eISSN 2076-6327

IJMS

International Journal of Medical Students

Year 2022 | Months Oct-Dec | Volume 10 | Issue 4

IJMS

International Journal of Medical Students

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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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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 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.

The *IJMS* receives submissions where there is at least one author enrolled as a medical student in any medical school in the world or a recently graduated physician worldwide. For research articles, early-career scientists must be accompanied by a senior researcher that must be also responsible for the research, guaranteeing the quality of the work. We publish Original Articles, Short Communications, Reviews, Case Reports, Interviews, Experiences, and Letters, which follow an innovative and unique two-step, double-masked peer-review process, in brief:

> *The first step of revisions is carried out by two Student Editors (medical students with publications indexed in the US National Library of Medicine (NLM) with the supervision of an Associate Editor. The aim of this step is to improve the quality of articles and identify those that can proceed to external peer-reviews. The second step of revisions is carried out by external peer-reviewers who are researchers with publications indexed in the NLM related to the topic of the submission.*

The time between submission and final publication in most cases has been two to four months depending on the diligence of Peer-Reviewers and Authors.

The *International Journal of Medical Students* is published online quarterly (March, June, October, December) by the University of Pittsburgh Library System, a member of the Open Access Scholarly Publishers Association, as part of its Pitt Open Library Publishing imprint.

The journal main office is located in the United States of America (USA). Any publication, dissemination or distribution of the information included in the Journal is permitted if the source is cited (*Int J Med Stud*).

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The *IJMS* acceptance rate is 18% of the almost 350 annual submissions. Published articles in 2021 came from 32 different countries. The average days to a first decision is 14 days, 143 for acceptance, and 31 to decline a submission. The time between submission and final publication in most cases has been three to four months depending on the diligence of Peer-Reviewers and Authors.

The journal's website got over 75 thousand visits only in 2021. The *IJMS*'s reach includes a growing social media presence (more than 19,000 followers on Twitter, Facebook, Instagram, YouTube, and LinkedIn). Only in the last 2 years, the Journal has been visited from nearly every place in the world (+190 countries). You can find more of the *IJMS* statistics here.

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There are no article processing charges, submissions fees, or any other costs required of authors to submit, review or publish articles in the IJMS.

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All papers submitted to the International Journal of Medical Students will undergo a two steps peer-reviewers process. The first step of revisions is carried by two anonymous Student Editors who will work together with one Associate Editor. In the second step, the manuscript will be reviewed by two anonymous reviewers (Editorial Board members, Associate Editors and/or invited reviewers with expertise in the subject matter). Authors will remain anonymous to all the referees.

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

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Suite 3103
Pittsburgh, PA 15219.
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e-ISSN 2076-6327 (Online)

International Journal of Medical Students

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IJMS INTERNATIONAL JOURNAL of MEDICAL STUDENTS

Editorial

Advancing Research Through Early-Career Scientists' Publications and Training the Next Generation of Medical Editors: The First 10-Years of the International Journal of Medical Students

Sebastian Diebel,[1] Diego Carrion-Alvarez,[2] Wah Praise Senyuy,[3] Marina Shatskikh,[4] Juan C. Puyana,[5] Francisco J. Bonilla-Escobar.[6]

Introduction

The International Journal of Medical Students (IJMS) has reached a new milestone. This historic issue will mark the final publication for the IJMS in the first 10-years of uninterrupted publications.[1] The IJMS started following a discussion in 2009 at an international medical student congress where a conversation pertaining to student research was held. The discussion centered around the need for medical students to be acknowledged for their research, which in turn would lead to an improved research impact for the next generation in the medical-scientific community.[2] By 2013 the ideas from the discussion at the congress had reached fruition and the IJMS published its first issue.

From its humble origins that started as an international project in Latin-America, the journal that is now an institution boasts a team of over 300 medical students, with representation from thirty-four different nationalities from all seven continents.[1,3,4] This teamwork is being seen around the globe. In 2022, more than 250,000 website views were counted from more than 85,000 users (https://ijms.info/IJMS/statistics). In addition to the journal being widely disseminated, another accomplishment is that the journal has experienced long-term success when it comes to publishing. The IJMS is the longest-standing, non-interrupted international medical student journal that went from publishing three issues annually to four in 2021.[1]

Other accomplishments that are noteworthy in the journal's first decade of existence include the indexing of multiple publications in PubMed Central (PMC).[1,5-11] Another major accomplishment can be appreciated when looking at the journal's success as it pertains to funding of the research that is published. Medical students under the mentorship of investigators with funding from the National Institute of Health (NIH) of the United States have specifically chosen the IJMS to publish their work.[12]

This year the IJMS also ventured into another side of the academic world with the first World Conference of Medical Students Research (WCMSR), which took place in November 2022 and aimed to reduce barriers such as time, transportation, registration costs, and limitations related to the role of medical students in this type of event. Held virtually, it attracted more than one hundred abstract submissions, which ended up in forty-one student presentations and over 1,200 viewers during that day, a number that is still growing, marking another staple in this ten-year celebration (First IJMS WCMSR link: https://www.youtube.com/watch?v=0JIMP5Fyl7s&t=0s). The editorial of the Conference has a better insight on the work behind this event and will be found in the Supplement of this volume, together with the abstracts from the Conference itself.[13] The Supplement includes six different medical student-led conferences that are locally incentivizing the relevance of training in research and the visibility of student work, including:

- Abstracts of the 2022 American Physician Scientist Association (APSA) Northeast Regional Conference (NERC).[14]
- Abstracts of the Lagos State University Medical Students Association Research Conference.[15]
- Abstracts of the Medical University Congress of Mogi das Cruzes, COMUMC.[16]
- Abstracts of the Medical Academical Conference of Piauí (COMAPI) 2021.[17]
- Abstracts of the 2021 Yorkshire International Imaging and Interventional Radiology Symposium at the University of Leeds.[18]
- Abstracts of the Medical Academical Conference of Piauí (COMAPI) 2022.[19]

As the IJMS continues to progress and evolve, it is always seeking contemporary ideas in order to advance the Journal. As a result, 2022 saw the launch of MedEd Research Webinars. These are monthly research webinars that serve to develop a positive culture of virtual mentorship for medical students that may not have the opportunity to attend such events in their home countries. These webinars are specifically designed for medical students who want to improve their research skills. The overall

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mission and vision of the webinars is to be the leading diffusion platform for early career medical research (Link to the webinars: https://www.youtube.com/channel/UCoUYNIPrknOofTbP2WnioIA). These certainly are exciting times and the IJMS is additionally planning an online series that will be released in 2023 and disseminated on its YouTube platform entitled "Research Pathways." It will be a space for top-tier researchers to share their stories and provide guidance on how to get there, together with their research career development.

This issue is truly a highlight of what the last 10-years has been for the IJMS. The Journal is publishing works from ten different countries that consists of seven original articles, two reviews, two case reports, one letter to the Editor, two editorials, one interview and four experiences.

