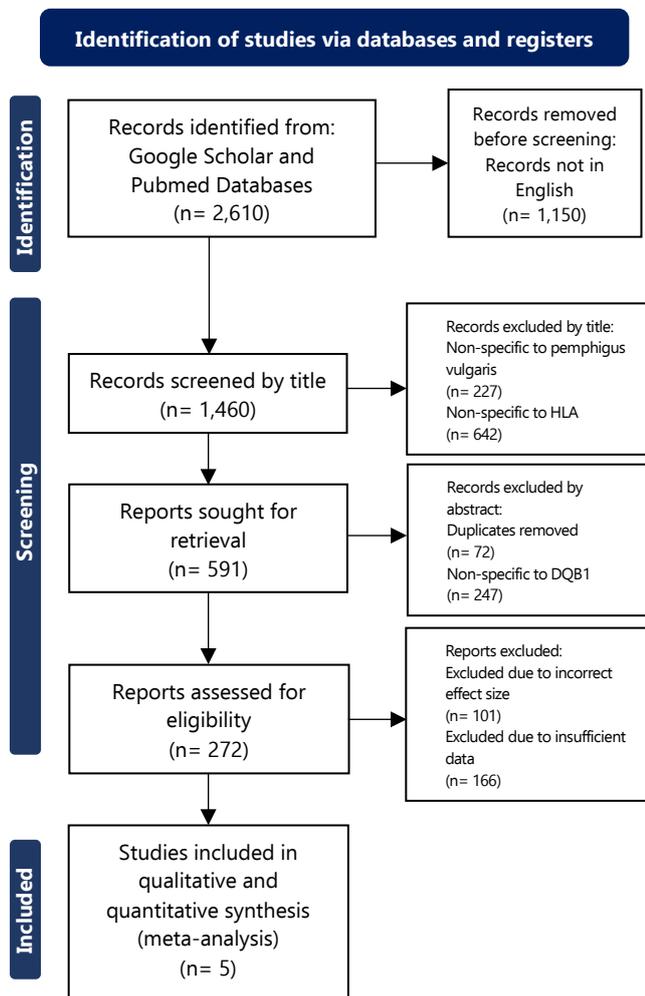


Luis Furuya-Kanamori index (LFK index) was determined and a Doi plot was created for each of the analysis as a means of assessing publication bias.¹³ Doi plots combined with LFK index allows for a quantitative and visual representation of bias. The Doi plot represents included studies in a graph form while LFK index measures the asymmetry of the created plot. Ideally, plots should show no asymmetry or minor asymmetry (a value between -1 to +1), with larger values indicating inconsistency across included studies. The inclusion of Doi plot and LFK index provides an additional layer to determine consistency of findings across studies.

Additionally, the NIH Quality Assessment Tool was used to evaluate individual studies included in the analysis; if a particular study was found to have a majority of the questions on the bias assessment as "no", it was specifically removed for inclusion and mentioned.¹⁴ The effect size was measured using the odds ratio, no other effect sizes were included in the meta-analysis. When determining the eligibility of each study used in the meta-

analysis, studies that provided enough data to calculate the effect size were included and used to calculate the odds ratio. Data collected from studies that failed to provide sufficient data to calculate effect size or those who did not meet inclusion criteria were not included in the study. Data was collected by researchers and compared; this data was then combined into a table to visually display the results of individual studies. In order to synthesize results, MetaXL software was used to generate a forest plot and conduct the meta-analysis.¹⁵ This analysis used the IVhet model. Heterogeneity was calculated using Cochran's Q and an I^2 value. A result with a P value <0.05 or an I^2 value greater than or equal to 25% were significant for heterogeneity. Sensitivity testing was performed using pooled odds ratios and subgroup analysis.¹⁶ To report bias assessment, literature heterogeneity was noted in the results. The odds ratio obtained from the forest plot analysis as well as its 95% confidence interval were used to evaluate the outcome in this study. All research was conducted under appropriate ethical guidelines for research set by the institution the research was performed at.

Figure 2. PRISMA Flow Diagram for HLA-DQB1*0301 in Pemphigus Vulgaris.



Results

Nine studies conducted between 1996 and 2021 met study selection criteria for the BP HLA-DQB1*0301 meta-analysis.^{7, 17-24} One study seemingly met all criteria for the BP analysis, though due to its usage of deceased patients as a control group, was excluded due to selection criteria not allowing animals, deceased patients, or microorganisms as a studied sample for comparison.²⁵ A combined total of 1,340 patients with BP and 6,673 controls were included from the nine studies. Several different demographic groups were examined in these studies including German, Caucasian, Han Chinese, Japanese, Iranian, and Northern Chinese. For the PV analysis, five studies conducted between 1999 and 2021 met selection criteria.²⁶⁻³⁰ Despite meeting most inclusion criteria, one study was removed from the PV analysis due to its usage of animals, deceased patients, or microorganisms as a sample for comparison.³¹ Due to exclusion criteria prohibiting past meta-analyses to be incorporated into this study's meta-analysis, an additional study was also removed.³² A total of 247 PV patients and 2,435 controls were used in this five-study analysis. Demographic groups included in these studies consisted of Vietnamese, Serbian, Slovak, Venezuelan, and Italian groups.

Odds ratio, 95% confidence interval, size of patient sample, size of the control sample, and the group being tested were recorded for all studies used for the meta-analyses. Recorded details collected from the studies of both analyses are summarized in [Table 1](#). To test for publication bias, a Doi plot was generated for each analysis. The BP analysis showed no asymmetry with an LFK index of 0.83. Minor asymmetry was found in the PV analysis, with an LFK index of -1.43.

To calculate a combined odds ratio for the various studies, an inverse variance heterogeneity (IVhet) model was used via MetaXL software to generate corresponding forest plots ([Figure 3](#)).¹⁵ Odds of BP was higher given a person had HLA-DQB1*0301 (OR= 1.64, 95% CI [1.44, 1.87], $I^2= 0\%$) while odds of PV was lower given the person had HLA-DQB1*0301 (OR= 0.60, 95% CI [0.40, 0.89], $I^2= 34\%$). This finding suggests that HLA-DQB1*0301 has opposite effects in each condition, increasing odds of BP while reducing odds of PV. Note that the heterogeneity of the PV analysis is above 25% and should be interpreted with a level of caution that some studies may have influenced the results ($I^2= 34\%$).

Sensitivity testing was performed via the exclusion of each study individually and sequentially. For the BP analysis, two studies contributed most to the pooled OR.^{18, 19} No substantial heterogeneity result was found on analysis, and $I^2=0.0$ for all studies analyzed for it. Regarding the PV analysis, two studies were found to most effect pooled OR.^{26, 28} Heterogeneity testing in this case showed two values to note: Párnická et al.'s $I^2= 50.11$ and Lombardi et al.'s $I^2= 49.65$.^{27, 29} Though no Q value was considered significant for these two studies, minor asymmetry found in the Doi plot was a result.

Table 1. Characteristics of Studies of HLA-DQB1*0301 in Bullous Pemphigoid and Pemphigus Vulgaris.

Author	OR	CI lower	CI upper	Patient	Control	Group
Bullous Pemphigoid						
Schwarm et al., 2021	1.84	1.01	3.35	446	433	German
Lindgren et al., 2019	2.76	1.42	5.35	23	2991	Caucasian
Fang et al., 2018	1.69	1.19	2.39	105	420	Han Chinese
Sun et al., 2018	1.58	1.33	1.88	575	976	Han Chinese
Ujiie et al., 2018	1.60	0.90	2.90	72	873	Japanese
Esmaili et al., 2013	1.82	1.13	2.92	50	180	Iranian
Gao et al., 2002	1.29	0.50	3.31	25	57	Chinese
Okazaki et al., 2000	1.48	0.57	3.85	23	525	Japanese
Delgado et al., 1996	1.38	0.70	2.70	21	218	Caucasian
Pemphigus Vulgaris						
Vuong et al., 2021	1.05	0.49	2.11	22	101	Vietnamese
Zivanovic et al., 2016	0.42	0.21	0.85	72	1992	Serbian
Párnická et al., 2013	0.65	0.34	1.25	43	113	Slovakian
Sáenz-Cantele et al., 2007	0.25	0.09	0.73	49	101	Venezuelan
Lombardi et al., 1999	0.66	0.36	1.22	61	128	Italian

Discussion

Despite the relative similarity of BP and PV, the findings of this meta-analysis support that HLA-DQB1*0301 has opposing effects in each condition. While it was found to increase odds of BP in those with HLA-DQB1*0301 (OR= 1.64, 95% CI [1.44, 1.87]), there are decreased odds of PV in those with the HLA (OR= 0.60, 95% CI [0.40, 0.89]). With this finding of opposing results in these conditions, a question as to why there are differing effects despite similarity in symptoms must be asked.

With HLA-DQB1*0301 being more common in BP according to this study's findings, there is a need to understand what to expect this association to mean clinically. Regarding autoimmune consequence parallels in other autoimmune conditions, the DQB1*0301 allele was found to be associated with more severe outcomes in patients with multiple sclerosis, type 1 diabetes mellitus and celiac disease.³³⁻³⁵ Regarding DQB1*0301 association with skin disorders, it was found to be correlated with the development of cutaneous melanoma, erythema multiforme, as well as ocular cicatricial pemphigoid.³⁶⁻³⁸ Membranous

pemphigoid also shows this increase as well.³⁹ It has been postulated that the HLA class II antigen presentation seen in higher amounts within keratinocytes may stimulate a T-cell inflammatory response, contributing to the increased susceptibility of skin disorders with the HLA-DQB1*0301 allele.³⁸

PV did not follow this deleterious effect, instead showing an opposite, seemingly protective role. Unfortunately, the heterogeneity of $I^2= 34\%$ calls into question whether this finding is a result of not including a sufficient number of studies. A more global inclusion of different samples may help understand this connection more completely. Other epithelial tissues outside of blistering skin conditions have shown a potential effect, such as in gastric cancer.⁴⁰ Autoimmune disorders that are not skin related, such as autoimmune hepatitis, similarly show HLA-DQB1*0301 as protective.⁴¹

Among multiple autoimmune diseases, there is a diverse set of HLA antigens with an association yet to be discovered. Clinically in the future, HLA antigen sequencing could perhaps be a standard of care in diagnosing new patients. This data may lead to the ability to increase the pathological predictive ability of medical geneticists in the future.

Strengths and Limitations

The meta-analysis conducted to evaluate the impact of HLA-DQB1*0301 on the prevalence of BP and PV considered various variables and limitations of the pooled studies. However, it is important to acknowledge certain strengths and limitations of this analysis. While the meta-analysis involved a comprehensive approach by including multiple studies, no single methodology encompassed a representative global population. Instead, individual studies primarily focused on specific ethnicities, leading to variations in the significance of the results. The study utilized strict inclusion and exclusion criteria, with pre-defined methods of data utilization and data storage which would help avoid post-hoc analysis bias.

However, the analysis was primarily conducted by two medical student researchers with PhD oversight, and thus the study lacked a dedicated statistician. Regarding the quality of the genes analyzed, the majority of the studies concentrated solely on the effect of a single haplotype on BP and PV prevalence, with limited exploration of the effects of linkage disequilibrium or the combined impact of HLA allele frequencies on disease prevalence. Consequently, these factors impose limitations on the extent to which the current analysis can accurately predict the global impact of HLA-DQB1*0301. Furthermore, the reliance on only two broad databases restricts the generalizability and applicability of the research findings.

While heterogeneity was 0% for the BP comparison, it was a factor influencing the PV analysis ($I^2= 34\%$), making the result of the PV analysis more challenging to interpret. Additionally, while bias assessment found the included studies to overall be well designed, there was minor asymmetry in LFK index findings for the PV analysis. Both the heterogeneity findings and this minor asymmetry suggest that some of the included studies in the PV

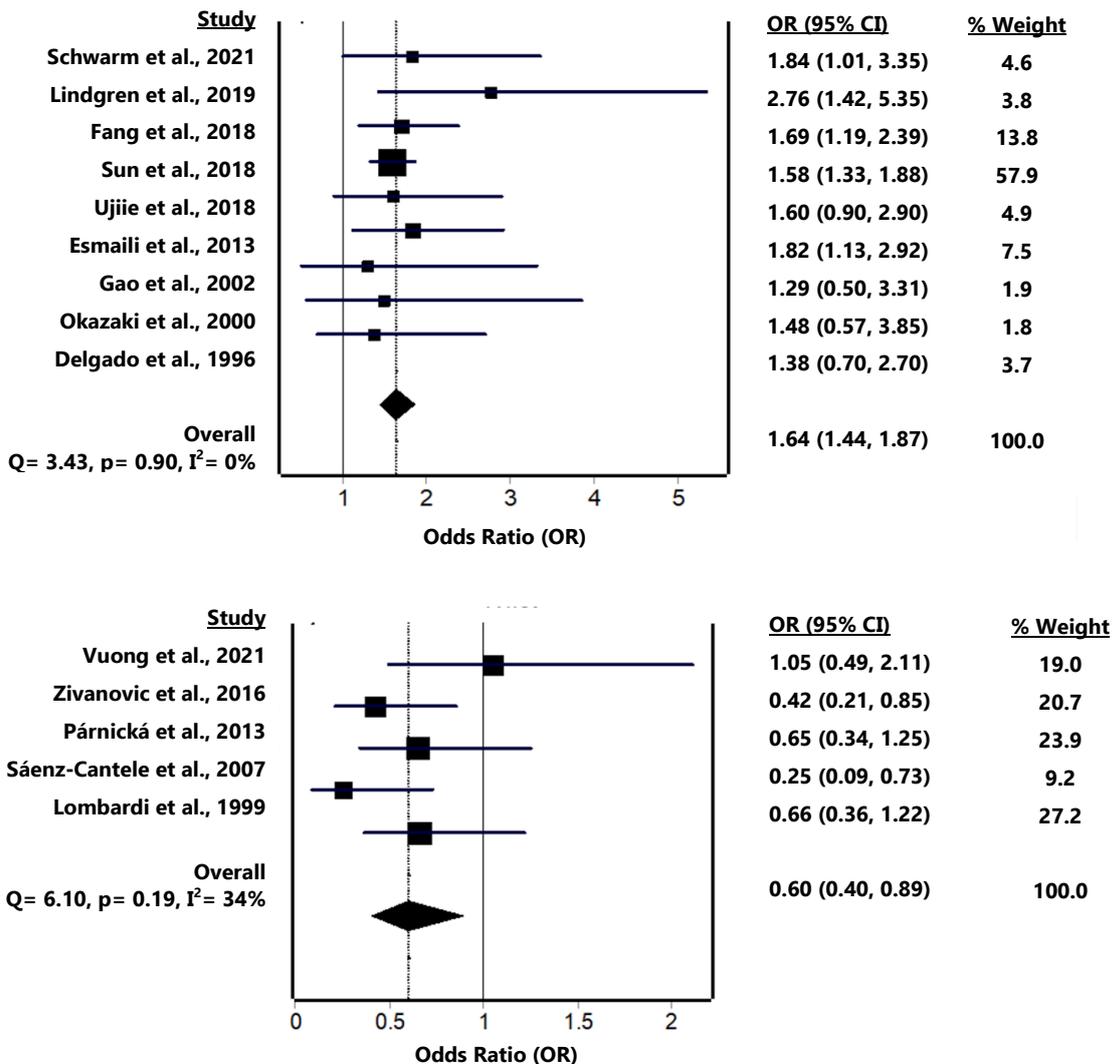
analysis may not have been as high quality. This may have influenced the findings.

Conclusion

Autoimmune blistering diseases, such as BP and PV, involve the formation of autoantibodies against the skin, leading to damage. These conditions are characterized by a T2 hypersensitivity reaction, with each condition targeting different proteins despite a similar immunologic mechanism. The human leukocyte antigen (HLA) genes, particularly HLA-DQB1*0301 allele, have been associated with various pathologies. Understanding the role of

HLA alleles is crucial for understanding the development and treatment of BP and PV. This analysis included nine studies for BP and five studies for PV which collectively showed that HLA-DQB1*0301 allele increased the odds of BP and reduced the odds of PV. These findings suggest that HLA-DQB1*0301 has opposing effects in these two conditions. However, caution should be exercised due to some heterogeneity in the PV analysis. Further research is needed to explore the specific mechanisms underlying these associations and their implications for the diagnosis and treatment of BP and PV.

Figure 3. Forest Plot for Bullous Pemphigoid (Top) and Pemphigus Vulgaris (Bottom).



Summary – Accelerating Translation

Title: HLA-DQB1*0301 in Bullous Pemphigoid and Pemphigus Vulgaris: A Meta-Analysis

Main problem to solve:

Human Leukocyte Antigen (HLA) is something which takes up parts of the environment around or inside of cells. These parts, antigens, are then

shown to immune cells by the HLA. Some specific types of these HLA have been linked to autoimmune problems. Bullous pemphigoid (BP) and pemphigus vulgaris (PV) are two examples of autoimmune blistering skin problems. These conditions both cause similar symptoms. Despite being similar, research shows that different HLAs are linked to each. Some HLAs can make it more likely to get one of the blistering skin problems and some HLAs can make it less likely to get one of the blistering skin

problems. One specific HLA, HLA-DQB1*0301, has increased odds of certain autoimmune skin problems and has decreased odds of other autoimmune skin problems.

Aim of study:

In this study, the odds of bullous pemphigoid and pemphigus vulgaris depending on whether a patient has HLA-DQB1*0301 is found through a meta-analysis. This is done so that the relationship between these autoimmune conditions and HLA-DQB1*0301 can be found.

Methodology:

In this systematic review, HLA-DQB1*0301 and the odds of developing bullous pemphigoid and pemphigus vulgaris were explored. Google Scholar and Pubmed were used for searching. Articles were used if they had living subjects only, odds ratio was in the study or could be found from the study, and if the study was not a meta-analysis. MetaXL software

was used to make a forest plot for bullous pemphigoid and for pemphigus vulgaris. Nine studies that were done between 1996 and 2021 had the required data for the bullous pemphigoid HLA-DQB1*0301 meta-analysis (1,340 patients and 6,673 controls) and five studies (247 patients and 2,435 controls) had the required data for pemphigus vulgaris meta-analysis.

Results:

HLA-DQB1*0301 increased the odds of developing bullous pemphigoid (OR= 1.64, 95% CI [1.44, 1.87], I²= 0%). HLA-DQB1*0301 decreased the odds of pemphigus vulgaris (OR= 0.60, 95% CI [0.40, 0.89], I²= 34%).

Conclusion:

Results suggest that HLA-DQB1*0301 has opposite effects in bullous pemphigoid and pemphigus vulgaris. There are increased odds for getting bullous pemphigoid and lower odds for getting pemphigus vulgaris if a patient has HLA-DQB1*0301.

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From Student to Physician: Determining Which Lifestyle Behaviors May Be Risk Factors for Burnout at a South Florida Medical School

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Abstract

Background: Compared to other professions, physicians have significantly higher rates of burnout and poor lifestyle behaviors, including inadequate sleep, poor diet, limited exercise, and lack of supportive social relationships. Among physicians in training, burnout and increasingly poor lifestyle behaviors can begin as early as the preclinical years of medical school. **Methods:** A cross-sectional survey composed of questions from standardized surveys measuring diet (Yaroch's FVS), exercise (NPAQ-S), sleep (NHANES), stress management (HRQOL), social support (BRFSS), substance use (AUDIT-QF, WHO), and burnout (Mini-Z) was conducted on a South Florida medical school in May 2021. One hundred forty-four students fully completed the survey for a response rate of 16%. Descriptive analysis was performed via SPSS to determine the effects of these lifestyle factors on the likelihood of student burnout. **Results:** In this sample of medical students, over half (61%) experienced burnout per the Single Item Burnout Measure. Independently, lack of sleep ($p < 0.02$) and decreased social support ($p < 0.001$) were lifestyle factors positively associated with increased risk of burnout. Furthermore, students who experienced burnout reported more poor mental health days and decreased life satisfaction ($p < 0.001$). **Conclusion:** Over half of the medical students experienced burnout. Lack of sleep and lack of social support were significantly associated with increased risk of burnout. In addition, burned-out students showed significantly increased levels of poor mental health and decreased life satisfaction. These findings help us identify specific lifestyle factors that institutions could use to further combat medical student burnout.

Introduction

Physicians are burned-out, and it starts in medical school. Nearly half of all physicians report experiencing burnout, defined as work-related stress leading to emotional exhaustion, depersonalization, and decreased sense of personal accomplishment.¹ The emergence of COVID-19 only deepened this occupational risk.¹ Burnout is a growing healthcare concern because it has been associated with lower patient satisfaction, decreased medication adherence, and increased rates of medical errors.^{1,2} The physical and cognitive impairment of burnout also lead to professional consequences; including medical errors, career regret, and lack of empathy towards patients.¹⁻⁴ Furthermore, burnout impacts physician wellness and is linked to personal ramifications such as obesity and increased suicidal ideations.³

Burnout can begin as early as the preclinical years of medical school.^{5,6} A 2013 literature review estimates 45-71% of medical students experience burnout.⁶ Burnout interventions have a reported range of benefits.^{5,7,8} For example: (1) those who participate in burnout prevention programs report decreased

burnout; and (2) those who completed personal health interventions were more likely to counsel patients on healthy lifestyle behaviors.^{7,8}

While prior studies have examined burnout among medical students, less is known about their lifestyle behaviors. Studies that explore the role of lifestyle factors on burnout mostly emphasize individual behaviors such as sleep or exercise.^{5,9,10} To better understand lifestyle behaviors and burnout among US medical students, data was collected from a cohort of medical students at an LCME-accredited institution to determine (1) burnout prevalence; and (2) lifestyle behaviors, including social support, of South Florida medical students. The objective of this study is to identify specific lifestyle behaviors among undergraduate medical students that may be associated with burnout.

Methods

Between May and June 2021, a cross-sectional survey was conducted at the University of Miami Miller School of Medicine (UMMSM) to explore medical student burnout and lifestyle factors. All currently enrolled medical students ($n=892$) were sent

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an email that included an anonymous link to a Qualtrics survey hosted on a privacy-protected, cloud-based server. The electronic consent form stated participation was voluntary and anonymous. Parameters were set to prevent repeat entries from students. A reminder was sent 21 days later. This research was approved by UMMSM Human Subject Research Office (IRB: 20210170).

Measures

Demographic questions on the survey captured the student's race and medical school year. Ten questions measured burnout and lifestyle factors on diet, exercise, sleep, substance use, stress management, and social support. Diet was assessed with Yaroch's 2-item survey for fruit and vegetable servings, which has adequate reliability but has not been validated.¹¹ Exercise was measured by the validated Nordic Physical Activity Questionnaire-Short (NPAQ-S).¹² Sleep was measured by adapting NHANES question SLD012. Substance use and substance-related stress management included the validated Alcohol Use Disorder Identification Test (AUDIT-QF) for alcohol and modified questions from WHO for tobacco.¹³ Poor mental health days and life satisfaction were measured by adapting questions from Health-Related Quality of Life (HRQOL). Social support was measured through the Behavioral Risk Factor Surveillance System (BRFSS) question: "How often do you get the social and emotional support you need?"²⁰ Possible responses were: "Always", "Usually", and "Sometimes." Presence of social support was denoted for participants who answered "Always."

Burnout

The key outcome variable measured in this study was emotional burnout. Burnout was measured by the Single Item Burnout Measure from the Mini-Z, which measures emotional exhaustion and has been validated against the Maslach Burnout Index (MBI).^{14,15} Answers were dichotomized into burnout and no burnout. Students answering: "The symptoms of burnout that I'm experiencing won't go away. I think about frustration at work a lot", "I am definitely burning out and have one or more symptoms of burnout, such as physical and emotional exhaustion", "I feel completely burned-out and often wonder if I can go on", and "I am at the point where I may need some changes or may need to seek some sort of help," were considered to have burnout.^{14,15}

Data Analysis

Only fully completed surveys were included for analysis. Data was exported from Qualtrics to Microsoft Excel. Descriptive statistics were conducted to characterize demographic and lifestyle factors. Bivariate analyses including Chi-square were conducted to examine associations among demographic and lifestyle variables. Items with a p-value less than 0.05 were considered significant.

Results

One hundred forty-four students out of 892 completed the survey for a response rate of 16%. First-year medical students (49%) accounted for most respondents, followed by third-year medical students (35%). Almost half of the respondents (47%)

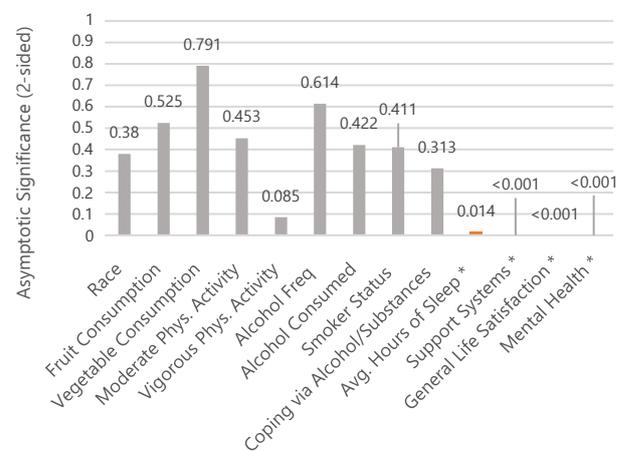
identified as non-white, representing Hispanic/Latinx (17%), Asian or Pacific Islander (15%), Black/African-American (7%), and other (8%). This is reflective of the racial demographic layout of this institution.

Burnout and Life Satisfaction

Eighty-eight medical students (61%) met the burnout criteria per the Single-Item Burnout Questionnaire. Only 5% of students reported no symptoms of burnout.

Most students were satisfied (64%) or very satisfied (26%) with their life; only 10% reported dissatisfaction. Over half (56%) of participants had 7 or more days of poor mental health in a month. Both life satisfaction ($p < 0.001$) and days of poor mental health ($p < 0.001$) were significantly associated with student burnout ([Figure 1](#)).

Figure 1. Chi-Square Results of Medical Student Burnout and Lifestyle Factors for 144 South Florida Medical Students, 2021.



* indicates significance at a $p < 0.05$ level

Lifestyle Behaviors

Most students (63%) averaged 7-9 hours of sleep per night while 36% got 6 hours of sleep or less per night.

Most students reported eating at least 1 serving of fruits (86%) and vegetables (94%) daily. Most students (54%) exercised less than 150 minutes per week, with 29% having less than 30 minutes of vigorous exercise per week. Nearly all students reported abstaining from tobacco use (92%). Of the students who drank alcohol (88%), 60% drank no more than 4 times a month. Typically, 1-2 drinks were consumed per sitting (57%); however, 10% of students averaged 5 or more drinks per sitting. Twenty-nine percent of students mentioned using substances as a stress-coping mechanism. Thirty percent of students reported "always" receiving emotional support. The largest category of students (43%) reported "usually" receiving emotional support, whereas 27% stated only "sometimes" receiving emotional support.

Table 1. Demographics and Lifestyle Behaviors of Participating South Florida Medical Students, 2021.

Behavioral Factors	Frequency (n)	Percent (%) (n = 144)
What year of medical school are you in?		
M1	71	49.3
M2	19	13.2
M3	50	34.7
M4	4	2.8
Which best describes your race?		
Asian or Pacific Islander	22	15.3
Black or African American	10	6.9
Hispanic or Latino	24	16.7
Other	11	7.6
White	77	53.5
How many servings of fruit do you usually eat or drink each day? Think of a serving as being about 1 medium piece, or ½ cup of fruit, or ¾ of cup of fruit juice.		
0	20	13.9
1	54	37.5
2	54	37.5
3+	16	11.1
How many servings of vegetables do you usually eat or drink each day? Think of a serving as being about 1 cup of raw leafy vegetables, ½ cup of other cooked or raw vegetables, or ¾ cup of vegetable juice.		
0	8	5.6
1	48	33.3
2	53	36.8
3+	35	24.3
On a typical week, how much time do you spend in total on moderate and vigorous physical activities where your heartbeat increases and you breathe faster (e.g., brisk walking, cycling as a means of transport or exercise, heavy gardening, running or recreational sports). <i>Only include activities that lasted at least 10 minutes at a time.</i>		
Less than ½ an hour (less than 30 minutes)	26	18.1
½ an hour - 1 ½ hours (30-90 minutes)	22	15.3
1 ½ - 2 ½ hours (90-150 minutes)	30	20.8
2 ½ - 5 hours (150-300 minutes)	36	25.0
More than 5 hours (more than 300 minutes)	30	20.8
How much of the time that you spend on physical activities in a typical week, which you indicated above, do you spend in total on vigorous physical activities? This includes activities that get your heart racing, make you sweat, and leave you so short of breath that speaking becomes difficult (e.g., swimming, running, cycling at high speeds, cardio training, weight-lifting or team sports such as football). <i>Only include activities that lasted at least 10 minutes at a time.</i>		
Less than ½ an hour (less than 30 minutes)	42	29.2
½ an hour - 1 ½ hours (30-90 minutes)	32	22.2
1 ½ - 2 ½ hours (90-150 minutes)	31	21.5
2 ½ - 5 hours (150-300 minutes)	23	16.0
More than 5 hours (more than 300 minutes)	16	11.1
How often do you have a drink containing alcohol?		
Never	17	11.8
Monthly or less	34	23.6
2-4 times a month	52	36.1
2-3 times a week	36	25.0
4 or more times a week	5	3.5
How many drinks containing alcohol do you have on a typical day when you are drinking?		
0	12	8.3
1 or 2	82	56.9
3 or 4	35	24.3
5 or 6	11	7.6
7 or 8	4	2.8
Do you smoke or use tobacco products (including e-cigarettes)?		
No	133	92.4
On occasion	8	5.6
Yes	3	2.1
In the last 30 days, did you use alcohol, tobacco products, or other substances as a stress-coping strategy?		
No	99	68.8
Unsure	4	2.8
Yes	41	28.5
How many hours do you usually sleep on weekdays or workdays?		
5 hours or less	5	3.5
6 hours or less	47	32.6
7-9 hours	90	62.5
9 hours or more	2	1.4
How often do you get the social and emotional support you need?		
Always	43	29.9
Usually	62	43.1
Sometimes	39	27.1

Table 1. (Continued).

In general, how satisfied are you with your life?		
Dissatisfied	14	9.7
Satisfied	92	63.9
Very satisfied	38	26.4
Now thinking about your mental health, which includes stress, depression, and problems with emotions, for how many days during the past 30 days was your mental health not good?		
0-6 days	64	44.4
7-13 days	43	29.9
14-20 days	17	11.8
21-30 days	20	13.9
Overall, based on your definition of burnout, how would you rate your level of burnout?		
I enjoy my work. I have no symptoms of burnout	7	4.9
Occasionally I am under stress, and I don't always have as much energy as I once did, but I don't feel burned-out	49	34.0
I am definitely burning out and have one or more symptoms of burnout, such as physical and emotional exhaustion	60	41.7
The symptoms of burnout that I'm experiencing won't go away. I think about frustration at work a lot	13	9.0
I feel completely burned-out and often wonder if I can go on. I am at the point where I may need some changes or may need to seek some sort of help	15	10.4
Presence of Burnout		
No	56	38.9
Yes	88	61.1

To determine the effects of specific lifestyle factors on burnout, a bivariate Chi-squared analysis was performed (Figure 1). Lack of social support, increased days of poor mental health, and decreased life satisfaction was significantly associated with student burnout ($p < 0.001$). In addition, we found a significant association between decreased hours of sleep per night and burnout ($p < 0.02$). There was a decreased trend between minutes of vigorous exercise and burnout ($p = 0.085$). No association was found between burnout and diet, exercise, or alcohol/tobacco use. Separately, no association between race and burnout was found in this sample.

Table 2. Chi-Square Results of Medical Student Burnout and Lifestyle Factors for 144 South Florida Medical Students, 2021.

Burnout Chi-Square Test	Value	Df	Asymptotic Significance (2-sided)
Race Pearson χ^2	4.196	4	0.38
Fruit Consumption Pearson χ^2	2.236	3	0.525
Vegetable Consumption Pearson χ^2	1.043	3	0.791
Moderate Phys. Activity Pearson χ^2	3.669	4	0.453
Vigorous Phys. Activity Pearson χ^2	8.187	4	0.085
Alcohol Freq Pearson χ^2	2.671	4	0.614
Alcohol Consumed Pearson χ^2	3.886	4	0.422
Smoker Status Pearson χ^2	0.676	1	0.411
Coping via Alcohol/Substances Pearson χ^2	2.325	2	0.313
Avg. Hours of Sleep Pearson χ^2	8.486	2	0.014*
Support Systems Pearson χ^2	13.183	2	<0.001*
General Life Satisfaction Pearson χ^2	21.983	2	<0.001*
Mental Health Pearson χ^2	28.633	3	<0.001*

Legend: * Indicates significance at a $p < 0.05$ level. Df, degrees of freedom.

Discussion

This study is one of the first to examine all six pillars of lifestyle medicine per the American College of Lifestyle Medicine (ACLM) in medical student burnout, which future studies can build upon.¹⁶ In our study, 61% reported burnout, consistent with previous studies that estimate half of American medical students experience burnout.⁶ Burnout has serious consequences, as

shown in our study where burnout was significantly associated with poor mental health and decreased life satisfaction. Sleep and social support were lifestyle factors that showed a significant association with burnout. No significant association between diet, exercise, or risky substance use and burnout was found, however, a decreased trend between vigorous exercise and burnout was seen which reflects other studies.^{8,9} Tobacco and binge alcohol use were rare in our sample. These findings do not diminish the importance of diet, exercise, or risky substance use. Rather, this study introduces new factors that lifestyle-based interventions can target to address burnout among medical students.⁵

Students who slept 6 or fewer hours reported higher levels of burnout than those who slept 7-9 hours, the amount recommended by the ACLM and CDC.¹⁷ This corroborates prior research showing burned-out medical students are more likely to experience sleep deprivation, often due to stress and academic demands.^{9,18} Chronic sleep deprivation can lead to depression, anxiety, and even substance abuse, all of which can decrease the quality of life and wellbeing of students who have barely begun their medical careers.^{8,9,18} Sleep deprivation may impact students' ability to learn and diminish empathy towards patients and classmates, which can damage their ability to build rapport and relationships.^{9,18}

While the connection between sleep and burnout is well-established, limited studies address the relationship between social support and burnout. This could be attributed to difficulty defining support but may also reflect the medical community's disregard for social support as a critical aspect of health. Only half of Americans claim to have "support all or most of the time."¹⁹ Medical school's academic demands worsen the availability of social support, leading to professional consequences.^{20,21} US medical students without social support are less likely to feel confident in their medical skills.^{7,10} Like US students, half of Trinidadian medical students (52%) experienced burnout, but those who lacked emotional support exhibited higher burnout and depressive symptoms.²⁰ Another study found poor social support in medical students was positively associated with psychological distress and poor academic self-perception.²²

In parallel, our study found that students who reported consistent access to emotional support were significantly less likely to experience burnout. These findings suggest the need for more peer-to-peer support in medical schools by prioritizing a program's social aspects, such as school-sponsored extracurriculars.^{21,22} Additionally, medical students should be encouraged to nurture social relationships that existed before medical school. This includes scheduled breaks and absence policies enabling students necessary time off without repercussion, particularly in times of personal tragedy when risk of burnout increases.²³

The availability of support—or lack thereof—may influence important lifestyle factors such as sleep and impact medical students' interpersonal relationships.²¹ The role of social support in burnout underscores the importance of diverse campuses. The ability to find support in shared communities may be critical to preventing burnout and promoting academic success, as studies

show lack of support contributes to a negative learning environment.^{7,22}

The concept of social support as a vital sign is gaining popularity as studies show social support is a reliable predictor of longevity comparable to traditional risk factors.²⁴ Previous research on student burnout and lifestyle factors noted lack of a social support measurement as a study limitation.²⁵ Our study addresses this, reiterates social support's role in mitigating medical school burnout, and highlights it as a potential target for intervention.

Overall, our findings may support the use of lifestyle interventions to reduce the risk of burnout in medical students.^{1,17-19} Incorporating individual and structural interventions in medical schools to reduce burnout in medical students has been shown to be effective in reducing it.²⁶ Perhaps a prescription for social support could be added to supplement wellness.²⁴ However, the effectiveness of this would need to be further evaluated.

Strengths and limitations

We note our study is limited in response rate and lacks demographic details regarding gender and age. In addition, the COVID-19 pandemic introduced a landmark change in the medical school experience that may have been captured in this study. Classes were conducted virtually, and students had limited opportunities to socialize with peers and faculty, which may have contributed to a lack of social support. Additionally, generalization may not apply due to low response rates leading to potential selection bias, as the study was conducted at a single private medical school in Florida, and burned-out students may be more likely to respond to a burnout survey. Furthermore, self-reported data confers a response bias which may falsely represent the true practice of lifestyle behaviors or level of burnout in students. While validated using the Single Item Burnout Measure limits result details, medical student burnout could be more thoroughly described with a full MBI survey. Lastly, as a cross-sectional study, this study does not account for how fluctuating academic stressors impact levels of burnout or lifestyle behaviors. However, this study captured a racially diverse medical student population, which contrasts with other American medical education research which historically has captured the white-predominant population of US medical schools.

Conclusion

Early preliminary data suggests that lifestyle factors such as sleep and social support may significantly influence burnout rates in medical students. Further studies are needed to expand on the role social support play in medical student burnout.

Summary – Accelerating Translation

Title: From Student to Physician: Determining Which Lifestyle Behaviors May Be Risk Factors for Burnout at a South Florida Medical School

Main Problem to Solve: Burnout is a growing issue among American healthcare providers. Burnout is defined as physical, emotional, or mental exhaustion and is often seen as a type of work-related stress. In medicine, burnout can lead to decreased empathy for patients, increased medical

errors, and career regret. However, burnout is not just limited to physicians. Medical students training to become medical doctors experience burnout even before entering the workforce. A survey of medical students estimated around half of medical students experienced burnout. With the national healthcare shortage in a critical stage, it is important to identify and mitigate potential burnout risk factors in these budding physicians.

Aim of Study: Therefore, a study was conducted to better understand lifestyle behavior and rates of burnout among US medical students. The goal was to identify the rates of burnout and types of lifestyle behaviors in medical students and see if there were any specific lifestyle behaviors that might be linked to burnout.

Methodology: In 2021, a survey was distributed to all students in a South Florida medical school. This survey compiled questions for validated surveys measuring lifestyle behaviors such as diet, exercise, sleep, stress management, social support, and risky substance use. Another validated question was included to measure burnout. One hundred forty-four students responded to this voluntary survey, and the data was analyzed to determine the effects of these lifestyle behaviors on the likelihood of student burnout.