The second editorial is a particularly important piece as it is a real call for global climate change efforts. This issue will highlight the third call for global action and collaboration for climate change. The IJMS remains the only medical student journal involved in this initiative. The editorial touches on the 2022 Report of the Intergovernmental Panel on Climate Change (IPPC) and the burden of the effects of climate change specially in Africa and other vulnerable regions.[20]

Some of the original articles in this volume continue to demonstrate both the tradition of international work and social accountability that has been on display in the IJMS in the past.[21] The first original article to continue with the international theme was a study conducted by Bandyopadhyay et al., which set out to examine personality traits of medical students and how they evolve over the course of undergraduate medical training in India. Interestingly, the authors reported that the students became more introverted as time went on.[22] Other international studies that examined low- and middle-income areas include the work by Johnson et al., which examined traumatic brain injuries in Honduras to better understand their etiology and severity, and finally the work by Amo-Tachie et al., which examined the health practices of blood donors in Ghana.[23,24]

As we head into 2023, it is important to note that the global pandemic of COVID-19 is still ever present. Two of the original studies had COVID-19-related research questions. Hardoon et al. look into the effects of COVID-19 lockdowns and fatality rates in the United-States during the first year of the global pandemic. They found that implementing safety protocols and lifting these protocols in phases reduced the spread of the virus, and ultimately the fatality rate.[25] The second study, by Skoczek et al., examined the impact of the pandemic on medical learners and how it affected their education. The study found that International medical students reported more restrictions in their country and a larger mental health impact, while United States medical students were more likely to express a decrease in academic opportunities and academic performance.[26]

The last two original articles in this volume demonstrated novel techniques to answer fascinating research questions. El-Jack et al. performed research using the social media platform Reddit to gain better insight into the type of questions that patients may be posing about anesthesia.[27] The last original article was conducted by Simões et al. and set out to explore if renal disease in the context of diabetic patients could be predicted by looking at specific gene expression.[28]

This issue also features two reviews. Rossi et al. performed a narrative review addressing the need for young physicians to be part of global surgery, a neglected but essential part of global health. They conclude with a strong proposal based on their setting and the need to have a broader approach to medical school curriculum.[29] Campbell et al. performed a narrative review on the management for myelomeningocele, a study that explores and describes how the advancement in biomedical engineering can change these patients lives.[30]

Clinical cases in this issue were focused on anatomic findings. One article reported two cases of headaches associated with coughing, whose etiology was jugular venous insufficiency.[31] The other case examined a post-mortem finding during an anatomy class, describing an aberrant right subclavian artery which occurs in less than 1% of the population.[32]

Understanding the importance of physicians' role in addressing healthcare disparities, Lahiri et al. engaged with at-risk K-5th graders via an after school science program to increase students' exposure to Science, Technology, Engineering, and Mathematics (STEM). Through hands-on projects the kids were inspired while participants gained skills to advocate for vulnerable patient populations in the future.[33] Across Ghana, Dr. Amo-Tachie was struck by the disproportionate impact of a recent poliomyelitis outbreak. His insights into the significance of the outbreak, particularly in the context of concurrent stressors on the healthcare system posed by COVID-19, highlight the importance of remaining vigilant about controlling preventable infectious disease outbreaks to avoid unnecessary suffering and loss of life.[34] Shah et al. shared their experience within an international peer research mentorship program, which was meant to equip medical students with the tools to become competent researchers and communicators upon graduation. The authors' positive experiences within the program highlight the need for more widespread incorporation of such initiatives across medical schools globally.[35] Equally important to obtaining research experiences are early clinical exposures to both specialties and geographic regions where medical students may envision themselves practicing post-graduation. In two articles we gain insight into rural medicine from a clerkship in rural Australia,[36] and about mental health provision in rural settings through the interview of Dr. Van Gilder-Pierce.[37] Finally, the Letter to the Editor acts as a reminder that *"Primum non nocere"* or *"do no harm"* should not only be applied to serving patients but also be a key commitment of healthcare providers to themselves—to prioritize mental and physical wellbeing, which will in turn aid in provision of better care to patients.[38]

The last decade of consistent and quality publications would not have been possible without the tireless efforts and hard work of all the members both past and present of the IJMS Editorial Team and

Editorial Board. A special acknowledge goes to the **Student Editor of the Year 2022:** Dr. Lourdes A. Medina Gaona, Instituto Tecnológico y de Estudios Superiores de Monterrey, Mexico; **Raising Star Student Editor 2022:** Dr. Rebecca N. Murerwa, University of Nairobi; Kenya; and the **Associate Editor of the Year 2022:** Dr. Sohaib Hasseb, James Cook University, Queensland, Australia. The IJMS looks forward to what the next decade will bring.

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Conflict of Interest Statement & Funding

The Authors have no funding, financial relationships or conflicts of interest to disclose. Dr. Juan C. Puyana work is partially funded by the National Institute of Health (NIH) of the United States with the grant R21TW011151. The opinions expressed in this article are the author's own and do not reflect the view of the National Institutes of Health, the Department of Health and Human Services, or the United States government.

Cite as

Diebel S, Carrion-Alvarez D, Senyuy WP, Shatskikh M, Puyana JC, Bonilla-Escobar FJ. Advancing Research Through Early-Career Scientists' Publications and Training the Next Generation of Medical Editors: The First 10-Years of the International Journal of Medical Students. Int J Med Stud. 2022 Oct-Dec;10(4):341-43.

ISSN 2076-6327

This journal is published by Pitt Open Library Publishing

IJMS INTERNATIONAL JOURNAL of MEDICAL STUDENTS

Editorial

COP27 Climate Change Conference: Urgent Action Needed for Africa and The World

Gregory E. Erhabor,[1] Aiah A. Gbakima,[2] Abraham Haileamlak,[3] Jean-Marie Kayembe Ntumba,[4] James Kigera,[5] Bob Mash,[6] Joy Muhia,[7] Fhumulani Mavis Mulaudzi,[8] David Ofori-Adjei,[9] Friday Okonofua,[10] Arash Rashidian,[11] Siaka Sidibé,[12] Abdelmadjid Snouber,[13] James Tumwine,[14] Mohammad Sahar Yassien,[15] Paul Yonga,[16] Lilia Zakhama,[17] Chris Zielinski.[18]

Wealthy nations must step up support for Africa and vulnerable countries in addressing past, present, and future impacts of climate change.

The 2022 report of the Intergovernmental Panel on Climate Change (IPCC) paints a dark picture of the future of life on Earth, characterised by ecosystem collapse, species extinction, and climate hazards such as heatwaves and floods.[1] These are all linked to physical and mental health problems, with direct and indirect consequences of increased morbidity and mortality. To avoid these catastrophic health effects across all regions of the globe, there is broad agreement—as 231 health journals argued together in 2021—that the rise in global temperatures must be limited to less than 1.5°C compared with pre-industrial levels.

While the Paris Agreement of 2015 outlines a global action framework that incorporates providing climate finance to developing countries, this support has yet to materialize.[2] COP27 is the fifth Conference of the Parties (COP) to be organised in Africa since its inception in 1995. Ahead of this meeting, we—as health journal editors from across the continent—call for urgent action to ensure that the COP finally delivers climate justice for Africa and vulnerable countries. This is essential, not just for the general health of those countries, but for the health of the whole world.