Results: In our study, 61% of the medical students met the criteria for burnout. Only 5% of students reported absolutely no symptoms of burnout. Regarding lifestyle factors, 86% of students ate at least 1 serving of fruit daily, while 94% ate at least 1 serving of vegetable daily. Fifty-four percent of students exercised less than 150 minutes per week, with 29% of students having less than 30 minutes of vigorous exercise per week. Most students averaged 7-9 hours of sleep nightly, but 36% got 6 hours or less. Only 8% reported tobacco use, while 88% reported alcohol use. Of those who drank, 60% drank no more than 4 times a month. Typically 1-2 drinks were consumed per sitting; however, 10% of students averaged 5 or more drinks per sitting. Twenty-nine percent of students mentioned using substances as a stress-coping mechanism. Only thirty percent of students reported they consistently received emotional support. Forty-three percent of students reported "usually" receiving emotional support, whereas 27% stated only "sometimes" receiving emotional support.

Medical students who were burned out were significantly more likely to have poor mental health and decreased life satisfaction. In terms of lifestyle factors, medical students who had less than the recommended 7 to 9 hours of sleep had increased rates of burnout. In addition, medical students who reported having less social support also had increased rates of burnout. There was no link between the number of fruits and vegetables eaten, the frequency of exercise, or tobacco and alcohol use and burnout in this study.

Conclusion:

In our study, 61% reported burnout, consistent with previous studies that estimate half of American medical students experience burnout. Burnout has serious consequences, as shown in our study where burnout was significantly associated with poor mental health and decreased life satisfaction. Sleep and social support were the lifestyle factors that showed a significant association with burnout in our study. Lack of sleep is a well-established factor in burnout. Chronic sleep deprivation is known to cause decreased quality of life by increasing stress, anxiety, and depression. These feelings may affect a student's ability to perform academically or build relationships with patients or peers. Social support as another factor in burnout is significant because social support is increasingly being viewed as a critical aspect of health. Studies show social support is a reliable predictor of longevity, as much as other traditional risk factors like smoking. The role of social support in burnout underscores the importance of diverse campuses. The ability to find support in shared communities may be critical to preventing burnout and promoting academic success, as studies show lack of support contributes to a negative learning environment, decreased confidence, and higher rates of depression.

Previously, lifestyle-based interventions have been effective in reducing burnout in medical students. Our findings suggest using lifestyle interventions to specifically target lack of sleep and lack of social support in medical school may help reduce the risk of student burnout. However, further studies are needed to expand on the role social support plays in medical student burnout.

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Walking the Walk: A Review of Medical Students' Perspective of a Surgical Theatre as the New Classroom

Tamara A. Mallia,¹ Sarah Cuschieri.²

Abstract

Medical school trains eligible students for a medical degree (MD). As part of the clinical years in the MD program, students attend surgical theatre sessions to learn medical concepts from hands-on experience in the theatre. This review aims to provide a comprehensive overview of the role surgical theatre plays in the learning process and clinical experience of medical students. Google Scholar, PubMed and NCBI databases were searched for articles from 1990 to March 2022 using the search terms 'Operating Room' or 'Operating Theatre' or 'Surgical Theatre' and 'Learning', 'Medical Students' and 'Surgeons'. Only articles on medical students' perceptions on their learning experience in the surgical theatre were included. Thirty-four articles were eligible for inclusion. Unpreparedness, anxiety, lack of clear learning outcomes, fear and intimidation were the most common reported experiences by students. These demotivate medical students from attending theatre, along with poor surgical field visibility, resulting in a negative learning experience. Positive experiences during theatre time were more likely to attract students to choose a future surgical career. Limitations include the inclusion of surgical residents' perspectives and the exclusion of other surgical team members' perspectives. Studies included students across different clinical years, and results were primarily based on subjective perceptions. Evidently, the surgical theatre is a great learning opportunity for medical students. However, for this learning environment to be beneficial, students need to be included during surgical discussions and procedures. Additionally, clear learning outcomes need to be present whilst adequately training students prior to their first surgical attendance.

Introduction

Medical school is an opportunity for medical students to acquire new skills and practical competencies. This five-year journey includes being exposed to different specialties, which enables the formation of career preferences.^{1,2} Surgical competence comprises several elements, namely anatomical, physiological and clinical knowledge, technical skill, clinical judgement and professionalism.³ As a result, surgical exposure through surgical rotations is vital in medical education since the operating theatre is rich in educational resources. The operating theatre enables a change in the teaching domain, which in turn, allows for the heightening of the senses. The various stimuli present in a theatre welcome all medical students of any learning style.³ However, current literature not only addresses the benefits of surgical rotations but also its challenges in optimizing medical education.^{3,4}

A medical student's perspective and clinical experience of medical school changes once one steps into the surgical theatre for the first time. The monitors' sounds, the nurses all neatly walking past each other, and the "smell of burning flesh" heighten the senses, making the surgical theatre an unforgettable experience.^{3,5,6} As a result, the surgical theatre has become a

significant teaching tool among medical students whereby surgical conditions and procedures are discussed, observed, and, if possible, participated upon. Thus, the surgical theatre environment can enhance medical student pro-activity for their own learning and knowledge retention. Given the aforementioned stimuli, it targets all forms of senses, enabling all students with different learning styles (visual, auditory, sensory) to find the surgical theatre fruitful.⁵

Medical education, as defined by the General Medical Council (GMC), is there to certify graduates who are able to make effective decisions and function properly in their first year as a physician.⁷ Despite such regulations, studies show that 27.4% of medical students do not believe they will be taught suturing skills by the end of their medical education.^{8,9} The surgical theatre has unfortunately been perceived as a poor "teacher" because first-year doctors do not perform surgical procedures alone. As a result, medical students find this teaching irrelevant to their near future job.^{10,11} Conversely, generic clinical skills are a recommended priority and are a focus point for medical students.^{8,10,12}

This literature review aims to provide a comprehensive overview of the role the surgical theatre plays as part of the learning

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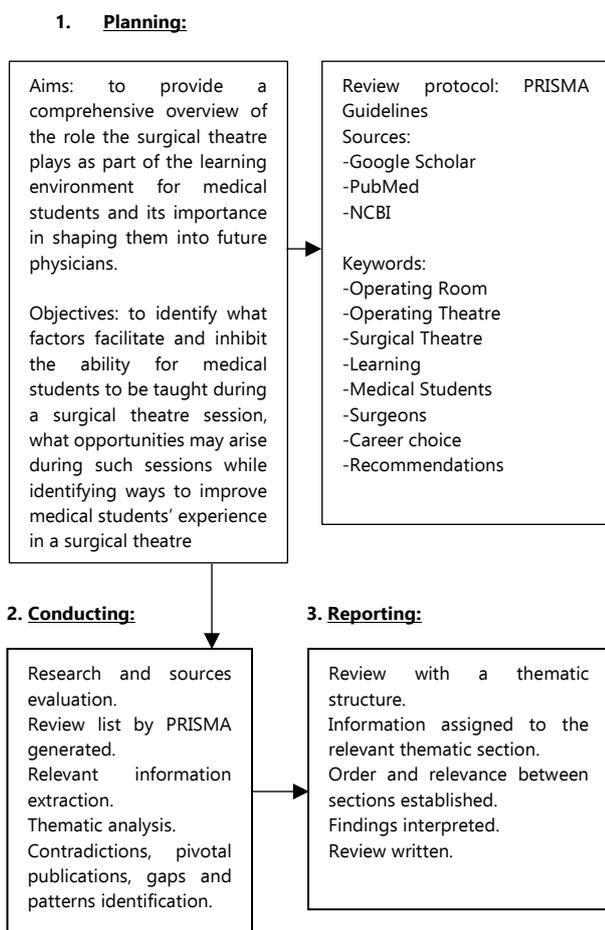
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environment for medical students and its importance in shaping them into future physicians. The objective is to identify what factors facilitate and inhibit the ability of medical students to be taught during a surgical theatre session and what opportunities may arise during such sessions while identifying ways to improve medical students' experience in a surgical theatre.

Methods

A critical narrative analysis was followed by undergoing systematic identification of the articles related to surgical theatre learning by medical students and teaching by surgeons while identifying factors that may facilitate or hinder this interaction.

Figure 1. Study Flow Diagram.



As shown in [Figure 1](#), literature searches were performed through Google Scholar, PubMed and the National Library of Medicine databases. The keywords and terms used included 'Operating Room' or 'Operating Theatre' or 'Surgical Theatre' and 'Learning' and 'Medical Students'. The latter term was switched to 'Surgeons' to assess the surgeons' perspective of medical students learning in the surgical theatre. The 'Career Choice' term was used to assess the effect of the theatre learning experience on medical students when choosing a specialty. The 'Recommendations' term was used to analyze any tips other

medical students or surgeons gave to facilitate learning in the surgical theatre. Screening of papers [1990-2022] was done by both authors during July 2022.

Inclusion criteria included research papers originating from any study design published between 1990 and 2022. The only exception was an early study done in 1908 that paved the way for later studies that confirmed the main results of the study in 1908. Opinion articles written by medical students pertaining to their perspective of surgical rotations were included. Exclusion criteria include papers not written in English, opinion articles from other health care workers' (HCW) perspectives and articles targeting other health care student perspectives. Furthermore, published abstracts without access to the full text were also excluded. Search results identified 508 papers. After duplicate removal and selection according to the aforementioned inclusion and exclusion criteria, 34 articles were included. The article selection process is shown in [Figure 1](#).

Papers included underwent a full thematic analysis. Additionally, data extracted included the year of publication, country of origin, themes identified, research method and results. The themes identified were grouped according to relevance and then integrated to address all themes discussed by the current literature in the most cohesive way possible. These are shown in table 1 in the results section.

Results

Thirty-four papers were included and underwent full-text analysis and thematic review. [Table 1](#) illustrates the themes identified in the articles used.

The Sterility Procedure and the Surgical Experience

Sterility techniques and protocols, namely, environmental cleaning, hand hygiene, pre-operative patient skin preparation, surgical gowning and general techniques of maintaining a sterile field, were described among studies.^{13,14} Additionally, sterility accommodations are available for various religious views to prevent embarrassment due to inadequate preparation.¹⁵

The surgical theatre is perceived as uncomfortable by medical students due to pre-established relationships among surgical team members.¹⁶⁻¹⁸ Additionally, students report fear of contaminating sterile equipment¹⁹ and feeling insecure about their behavior during theatre.^{20,21} Others report fear, anxiety and shame of syncope or protocol violation.²² Other studies report fear of incompetence and insecurity, humiliation and intimidation.^{3,23,24} Evidently, only a minority of medical students reportedly described a positive theatre experience.²⁵ The surgical theatre experience was also perceived as multi-disciplinary.⁵

Medical students were reported to focus more on generic clinical skills^{10,12} and perceived the surgical theatre as a relatively poor "teacher" of medical education.¹⁰ Additionally, medical students report perceiving their medical education as less likely to teach suturing skills.

Table 1. Primary Sources and Summary of Information in the Review of Medical Students' Perspective about Surgical Theatres.

Author	Year	Country	Themes Identified
Yerkes RM. <i>et al</i> ⁶⁰	1908	USA	Students report fear of contaminating sterile equipment especially those unfamiliar to theatre etiquette.
Lewis L. <i>et al</i> ⁶⁷	2000	USA	Recorded surgeries incorporated in tutorials or lecture may aid learning.
Taylor I. ¹¹	2003	UK	Medical students focus on generic clinical skills. Active participation aids visibility during theatre, hence, is to be discussed by the surgeon and students. Topics taught by other staff members will depend on their specialty, this aids students' learning.
Lyon PM. <i>et al</i> ⁶	2003	Australia	Surgical theatre is perceived as uncomfortable due to pre-established relationships between team members.
Lyon PM. ¹⁸	2003	Australia	Surgical theatre is perceived as uncomfortable due to pre-established relationships between team members. Medical students commonly feel unwelcome in theatre. Clear learning objectives are commonly absent. Shifting positions and eating before theatre are preventive of syncope.
Stark P. ³⁶	2003	UK	Longer procedures negatively correlate with medical student attendance.
Schwind CJ. <i>et al</i> ⁸	2004	USA	A positive learning experience is enhanced if the surgeon acts as a positive role model and the staff supportive in teaching medical students.
Agha RA. <i>et al</i> ⁸	2005	UK	The surgical theatre is perceived by students as a poor "teacher" in their medical education. Medical students focus on generic clinical skills.
Fernando N. <i>et al</i> ²	2007	UK	Surgeons' and students' opinions of their learning objectives and what the level of student participation in theatre differ. "Friendliness and approachability" were ranked vital towards a positive learning experience whilst, most students report feeling burdensome in theatre.
Fernando N. <i>et al</i> ⁴	2007	UK	Consultants are unsure of the learning objectives to be covered during theatre. A minority of students describe a positive theatre experience. Unable to visualize the procedure negatively impacted students' learning.
Lupien SJ. <i>et al</i> ⁵	2007	Canada	Anxiety negatively impacts students' performance and learning.
McIntyre TP. <i>et al</i> ⁸	2008	USA	Teleconferencing guarantees visibility and students' learning without disturbing the surgeon's work.
Karle H. ¹	2010	Denmark	Medical degree (MD) program organization.
Wilhelmsson B. ⁴	2012	Sweden	Outdoor environment reinforces learning.
Knight WR. <i>et al</i> ⁷	2013	UK	Surgical theatre is perceived as uncomfortable due to pre-established relationships between team members. Feeling unsafe or awkward prohibits learning. Students cautiously reflect on how worthwhile it is to attend long periods of surgery in comparison to other methods of learning.
Ravindra P. <i>et al</i> ⁷	2013	UK	Students taught by theatre staff found the surgical theatre more beneficial. Teaching should be delegated among all team members. Surgical theatre attendance was reported as poor and mainly hindered by absent learning objectives, absent participation opportunities, insufficient preparation during procedures and feeling unwelcome. Longer procedures negatively correlate with medical student attendance.
Chapman SJ. <i>et al</i> ³²	2013	UK	Students report feeling insecure about their behavior in theatre. Most students report feeling burdensome on theatre staff.
Nagji A. <i>et al</i> ⁴	2013	Canada	Students report feeling insecure about their behavior in theatre. An optional theatre module can positively impact students' learning experience and personal development.
Bowrey DJ. <i>et al</i> ⁹	2014	UK	Anxiety, fear and shame are commonly felt by students in theatre mainly due to concerns of violating theatre protocols or fear of syncope. Students who felt welcome in theatre were more likely to attend and learn.
Stone JP. <i>et al</i> ¹	2015	Canada	Students report fear of seeming incompetent.
Zundel S. <i>et al</i> ³	2015	Germany	Students report feeling insecure about their behavior in theatre. Knowing patients prior to surgery can positively impact learning.
Hartmann EK. ³	2016	Australia	Student's perspective of the first surgical theatre experience. Australian universities introduced a "surgical skills" module to prepare students prior to surgery.
Gaines S. <i>et al</i> ³	2017	USA	Sterility protocols.
Barnum TJ. <i>et al</i> ⁰	2017	USA	A Chicago university organizes orientation days to prepare students prior to theatre. The surgeon should remain updated with academic curricula. The surgeon introducing the students to the staff, aids their multi-disciplinary learning.
O'Neill R. <i>et al</i> ¹	2018	USA	Surgeons' and students' opinions of their learning objectives in theatre differ. A significant number of surgeons and residents report students' presence in theatre as an asset.
Hexter AT. <i>et al</i> ³	2018	UK	A curriculum ensures adequate preparation of students prior to theatre and discussion of relevant topics by surgeons.
Jensen RD. <i>et al</i> ⁶	2018	Germany	Students ought to focus more on learning the surgeon's behavioral attitudes rather than surgical technique.
Croghan SM. <i>et al</i> ⁶	2019	UK	Students' surgical theatre experience: lack of clear learning objectives, fear, anxiety, humiliation, intimidation, lack of participation and visibility hinder their learning experience. The experience is perceived as multi-disciplinary. Burdensome and welcoming environments significantly impact learning. Display units can aid visibility of procedures, enhancing learning. Shorter surgeries may provide more teaching per unit time.
Twigg V. <i>et al</i> ⁶	2020	UK	Medical education is perceived by students as less likely to teach suturing skills.
Kent F. <i>et al</i> ⁰	2021	Scotland	The surgical theatre is perceived by students as a poor "teacher" in their medical education. It is perceived as an uncomfortable environment. Feeling unsafe or awkward prohibits learning. Medical students commonly feel unwelcome in theatre. Clear learning objectives are commonly absent. Participation aids learning during theatre.
Abdelwahab R. <i>et al</i> ⁵	2021	USA	Sterility accommodations for students of various religions to prevent embarrassment due to inadequate preparation.
Hunukumbure AD. <i>et al</i> ⁹	2022	UK	Acquiring knowledge on sterility and theatre etiquette, planning ahead via theatre lists prior to theatre, and follow-up after surgery aid students' learning.
Azevedo Sansoni G. <i>et al</i> ⁵	2022	Italy	Practical knowledge namely, suturing, scrubbing in and good surgical practice enhanced medical students' surgical education.

Preparing Medical Students for Better Surgical Education

Studies report that medical students perceive the theatre as uncomfortable and stimulate feelings of unsafety and awkwardness. As a result, students report feeling inhibited from learning and overall unwelcome.^{11,16-18}

Hartmann EK (2016) reports how Australian universities have introduced a "surgical skills" module to better prepare students prior to surgery.⁵ Notably, a Chicago university was reported to organize orientation days to prepare students for theatre.²⁶

Surgical Theatre Attendance

A study reports how students describe their ongoing reflections about how worthwhile it is to attend long hours of surgery compared to other learning methods.¹⁷ In fact, further studies report longer procedure hours as negatively correlated to medical student attendance at surgical theatres.^{4,27} The former study also reports other attendance hindrances, namely, absent learning objectives, absent participatory opportunities, insufficient preparation prior to procedures and the aforementioned unwelcoming feeling.²⁷

The Perception of Medical Students, Surgeons and Surgical Residents about the Theatre Experience

Various literature reports how surgeons, surgical residents and students have different perspectives.²⁸ Namely, the learning objectives and level of participation in theatre.²⁹ Also, whilst a significant proportion of surgeons and surgical residents perceive students' presence in theatre as an asset,²⁸ a significant proportion of medical students report feeling unwelcome.¹¹

Factors Affecting Surgical Education in Theatre

Various studies report elements that aid learning during surgical theatre, namely, active participation,^{11,12} multi-disciplinary teaching,^{12,27} recorded surgeries incorporated in tutorials or lectures³⁰ or teleconferencing,³¹ clear learning objectives¹⁸ or curricula³² availability, "friendliness and approachability",²⁹ the overall stimulatory environment,⁶ optional theatre modules,²¹ feeling welcome,²² better visibility,¹² adequate preparation prior to surgery,³³ and shorter surgery times.³ Additionally, knowing the patient pre-operatively²⁴ and following up post-operatively³³ were also reported as positive factors in medical education. Conversely, poor procedure visualization,²⁵ anxiety,³⁴ feelings of unsafety or awkwardness,¹⁷ among others aforementioned, were reported as significant inhibitors of learning in theatre sessions.

Students report clear learning objectives are commonly absent^{11,18} and tend to feel burdensome or unwelcome in theatre.²⁹ In fact, literature reports consultants are unsure of the learning objectives to be covered.²⁵ Nonetheless, medical students emphasize how the discussion of relevant topics and surgeons remaining updated to curricula aid their learning during theatre sessions.²⁶ Medical students recommend eating before theatre sessions and shifting positions to prevent syncope.¹⁸ Additionally, surgeons acting as positive role models and

supportive staff members were deemed a positive learning influence during theatre.³⁵ The latter was found to be better facilitated if surgeons introduced the students to the surgical team members.²⁶ In fact, students were recommended to focus more on learning the surgeon's behavioral attitudes rather than surgical technique during theatre sessions.³⁶ Additionally, display units can aid the visibility of procedures.³

Discussion

The Surgical Theatre Experience

On visiting the surgical theatre for the first time, most medical students experience anxiety as they find it challenging to fit into the coordinated teamwork set out by the surgical team.⁵ Upon stepping into the scrubbing room, a new medical student will face a range of specific sterility protocols and procedures they may have never encountered before, which may be daunting.

Sterility is defined as an object free from any microorganisms.³⁷ Sterile techniques are there to reduce the rate of surgical site infections (SSIs), and despite some variations among clinical institutions and situations, all try to maintain an aseptic surgical theatre. Such techniques include environmental cleaning, hand hygiene, pre-operative patient skin preparation, surgical gowning and general techniques of maintaining a sterile field.^{13,14} Generally, every person entering the surgical theatre has to change into scrubs, wear hair caps, change shoes and ensure bareness below the elbow, among other sterility protocols, namely, scrubbing in.^{13,14} Furthermore, accommodations are made for hijab wearers among other religious variations as to maintain sterility without affecting the sterility process.¹⁵

Preparing Medical Students for a Better Teaching Experience

Medical students have frequently reported that the theatre environment is uncomfortable due to the aforementioned etiquette and pre-established relationships between surgical team members.^{11,16-18} Therefore, medical students may feel unsafe or awkward because of the surgical team's attitudes, which might prohibit their learning and surgical interest.^{11,17} In fact, a common theme mentioned by medical students was found to be the feeling of being unwelcome in a theatre.^{11,18}

Ensuring a positive learning experience by attending theatre sessions was attempted by many medical schools. Australian universities introduced a module entitled "surgical skills" as part of their pre-clinical programs with the aim to incorporate theatre experience with medical education. The program teaches medical students how to scrub for a surgical operation whilst it also teaches students the theatre team's various roles. This ensures that medical students acquire knowledge on sterility, scrubbing in and gowning among other theatre etiquette which will enable the students to focus on surgical knowledge acquisition during the actual surgical procedures.^{5,33} Moreover, a Chicago university provides students with orientation days to address topics on theatre etiquette and answers any questions the students may have before attending their first surgery.²⁶ Notably, additional accommodations are made for all religious and cultural attitudes

to prevent embarrassment or humiliation due to inadequate preparation for the surgical theatre protocols.¹⁵

Learning Objectives and Opportunities at the Surgical Theatre

Setting clear learning outcomes by medical schools is vital to emphasizing the importance of teaching in the theatre. However, a study conducted by a New Jersey medical school reveals that learning outcomes for surgeons and medical students differ.²⁸ Namely, surgeons intend to discuss the clinical application of medical conditions, whilst medical students aim to learn surgical skills.^{28,29} A survey noted that surgeons were more inclined to cover the importance of medical decisions and the understanding of pathology during surgical theatre, which contrasted with what medical students were inclined to discuss during this period. Yet, surgeons and medical students identified that anatomy teaching is valuable and should be discussed during surgery.²⁸ Therefore, the establishment of a clear outline of the learning objectives with an official curriculum by medical schools ensures that important and relevant topics are discussed by the surgical team during theatre. This will also provide a guide for medical students and ensures that they are well-prepared before attending a surgical operation.³² Unfortunately, a survey reports that less than half of the surveyed medical students confirmed the presence of clear learning objectives in their curricula.^{11,18} Interestingly, another study noted that consultants are also unsure of the learning objectives that should be covered during theatre sessions.^{10,24}

Furthermore, medical students perceive active participation during surgical theatre sessions as essential to their learning experience.³⁸ This was termed a "hidden curriculum".¹¹ In fact, studies suggest that students should focus more on observing the surgeon's behavioral attitudes when interacting with staff, patients and difficult circumstances as opposed to surgical techniques.³⁶ A survey reveals that medical students' and surgeons' opinions of how much participation should be allowed varies.²⁹ Actively participating or "scrubbing in" allows a better view of the operation and better teaching of practical skills, namely, suturing.¹² Studies recommend that the level of participation is to be discussed whilst setting the learning outcomes between the surgeon and the students. This should also depend on the faculty's curriculum and the surgical case at hand.¹² As a result, it is important for the attending surgeon to remain updated with the academic curricula and choose the right cases for his students both for observation and participation purposes.²⁶

Other studies propose that students acknowledge the surgical theatre as a holistic learning experience, enhancing students' ability to adapt to their expectations and overall satisfaction while attending the surgical theatre.³ On busy theatre days, when the surgeon is unable to attend to students, it would aid if the surgeon was to introduce his students to the surgical team. As a result, students would be more confident to maximize their learning by seeking the teaching provided by the other team members. In fact, studies have outlined how a surgeon portrays that when s/he is unable to teach, the students should ask the other team members to teach them during the surgery.²⁶

Moreover, the teaching contributed by the different staff members will depend on their specialty. Therefore, whilst a scrub nurse can teach the students about surgical instruments and sterility procedures, an anesthetist can teach students about anesthetic choice and intraoperative monitoring.¹² As a result, interprofessional learning is enhanced, and medical students can better appreciate the multi-disciplinary approach taken towards the patient's safety and well-being.^{12,26} In fact, it was reported that students who were taught by theatre staff found the surgical theatre experience more beneficial.²⁷ The same study suggested that teaching should be the responsibility of the whole surgical team. Proper teaching delegation among staff members can provide the students with a more efficient and consistent learning experience.¹²

Attendance at the Surgical Theatre

Studies have recommended that medical student attendance to surgical theatre ought to be mandatory, yet 59% of medical students reported poor attendance, with less than 50% of medical students presented with opportunities to go to the surgical theatre.²⁷ The hindering factors that affect the attendance rate in a surgical theatre were noted to be the lack of clear learning goals, the lack of opportunity for medical students to scrub in, insufficient participation during procedures and feeling unwelcome in theatre. Interestingly, induction sessions prior to the surgical theatre attachments had no effect other than adequately preparing medical students for the surgical theatre. Moreover, receiving negative comments from surgeons did not inhibit attendance but affected their learning experience.²⁷

What impacts learning in the Surgical Theatre?

Various factors contribute to the effectiveness of the surgical theatre as a learning environment. Overall, a positive learning experience is enhanced if the surgeon acts as a positive role model to the students by being friendly and interactive with students and explaining the surgical procedure. The rest of the surgical team is recommended to be helpful and supportive in the medical students' learning experience.³⁵

Emotions and Feelings

Interviews with clinical medical students revealed that negative feelings around the surgical theatre, namely, anxiety, fear and shame were common.²² These commonly originate from students' concerns about violating theatre protocols and fear of syncope.^{5,22} Although shifting positions and eating before theatre prevent episodes of syncope.^{18,22}

Fear is a strong emotional response to actions that can have a detrimental impact on the patient. In the surgical theatre setting, medical students report fear of contaminating sterile equipment especially those unfamiliar to the theatre etiquette, including where to stand during a procedure and which doors are an entrance or an exit into the surgical theatre.^{3,19,32,36} Some students have also noted the fear of seeming incompetent.²³ Insecurity towards the surgical theatre is quite a general emotion, as various studies describe how insecure medical students feel regarding their own behavior in the surgical theatre.^{18,20,21,24} Similar feelings include embarrassment. Naturally, the aforementioned feelings

bring about anxiety which negatively affects medical students' performance and learning.^{3,19,22,34}

Attitudes Towards Medical Students During Theatre

Studies show that students who are made to feel welcome during surgical theatre sessions were more likely to attend theatre while enhancing their opportunities to learn.^{22,27} Yet, it was noted that only 7% of medical students describe a positive, welcoming experience in theatre.²⁵ Despite such studies not emphasizing the factors that define this welcoming environment, another study reports that 74% of medical students rank "friendliness and approachability" as the vital requirements towards positive theatre-based teaching.²⁹ Medical students reported feeling burdensome on the surgical staff.^{20,29} Notably, this feeling may not be mutual as 55% of surgeons and 66% of residents report medical students' presence as an asset.²⁸ Evidently, burdensome and welcoming environments can have a significant impact on learning.³

Visualization and Time Expenditure

Two important factors medical students value include the visibility of the surgical procedure and the time management surgical theatre demands against other learning modalities. It was noted that approximately 30% of students were unable to visualize "most of the operation", which significantly impacted their learning ability.²⁵ Indeed, it was emphasized how helpful display units can be through a head camera worn by the attending surgeon. Visibility is especially problematic in open surgeries since endoscopic procedures or those who use intraoperative imaging, like orthopedics and vascular surgery, may naturally provide adequate visibility. Despite their aid, such accommodations may be restricted due to costs or surgeon preferences. Nonetheless, good visibility can make the surgical theatre more enjoyable, and students tend to feel more welcome.³

Notably, time management is of utmost importance to medical students. Knight et al. (2003) confirmed that students cautiously reflect on how worthwhile it is to attend hours on end of surgeries against other learning modalities.¹⁷ Medical students' main objective throughout medical school is to ensure they pass their exams.³ Therefore, they frequently assess which learning tool is most efficient to reach their goal.^{3,18} In fact, a negative correlation between longer procedures and medical student attendance was established as this was perceived as "absolutely pointless".^{4,27} Another study hypothesized that shorter procedures might provide more teaching per unit time since they are associated with a less stressful environment whereby the student feels more comfortable to learn and the surgeon has plenty of time to teach.³

Alternatively, recorded surgeries incorporated in tutorials or lectures may aid learning.^{3,30} Open communication about whether or not the surgeon will be able to teach anything during surgical theatre time can also help students manage their time effectively.³ More novel interventions include teleconferencing for medical students to see a live procedure from the classroom.³¹ Such a modality will guarantee visibility and teaching without disturbing the surgeon's work.³¹

Recommendations for Better Learning and Teaching

A number of recommendations have been put forward as to how to enhance medical students learning outcomes during surgical theatre sessions. Medical students recommend planning ahead in accordance with the scheduled theatre lists. Knowing the patients prior to the procedure can positively impact learning.^{24,33} In fact, a medical student's personal reflection described not having enough time to prepare before theatre and finding the whole theatre experience "demoralizing." He narrates that not knowing answers to questions left him feeling "stupid", resulting in an overall negative learning experience.³³ Furthermore, following the whole patient journey from pre-operative assessment to the actual procedure and follow-up later on enhances the understanding and learning process for that particular surgery.³³ Hence, preparation is pivotal in the medical students' learning experience. An optional theatre module will enhance the understandability and enjoyability of the surgical experience as students will be able to engage during the sessions while enriching their learning. This also aids in the students' personal growth.²¹

Limitations

Naturally, this review is not short of its own limitations. Firstly, the aim was to identify articles targeting the perception of medical students and surgeons on the surgical theatre as a teaching tool. However, most research available includes medical students' perspectives only. Thus, surgical residents' perspectives were also included. Nonetheless, the surgical theatre is also an effective classroom for other health care students, namely, nursing and anesthesia students. However, including such health care professions was beyond the scope of this review. The studies chosen occurred in different countries and included medical students across different clinical years, resulting in restricted generalizability of perceptions. However, similar results were found across different universities and provide a global relevance. Furthermore, most articles use students' perceptions to measure the learning experience. Nonetheless, this qualitative factor can deem a poor objective measuring tool but seems a realistic aim of attaining what inhibits and facilitates learning.

Conclusion

Medical students experience unpreparedness, anxiety, lack of clear learning outcomes as part of their curricula, fear and intimidation when visiting the surgical theatre. However, there are different factors that can motivate and enhance the learning experience of medical students during a surgical operation, including increased visibility and inclusion during the procedure, among others. Surgical faculties can utilize the multi-disciplinary set-up and healthcare experience to formulate plans that better accommodate medical students on their path to becoming physicians. Additionally, both the faculty and students need to respect each other's perspectives to ensure that a teacher-student relationship is formed. Ultimately, a positive surgical theatre experience is more likely to attract students to choose a surgical career.

Future research is recommended targeting the different learning and teaching quality among different surgical specialties while

considering the different surgical theatre perspectives shared by both students and professionals concerning the integration of inter-professional teaching as part of the healthcare students' learning experience.

Summary – Accelerating Translation

The study entitled "Walking the Walk: A Review of Medical Students' Perspective of a Surgical Theatre as the New Classroom" was conducted at the University of Malta, Msida, Malta. This was authored by Tamara Attard Mallia and Dr Sarah Cuschieri to address the pivotal role the surgical theatre plays in medical and surgical education and the overall clinical experience for medical students. The objective is to identify what factors facilitate and inhibit medical students' learning during a surgical theatre session, and what opportunities may arise when attending such sessions whilst identifying ways to improve medical students' experience based on the readily available literature.

A critical narrative analysis was followed by undergoing systematic identification of the articles related to surgical theatre learning by medical students and teaching by surgeons, while identifying factors that may facilitate or hinder this interaction. Literature searches were performed through Google Scholar, PubMed and NCBI databases. The keywords and terms used included 'Operating Room' or 'Operating Theatre' or 'Surgical Theatre' and 'Learning' and 'Medical Students'. The latter term was switched to 'Surgeons' to assess the surgeons' perspective of medical students learning in the surgical theatre. The 'Career Choice' term was used to assess the effect of the theatre learning experience on medical students when choosing a specialty. The 'Recommendations' term was used to analyze any tips other medical students or surgeons gave to facilitate learning in the surgical theatre. Inclusion criteria included research papers originating from any study design published between 1990 and March 2022. The only exception was an early study done in 1908

that paved the way for later studies that confirmed the main results of the study in 1908. Opinion articles written from other HCW perspectives and articles targeting other health care student perspectives were excluded. Furthermore, published abstracts without access to the full text were also excluded. After careful selection depending on the aforementioned inclusion and exclusion criteria, 34 articles were included.

These articles underwent full-text analysis and thematic review to identify the relevant information provided by every article included in the review. Literature reports that medical students perceive the theatre as uncomfortable and anxiety-provoking due to surgical etiquette and pre-established relationships between the surgical team members. The poor attendance to theatre reported by several studies was mainly due to a lack of clear learning outcomes, opportunities, feeling unwelcome and insufficient preparedness. Medical students experience unpreparedness, anxiety, fear and intimidation when visiting the surgical theatre, all of which inhibit medical education. Factors facilitating learning during surgical theatre sessions include increased visibility, inclusion during the procedure, feeling welcome and previously set learning objectives. A number of recommendations have been put forward as to how to enhance medical students' learning outcomes during surgical theatre sessions. These include planning ahead using theatre lists, assessing the patient pre-operatively and following up post-operatively and sufficient preparation beforehand.

In conclusion, surgical faculties can utilize the multi-disciplinary set-up and healthcare experience to formulate plans that better accommodate medical students on their path to becoming physicians. Additionally, both the faculty and students need to respect each other's perspectives to ensure that a teacher-student relationship is formed. Ultimately, a positive surgical theatre experience is more likely to attract students to choose a surgical career.

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Pseudo-Chilblains in Adult Patients with Confirmed COVID-19: A Systematic Review

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Abstract

Background: Pseudo-chilblains have been associated with COVID-19. Many reports, however, lack confirmation of COVID-19 infection. While likely associated, all chilblains/chilblain-like lesions during this time should not be assumed to be COVID-19 related. This study examines the characteristics of adults with pseudo-chilblains and confirmed COVID-19. **Methods:** A systematic review of PubMed/MEDLINE database was performed using the PRISMA guidelines. Adults (>18 years) with confirmed COVID-19 were included. De-identified registries were excluded to avoid duplication. We extracted study design, age, sex, race, geographic location, relationship of COVID-19 diagnosis to chilblains onset, confirmatory testing, hospitalization status, anatomical location, cold/damp exposure, presence/absence/description of pseudo-chilblains symptoms, presence/absence of biopsies/histopathologic findings, tissue IHC/PCR, presence/absence/details of extracutaneous COVID-19 disease, pre-existing chilblains, treatment and resolution timeline. The search was completed in July 2022. **Results:** We identified 13 studies (29 patients). In COVID-19-infected adults, pseudo-chilblains were reported primarily from North America and Europe, occurring in both sexes over a wide age-range, affected well and ill patients, favored the hands and feet and could be symptomatic or asymptomatic. Most patients had extracutaneous symptoms. Resolution time ranged from <1 week to >50 days. There was marked variation in treatment strategies and appearance of pseudo-chilblains relative to entire disease course. Biopsies were infrequently performed but findings similar to classical chilblains were described. **Conclusions:** Many patients reported as pseudo-chilblains of COVID-19 lack confirmed infection. Infection confirmation, photographic documentation and histopathology are critical to establish homogeneity in reported pseudo-chilblains during this global pandemic. Further work clarifying the relationship of acral eruptions and COVID-19 is necessary.

Introduction

Recent reports document cutaneous manifestations of coronavirus disease of 2019 (COVID-19) infection including exanthematous, urticarial, papulovesicular and vascular-related eruptions.¹ Acral lesions described early in the pandemic were designated 'pseudo-chilblains', 'COVID-toes' or 'chilblain-like' due to their resemblance to classical chilblains. Compared with classical chilblains, these patients lacked cold exposure but reported COVID-19 infection/exposure.¹⁻³ The diagnosis has typically been made clinically in patients with erythematous to violaceous papules, plaques or occasionally blisters in confirmed or clinically suspicious cases of COVID-19 or in patients with compatible lesions and a recent exposure to known COVID-19 infection.¹⁻⁵ The lesions may be painful, pruritic or asymptomatic and occur in both children and adults, with equal distribution between sexes. While the pathophysiology of pseudo-chilblains is still unclear, viral infection associated increased interferon- α , a strong cytotoxic T-cell and natural killer cell response, along with IgA anti-neutrophil cytoplasmic antibodies have been described.⁶

This immune response likely contributes to the dense perivascular and periadnexal lymphocytic infiltrate seen on histopathologic sections.⁶ Cryofibrinogenemia with potential resultant vascular microthrombi has also been reported as a potential pathomechanism.⁷ In addition to being a marker of COVID-19 positivity, prognostic implications have been suggested,⁴ with pseudo-chilblains reportedly associating with mild disease.⁴ One challenge with the data regarding its association with COVID-19 is the lack of confirmed infection in many studies and whether this eruption is a true manifestation of COVID-19 infection remains controversial.⁸ In many reports, infection was inferentially deduced using known contact exposure or previous suggestive clinical symptoms rather than confirmed laboratory testing.⁵ Although little doubt exists that pseudo-chilblains are a manifestation in some patients with COVID-19 infection, it should not be assumed that it is exclusively seen in COVID-19 infected patients.⁹ Lack of clinical criteria, variation in appearance and infrequently performed biopsies raise the possibility that pseudo-chilblains may not be a homogenous condition, potentially

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representing a variety of livid-appearing eruptions with differing pathomechanisms or prognostic implications. Thus, our study aims to describe the demographic, clinical and laboratory features of adult patients with pseudo-chilblains and confirmed COVID-19 infection.

Methods

A systematic review search strategy was performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A literature search was done on July 14, 2022 and July 17, 2020 using PubMed/MEDLINE and Web of Sciences databases respectively. Following PRISMA 2015.10 which requires at least two databases, we used those detailed above. We restricted data to scientific peer reviewed journals. We did not include gray literature. Gray literature is not formally peer reviewed work and thus did not meet our inclusion criteria. Many would also not have COVID-19 diagnostically confirmed. Our included keywords with Boolean terms were "Chilblains" OR "COVID toes" AND "COVID-19", as well as "COVID-19" AND "Chilblains" AND "immunohistochemistry". The search was filtered to only include journal articles, human adult studies (>18 years), written in English and published between January 2020 and June 30 2022. An additional search on Web of Science using the same Boolean terms was completed on July 17, 2022. Archiving of the review protocol was not previously done.