Africa has Suffered Disproportionately Although it has Done Little to Cause the Crisis

The climate crisis has had an impact on the environmental and social determinants of health across Africa, leading to devastating health effects.[3] Impacts on health can result directly from environmental shocks and indirectly through socially mediated effects.[4] Climate change-related risks in Africa include flooding, drought, heatwaves, reduced food production, and reduced labour productivity.[6]

Droughts in sub-Saharan Africa have tripled between 1970-79 and 2010-2019.[7] In 2018, devastating cyclones impacted three million people in Malawi, Mozambique, and Zimbabwe.[7] In West and Central Africa, severe flooding resulted in mortality and forced migration from loss of shelter, cultivated land, and livestock.[5] Changes in vector ecology brought about by floods and damage to environmental hygiene has led to increases in diseases across sub-Saharan Africa, with rises in cases of malaria, dengue fever, Lassa fever, Rift Valley fever, Lyme disease, Ebola virus, West Nile virus, and other infections.[8,9] Rising sea levels reduce water quality, leading to water-borne diseases, including diarrhoeal diseases, a leading cause of mortality in Africa.[8] Extreme weather damages water and food supplies, increasing food insecurity and malnutrition, which causes 1.7 million deaths annually in Africa.[10] According to the Food and Agriculture Organization of the United Nations, malnutrition has increased by almost 50% since 2012, owing to the central role that agriculture plays in African economies.[11] Environmental shocks and their knock-on effects also cause severe harm to mental health.[12] In all, it is estimated that the climate crisis has destroyed a fifth of the gross domestic product (GDP) of the countries that are most vulnerable to climate shocks.[13]

The damage to Africa should be of supreme concern to all nations. This is partly for moral reasons. It is highly unjust that the most impacted nations have contributed the least to global

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cumulative emissions, which are driving the climate crisis and its increasingly severe effects. North America and Europe have contributed 62% of carbon dioxide emissions since the Industrial Revolution, whereas Africa has contributed only 3%.[15]

The Fight Against the Climate Crisis Needs All Hands on Deck

It is not just for moral reasons that all nations should be concerned for Africa. The acute and chronic impacts of the climate crisis create problems like poverty, infectious diseases, forced migration, and conflict that spread through globalised systems.[6,14] These knock-on impacts affect all nations. COVID-19 served as a wake-up call to these global dynamics and it is no coincidence that health professionals have been active in identifying and responding to the consequences of growing systemic risks to health. But, the lessons of the COVID-19 pandemic should not be limited to pandemic risk.[16,17] Instead, it is imperative that the suffering of frontline nations, including those in Africa, be the core consideration at COP27: in an interconnected world, leaving countries to the mercy of environmental shocks creates instability that has severe consequences for all nations.

The primary focus of climate summits remains to rapidly reduce emissions so that global temperatures rises are kept to below 1.5 °C. This will limit the harm. But, for Africa and other vulnerable regions, this harm is already severe. Achieving the promised target of providing $100bn of climate finance a year is now globally critical, if we are to forestall the systemic risks of leaving societies in crisis. This can be done by ensuring that these resources focus on increasing resilience to the existing and inevitable future impacts of the climate crisis, as well as on supporting vulnerable nations to reduce their greenhouse gas emissions: a parity of esteem between adaptation and mitigation. These resources should come through grants, not loans, and be urgently scaled up before the current review period of 2025. They must put health system resilience at the forefront, as the compounding crises caused by the climate crisis often manifest in acute health problems. Financing adaptation will be more cost-effective than relying on disaster relief.

Some progress has been made on adaptation in Africa and around the world, including early warning systems and infrastructure to defend against extremes. But, frontline nations are not compensated for impacts from a crisis they did not cause. This is not only unfair, but also drives the spiral of global destabilisation, as nations pour money into responding to disasters, but can no longer afford to pay for greater resilience or to reduce the root problem through emissions reductions. A financing facility for loss and damage must now be introduced, providing additional resources beyond those given for mitigation and adaptation. This must go beyond the failures of COP26 where the suggestion of such a facility was downgraded to "a dialogue".[18]

The climate crisis is a product of global inaction, and comes at great cost not only to disproportionately impacted African countries, but to the whole world. Africa is united with other frontline regions in urging wealthy nations to finally step up, if for no other reason than that the crises in Africa will sooner, rather than later, spread and engulf all corners of the globe, and at that time it may be too late to effectively respond. If, so far, they have failed to be persuaded by moral arguments, then hopefully, their self-interest will now prevail

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Conflict of Interest Statement & Funding

The Authors have no funding, financial relationships or conflicts of interest to disclose.

Cite as

Erhabor GE, Gbakima AA, Haileamlak A, Kayembe Ntumba JM, Kigera J, Mash B, et al. COP27 Climate Change Conference: Urgent Action Needed for Africa and The World. Int J Med Stud. 2022 Oct-Dec;10(4):344-46.

ISSN 2076-6327

This journal is published by Pitt Open Library Publishing

IJMS INTERNATIONAL JOURNAL of MEDICAL STUDENTS

Original Article

Assessment of Personality Traits and Their Changes Over the Undergraduate Medical Course: A Pseudo-Longitudinal Analysis Among Indian Medical Students

Alapan Bandyopadhyay,[1] Arup J. Rout,[2] Mabel Das,[3] Debajyoti Das.[3]

Abstract

Background: Personality traits of medical students have been shown to affect both their academic performance as well as their capabilities to develop rapport with patients, with evidence that they change through the medical course. This research aimed to explore the personality traits of undergraduate medical students and assess whether personality parameters changed throughout the medical education course. **Methods:** A pseudo-longitudinal design was utilized for this study. A total of 346 MBBS. students studying in a Medical College of Eastern India were recruited at different stages of their coursework. These participants were similar in their sociodemographic makeup and differed only with respect to their year of MBBS study. The personality characteristics were assessed among these participants using the short-form revised Eysenck personality inventory. **Results:** The minimum possible score for each subscale was 0, and the maximum was 12. Mean scores of the participants for the extraversion, neuroticism, psychoticism, and lie scales were 6.17±3.09, 7.51±3.16, 3.40±1.61, and 4.98±2.48, respectively. Females scored significantly higher in neuroticism and lie dimensions. There were significant differences of psychoticism scores between participants with rural and urban backgrounds. A significant negative trend was seen from the first to the final year of study in the extraversion dimension (Kendall's tau =-0.094, p-value=0.025). **Conclusion:** Medical students in India scored higher on the neuroticism and lower on the psychoticism scales of personality with a trend of increasing extraversion over the years of their coursework.

Key Words: Extraversion (Psychology); Medical Education; Neuroticism, Personality; Social Desirability (Source: MeSH-NLM).

Introduction

A physician's mannerism and personality help build rapport with their patients. It has been observed that physicians with personality characteristics complimentary to that of their patients reported better clinical outcomes and vice versa.[1] Therefore, it is important to assess and understand the personality characteristics of medical students as they enroll in and progress through their medical coursework to ensure better doctor-patient interactions in the future.