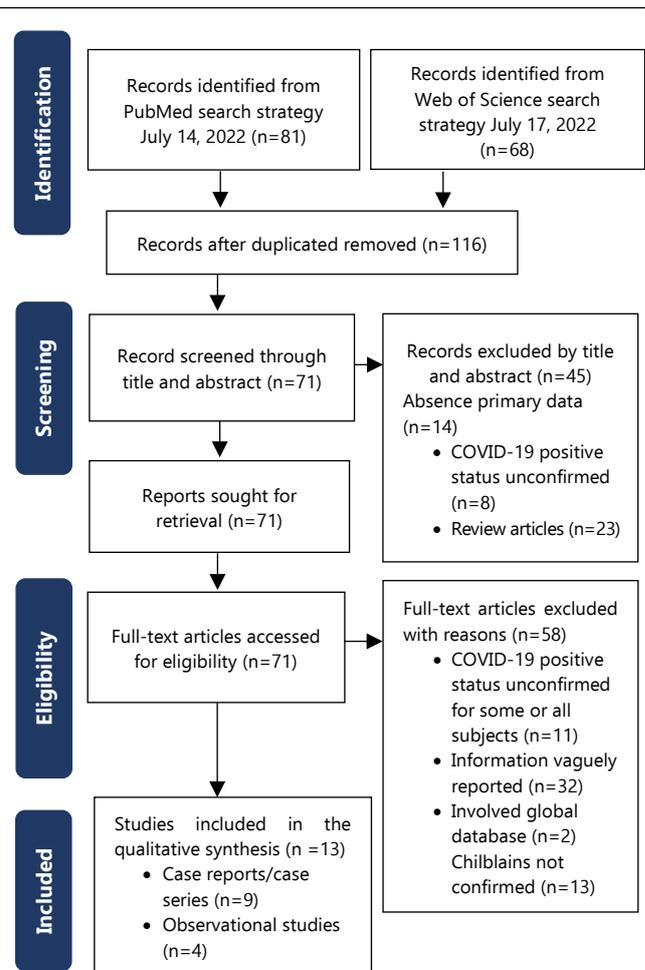
Study Selection

Two authors (SH, MG) independently screened titles/abstracts identifying and including articles describing pseudo-chilblains in patients with confirmed COVID-19 infection (defined as positive reverse transcriptase polymerase chain reaction (RT-PCR), positive serology for IgG/IgM or detection of COVID-19 on biopsies via immunohistochemistry/immunofluorescence (IHC/IF), in situ hybridization (ISH) or tissue PCR. Where there was disagreement on inclusion/exclusion a third author (KW) was consulted for consensus. Eligibility of study based on data available for extraction was determined through full-text review with consensus between two authors (SH, KW, NT, JM) and final review by consultant dermatologist (JH). Studies involving data extracted from de-identified patient registries, such as the American Academy of Dermatology Association COVID-19 Dermatology Registry (<https://www.aad.org/member/practice/coronavirus/registry>) were excluded to avoid duplicated patient representation. The inclusion/exclusion criteria were decided and vetted using multiple practice runs during planning meetings prior to July 14th. With the criteria decided, a single run was completed on July 14th, 2022 for PubMed and July 17th, 2022 for Web of Science. Microsoft Word was used to organize and manage the yielded citations. Once there was consensus on the included studies, Microsoft Excel was used to extract the required data from the papers.

Data Extraction

Data extracted included study design, number of patients with confirmed COVID-19 and pseudo-chilblains, age, sex, race, geographic

Figure 1. Study Identification PRISMA Flow Chart; Template Adapted from Page et al.⁸



location, temporal relationship of COVID-19 diagnosis to onset of chilblains, confirmatory test used, hospitalization status, anatomical location, exposure to cold/damp, presence/absence and description of pseudo-chilblains related symptoms, presence/absence of a biopsy and where reported, histopathologic findings, tissue IHC/PCR, the presence/absence and details of extracutaneous COVID-19 disease, history of conventional chilblains, treatment and resolution timeline.

Quality Assessment

The Joanna Briggs Institute critical appraisal checklists (2017) for case reports, case series, cross-sectional and cohort studies¹¹ were utilized to assess the overall quality of the included studies and estimate the risk for bias. For example, we assigned "Yes" to the question "Was the patient's history clearly described and presented as a timeline?" only if there was well-detailed chronology and timing of events reported. Similarly "Yes" would be assigned to "Were valid methods used for identification of the condition for all participants included in the case series?" only if a standard method of diagnosis was utilized (PCR, antibody testing etc.). All of our case reports and series had at minimum

"Yes" assigned to criteria 1-4 and for cohort and cross-sectional studies, at minimum "Yes" assigned to criteria 1-3 and 7.

Results

General study details

The flow diagram of the search and study selection process is shown in [Figure 1](#). The literature search resulted in 116 articles which were evaluated for relevancy based on their titles and abstracts. Following title and abstract review, 45 studies were excluded for lack of confirmed infection (n=8) or absence of primary data (n=14). Review articles were also excluded (n=23). Seventy-one articles remained for full text reading. Of these, 58 were excluded for lack of confirmed infection in some/all subjects

(n=11), inability to extract data due to vague reporting (n=32), lack of confirmed clinical features of chilblains-like lesions (n=13) and global databases (n=2). The subsequent review of full texts yielded 13 articles which fulfilled the selection criteria to be included in the systematic analysis.¹³⁻²⁵ Extracted data is shown in [Table 1](#) and [Table 2](#). There were four observational studies and nine case reports/case series. As it relates to confirmation of COVID-19 infection, five studies used both nasopharyngeal RT-PCR and serologic IgM/IgG testing for COVID-19, four with RT-PCR only, one study solely through serologic antibody testing, two via positive spike protein IHC/IF on biopsies and one study used all three methods.

Table 1. Clinical/Laboratory Characteristics of Chilblain-like Lesions in Adults with Confirmed COVID-19 Infection (Part A).

Authors	Country (C) Ethnicity (E)	Study Design & Number of cases (n)	Sex (M: F) & Age (years)*	Type of COVID- 19 confirmatory test	Hospitalization status	Pseudo-chilblains presentation relative to overall course of COVID- 19 infection
Almeida et al. (2021) ¹⁴	C: Brazil & USA E: NR	Case Series n=4	4M 25,49, 62,66	RT-PCR/antibody serology	Outpatient	NR
Alramthan and Aldaraji (2020) ²¹	C: Qatar E: NR	Case report n=2	2F 27,35	RT-PCR	Outpatient	NR
Brancaccio et al. (2021) ²²	C: Italy E: NR	Cross-sectional n=2	1M:1F 19,29	IgG/IgM serology (RT-PCR negative)	Outpatient	Days 3 and 13 after onset of COVID-19 symptoms
Gambichler et al. (2020) ²³	C: Germany E: NR	Case report n=1	1F 80	RT-PCR/IgG antibody serology/IHC	Inpatient	3 weeks
Ko et al. (2021) ²⁵	C: USA E: NR	Case series n=3	1M:2F 82,62,76	IHC tissue	NR	NR
Mendez-Maestro et al. (2020) ¹⁸	C: Spain E: NR	Cross-sectional n=6	NR 64-70	RT-PCR/antibody serology	Inpatient	NR
Proietti et al. (2020) ²⁴	C: Italy E: White	Case report n=1	F 35	RT-PCR	Outpatient	14 days after positive PCR
Recalcati et al. (2021) ¹⁶	C: Italy E: NR	Observational Retrospective cohort n=2	2F 31, 33	RT-PCR (n=1), ELISA (n=1)	Outpatient	2 weeks after extracutaneous COVID-19 symptoms (n=1) First day of presentation (n=1)
Rekhtman et al. (2021) ¹⁷	C: USA E: White, Black, Asian, Native American, Hispanic, Multiracial (not specifically stated for each case)	Observational Prospective cohort n=4	NR 55-77	RT-PCR/antibody serology	Inpatient	NR
Rubin et al. (2020) ¹⁵	C: USA E: NR	Case report n=1	1F 27	RT-PCR	Outpatient	6 weeks after extracutaneous symptoms
Santonja et al. (2020) ¹³	C: Spain E: NR	Case report n=1	1F 36	IHC tissue (RT-PCR + IgG/IgM serology negative)	Outpatient	First day of presentation
Shah et al. (2021) ²⁰	C: USA E: NR	Case report n=1	1M 19	Antibody serology	Outpatient	First day of presentation
Wee and Tey (2020) ¹⁹	C: Singapore E: Asian (Indian)	Case report n=1	1M 26	RT-PCR	Outpatient	NR

Legend: *Where specific ages not available, age-range of cohort reported; IHC, Immunohistochemistry; NR, Not reported; RT-PCR, reverse transcriptase polymerase change reaction.

Table 2. Clinical/Laboratory Characteristics of Chilblain-like Lesions in Adults with Confirmed COVID-19 Infection (Part B).

Authors	Extracutaneous COVID-19 symptoms/cases number	Cold/damp exposure	Anatomical location(s)**	Symptoms related to pseudo-chilblains	Histopathologic findings	Pseudo-chilblains specific treatment	Time to resolution
Almeida et al. (2021) ¹⁴	Fever, headache and diarrhea (1/4 cases) Asymptomatic (3/4 cases)	NR	Toes (n=4) Fingers (n=1) Ears (n=1)	Pruritus (n=1) Asymptomatic (n=3)	-Spongiotic dermatitis with vesicles -Keratinocyte necrosis (dyshidrotic pattern) -Superficial perivascular lymphocyte infiltrate	NR	Day: 7, 11, 12, 15 days
Alramthani and Aldaraji (2020) ²¹	Asymptomatic (2/2 cases)	NR	Fingers on bilateral hands (n=2)	Asymptomatic (n=2)	Not performed	NR	NR
Brancaccio et al. (2021) ²²	Mild symptoms not otherwise described (2/2 cases)	NR	Toes and fingers (n=1) Toes (n=1)	Pain (n=2)	Not performed	None (2/2 cases)	Day: 14, 7
Gambichler et al. (2021) ²³	Fever, cough shortness of breath, COVID pneumonia (1/1 cases)	NR	Thumb (n=1)	Asymptomatic (n=1)	-Parakeratosis, acanthosis -Perivascular and diffuse lymphohistiocytic infiltrate -Fibrinoid deposits and occlusion of mid-dermal blood vessels -IF positive for SARS-CoV-2 spike protein	None	NR
Ko et al. (2021) ²⁵	NR (3/3 cases)	NR	Fingers and toes (individual case details not specified)	NR	Perivascular lymphocytic infiltrate IHC: + spike protein	NR	NR
Mendez-Maestro et al. (2020) ¹⁸	NR (6/6 cases)	Unrelated to exposure	Toes and fingers (individual case details not specified)	Asymptomatic (n=6)	Not performed	Observation (6/6 cases)	Resolved, but timeline not reported
Proietti et al. (2020) ²⁴	Asymptomatic (1/1 cases)	NR	Right auricle	Pain	Not performed	Methylprednisolone Heparin (1/1 cases)	5
Recalcati et al. (2021) ¹⁶	Fever (1/2 cases) Asymptomatic (1/2 cases)	Unrelated to exposure	Hands (n=1) Feet (n=2)	Asymptomatic (n=2)	-Dense coat-sleeve-like perivascular and perieccrine lymphocytic infiltrate	Observation (2/2 cases)	Day: 20, 21
Rekhtman et al. (2021) ¹⁷	NR (4/4 cases)	NR	Hand (n=1) Fingers (n=3) Feet (n=1) Toes (n=2)	NR	Not performed	NR	NR
Rubin et al. (2020) ¹⁵	Anosmia, Ageusia (1/1 cases)	Unrelated to exposure	Toes	Swelling, pruritus	None performed	Observation	3 months
Santonja et al. (2020) ¹³	Fever, cough (1/1 cases)	NR	Toes	NR	-Perivascular and periadnexal lymphocytic infiltrate -Focal thrombosis -Focal endothelial damage -DIF: perivascular C3 C1q and C5b-9 -IHC: + spike protein	LMW heparin Aspirin	Day 54
Shah et al. (2021) ²⁰	Asymptomatic (1/1 cases)	Unrelated to exposure	Toes	Pain, blisters, tightness	Not performed	NSAID	Day 40 (faint cyanosis remained)
Wee and Tey (2020) ¹⁹	Asymptomatic (1/1 cases)	NR	Left thumb and palm (n=1)	Pain, swelling	Not performed	Paracetamol	Day 12 (palm)

Legend: **An individual case may have more than one anatomic location involved; IF, Direct immunofluorescence; IHC, Immunohistochemistry; IF, immunofluorescence; LMW, low molecular weight; NR, Not reported; NSAID, Non-steroidal anti-inflammatory drug.

Quality Assessment/Risk of Bias

The majority of included studies fulfilled most of the study-type appropriate Joanna Briggs Institute Critical Assessment checklist parameters (Tables 3-4). For case reports/series missing information was primarily related to the adverse reactions which were generally not relevant based on the subject being studied. Similarly, for observational studies (cohort and cross-sectional studies), information on confounders was not generally available. Overall, based on the assessment of the critical appraisal checklists, all but one of our studies had >70% "yes" answers to relevant/applicable criteria (See Table 3-4). Therefore, while not negligible, we assessed the risk of bias as relatively low.

Patient Demographics

The included studies yielded information on 29 patients. Sex and specific ages were evaluable for eleven of the thirteen studies (19 cases). There were 8 males and 11 females. Ages ranged from 19-82 years. The remaining studies provided age ranges for their entire cohorts and minimum (55) and maximum (77) ages could be deduced. Race was generally unreported. Regarding geographic distribution, four studies included nine patients exclusively from United States of America,^{15, 17, 20, 25} while six studies (13 patients) were reported from continental Europe (Spain, Germany and Italy).^{13, 16, 18, 22-24} Four patients were collaboratively reported between the United States of America and Brazil,¹⁴ one study detailing 2 patients from Qatar¹⁷ and a single patient was reported from Southeast Asia (Singapore).¹⁹

Clinical Characteristics

Regarding clinical presentation, twelve studies reported hospitalization status,^{13-24, 15} outpatient and 16 inpatient cases were reported (unreported in one study of three patients).²⁵ Details regarding temporal relationship of the eruption to the overall course of disease was available for 9 cases with pseudo-chilblains occurring on day 1 (n=3), day 3 (n=1), day 13 (n=1), 2 weeks (n=2), 3 weeks (n=1) and 6 weeks (n=1) after onset of other COVID-19 related symptoms.^{13, 14, 16, 20, 22-24} Exposure to cold/damp was excluded in four studies, (10/29 cases) and unreported in the remainder.^{15, 16, 18, 20} Anatomical locations included toes/feet, hand/fingers, ears, arms and legs. 28/29 patients had involvement of hands/feet/digits. There were two reports of ear involvement, one patient with an ear-only lesion.^{14, 24} Toes/feet were the most commonly reported single location. Chilblains-related symptomatology was reported in 21 patients (nine studies), with 7 experiencing symptoms (pain/pruritus/swelling) and 14 were asymptomatic.^{14, 15, 18-24} Presence of extracutaneous symptoms of COVID-19 was evaluable for twelve studies. Although specific details were only provided for ten studies,^{13-16, 19-24} two studies were taken from inpatient cohorts of subjects admitted for COVID-19-related complications,^{17, 18} and so had extracutaneous features. One study did not comment on symptoms.²⁵ Extracutaneous COVID-19 symptoms were experienced in 17 cases (including fever, headache, diarrhea, respiratory symptoms and sensory disturbances) and 9 cases lacked extracutaneous manifestations.

Resolution timelines could be assessed in eight studies (13 cases).^{13-16, 19, 20, 22, 24} Three cases resolved at < 7 days, 4 cases between 8-14 days, 2 cases between 15-21 days and 4 cases took >21 days (maximum of >50 days). Pseudo-chilblains management was detailed in eight studies with 2 patients receiving analgesics (non-steroidal anti-inflammatory drug and paracetamol), 1 receiving low molecular weight heparin and aspirin, 1 receiving heparin and methylprednisolone and 11 observed.^{13,16-20,22,23} Five studies (5 cases) highlighted the temporal relationship of pseudo-chilblains to COVID-19 testing; recognition of eruption triggered COVID-19 testing in 4 of these patients.^{13, 15, 19, 20,24}

Table 3. Results of Joanna Briggs Institute Critical Appraisal Checklists for Case reports and Case Series.

Study Type (CS/CR), Author	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
CS, Almeida et al. (2021) ¹⁴	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A
CR, Alramthan and Aldaraji, (2020) ²¹	Y	Y	Y	Y	N	N	N/A	Y	-	-
CR, Gambichler et al. (2020) ²³	Y	Y	Y	Y	Y	Y	N/A	Y	-	-
CS, Ko et al. (2021) ²⁵	Y	Y	Y	Y	Y	Y	U	N	Y	N/A
CR, Proietti et al. (2020) ²⁴	Y	Y	Y	Y	Y	Y	N/A	Y	-	-
CR, Rubin et al. (2020) ¹⁵	Y	Y	Y	Y	Y	Y	N/A	Y	-	-
CR, Santonja et al. (2020) ¹³	Y	Y	Y	Y	Y	Y	N/A	Y	-	-
CR, Shah et al. (2021) ²⁰	Y	Y	Y	Y	Y	Y	N/A	Y	-	-
CR, Wee and Tey (2020) ¹⁹	Y	Y	Y	Y	Y	Y	N/A	Y	-	-

Legend: CR, Case Report; CS, Case series; Y, Yes; N, No; N/A, Not applicable; U, Unclear; Dash (-), no response necessary based on study type; Q1 (CR), Were patient's demographic characteristics clearly described?; Q1 (CS) Were there clear criteria for inclusion in the case series?; Q2 (CR) Was the patient's history clearly described and presented as a timeline?; Q2 (CS) Was the condition measured in a standard, reliable way for all participants included in the case series?; Q3 (CR) Was the current clinical condition of the patient on presentation clearly described?; Q3 (CS) Were valid methods used for identification of the condition for all participants included in the case series? Q4 (CR) Were diagnostic tests or assessment methods and the results clearly described?; Q4 (CS) Did the case series have consecutive inclusion of participants?; Q5 (CR) Was the intervention(s) or treatment procedure(s) clearly described?; Q5 (CS) Did the case series have complete inclusion of participants?; Q6 (CR) Was the post-intervention clinical condition clearly described? Q6 (CS) Was there clear reporting of the demographics of the participants in the study? Q7 (CR) Were adverse events (harms) or unanticipated events identified and described? Q7 (CS) Was there clear reporting of clinical information of the participants? Q8 CR Does the case report provide takeaway lessons? Q8 (CS) Were the outcomes or follow up results of cases clearly reported? Q9 (CS only) Was there clear reporting of the presenting site(s)/clinic(s) demographic information? Q10 (CS only) Was statistical analysis appropriate?

Table 4. Results of Joanna Briggs Institute Critical Appraisal Checklists for Cross-Sectional and Cohort studies.

Study type, Authors	Q 1	Q 2	Q 3	Q 4	Q 5	Q 6	Q 7	Q 8	Q 9	Q 10	Q 11
Cross-sectional, Brancaccio et al. (2021) ²²	Y	Y	Y	Y	N	N	Y	N/A	-	-	-
Cross-sectional, Mendez-Maestro et al. (2020) ¹⁸	Y	Y	Y	Y	N	N	Y	Y	-	-	-
Retrospective cohort, Recalcati et al. (2021) ¹⁶	Y	Y	Y	N	N	N	Y	N/A	N/A	N/A	Y
Prospective cohort, Rekhman et al. (2021) ¹⁷	Y	Y	Y	N	N	N	Y	Y	Y	N/A	Y

Legend: Y, Yes; N, No; N/A, Not applicable; Dash (-), no response necessary based on study type; Q1 (Cross-sectional) Were the criteria for inclusion in the sample clearly defined? Q1 (Cohort) Were the two groups similar and recruited from the same population? Q2 (Cross-sectional) Were the study subjects and the setting described in detail? Q2 (Cohort) Were the exposures measured similarly to assign people to both exposed and unexposed groups? Q3 (Cross-sectional) Was the exposure measured in a valid and reliable way? Q3 (Cohort) Was the exposure measured in a valid and reliable way? Q4 (Cross-sectional) Were objective, standard criteria used for measurement of the condition? Q4 (Cohort) Were confounding factors identified? Q5 (Cross-sectional) Were confounding factors identified? Q5 (Cohort) Were strategies to deal with confounding factors stated? Q6 (Cross-sectional) Were strategies to deal with confounding factors stated? Q6 (Cohort) Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)? Q7 (Cross-sectional) Were the outcomes measured in a valid and reliable way? Q7 (Cohort) Were the outcomes measured in a valid and reliable way? Q8 (Cross-sectional) Was appropriate statistical analysis used? Q8 (Cohort) Was the follow up time reported and sufficient to be long enough for outcomes to occur? Q9 (Cohort only) Was follow up complete, and if not, were the reasons to loss to follow up described and explored? Q10 (Cohort only) Were strategies to address incomplete follow up utilized? Q11 (Cohort only) Was appropriate statistical analysis used?

Histopathology

Biopsies were performed in five of 13 studies,^{13, 14, 16, 23, 25} although it was unclear whether all patients were sampled in two of these reports.^{14, 16} Two patterns were seen; 1) spongiotic/dyshidrotic dermatitis, necrotic keratinocytes and a superficial perivascular lymphocytic infiltrate and 2) a perivascular +/- periadnexal lymphocytic infiltrate. The latter pattern accounted for at least five cases.^{13, 16, 25} Immunohistochemistry/immunofluorescence was performed in three studies (5 cases) using antibodies against the COVID-19 spike protein (SARS-CoV/SARS-CoV-2 spike 1A9; GeneTex, Inc., Irvine, CA, USA and Sino Biological, 40 150-T62-COV) while ISH was concurrently performed in one paper (Advanced Cell Diagnostics anti-SARS-CoV-2 SP probe V-

nCoV2019-S, performed on the Leica BOND-III platform, Wetzlar, Germany).^{13, 23, 24} Although ISH was negative, IHC detected SARS-CoV-2 spike protein (granular staining pattern) localized to vascular endothelium in all five cases with concurrent eccrine gland positivity in 3 patients. Direct immunofluorescence performed in one patient revealed perivascular deposition of C3, C5b-9 and C1q.¹³

Discussion

While from an epidemiologic perspective, the rise in chilblain-like lesions during the onset of the COVID-19 pandemic points to an association with COVID-19, the lack of confirmatory testing is a significant limitation.^{2, 26-28} As in other viral eruptions (e.g., unilateral laterothoracic exanthem), numerous agents may produce similar findings and care must be taken in ascribing causality. Furthermore, the frequent lack histopathologic confirmation, variation in clinical appearance and microscopic features, and absence of clinical photographs for many reports raises the possibility that the designation pseudo-chilblains/"COVID-toes" may represent a heterogenous group of conditions with similar anatomic distribution. This study aims to contribute to our evolving understanding of COVID-19-associated skin disease by specifically examining the features of pseudo-chilblains in adults from studies where patients were definitively infected. It should be noted a positive serologic test or RT-PCR for COVID-19 is not necessarily an indicator of active infection in otherwise asymptomatic patients, as both may remain positive for some time after infection.²⁹ Perhaps in some patients, pseudo-chilblains represent a delayed reaction to recent but inactive infection.³⁰

Our analysis suggests that many reported cases of pseudo-chilblains do not detail laboratory confirmation of COVID-19 infection. In studies meeting our inclusion criteria, we found pseudo-chilblains in adults occurred in both sexes over a wide age range (2nd-9th decades). Most cases were reported from non-equatorial countries. The apparent geographic distribution and acral localization may implicate environmental factors as concomitant triggers.³

Pseudo-chilblains have been suggested as a marker for mild disease.⁴ While the number of cases evaluated in this study is too small to confirm or refute this, it is noteworthy that pseudo-chilblains occurred in both well outpatients and persons hospitalized with COVID-19 complications.^{17, 18} While details of the onset of pseudo-chilblains relative to overall disease-course were not clear in most studies, where evaluable, pseudo-chilblains could occur from Day 1 of illness to six weeks from initial symptoms, suggesting its potential appearance in acute and more chronic phases of infection, or perhaps in patients with recent but inactive infection. Cold/damp exposure was excluded in 10/29 of the cases. Unfortunately, a history of previous conventional chilblains was generally unreported. Currently pathomechanistic similarities/differences of conventional and pseudo-chilblains are not known.

Pseudo-chilblains could be either asymptomatic or symptomatic. Extracutaneous symptoms were present in greater than two thirds of cases analyzed but no characteristic pattern could be elucidated with respiratory, sensory, gastrointestinal, headache and fever being represented. Resolution time was likewise heterogeneous some patients resolving within a week and others longer up to 50 days. Therapeutic approach was not standard and included anti-inflammatory and analgesic agents, anticoagulants, and observation.

Regrettably, biopsies were not performed in the majority of cases examined nor in larger global registry reported cases.⁵ Reported histopathologic features include vacuolar change, spongiosis, necrotic keratinocytes, a superficial and deep perivascular and perieccrine lymphocytic/lymphohistiocytic infiltrate, lymphocytic vasculitis, subepidermal blister formation, papillary dermal edema, extravasation of erythrocytes, increased intradermal mucin and microthrombi.^{5,31} In our included cases, intraepidermal vesicular (dyshidrotic-like) dermatitis and a superficial and deep perivascular and perieccrine lymphocytic infiltrate were described. While further work outlining histopathologic changes is needed, a perivascular and periadnexal lymphocytic infiltrate similar to conventional chilblains appears to be common, though not universal.^{13, 25, 32} Interestingly, biopsies may aid in tissue-based confirmation of infection.²⁵ In 4 out of 5 cases, COVID-19 spike protein was visualized via IHC/IF in vascular endothelium and in eccrine epithelium despite negative nasal PCR and/or serology. It is important to note that like nasal/nasopharyngeal RT-PCR and serology, spike protein identification may not equate to active infection. The spike protein is thought to be cleaved, entering endothelium/epithelium via the angiotensin converting enzyme type two receptor²⁵ but how long it remains within these cells is unclear.

Based on our analysis, features of classical chilblains and pseudo-chilblains in adults with confirmed COVID-19 infection were compared. Typical chilblains present with painful, acral, erythematous/livid lesions in young, predominantly female patients within the Northern Hemisphere after exposure to cold/damp conditions.³³ Microscopic features include superficial and deep perivascular and perieccrine lymphocytic infiltrates, papillary dermal edema and extravasation of erythrocytes.³⁴ Similarities include anatomical and perhaps geographic distribution, morphology and some histopathologic findings. Differences include the often asymptomatic nature, potential for chronicity, lack of exposure to cold/damp, variability in histopathologic findings and the occurrence over a broad age range in both sexes in COVID-19 related lesions compared with classical chilblains. Limitations to this study include the retrospective nature of systematic reviews, occasional methodologic gaps in some of the included studies and the exclusion of cases from large databases where confirmation of COVID-19 status was unavailable and where specific clinical data is often limited at best may have resulted in some true cases of COVID-19 related chilblains being unavailable for analysis.

Conclusion

Many patients reported as pseudo-chilblains of COVID-19 do not have confirmed infection. In adult patients with confirmed

COVID-19, chilblain-like lesions have been reported primarily from North America and Europe, occur across the spectrum of age in males and females, favor acral surfaces, may be symptomatic or asymptomatic, lack relationship to cold/damp exposure, display variability in resolution time and association with extracutaneous COVID-19 manifestations, occurs in both well and ill patients and may serve as a trigger for COVID-19 testing. Histopathologic features resemble that of classical chilblains but less common patterns may occur. Further work is needed to clarify the relationship of acral eruptions and COVID-19. Infection confirmation, photographic documentation and histopathology are critical to establish homogeneity in reported pseudo-chilblains during this global pandemic.

Summary – Accelerating Translation

Pseudo-Chilblains in Adult Patients with Confirmed COVID-19: A Systematic Review

Many organs can be affected by infection with COVID-19. The skin is no different. One of the earliest skin signs of COVID-19 infection was labeled "COVID-toes", where patients get red-to-purple spots/rashes, primarily on their toes or fingers. In the dermatology world, the preferred name for "COVID-toes" is 'pseudo-chilblains' referencing the similarity in appearance of the rash to a condition called chilblains affecting fingers and toes of people who have been exposed to cold and wet conditions for a relatively prolonged time. While little doubt exists that this peculiar rash may be a manifestation of infection with COVID-19, we were struck by the fact that many of the reported cases did not have confirmed infection. In the future, as we look back at the science and data generated during this period, the lack of laboratory confirmation of infection may render some of the conclusions drawn invalid, or at least uncertain. We wished to examine the clinical and laboratory characteristics of adult patients with COVID-toes (pseudo-chilblains) with confirmed infection.

To do this, we performed a systematic review of the published literature on the PubMed/Medline database following the standard guidelines for this type of research (Preferred Reporting Items for Systematic Reviews and Meta-Analyses, PRISMA). We used studies reporting adults (>18 years) with confirmed COVID-19. We recorded the type of study performed, which country the patients came from, age, sex and race of the patients reported, how close the onset of COVID-toes was to the diagnosis of COVID-19 infection, the type of testing used to confirm infection, whether the patient was kept in hospital or not, where on the body the rash occurred, whether the patient had a history of being exposed to cold or wet conditions, whether the rash had any symptoms, whether the patients had any non-skin manifestations of COVID-19 infection, how long the rash took to go away and what treatment if any was prescribed to patients with COVID-toes. We also documented if small pieces of skin were taken (biopsies) to describe what the rash looks like microscopically.

Our search identified only 13 studies giving us details on 29 patients. In COVID-19-infected adults, "COVID toes" were most commonly reported from North America and Europe, occurred in both males and females over a wide age-range. Both well people and ill patients who were admitted to hospital could be affected. The hands and feet were most commonly affected but lesions on the ear could also be seen. "COVID-toes" could be symptomatic or not. Many patients had evidence of COVID-19 infection besides rash (e.g. cough or diarrhea). "COVID-toes" could take <1 week or up to greater than 50 days to resolve. No standard treatment for the rash was found. Biopsies are infrequently performed but when done, findings similar to classical chilblains are described.

In summary, many patients reported as pseudo-chilblains of COVID-19 do not have confirmed infection. Infection confirmation, photographs and biopsies are recommended if we are to be sure that every person reported

as “COVID-toes” has the same rash. Further work clarifying the relationship of rashes on the hands and feet with COVID-19 infection is necessary.

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Early Point of Care Ultrasound Training in Medical Education, Making the Case with a Case Report

James Wilcox,¹  Bret Lawson,²  Andrew Gauger.³ 

Abstract

Background: Point of Care Ultrasound (PoCUS) emerged in the early 1990's as a promising clinical and educational tool that allows for quicker diagnosis at the bedside. Our PoCUS program at Indiana University School of Medicine uniquely exposes students to training during their first weeks of medical school, with training continuing through all 4 years. Our paper demonstrates the portability and efficiency of PoCUS devices to benefit student run clinics, where vulnerable patients come to seek free medical care. **Case:** We report the case of a 48-year-old man presenting to our student run clinic with shortness of breath and cough. He recently immigrated from Nigeria, had no prior interaction with United States healthcare, and faced a significant language barrier. Physical examination conducted by the medical students revealed mild bibasilar crackles and 1+ pitting edema in the lower extremities. This prompted the students to suspect heart failure, and the first-year medical student used bedside ultrasound to reveal a reduced ejection fraction of approximately 15%, which resulted in expedited and escalated medical care. **Conclusion:** This case report demonstrates how incorporating PoCUS early into the undergraduate medical curriculum might improve patient care by expediting the diagnosis, while also enhancing student education. The use of bedside ultrasound rapidly updated the team to the severity and type of heart failure present. Therefore, the care team quickly escalated the appropriate treatment, and impressed the importance of follow up care to the patient.

Introduction

Point-of-Care Ultrasound (PoCUS) is a novel use of a tool that has been available for decades. With the invention of smaller and more portable units, physicians can deliver quicker diagnoses and guide management at the bedside. Several studies in Emergency Medicine and in Primary Care demonstrate the utility of ultrasound in bedside patient management.¹ As early as the 1990's, Emergency Medicine Departments in the United States started using PoCUS to assist with evaluation of trauma patients with the FAST exam.⁶ In 1990, a school in Hanover, Germany first introduced PoCUS in medical education as a pilot program, an adjunct to existing anatomy education.⁴ Since then, schools across the United States, and the world, started adopting and expanding on the utility of bedside ultrasound for medical education. However, only about 57% of medical schools across the United States offer PoCUS training as of 2020. Additionally, less than 10% of schools offer a 4-year longitudinal curriculum which includes clerkship POCUS training.⁵ The opportunity for improved patient care afforded with PoCUS still lies untouched in many medical schools.

At Indiana University School of Medicine, in Indianapolis, we implemented a comprehensive 4-year PoCUS curriculum in 2019.

Training in Point-of-Care Ultrasound started as early as the first week of school. Students received a mixture of online training and

Highlights:

- Use of bedside ultrasonography in a student run free clinic for underserved populations.
- Bedside ultrasonography allows identification and estimation of disease severity in clinics for underserved populations.
- Early integrated 4-year ultrasonography curriculum helped students identify use of ultrasound in clinical setting

in person practice sessions scattered throughout their pre-clinical and clinical training years. Alongside their education, students may volunteer to serve at the free Student Outreach Clinic based in the urban center of Indianapolis, Indiana. Each patient in the outpatient clinic gets a clinical care team of a junior medical student, senior medical student, resident, and attending physician, all providing quality care. Recently, students utilized bedside ultrasound, in large part due to the new PoCUS program, to aid in the diagnosis and management of vulnerable patients. This much needed imaging application saves time and impresses the importance of follow up care for the medical team and the patients themselves.⁸ We would like to present one such case to highlight the importance of teaching PoCUS early and comprehensively in medical education.

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The Case

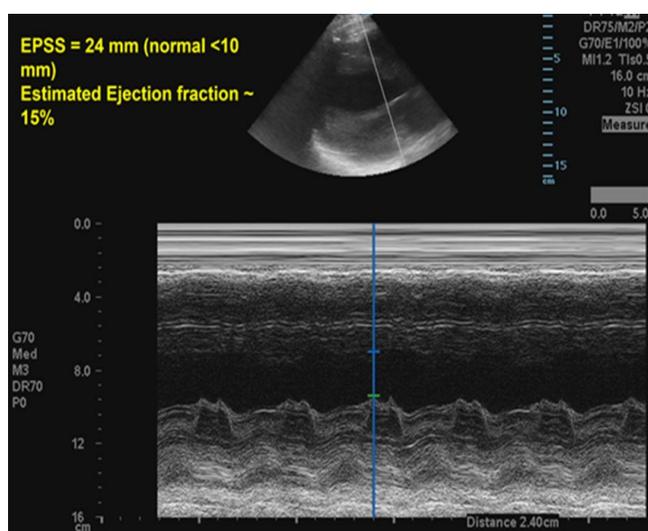
The CARE guidelines were used for reporting our case. Consent from our patient was obtained verbally via a trained Yoruba interpreter. A 48-year-old man who recently immigrated from Nigeria presented to the student-run free clinic in Indianapolis with the complaint of shortness of breath and cough. The shortness of breath was reported at his work and was relieved by drinking water. The language barrier made history taking difficult; however, he was able to communicate that he had dyspnea on exertion for the last 7 months. He denied any past medical history and took no medication as he had not had the financial resources to interact with healthcare since immigrating. Family history was unremarkable. He denied use of tobacco, alcohol, and illicit substances. The physical exam performed by the medical students identified mild bibasilar crackles and 1+ pitting edema in the bilateral lower extremities. The students, concerned for heart failure, initiated an EKG which revealed evidence of atrial overload and left ventricular hypertrophy. The first-year medical student had received training on cardiac ultrasound the week prior, allowing the students to perform point of care ultrasound. Hypokinetic left ventricular walls were visualized with bedside ultrasound and the cardiac PoCUS trained attending physician assisted with estimating the ejection fraction at 15% (normal 50%-70%), seen in [Figure 1](#). The patient was diagnosed with heart failure with reduced ejection fraction, labs were drawn, appropriate medication was started, and urgent cardiology consultation was scheduled. At the outreach clinic, he was started on furosemide, lisinopril and metoprolol. Furosemide was subsequently discontinued due to elevation in serum creatinine and hypokalemia during follow-up visits at the outreach clinic. The patient followed up with the attending physician at his primary clinic 4 months later, where a formal echocardiogram confirmed the diagnosis of heart failure with reduced ejection fraction. After 7 months of medical treatment at the student outreach clinic, his systolic ejection fraction improved to 49% on formal transthoracic echocardiogram. At the county hospital, he met with a cardiologist who adjusted his medication and scheduled him for a stress test to be completed. His symptoms improved, and his prognosis from congestive heart failure improved significantly.

On reflection with his primary care provider, using a Yoruba interpreter, he expressed gratitude for the student outreach clinic and staff accurately diagnosing his condition, and connecting him with specialist care. He was unable to afford medical care and was grateful for the assistance at the free clinic. The first-year medical student reflected, "I was especially impressed with how ultrasound in this context could rapidly correlate our patients' clinical status with an anatomical picture of heart failure. It felt empowering to have a tool readily accessible to deliver quality care to an underserved patient. Our free clinic is limited in resources and time, but I felt that the use of ultrasound exceeded this barrier and allowed us to rapidly and accurately diagnose our patient and guide in their management."

Discussion

In our case, we highlighted how Point-of-Care Ultrasound afforded rapid diagnosis of a patient with characteristics indicative of heart failure. Bedside ultrasound confirmed the diagnosis of heart failure and further characterized the type of heart failure, so that appropriate medical management could be initiated promptly; the formal echocardiogram was scheduled 4 months later due to staffing shortages. Findings of heart failure can be supported by x-ray imaging, but this also often requires the patient to leave the initial clinical space to obtain the x-ray, whereas Point-of Care Ultrasound is performed at the bedside. Student staffed clinics allow both clinical and pre-clinical students to hone their medical skills. In our case, the use of bedside ultrasound by the first-year medical student allowed for the students and staff to escalate the urgency of the care for this patient.