Studies conducted internationally have shown that students who opt to pursue medical education differ significantly in personality traits as compared to their peers studying in other fields such as engineering, commerce, and the arts. For example, Lievens F. et al. reported that medical students in Belgium were among the highest scorers in extraversion when compared to other majors.[2] Another study done in Singapore by Lean L.L. et al. found that medical students scored lower in neuroticism and higher in extraversion.[3] It has also been observed that over time, the personality traits of a person can change due to the influence of external factors.[4] Thus, knowledge about the baseline personality traits of medical students and their changes throughout the coursework can not only contribute more information about the people entering the stream, but also provide valuable insights to the traits that are amenable to change during the course of their study. This knowledge can be translated into curriculum development and integration of skills training that would help medical students develop a stronger rapport with their patients, in the future, as physicians.

However, data on the personality characteristics of medical students is difficult to obtain in the Indian subcontinent. In India, there is no documentation or assessment of personality parameters of medical students during their enrollment to a medical course. It was noted that only one study explored the personalities of medical students at the time of admission.[5] Furthermore, research regarding the gradual change of personality characteristics of college students as their courses progress is scarce,[6] with no research investigating this particular aspect among medical students of India. This study aimed to assess the prevalent personality traits of medical students enrolled in the MBBS course in an Indian medical institute and to

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Layout Editor: Ana Maria Morales

Submission: Dec 26, 2021
Revisions: Feb 13, 2022, Aug 15, 2022
Responses: Feb 14, 2022, Aug 20, 2022
Acceptance: Aug 29, 2022
Publication: Dec 2, 2022
Process: Peer-reviewed

determine any existing change in personality traits from the first to the final year of the course.

Methods

In this study, an observational, descriptive study with a pseudo-longitudinal design was conducted at a tertiary care teaching hospital located in the state of West Bengal of Eastern India from April to June 2020.[7] Medical students enrolled in the MBBS course at the hospital formed the study sample.

The pseudo-longitudinal design of the current study enabled the identification trends in personality traits from the first through the final year MBBS students. Pseudo-longitudinal studies are performed when it is not possible to follow the same individuals over time. Then, researchers can carry out a comparison of cross-sectional studies of different groups of students at different stages of development (with regards to the age, proficiency, and exposure to certain conditions). This generates an effect where "time" (which is accounted for directly in longitudinal studies) is measured by a proxy such as proficiency level or age. These groups, while consisting of different participants, often share some characteristics to have homogeneity and hence, mimic a cohort. Pseudo-longitudinal or quasi-longitudinal studies are uncommon, but not unknown in medical sciences.[9-10]

The selection procedure for MBBS courses in India is merit-based, multiple-choice, all-India examination. This ensures that similar groups of students are admitted to the course every year. Due to the nature of the exam itself as well as the college-allotment processes (which are online and choice-based), each batch of students entering a medical college approximates a random sample drawn from all medical students in the country. Therefore, the personality scores obtained by a cross-sectional assessment of Indian medical students in different course years is equivalent to assessing random samples of the country's medical student population. This provides data that is fairly similar to that observed in a true longitudinal study design, where a single random sample of undergraduate medical students is followed throughout the course. This made a pseudo-longitudinal design a viable study design for the current research.

Data was collected from the participants using an anonymized, self-administered online questionnaire consisting of two parts. The first part contained eight sociodemographic questions followed by the short-form revised Eysenck personality questionnaire (EPQR-S).[11] The latter consisted of forty-eight yes/no questions that assessed individual personalities across four distinct dimensions: extraversion-introversion, neuroticism-stability, psychoticism, and lie dimensions. Each dimension was assessed by twleve yes/no questions. Participants who scored less than six were considered to have a low score in that particular dimension of interest, and a high score if scored more than six. For example, a participant scoring two out of twelve in the extraversion-introversion dimension was considered to be more introverted than extraverted. The questionnaire also included an Instructional Manipulation Check (IMC) question to check whether the participants were paying attention to individual questions.[12] The IMC included was a yes/no question where only the participants who responded 'yes' were included. Participants who answered 'no' were not included in the analysis.

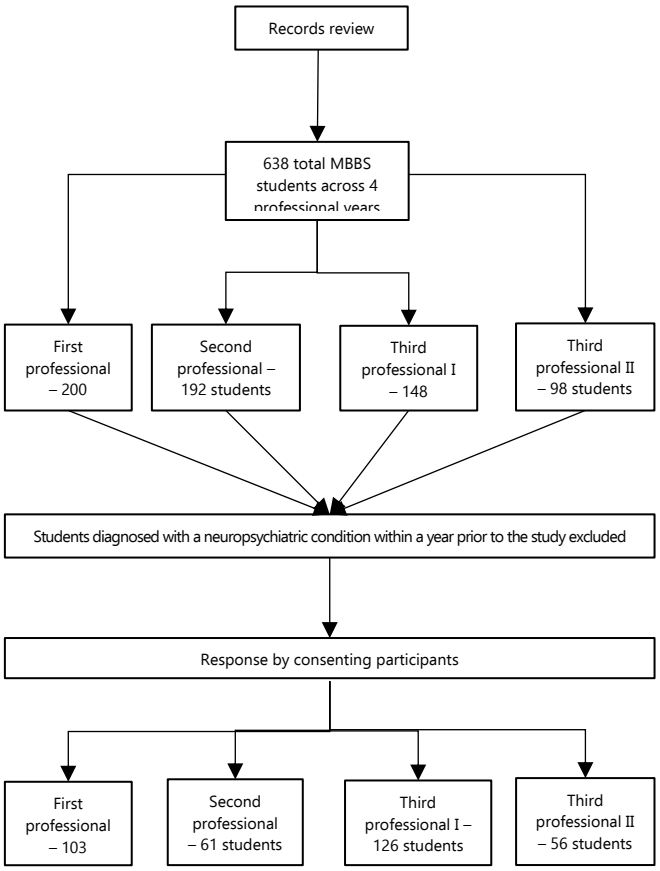
Review of the records showed that there was a total of 638 MBBS students in the medical college at the time of the study. Of them, 200 students (31.3%) were enrolled in their first professional year, 192 students (30.1%) in the second professional year, 148 (23.2%) students in third professional year (Part – I), and 98 students (15.4%) in their final year (Third Professional Year Part – II). All students were selected for the MBBS course through a pan-India, multiple choice question examination. Therefore, we approached all 638 students to participate in the study. Those who were unwilling or incapable of giving informed consent, and those that were diagnosed with a neuropsychiatric condition in the year prior to the study were excluded from the study.

This study aimed to include the total student population. To that effect, a complete enumeration sampling technique was employed for the study. Of the 638 enrolled students, a total of 391 students provided informed consent to participate in the study. A total of 39 students who had been diagnosed with neuropsychiatric conditions such as depressive disorders, anxiety disorders, cyclothymia, and bipolar disorders in the past one year (6 students in their first professional year, 9 students in their second professional year, 13 students in their third professional year part I, and the remaining 11 students in their final year) were excluded. This resulted in a final sample size of 352 participants (***Figure 1***).

Personality parameters of the participants as per the EPQR-S questionnaire (extraversion, introversion, neuroticism, psychoticism, and lie) in each course year were the outcome variables of the study. Socio-demographic factors of the study population like age, sex, socioeconomic status, and residence, as well as the year of study, for each participant were considered as explanatory variables.

The data collected was sorted in a spreadsheet. For statistical analysis, the Statistical Package for the Social Sciences (SPSS) version 25 (IBM corp.) was used. Descriptive statistics, such as frequency, percentage, mean, median, and standard deviation were applied to observe the trend in the data collected. The scores of each subscale of the EPQR-S were found to be non-normally distributed as per the Shapiro-Wilk's test. Therefore, the median scores were considered as the measure for central tendency and non-parametric tests were used for analyses. For non-normally distributed variables, Jonckheere-Terpstra test for trends and Kendall's tau-b test for correlation were used to identify trends in the observed data and the direction and strengths, respectively. The analysis of categorical variables was performed using Chi-Square test. All statistical tests performed were two-tailed, with a statistical significance level considered as *P*-value of <0.05.

Figure 1. Data Collection Protocol for the Study.



This study was conducted after obtaining formal ethical clearance from the Institutional Ethics Committee of the North Bengal Medical College and Hospital, IEC/NBMC/2020-21/11.

Results

Of the 352 participants, 6 (1.7%) answered the IMC question as 'no' and were therefore excluded, resulting in 346 respondents; of which, 167 (48.3%) were men (***Table 1***). The mean age of the participants was 20.99 ± 1.46 years. The majority of the respondents were in their pre-final year of the course (3rd Professional Part I) (36.4%), followed by the first years, second years, and final years, respectively. 198 (57.2%) of the participants were from an urban residential background. When the socio-economic background of the participants was considered, a majority came from families belonging to the Class I (upper class) of the Modified B. G. Prasad Scale for Socioeconomic status (SES) updated with the All-India Consumer Price Index (AICPI) for January 2020. It was followed closely by the Class II (29.2%), III (13.6%), IV (13.6%), and then, Class V (9.3%). All respondents were unmarried. The participants included in the study differed in their ages, which showed a statistically significant increase over the course years (*P*-value = 0.00003*, Pearson's r = 0.712). However, no statistically significant differences between the analyzed groups with respect to sex, socioeconomic status, and residence, were observed (***Table 1***).

Table 1. Table Showing the Socio-demographic Characteristics of the Study Participants (n=346).

Parameters n (%)	Total	1st Professional	2nd Professional	3rd Professional Part I	3rd Professional Part II	p-value
	346 (100)	103 (29.77)	61 (17.63)	126 (36.42)	56 (16.18)	-
Age (Years)						
Mean	20.99	19.51	20.92	21.61	22.39	<0.001*
SD	1.46	0.97	1.14	1.03	0.95	
Sex						
Male	167 (48.27)	51 (49.52)	31 (50.82)	60 (47.62)	31 (55.36)	0.91
Female	179 (51.73)	52 (50.48)	30 (49.18)	66 (52.38)	25 (44.64)	
Socioeconomic Status						
I (>₹7532)	119 (34.39)	39 (37.87)	16 (26.23)	43 (34.12)	21 (37.50)	0.82
II (₹3766 - ₹7532)	101 (29.19)	25 (24.27)	19 (31.15)	41 (32.54)	16 (28.57)	
III (₹ 2260 - ₹3765)	47 (13.58)	11 (10.68)	9 (14.75)	19 (15.08)	8 (14.29)	
IV (₹1130 - ₹2259)	47 (13.58)	18 (17.47)	10 (16.39)	13 (10.32)	6 (10.71)	
V (<₹1130)	32 (9.26)	10 (9.71)	7 (11.48)	10 (7.94)	5 (8.93)	
Residence						
Urban	198 (57.23)	60 (58.25)	37 (60.66)	67 (53.18)	34 (60.71)	0.69
Rural	148 (42.77)	43 (41.75)	24 (39.34)	59 (46.82)	22 (39.29)	

Legend: *Statistically significant

It was observed that women scored significantly higher than men in the neuroticism (Mann-Whitney U test statistic = -3.783, *P*-value=0.000) and lie subscales (Mann-Whitney U test statistic = -3.364, *P*-value=0.001). There was no difference in the scores with respect to the participants' socioeconomic status. However, a statistically significant difference in psychoticism scores between participants hailing from rural and urban backgrounds (Mann-Whitney U test statistic = 2.342, p-value=0.019) was observed (***Table 2***).

A Jonckheere Terpstra test for trends was used to determine any existing trend in scores of each personality subscale. It was found that there was a significant negative trend in the extraversion scores from the first to the final years (TJT = 19,306.5, z = -2.235, Kendall's tau-b correlation coefficient= -0.094, p-value=0.025). However, no significant trend was observed in the other subscale scores (***Table 3***).

Discussion

Personalities are amenable to change depending on the environment.[4] Over the course of their medical training, certain personality traits among medical students may develop or change from the day of enrollment. It can be postulated that this could be due to increased stress, length and difficulty of course, or from increasing exposure to clinical scenarios involving significant mortalities and morbidities. Prior studies have provided some evidence in favor of this assertion, such as Gough H.G. et al. whose study found significant changes in personality traits as medical students advance in the years of their study. A study conducted in Malaysia found that final year medical students had lower scores in neuroticism as compared to students enrolled in other years. A longitudinal study performed on pharmacy and medical students of Malta also reported the shifting of certain personality traits from their baseline at the time of enrollment.

Background characteristics of the participants

One of the primary assumptions of a pseudo-longitudinal design is that the groups selected for the study should be similar to each other in their background characteristics, except for the time of exposure to the risk factor under observation.[8] In this study, this assumption was corroborated as the analysis of the different socio-demographic variables showed that the four primary groups of students had similar socio-demographic characteristics except for their ages, which, as expected, increased from the first to final years.

Neuroticism

It was found that medical students scored on the higher end of the neuroticism scale, with a median score of 8. This is higher than the median score of 5 reported by Kuriata et al. in their study done in Poland, and differs from the findings of Lean et al. in Singapore, who reported medical students to be less neurotic as compared to their non-medical peers.[3] This discrepancy, compared to international research, needs to be explored in detail, especially in the Indian context, as there are conflicting reports of the effect of higher neuroticism on the performance of medical students in their course. The higher scores of neuroticism among medical students can be explained by the unique and highly competitive entrance examinations to the medical courses, where competitiveness and cognitive function are rewarded. The fact that neuroticism has been positively correlated with competitiveness as well as academic achievement in medical schools also supports this assumption. However, the significantly higher scores of women in the neuroticism subscale than their male counterparts is in line with previous research done on this subject.[20]

Social Desirability

Another finding of male-female difference in personality traits was seen in the case of the lie subscale scores, where women scored significantly higher than men. Social desirability bias, the factor assessed by the Eysenck lie subscale, is complex in its

Table 2. Table Showing the Differences in Personality Traits and Demographic Characters of Participants (n=346).

Characters	Extraversion (median)	p[a]	Neuroticism (median)	p[a]	Psychoticism (median)	p[a]	Lie (median)	p[a]
Sex								
Female	7	0.147	9	0.000*	3	0.259	6	0.001*
Male	6		7		3		4	
Socioeconomic Status								
I	6		8		3		5	
II	7		8		3		5	
III	7	0.676	9	0.454	4	0.971	6	0.51
IV	6		7		3		5	
V	6		7		3		5	
Residence								
Urban	6	0.831	8	0.656	3	0.019*	5	0.323
Rural	7		8		4		5	

Legend: [a] Kruskall-Wallis H test and Mann-Whitney U test for independent samples, wherever appropriate. *Statistically significant

Table 3. Table Showing the Difference in Subscale Scores of Participants According to their Academic Year of Study (n=346).