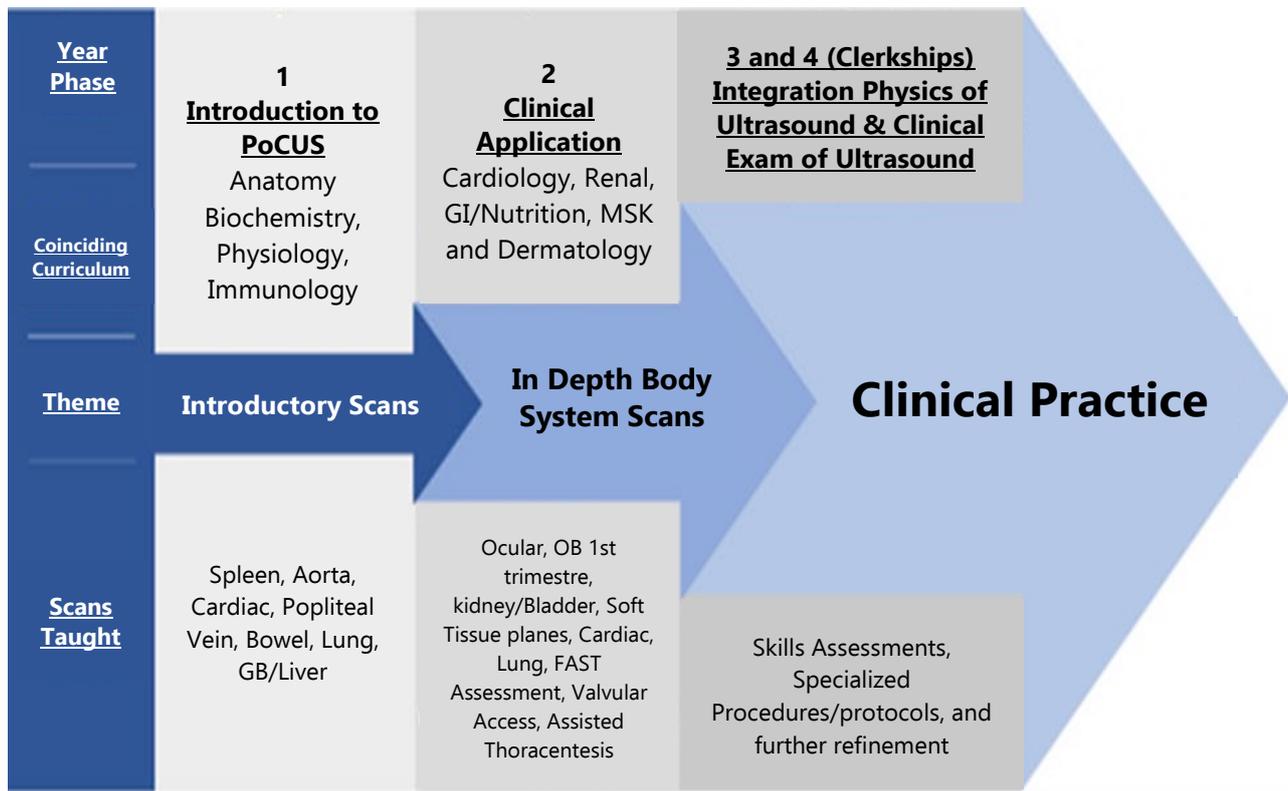
Figure 1. End Point Septal Separation (EPSS) Calculation: Distance Between the end Point Excursion of the Mitral Valve and the Interventricular Septum on m-mode Imaging in Parasternal Long Axis View.



Legend: The distance in millimeters is included in a formula ($EF = 75 - [EPSS \times 2.5]$), y and gives an estimate of the left ventricular ejection fraction.

With our comprehensive PoCUS training curriculum, seen in [Figure 2](#) our student was able to perform a bedside limited echocardiogram to evaluate the left ventricular function for our patient in the underserved clinic. With this added information, we were not only able to direct management but also impress the severity of his situation to him during his consultation. The limitations to our case report include that, although the student performed the ultrasound, the images were reviewed and interpreted by the staffing physician present. However, this should encourage support for staffing physicians to have protected time to train in PoCUS for improved patient care and medical student education.

Figure 2. Indiana University School of Medicine Point of Care Ultrasound Curriculum.



PoCUS training has rapidly spread in undergraduate medical education across the country with more than half of programs now instituting this training. Other papers demonstrate that student-performed PoCUS improves patient care at the bedside.⁷ However, our case demonstrates the benefit for patients when we train our medical students in clinical ultrasound early in their education. Our first-year student accurately identified the abnormal heart on his initial ultrasound scan and discussed treatment options promptly with the attending. This case highlights the importance of initiating early PoCUS training for medical students, and how PoCUS education can help students better treat patients even while still in training.

Summary – Accelerating Translation

Ultrasound use at the bedside by medical clinicians, called Point of Care Ultrasound (PoCUS), emerged in the early 1990's as a promising clinical and educational tool that allows for quicker diagnosis of medical problems. However, only a little more than half of medical schools in the United States teach PoCUS to their medical students; barely a tenth of schools teach this important tool over all four years of medical education. Our paper, Point of Care Ultrasound Early and Consistent in Medical Education, Making the Case with a Case Report highlights the need for medical schools to teach students clinical ultrasound early and

consistently throughout education. The PoCUS program at our local university uniquely exposes students to training during their first weeks of medical school, and training continues through all 4 years.

The portability and efficiency of PoCUS devices benefit free student-run clinics, where vulnerable patients come to seek free medical care while giving students the opportunity to practice hands-on clinical skills. We report the case of a 48-year-old man presenting to our studentrun clinic with shortness of breath and cough. He recently immigrated from Nigeria, had no prior interaction with United States healthcare, and faced a significant language barrier. Physical examination conducted by the medical students revealed abnormal lung sounds and swelling in the lower legs. This prompted the students to suspect heart failure, and the first-year medical student accurately used bedside ultrasound to reveal reduced cardiac function of approximately 15% (normal 50%-70%), which prompted expedited and escalated medical care.

We demonstrate in our paper how incorporating PoCUS early into the undergraduate medical curriculum improves patient care while enhancing student education. The use of bedside ultrasound rapidly updated the team to the severity and type of heart failure present. Therefore, the care team quickly escalated the appropriate treatment, and impressed the importance of follow up care to the patient. This case highlights the importance of initiating early PoCUS training for medical students, and how PoCUS education can help students better treat patients in training and beyond graduation.

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A Rare Case Report of Neurological Condition: Moersch-Woltman Syndrome with Positive Anti-GAD Antibodies

Aakanksha Pitliya.¹ 

Abstract

Background: Moersch-Woltman Syndrome (MWS), also known as Stiff person syndrome (SPS), is a rare, progressive condition of the central nervous system. Symptoms can include severe immobility, rigidity, and painful muscle spasms in the trunk and limbs. Muscle spasms can occur in MWS patients because they are more sensitive to noise, rapid movements, and mental disturbance. The condition affects women twice as frequently as it does males. It is a rare disease, affecting only 1-2 people per million. The case report aims to highlight the importance of the diagnostic challenges associated with MWS and the significance of glutamic acid decarboxylase (GAD) antibodies. **The case:** A 57-year-old female patient presents with history of migraine headaches, anxiety, and depression. The patient experienced widespread and distressing muscle spasms affecting the shoulders, upper and lower back, and limited range of motion in the neck. Physical examination revealed dense diffuse muscle stiffness throughout the body. Further investigations were ordered, including a comprehensive range of laboratory tests and imaging tests. A positive test for GAD antibodies confirmed the diagnosis of MWS. Treatment included administration of Clonazepam and Baclofen. A follow-up appointment, three weeks later, indicated a noticeable 15-20% reduction in spasticity. **Conclusion:** This case highlights the crucial role of anti-GAD antibodies in confirming the diagnosis of SPS. Healthcare professionals should consider testing for these antibodies in patients presenting with the described symptoms. A multidisciplinary approach involving neurologists, physical therapists, psychiatrists, and orthopedic surgeons is essential to provide comprehensive care and optimizing outcomes for individuals with MWS.

Introduction

Moersch-Woltman Syndrome (MWS), also known as Stiff person syndrome (SPS), is a rare, progressive condition causing increased muscular activity brought on by a decline in brain and spinal cord inhibition. It manifests as gradual muscle rigidity, usually in the axial muscles. However, rigidity can also occur in the extremities. Besides rigidity, the patient frequently experiences strong, sporadic muscle spasms that may be spurred by jarring noises, bright lights, or mental distress.¹ Although more recent studies have found several other antibodies associated with the disease, including antibodies against GlyR, GlyR-associated protein (GABARAP), and GlyT2, patients with MWS are most frequently positive for antibodies against glutamic acid decarboxylase (GAD 65).² Confirming the diagnosis of MWS can be challenging, as antibodies against GAD are most frequently reported and are positive in only 60-80% of patients.^{2,3} However, they are beneficial in confirming MWS when combined with the clinical picture.²

The quality of life of a patient is substantially impacted by MWS, which is also associated with neurological and psychiatric diseases.⁴ There is evidence of genetic influence on the risk of developing MWS; the HLA class 2 locus makes patients susceptible to the condition.⁵ Unfortunately, the diagnosis is

Highlights:

- This case report sheds light on the clinical manifestations of MWS.
- The case emphasizes the significance of considering MWS as a differential diagnosis in patients presenting with widespread muscle spasms, even in the absence of obvious abnormalities in imaging studies.
- The confirmation of GAD antibodies, highlights their crucial role in diagnosing Stiff-Person Syndrome and emphasizes the importance of testing for these antibodies in patients with muscle stiffness and spasms
- The successful reduction in spasticity with the administration of Clonazepam and Baclofen highlights the potential effectiveness of these medications in managing symptoms associated with MWS.
- The case underscores the importance of a multidisciplinary approach involving various healthcare professionals to provide comprehensive care and optimize outcomes for individuals living with MWS.

often delayed, with an average of six years passing from symptom onset to diagnosis.⁵ It is reported that diazepam and other benzodiazepines, corticosteroids, plasma exchange, and intravenous immunoglobulin have been effective in improving

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symptoms of the disease, but none alter the progression of the disease.⁶

The cause of this condition is rarely known, making it difficult to control disease progression. The reason behind GAD autoimmunity manifestation in MWS patients is unknown, and it is debatable whether MWS meets the criteria for classification as a neuro-autoimmune condition. It is also questionable whether these antibodies are pathogenic since the levels of antibody titers do not correlate to the severity of the condition.⁷ It has not been established that GAD antibodies are the only cause of MWS, and the possibility of GAD acting as a biomarker for the disease is doubtful.⁷ There is no evidence-based criterion for treating MWS, and the rarity of the disease complicates the efforts to establish guidelines.⁶

We present the case of a 57-year-old woman with a history of migraine headaches, anxiety, and depression who developed diffuse painful muscle spasms in her shoulders, upper and lower back, and inability to move her neck. Dense diffuse muscle stiffness was found throughout the body on examination. In addition to the clinical presentation, the diagnosis of MWS was confirmed by positive GAD antibodies.

Case

A 57-year-old woman presented to the neurology clinic with chief complaints of diffuse muscle stiffness, pain, and spasms in her head, neck, and back, persisting and slowly progressing for the past 15-20 years. These chronic and progressive symptoms have significantly impacted her activities of daily living, worsened by inadequate sleep but relieved by sleep and exercise.

During her time in the Air Force from 1980 to 1999, she experienced milder symptoms that have since worsened. She recalls a head injury in the 1990s without associated weakness. Her current symptoms include stiffness, bilateral arm numbness and tingling, burning fingertips, gluteal numbness with prolonged sitting, muscle twitches without fixed position, spine stiffness, balance loss, diffuse muscle spasms, and widespread pricking pain. She also experiences sleep difficulties, bending and turning issues, and autonomic symptoms like urinary urgency and constipation. Prolonged postures worsen her pain, and medications provide little relief. Her condition has impacted her intimate relationship.

The patient has known allergies to fish product derivatives, iodine-containing contrast media, porcine derivatives, shellfish, and erythromycin. Her mother had a history of colon cancer and osteoarthritis. She plans to retire early due to her condition, but her supervisors are unaware and unsympathetic. She experiences chronic pain that has worsened with age. She has a past medical history of migraine headaches, anxiety, and depression.

She takes multiple medications for her symptoms, including Albuterol, Budesonide-Formoterol, Eetirizine, Epinephrine, Famotidine, Fluticasone Propionate, fovatriptan, Gabapentin,

Ibuprofen, Lisinopril, Magnesium oxide, Naproxen, Ondansetron, Pantoprazole, Polyethylene glycol, Polyvinyl alcohol, Ropivacaine, Triamcinolone, and Zolmitriptan.

During the examination, she appeared stiff and moved rigidly without trunk twisting. She preferred standing due to stiffness. Weakness in her arms and legs, difficulty lifting her leg while walking, and occasional foot dragging were noted. Simple tasks are challenging due to poor hand grip, as tested. She perceives weakness as peripheral. Physical therapy has become more difficult, but she remains committed to exercising.

Neurological examination revealed spasms in the shoulders and back, limb muscle stiffness, normal reflexes, decreased distal muscle strength, 3/5 graded muscle tone, and broad-based gait. The ocular examination was normal, and the rest of the neurological examination was unremarkable.

Additional investigations included laboratory tests, MRI scan that revealed no abnormalities, and planned EMG and NCS. Notably, the patient's GAD antibody test confirmed a positive result, further supporting the diagnosis of MWS. The treatment regimen involves the administration of Clonazepam and Baclofen. At a 3-week follow-up, she reported 15-20% relief in spasms and improved daily living activities. Intravenous immunoglobulin therapy for quick relief is scheduled. After two months, she reported a 30-40% improvement in spasticity and activities of daily living.

Discussion

MWS is a rare disorder of the central nervous system characterized by rigidity and stimulus-triggered painful muscle spasms of predominantly axial and proximal limb muscles.² The differential diagnosis for MWS is broad, including disorders of the brain, spinal cord, and muscles such as myelopathies.⁷ [Table 1](#) summarizes the differential diagnosis of Moersch-Woltman Syndrome.

Even though the patient exhibited several symptoms that were quite typical for MWS, her co-morbid illnesses likely contributed to the delay in diagnosis. She had a long history of depression, anxiety, and migraines, to name a few. It does not seem unreasonable to suppose that her psychiatric history may have played some role in her presentation. However, it is crucial to remember that MWS and concomitant autoimmune disorders frequently cause anxiety.^{4,8}

MWS patients generally have GAD antibodies, which seldom occur in the general population.⁹ In addition to blood tests for GAD, an electromyography test can help confirm the condition's presence as it generally reveals continuous agonist and antagonist muscle motor activities.^{7,9} Benzodiazepine-class drugs are the most common treatment for symptom relief from stiffness.¹⁰ Intravenous Immunoglobulin and plasmapheresis, among other immunotherapies, may also be prescribed.¹⁰

Table 1. Summary of the differential diagnosis of Moersch-Woltman Syndrome.⁷

Serial number	Diagnosis	Differentiating Presentation	Diagnostic tests	Comparison with MWS
1.	Myelopathies	Upper motor neuron, lower motor neuron signs, sensory deficits	MRI confirms the diagnosis.	In MWS, MRI is normal.
2.	Dystonias	Variable abnormal posturing, significant muscle pain, and cramping.	(EMG shows pulsating nerve signals being transmitted to the muscles even at rest.	EMG shows continuous motor unit activity in agonist and antagonist muscles in MWS.
3.	Spinocerebellar Ataxia	Hypermetric, slow saccades, nystagmus, areflexia, tremors, intellectual disability	Genetic testing confirms the diagnosis.	No genetic testing is required. Preserved intelligence in MWS.
4.	Primary Lateral Sclerosis	Onset after 50 years of age, Spasticity, Hyperreflexia, Babinski sign positive.	Pringle's Criteria for diagnosis. ¹³	Anti-GAD for diagnosis of MWS.
5.	Neuromyotonia	Hyperhidrosis, muscle fasciculations, quivering of the muscle, myoclonic jerks, and myotonia-like symptoms	Fibrillation potentials and fasciculations on EMG.	EMG shows continuous motor unit activity in agonist and antagonist muscles in MWS.
6.	Multiple Sclerosis	Off and on UMN symptoms, Temperature sensitivity, Optic neuritis	MRI for diagnosis	MRI normal in MWS, no temperature sensitivity
7.	Parkinson's disease	Tremor, Rigidity, Akinesia	Clinical, DaT scan, MRI	DaT Scan is normal, no tremors are present in MWS.

Legend: MRI: Magnetic Resource Imaging, MWS: Moersch-Woltman Syndrome, DaT: Dopamine transporter, EMG: Electromyography, GAD: Glutamic Acid Decarboxylase; UMN: Upper Motor Neuron.

The prevailing and logical approach to therapy involves a combination of GABA-enhancing medications and immunotherapy. This is because these two treatment categories operate through distinct mechanisms: one addresses underlying pathological processes, while the other targets autoimmune responses.¹¹ Dalakas et al. (2023) recommended initiating antibody treatment without any delay, concurrently with the administration of antispasmodic medications.¹² The patient's condition was improved using a variety of treatments after the diagnosis. Diazepam, a GABA-enhancing medication, and Baclofen, an antispastic medicine, were first administered to the patient. According to Dalakas et al. (2009) and Dalakas et al. (2023), both are routinely suggested as possibilities for the first treatment.^{12,13} Although there is currently no treatment that cures MWS, working with a specialist and maintaining symptom control can make it easier to live with the condition.¹⁴

Strengths

In approaching this case, several strengths can be identified. Firstly, a thorough review of the relevant medical literature on MWS and its differential diagnosis was conducted, providing a comprehensive understanding of the condition and its diagnostic challenges. This allowed for a more informed assessment of the patient's symptoms and formulating a differential diagnosis. Additionally, the inclusion of relevant diagnostic tests, such as blood tests for GAD antibodies and electromyography, contributed to the confirmation of the MWS diagnosis.

Limitations

This case report represents a single patient, which limits the generalizability of the findings to a larger population. Further studies

involving larger sample sizes are needed to corroborate these observations. Additionally, the absence of long-term follow-up data restricts the assessment of treatment outcomes and prognosis.

Conclusion

The differential diagnosis for MWS is broad, highlighting the importance of thorough evaluation and ruling out other potential conditions. Further research and awareness are needed to enhance understanding and facilitate the development of more effective treatments for this challenging condition.

By recognizing the potential presence of MWS, accurate diagnoses can be made, leading to appropriate management and treatment strategies. This emphasizes the importance of maintaining a high index of suspicion for MWS to improve patient outcomes and prevent unnecessary delays in the appropriate management of this condition.

Summary – Accelerating Translation

The rare and progressive disorder Moersch-Woltman Syndrome (MWS), also known as Stiff Person Syndrome (SPS), is characterized by muscle rigidity and spasms and has a significant impact on a person's quality of life. This case report focused on shedding light on the difficulties in detecting and managing this complicated condition by examining the clinical presentation, diagnosis, and treatment of MWS. The study involved a comprehensive evaluation of a 57-year-old woman presenting with chronic muscle stiffness, pain, and spasms. Based on the patient's clinical condition and the presence of GAD antibody positivity, the diagnosis of MWS was established. Treatment options such as Clonazepam and Baclofen were administered, and the patient's response was evaluated. The patient presented signs of MWS, such as tight muscles, spasms, and sensory problems. The diagnosis was supported by laboratory studies that

revealed the existence of GAD antibodies. A partial improvement in the patient's spasticity and activities of daily living was seen after treatment with clonazepam and baclofen. MWS, a challenging neurological condition, manifests as crippling muscle rigidity and spasms. Because of its rarity and the lack of clear diagnostic markers, MWS diagnosis can be challenging. However, a comprehensive examination that includes clinical assessment and pertinent laboratory tests, including GAD antibody testing, can help to support the diagnosis. Although there is no cure, treatment plans attempt to reduce symptoms and enhance the patient's

quality of life. Further research and awareness are needed to enhance our understanding of MWS and develop more effective treatments.

This case report emphasizes the importance of early MWS diagnosis and treatment, as well as the necessity of multidisciplinary management involving neurologists, physical therapists, and other experts. Healthcare practitioners can better support people with this difficult condition, improving their outcomes and general well-being, by raising awareness about MWS.