Subscale Score	Total	Academic Year (n) 1st Professional	2nd Professional	3rd Professional Part I	3rd Professional Part II	τb[a]	p-value
	(346)	(103)	(61)	(126)	(56)		
Extraversion							
Mean	6.17	6.54	6.46	6.02	5.52		
SD	3.09	3.15	3.30	2.99	2.92	-0.094	0.025*
Median	6	7	7	6	5		
Neuroticism							
Mean	7.51	7.36	7.16	7.66	7.80		
SD	3.16	3.19	3.29	3.22	2.60	0.040	0.341
Median	8	8	8	8	8		
Psychoticism							
Mean	3.40	3.52	3.13	3.43	3.39		
SD	1.61	1.78	1.49	1.63	1.73	-0.004	0.921
Median	3	3	3	3	3		
Lie							
Mean	4.98	5.14	5.31	4.62	5.13		
SD	2.48	2.58	2.22	2.48	2.55	-0.041	0.339
Median	5	5	5	4	5		

Legend: [a]Kendall's tau-b correlation coefficient. *Statistically significant

interpretation and association with the other three subscales. However, a distinct relationship between the Eysenck neuroticism and the lie subscales has been identified. Jackson and Francis demonstrated that people who scored high in the neuroticism subscale also had high scores in the lie subscale, indicating a higher social desirability bias.[21] Likewise, it was expected that women, who scored higher in the neuroticism scale would also do the same in the lie scale, an assumption that was reinforced by the current study.

Psychoticism

It was found that psychoticism was low in medical students across all academic years, implying lower aggression, recklessness, and impulsiveness. However, even at that low score threshold, participants with an urban background scored significantly higher than their rural counterparts. This is consistent with previous research that suggested a link between urbanicity and risk for psychosis, a feature represented by higher psychoticism scores.

Introversion-extraversion

With a minimum score of 0, a maximum score of 12, and a median score of 6, it can be generalized that medical students are equally likely to be introverted as they are to be extraverted. However, the subgroup analyses showed that a significant trend existed towards introversion from the first through the final years. This could be due to increased stress levels and increased exposure to significant morbidities and mortalities as students advance through course. Prior researches have found that with increased clinical exposure, medical students become less empathetic, as they suffer from increased stress levels and distress associated with it. Some authors explained this negative coping mechanism as a result of medical students having to deal with these stressors alone, which lead to a sense of detachment, increased carefulness, and anxiety, which are the characteristics of introversion.[24]

Since this study was conducted with participants who volunteered, the data collection was prone to volunteer bias, which could have influenced the obtained results. Furthermore, the absence of a control group further limits this study to only describing the observed personalities among medical students, without any comparisons to non-medical students. Finally, a personality change over the years can be best observed by a prospective design; although the pseudo-longitudinal design of this study aimed to mimic a prospective design. It is less effective than a true longitudinal design as this study substituted a single group followed-up over time with similar group data examined with time taken as a proxy. However, even with these limitations, to our knowledge, this is the first study that analyzed the personality traits of undergraduate MBBS students in India. This is also the first study that observed the trends of change of those personality traits throughout the course years of the MBBS program. The main strength of the study was the pseudo-longitudinal research design, which made trends analyses possible.

It was found that medical students in India, without overt psychiatric illnesses, scored higher in neuroticism and lower in the psychoticism dimension of the Eysenck Personality Inventory. Furthermore, there was a positive trend in introversion from the first to the final years of their study. Women were more likely to have personalities rich in the neuroticism and social desirability traits than men.

Summary – Accelerating Translation

Title: Assessment of Personality Traits and Their Changes Over the Undergraduate Medical Course: A Pseudo-longitudinal Analysis among Indian Medical Students

Main problem to solve: What kinds of personalities do Indian students entering the undergraduate medical course possess? Do their personalities change as they progress through their course?

Aim of the study: This research was conducted with an aim of identifying the most common personality traits among MBBS students enrolled at an Indian medical institute and to observe any changes in their personality traits from the first to the final years of the MBBS course.

Methodology: A descriptive, pseudo-longitudinal study was conducted. A personality assessment questionnaire was completed by MBBS students in different academic years. Their personality traits were assessed under four parameters: extraversion-introversion, neuroticism, psychoticism, and lie or social desirability. Each parameter was assessed by a scoring system, ranging from 0 to 12. After the relevant data was collected, statistical analyses were applied to determine which personality traits were the most commonly observed among the students. Furthermore, personality traits were also analyzed to find out whether or not there was any significant changes in the traits of medical students over the course-years.

Results: It was observed that medical students scored on the higher end of the neuroticism trait and lower on the psychoticism and social desirability (lie) trait, and were equally likely to be introverted as they were extroverted. However, women scored much higher than men in the neuroticism trait, as well as in the social desirability parameter.

As for the trends of change of personality traits over the years, only the extraversion trait showed any change. It was seen that as the medical students progressed through their coursework, they become more introverted. This has been explained by some authors a result of a negative coping mechanism, where the students become more detached and anxious in response to the various stressful situations that they experience in their course of study.

Conclusion: Undergraduate medical students in India have personalities high in neuroticism and low in psychoticism and social desirability traits. However, as they progress through their MBBS course, they become more introverted as compared to their time of enrollment.

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Acknowledgments

None

Conflict of Interest Statement & Funding

The Authors have no funding, financial relationships or conflicts of interest to disclose.

Author Contributions

Conceptualization: AB, AJR. Data curation: AB. Formal Analysis: AB, AJR, MD. Investigation: AB, MD, DD. Methodology: AB. Project Administration: AJR. Resources: MD, DD. Software: AB. Supervision: AJR. Validation: MD, DD. Visualization: AB, AJR, MD, DD. Writing – Original Draft Preparation: AB. Writing – Review & Editing: AJR.

Cite as

Bandyopadhyay A, Rout AJ, Das M, Das D. Assessment of Personality Traits and Their Changes Over the Undergraduate Medical Course: A Pseudo-Longitudinal Analysis Among Indian Medical Students. Int J Med Stud. 2022 Oct-Dec;10(4):347-52.

ISSN 2076-6327

This journal is published by Pitt Open Library Publishing

IJMS INTERNATIONAL JOURNAL of MEDICAL STUDENTS

Original Article

Comparison of Multinational Medical School Students Experiences in the Face of the COVID-19 Pandemic: A Qualitative Analysis

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Abstract

Background: In the midst of the COVID-19 pandemic, countries, and governments around the world have implemented different measures and guidelines for the containment and mitigation of the COVID-19 virus. In addition to implemented policies and initiatives, social media and personal beliefs have affected medical students' social, emotional, financial, and academic stability and success both domestically and internationally. **Methods:** This qualitative study, recruited students enrolled in the Global Seminar for Health and Environment elective course in their respective medical schools to complete a weekly, non-graded journaling assignment for 6 weeks. To measure outcomes, open-ended questions were asked to students across four different countries (United States, El Salvador, Dominican Republic, and Honduras) regarding the COVID-19 pandemic including personal beliefs and knowledge, policies and initiatives within their country, global policies and initiatives, and social media presentations. Thematic analysis was then completed using the QCoder package in R Studio. **Results:** A total of 142 assignment submissions were collected and analyzed. International medical students reported more restrictions in their country, a larger mental health impact, and more individuals in their country showing a lack of regard for policies and initiatives. United States medical students were more likely to express a decrease in academic opportunities and academic performances. **Conclusion:** The COVID-19 pandemic continues to affect medical students globally. The pandemic has changed the medical school experience for both international and United States medical students, and affected them not only academically but also mentally, and socially.