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Addressing Bias among Medical Care Teams on the Wards: A Perspective from Asian Medical Students in the United States

Jesper Ke,¹ Ellen Zhang,² Kate Lee,³ Hueyjong Shih,⁴ Chin Hur.⁵

The Experience

As Asian American and Pacific Islander (AAPI) medical students who were preparing to enter clinical rotations in the United States, we heard general warnings from certain faculty mentors about difficult exams, demanding shifts, and burnout. More specifically, we were also told to be wary of another stressor our mentors had experienced as AAPIs: being mistaken for each other. For example, we heard stories of an AAPI female medical student mistaken for another AAPI female student on a four-person team. This persistent mix-up led one student to consider dyeing her hair or wearing glasses. At the end of the rotation, the two students realized they had received evaluations meant for the other student because of this continued mix-up, which caused significant stress.

These are not isolated incidents. We have faced similar events during our own training in different hospitals across different states. Moreover, harmful AAPI biases are not a novel issue. A recent study published in the *Journal of the American Medical Association (JAMA) Network Open*, AAPI medical residents reported the highest percentage of any race/ethnic subgroup (99%) of being confused for another team member of the same race/ethnicity within a year.¹ As AAPI students, we not only face the challenges of medical school, but we also worry about unconscious and conscious biases in the clinical setting that may impact our evaluations and careers.

Bias refers to the “implicit stereotypes and prejudices,” often negative, that individuals may hold toward other groups based on factors like race, gender, age, and occupation.² There has been an increased focus on the healthcare system’s role in addressing systemic bias and discrimination leading to poorer outcomes and experiences for minority patients.³ Other studies have assessed patient’s bias towards physicians and medical students.⁴ Yet, the

bias perpetrated within the medical team is frequently missed. As AAPI students, we have a unique perspective on this important and prevalent issue.

One day, one of us was asked by a resident if we spoke Korean as we approached a Korean-speaking patient. Upon realizing that we spoke Chinese, the resident expressed disappointment, saying, “That’s such a shame. It’d be so much easier if you spoke Korean.” This conversation could have been approached differently: asking the entire team if anyone spoke Korean rather than targeting the sole AAPI medical student. Incidents like these can also affect team dynamics by leaving a negative impression on a student for something outside of their control – speaking a particular language based on the assumption they may be Korean.

When considering bias among medical care teams, the issue is complicated for medical students: we are less inclined to speak up and advocate for ourselves given our position in the medicine hierarchy.⁵ For AAPI students, this manifests not just as receiving the wrong evaluations, but also being viewed from the lens of racial stereotypes: receiving feedback from faculty on the wards that we are “too quiet,” for example. These experiences pose an important question: how can we address the bias within our clinical teams towards medical students? From our perspective, education and representation are potential avenues for change.

To begin, educators can be equipped with resources to understand the complex cultural backgrounds of AAPI students to cultivate a safe environment. Educator bystander intervention workshops build skills for faculty to intervene if a patient or another team member make biased comments that create an uncomfortable environment. Implicit bias trainings could benefit both students and educators alike by alerting both parties to the unconscious societal biases that may influence how one evaluates

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another person’s performance. Bias is present from students toward faculty and from faculty toward students in evaluations^{5,6}, which emphasizes the need to offer interventions toward students as well.

Another way for microaggressions and discrimination to be recognized and addressed is through AAPI experiences to be incorporated into medical school curriculum.⁷ As AAPI medical students, we have attended many lectures regarding race as a factor for healthcare disparities. From our personal experience, stories and statistics of AAPIs are sometimes not mentioned alongside that of other race/ethnic groups; despite being the fastest-growing racial group in America, AAPIs have funding, structural, and social barriers to research participation.⁸ Thus, we encourage these educational trainings and lectures to include our voices and data. Representation also comes in the form of mentorship and structural change to diversify faculty to include AAPI individuals. A 2012 study found that AAPIs represented 3.52% of chairpersons, and 0% of deans in the U.S.⁹ Hence, we endorse a hiring toolkit for recruiting, supporting, and retaining faculty and staff from marginalized backgrounds.

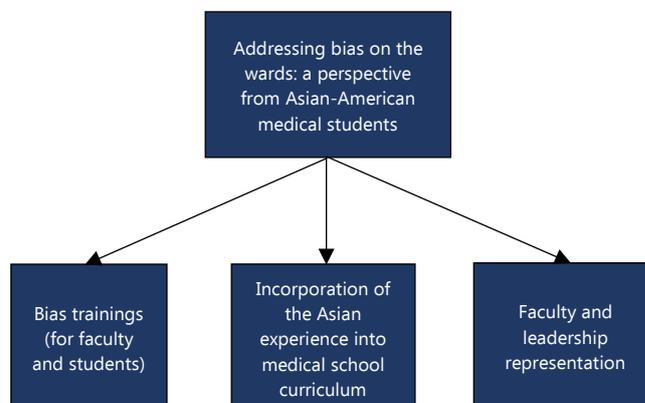
An example of these recommendations in practice, at one of our medical schools at the University of Michigan, we have advocated for bystander trainings to be offered to more faculty, staff, and students. We worked to add readings to an optional curriculum for incoming medical students related to the topic of bias toward AAPI students in medicine. Finally, we worked to help establish an AAPI faculty-staff-student support group across our health system to facilitate further conversation on these topics. While there remains more work to do at both Michigan and other institutions, these small steps have already led to progress.

Addressing general mistreatment of trainees includes addressing the biases medical colleagues perpetrate among each other. As conversations regarding systemic racism increase at bedside and

on the wards, it would be a blind spot to not do so. Just as Morbidity and Mortality conferences are seen as critical for ensuring high-quality patient care, so are discussions around how we can better support our hospital colleagues and medical students. Through interventions including implicit bias trainings, incorporation of health disparities in the AAPI population into medical school curriculum, and adequate leadership representation, we can create a more positive learning environment for AAPI students (*Figure 1*). Our hope is that this extends to the bias that trainees of other identities face as well.

As we look forward in our career, there is no better way to make us better educators and care providers than having exemplary models. Knowing our names is just one of many steps that mentors and supervisors in clinical settings can take to have medical students feel included. Now is the opportunity to set the precedent for addressing bias within clinical teams and positively shape the next generation of physicians.

Figure 1. Three Steps to Address Implicit Bias on the Clinical Wards.



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Decreasing Medication Delays: Maximizing the Efficiency of Patient Assistance Program Applications Through an Electronic System at a Student-Run Free Clinic

Jasmine A. Liu-Zarzuola,¹ Chelsea T. Nguyen,¹ Dominique B. Johnson.¹

The Experience

"I can barely breathe when I walk and I can't afford my inhaler," said one patient at our student-run free clinic. Time after time, we listen to our patients' struggles and try our best to support them, as many of them manage co-morbid, chronic conditions, but there is only so much we can do as students.

In 2019, more than 20% of Americans were unable to obtain prescription drugs due to excessive cost, a substantial cause of uncontrolled health conditions across all patient populations.¹ The combination of unregulated prices from pharmaceutical companies and limited patient access constitutes a public health crisis. To mitigate this crisis, patient assistance programs (PAPs) are sponsored by pharmaceutical manufacturers to provide free medications for patients that meet specific criteria.²

By guiding our patients through the PAP application process, we realized that students can alleviate some of the financial burden patients endure. Applications require various administrative steps, resulting in medication delays (see [Figure 1](#)).

Last year, an analysis of 100 randomly selected paper applications from 4/9/16 to 11/17/21 demonstrated that it takes an average of 62 days for an application to be approved at our clinic. More specifically, it took an average of 4 days to obtain patient signatures, 19 days to obtain prescriber signatures, 30 days to obtain proof of income (POI), 43 days to fax the application to the pharmaceutical company, and 105 days to receive rejection status. "When we saw the results of this analysis, my jaw dropped. I could not believe how long it took to get our patients life-saving medications. We knew there was some way to expedite the process, and our team was dedicated to discovering a way to achieve so."

To decrease the processing time of applications, we implemented a streamlined, secure, and electronic-based platform in November 2023. With Adobe Editor and Frevo applications, we

transformed electronic PDF applications to online forms. Students and faculty volunteers can access these forms on our clinic's main website. The forms were created so that patients and providers only provide their signature once. Moreover, when the volunteer is prompted to select an attending name as the prescriber, their licensing information (such as NPI number, DEA number, and clinic address) is automatically populated. This auto-population feature decreases the time needed to fill out an application and ensures that all fields are completed. If the patient has no income, there is an option to generate an automatic no income letter, which includes the patient's signature and the clinic's letterhead. When the volunteer submits the completed application, it is automatically uploaded to our secure Teams Channel, which is accessible for all volunteers of the clinic and allows us to fax the application within several minutes.

After three months of utilizing this electronic system, we analyzed 100 randomly selected electronic applications from 11/8/22 to 2/23/23, which revealed an average of 15 days to obtain approval, a 75.8% decrease from the amount of time it took for approval before implementation of the electronic system. Additionally, all applications received a patient signature on the same day of application initiation. It took an average of 1 day to obtain prescriber signature, 3 days to obtain POI, 6 days to fax the application to the pharmaceutical company, and 15 days to receive rejection status. All administrative steps significantly decreased with the implementation of the new system ($p < 0.01$).

The electronic system has significantly expedited the approval and overall process of applications. Automating income letters for eligible patients has decreased the time required to obtain POI. Likewise, online accessibility of applications has decreased time required to fax applications to companies. "It has been a tremendous achievement to see that our electronic system has helped patients get their medications faster," said one of our student volunteers who helped create the electronic system.

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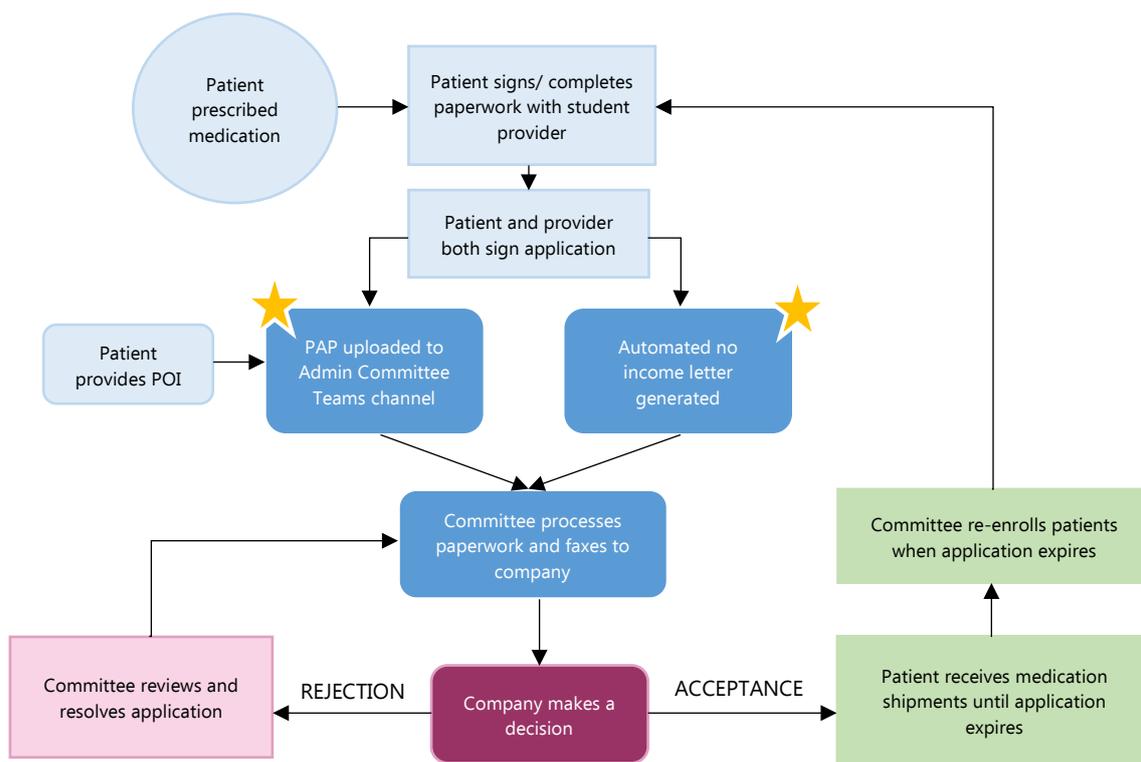
Obtaining POI and faxing applications are primary causes of delays, with missing POI being the main reason for rejection. Therefore, we plan to implement a new, faster method of obtaining POI where we text patients a link to safely upload documents. Moreover, we hope to automate faxing complete applications when submitted.

"We really try our best to provide patients with as many resources as possible, and these applications have not only saved our patient's a large amount of money, but that have also saved their lives. I feel extremely fortunate to be in a position where I am able

to help the lives of our underserved community," exclaimed one of the student volunteers in charge of handling PAPs.

Our goal is to share our findings with clinics utilizing PAPs and encourage others to implement similar interventions into their practices, ensuring continuity of patients' medication regimes and better management of their conditions, ultimately improving the healthcare of vulnerable populations. As MD/MPH students and future providers, we seek to provide accessible and quality healthcare that addresses the critical role of social determinants of health and optimizes patient care.

Figure 1. Administrative Steps for the Patient Assistance Programs (PAPs).



Summary – Accelerating Translation

Why Patients Wait Long for Medications from Patient Assistance Program Applications from Pharmaceutical Companies and Interventions to Decrease Wait Times

Many patients need medications to live. Thus, their health and wellbeing often depend on their medications. Patient assistance programs (PAPs) give uninsured and underserved patients medications that they might be able to afford on their own. However, it is often difficult to be approved

by these programs. The program's applications require many administrative steps, which results in delays for patients to receive their medications. Last year at our student-run free clinic, it took an average of 62 days for an application to be approved. To address this problem, we have implemented an electronic-based platform to complete these applications, which has decreased the approval time more than 75%. Our goal is to share our findings with similar clinics utilizing PAPs and encourage others to use them in their practices. As MD/MPH students and future providers, we want to increase access to quality healthcare for patients who are most in need.

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Global Surgery Research: An Overview and the Role of Medical Students and Surgical Trainees in Advancing Global Surgery Research in LMICs

Yvan Zolo.¹ 

Letter to the Editor

The Importance of Global Surgery Research

Global surgery research systematically investigates various facets of surgical care delivery, access, outcomes, and innovative solutions specifically tailored to low- and middle-income countries (LMICs) and disaster areas. Its scope involves in-depth examinations of the burden of surgical diseases, identification of barriers impeding access to care, development of sustainable strategies, evaluation of health systems, and promotion of equitable and effective surgical interventions.¹ By addressing the substantial burden of surgical diseases borne by LMICs, despite their limited healthcare workforce and infrastructural capacities, global surgery research plays a pivotal role in enhancing surgical care and outcomes in these regions.^{2,3} It achieves this by identifying key challenges, proposing innovative solutions, evaluating intervention effectiveness, addressing region-specific hurdles, and advancing global health equity.⁴ Given the unfortunate negative impact of surgical care on the environment, sustainability is at the core of global surgery research. Sustainable surgical care ensures that interventions benefit patients, minimize negative environmental impacts, and support long-term viability.⁵ Medical students and surgical trainees can significantly contribute to global surgery research, helping address the pressing needs of LMIC populations,^{6,7} hence, it is imperative to provide an overview of global surgery research and explore the avenues through which medical students and surgical trainees can make meaningful contributions to this critical field.

Research Priorities in Global Surgery

Global surgery research is pivotal in driving progress and fostering innovation in healthcare, particularly within LMICs.⁴ Research priorities form the foundational pillars upon which transformative advancements are built, paving the way for surgical care improvements and equitable health outcomes. Core areas of inquiry help generate evidence-based insights and strategic interventions that address the unique challenges LMICs face in global surgery. Some key research priorities in global surgery include the following:

- Assessing surgical disease burden in LMICs, including incidence, prevalence, and environmental impact of surgical care.
- Identifying barriers to accessing surgical care: financial, geographic, and cultural factors.
- Developing sustainable solutions to overcome barriers to accessible surgical care.
- Strengthening health systems and improving surgical care delivery in LMICs with sustainable practices.
- Evaluating the impact of surgical education and training programs in LMICs, enhancing sustainability education.
- Developing low-cost, high-impact surgical innovations aligned with sustainability for LMICs.

Medical Students and Surgical Trainees Can Contribute to Global Surgery Research

Medical students and surgical trainees in LMICs can make valuable contributions to global surgery research, despite being early in their careers. Some ways in which they can get involved include:

1. Participating in research projects led by experienced researchers in global surgery

Collaborating with seasoned researchers allows students to gain hands-on experience and contribute to ongoing studies in the field. Medical students and trainees can seek opportunities to collaborate with established researchers who are already leading projects in the field of global surgery. Seasoned researchers could benefit from involving medical students in research by gaining fresh perspectives, increasing productivity through task delegation, facilitating knowledge transfer and mentorship opportunities, and expanding their professional network.

2. Developing their research projects in collaboration with local partners in LMICs

Working closely with local partners fosters a deeper understanding of the specific healthcare challenges and needs in LMICs, leading to impactful research initiatives. Students can connect with local healthcare professionals, institutions, or non-

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governmental organizations (NGOs) in LMICs to identify research areas of mutual interest. Collaborating with local partners ensures the research aligns with the specific needs and priorities of the LMICs, increasing its relevance and impact.

3. Conducting literature reviews and meta-analyses to synthesize existing research in global surgery

By reviewing existing research in global surgery, students can synthesize and analyze available information, identifying knowledge gaps and potential areas for further investigation. Medical students and trainees can undertake comprehensive reviews of existing literature related to global surgery. They can summarize and analyze the findings from multiple studies, identify gaps in knowledge, and propose research questions or areas that require further investigation.

4. Collecting and analyzing data in LMICs, for example, by conducting surveys or interviews with patients and healthcare providers

Students can engage in primary data collection by conducting surveys or interviews with patients and healthcare providers, helping to generate new insights and evidence. Once the data is collected, students can assist with data analysis, interpretation, and drawing meaningful conclusions.

5. Disseminating research findings through academic publications, conference presentations, and social media

Sharing research outcomes through academic publications, conference presentations, and social media platforms raises awareness, promotes collaboration, and contributes to the broader global surgery community.

Challenges and Opportunities

Global surgery research in LMICs face several challenges, including limited human, infrastructural and financial resources, sociopolitical instability, language and cultural barriers, and

inadequate political engagement. Medical students and surgical trainees must be mindful of these challenges and work collaboratively with local partners to overcome them and mitigate their impact.

Medical students and surgical trainees are presented with unique opportunities to contribute significantly to the field of global surgery research. These opportunities are facilitated through various global surgery interest groups, such as the Association of Future African Neurosurgeons (AFAN), the International Student Surgical Network (InciSioN), the Association of Future African Cardiothoracic surgeons (AFAC), the African Research Society (ARS), and the Evidence-Based Scientific Consortium (EBASC), among others. These interest groups serve as platforms for medical students and surgical trainees in LMICs to cultivate their interest in global surgery research and foster the development of indispensable skills and experiences essential for their future careers and contributions to the field of global surgery. Additionally, numerous institutions within LMICs and the African continent offer research fellowships specifically dedicated to global surgery.⁸ By engaging in these research fellowships, medical students and surgical trainees can actively participate in hands-on global surgery projects, while simultaneously expanding their knowledge and expertise in the realm of global surgery research.

Conclusion

Global surgery research is an important area of study that aims to improve access to safe and effective surgical care for patients in LMICs. Medical students and surgical trainees can contribute by participating in research projects, collaborating with local partners, conducting literature reviews, collecting data, and disseminating findings. Despite challenges, there are opportunities to make a positive impact and develop valuable skills. Their involvement is essential for addressing healthcare disparities and promoting sustainable and equitable access to surgical care.

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