Key Words: COVID-19; Medical Student; Mental Health; Academic Performance (Source: MeSH-NLM).

Introduction

As the progression of the COVID-19 pandemic has tested the limitations of the healthcare systems throughout the world, medical students have been challenged to adjust to this new normal. The adjustment of online learning and social limitations have altered the social and mental well-being of the medical student.[1] At the height of the pandemic, there was a concern that students may be missing out on meaningful educational experiences and months of clinical training with unknown effects on their current well-being or professional trajectory.[2]

Among medical professionals, being a medical student has the highest odds of psychological symptoms of depression and anxiety.[3] Medical students are a vulnerable population globally and according to one study, are known to show higher rates of depression, suicidal ideation, and stigmatization around depression, and are also less likely to seek support.[4] Medical students are also more susceptible to report depressive symptoms compared to college and university students of similar age from the general population. Even though certain aspects of mental health (e.g., depressive symptoms) improve as students become residents and early career physicians, medical students are predisposed to have depression and other psychological distresses compared to their counterparts at different stages of life.[3]

Medical students use social media to not only obtain breaking news on the ongoing pandemic, but also cope with and express their emotions.[5] Social media platforms have played a positive and negative role during the COVID-19 pandemic. From a positive perspective, social media rapidly spreads necessary

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Editor:Francisco J. Bonilla-Escobar
Student Editors:Duha Shellah & Diego Carrion Alvarez
Copyeditor: Leah Komer
Proofreader: Laeeqa Manji
Layout Editor: Ana Maria Morales

Submission: Jul 20, 2022
Revisions: Aug 27, 2022, Sep 28, 2022
Responses: Sep 2, 2022, Oct 5, 2022
Acceptance: Nov 25, 2022
Publication: Dec 2, 2022
Process: Peer-reviewed

information to identify symptoms, share treatment plans/algorithms, and employ control measures from other countries, and adapt these measures with available resources.[6] Yet, from a negative perspective, the dissemination of information has also been linked to anxiety and depression.[7] As previously reported, social media has a significant correlation on spreading panic about COVID-19 amongst medical students, negatively impact their psychological health.[5]

The impact on psychological health is not just seen in the United States, but also globally. In previous pandemics, such as the 2003 SARS-CoV outbreak in Taiwan, it was reported that international medical professionals had negative effects on their wellbeing, including post-traumatic stress disorder (PTSD).[4,8] The effects of post-traumatic stress disorder (PTSD) primarily occurred due to the social distancing and isolation.8 At present, international nations such as the Dominican Republic, Honduras, and El Salvador continue to have an disproportionate impact on social well-being due to differences in policy and resources.[9] Latin America regularly faces widespread health problems due to overcrowding, limited sanitation, food insecurity and poor nutrition, and unpredictable environmental conditions that affect citizens with lower socioeconomic status.[9,10] Underfunded state-run hospitals are, in most cases, the only source of medical care available to these populations.[10]

This study sought to assess medical student's perspectives on domestic and global response and messaging, attitudes on how they have been personally affected, and insights on their personal understanding of the virus in the face of the COVID-19 pandemic and determine if differences exist between countries. Due to differences in global response and media portrayal, international medical students in countries such as El Salvador, Honduras, and the Dominican Republic will be impacted differently with regards to COVID-19 policy strictness, social and mental health, financial and academic stability, and overall attitude towards the pandemic than the United States medical students.

Methods

A qualitative phenomenological study on the COVID-19 pandemic was conducted using open-ended question responses from medical students from the United States and international medical schools to evaluate global impacts on medical education.

Setting and Participants

Over a 6-week period in the beginning of 2021, medical students enrolled in the Global Seminar for Health and Environment course at their respective medical schools were encouraged to complete a weekly writing assignment on their perspective on the COVID-19 pandemic. Participants attended one of the four Edward Via College of Osteopathic Medicine (VCOM) campuses in the United States, or one of three medical schools located in Central America and the Caribbean. VCOM campuses included VCOM-Virginia, VCOM-Carolinas, VCOM-Auburn, and VCOM-Louisiana. International medical schools included El Instituto Tecnológico de Santo Domingo (INTEC), Universidad Tecnológica Centroamericana (UNITEC), and Universidad Evangélica de El Salvador (UEES), located in the Dominican Republic, Honduras, and El Salvador respectively. Medical students were assigned an ID number to access the assignment questions and submit responses through the Qualtrics platform.[11] Researchers were never made aware of the participants ID numbers so that the study would remain confidential, anonymous, and voluntary. This study was reviewed and approved by the Edward Via College of Osteopathic Institutional Review Board (IRB # 2020-013)

Open-Ending Question Design

Open-ended questions were developed by the Global Seminar for Health and Environment course administration to analyze multiple aspects of the participants, lives regarding COVID-19. The goal of the questions was to provide the students with a platform to express multiple different perspectives on their beliefs and knowledge, perspectives on interventions and prevention methods within their country and internationally, and the impact social media had on the pandemic. The complete list of open-ended questions is available as Supplementary Material 1. The questions had been used in 2020 in the Global Seminar for Health and Environment course and modified as needed for clarity. A panel of experts including a retired CDC infectious disease physician with 8 years of experience in Central America, US physicians, and international physicians provided "Content Validity" instrument items to match research objectives. In addition to the open-ended question responses, demographic information was collected, including country of residency and year in medical school.

Study Outcomes and Analysis

Responses from students were analyzed by members of the research team to identify recurring themes in four different categories: personal beliefs and knowledge, policies and initiatives, international policies and initiatives, and social media presentations. Open-ended question responses and themes were then coded and compared to ensure consistency between theme usage. Qualitative analysis was completed using R and QCoder software and packages.[12-13] The number of times that a theme was expressed was divided by the number of total responses to determine the percentage of times a given theme was expressed. Data was then exported from QCoder and the number of times each theme was expressed, stratified by country, was compared.

Results

A total of 142 submissions were collected and analyzed from 76 participants. This included 19 submissions from INTEC, 30 submissions from UEES, 18 submissions from UNITEC, 28 submissions from VCOM Auburn, 18 submissions from VCOM Carolinas, 17 submissions from VCOM Louisiana, and 12 submissions from VCOM Virginia. The 67 submissions from INTEC, UEES, and UNITEC were considered international submissions, and the 75 submissions from VCOM Auburn, VCOM Carolinas, VCOM Louisiana, and VCOM Virginia were considered

as the United States submissions. Not all submissions contained answers to all the questions asked, making the total number of responses dependent on the question.

Table 1. Themes and Responses Corresponding to Personal Beliefs and Knowledge of COVID-19.

Theme	Country (% of responses)	Examples
Decrease in Academic Opportunities and Performance	International (14.5%)	"In a personaal level it affected me since I was finishing my internship at the beginning of the pandemic when precautions were taken to prevent covid 19 infections, I could observe a remarkable decrease of patients in the hospital, decreasing the opportunity to learn and provide medical care."
	United States (20%)	"It has effected my medical school experience significantly as we had online classes for months and months. "
Personal or Family Economic Impact	International (7.3%)	"My dad is a pilot who lost his job during the pandemic, even tho Im in last year of medical school, doing my social service, since my unviersity is private Im still paying so its been a difficult time."
	United States (6.7%)	"My father became unemployed. My sister's husband became unemployed. It was a very difficult time for my family."
Mental Health Impact	International (27.3%)	"My anxiety and panic have risen to such levels that it is hard for me to tolerate casual touch and proximity. I dont remeber the last time I hugged a friend."
	United States (1.7%)	"The COVID pandemic has increased my already heightened stressed induced by medical school studies."
Understanding of COVID19, Policies, and Preventative Methods	International (45.5%)	"The novel coronavirus 2019 has caused the worldwide pandemic of coronavirus disease 2019 (COVID-19). COVID-19 was initially identified as a cluster of pneumonia cases during late December 2019 in China and rapidly spread worldwide. The definite modes of SARS-CoV-2 transmission are not yet completely known; however, health officials suggest that it could primarily spread through droplets when an infected person coughs or sneezes, and by direct contact with infected individuals. Unfortunately, no drugs or vaccines have been officially approved for the treatment of COVID-19. Maintaining personal hygiene is an essential practice to protect against any type of respiratory illness, including COVID-19. Hand washing and social/physical distancing are effective measures to prevent transmission between individuals. Other major mitigating measures include isolation and quarantine, particularly of individuals with symptoms or confirmed COVID-19 cases."
	United States (43.3%)	"A novel virus typically presenting as fever/chills, dry cough, SOB, body aches, loss of taste or smell. Spread easily through respiratory droplets. Unknown about the long term side effects of being infected with COVID19."

Both internationally and in the United States, COVID-19 has had a large impact on medical students, with, their perspectives distinct in personal beliefs (*Table 1*), policies in their country (*Table 2*), policies in other countries (*Table 3*), and social media (*Table 4*). International medical students believed that their country's COVID-19 response contained more restrictions than the global response, with the theme being expressed in 16.4% of international responses compared to 1.3% of US responses. This was enforced by the US medical students' views that the United States had fewer COVID-19 restrictions.

Table 2. Themes and Responses Corresponding to Policies and Initiatives of COVID-19.

Theme	Country (% of responses)	Examples
Need better healthcare	International (5.6%)	"The health budget to cover the pandemic was used in the purchase of mobile hospitals, which were to be installed since July 2020, and which have not yet been established. The number of mechanical respirators needed for the number of people affected by the virus does not even cover 20% of the population. We were also affected by two hurricanes, IOTA and ETA, which caused many people to lose their homes, forcing them to crowd into shelters, increasing overcrowding and the spread of the virus, creating another high wave of mortality. if i could change anything, i would start with giving priority to the health of the population over the other things that are happening in the country, just as there was a budget for the voting campaigns, that money could have been well used in the purchase of vaccines or medicines for serious patients."
	United States (12.3%)	"I dont think the process of distribution was that great. We needed to be more effective with distribution. In my home town four months went by and they were still vaccinating elderly and priority workers. I think this could have been done in a more timely manner"
Need better initiatives and policies	International (42.6%)	"A would change a lot of this my country is not doing his best in prevention in covid they have been in responsables. They are not doing interventions in College in partys in beaches in hoteles "
	United States (52.6%)	"When the US decided to implement the lockdown, it was already too late. In addition, the US failed with the testing kits early on in the process. We did not have enough testing kits and the process was flawed in many ways. The presidential administration also discouraged the use of masks which further led to the spread. "
Individuals show a lack of regard	International (44.4%)	"People have stopped the fear of covid and do not respect the measures"
	United States (17.5%)	"My frustration that the COVID pandemic has gotten so bad is with the people who refused to be smart and take simple steps for the good of others even if it was a minor inconvenience to them."
Good healthcare	International (11.1%)	"Although we are a third world country, compared to the others we have advanced a lot with the vaccines. I wouldn't change anything."
	United States (26.3%)	"I think the vaccine is becoming more widely accepted and more available. Most people I know are able to receive the vaccine with no issue if they want one. It is available now in common pharmacies."
Good initiatives and policies	International (26.3%)	"There is many preventions that my country is taking, such as disinfecting our shoes, taking our temperature, the use of alcohol gel and the mask is mandatory, as well all public places are just with the 50% of people allowed. Personally I think it's a great plan that our government have applied because there is every area are cover."
	United States (38.6%)	"I am from New Orleans and I feel the city did pretty well when it came to preventive measures. The city canceled Mardi Gras and all other events. This led to a major fall in the tourists economy but at least the public health was given a priority. "

United States medical students had a higher number of responses with the theme "more restrictions internationally", which was present in 28% of the responses. An international student's

response with the theme "less restrictions internationally" is as follows:

"There are many variations of the preventions countries might have, but I think that there are many restrictions such as mask obligations that should be applied, as well as imposing a mandatory quarantine to people that have been exposed to the virus in the past days."

Table 3. Themes and Responses Corresponding to International Policies and Initiatives of COVID-19.

Theme	Country (% of responses)	Examples
Good Response Internationally	International (45.3%)	"I believe that everyone attempted to mitigate the pandemic as best they could, they just failed to calculate the potential length of it and hence ended up spending way more resources than necessary or wasted certain resources thinking the pandemic would be much shorter."
	United States (42.4%)	"South Korea did the best job when it came to testing its public. They implemented testing via a drive thru which was very effective and quick. Africa as a whole did very well as it had checkpoints set up at various points in the city to check people's temperature. India did very well in the beginning to control the virus. A family friend told me that the police were giving citations to anyone that was not wearing a mask. "
Poor Response Internationally	International (18.9%)	"In the case of Italy, in my opinion the government didn't took enough precautions and didn't close the borders when they had time and human resources to do so, just for the sake of keeping the countries economy, so, that wrong decision in my point of view took a lot of lives not just from civils but from doctors that had to exceed their energies to fulfill their duty to save as many lives as possible or help those in need."
	United States (16.9%)	"I know the vaccine is hard to receive in other countries, especially third world countries. I've also read and heard from relatives in a third world country that they had to pay in order to receive the vaccine. To me that does not seem right because this is a pandemic. "
More Restrictions Internationally	International (7.5%)	"With what respects other countries is that most have taken more biosecurity measures on their own to protect their citizens, from what I can say about their information is that they have been able to obtain better results in the case of European countries as Americans, among others who enjoy a good economic as well as social situation, etc., compared to other third world countries"
	United States (28.8%)	"I know some countries in Europe took stricter precautions at the beginning of the pandemic, as well as some countries in Asia (like China). For example, I have a ton of family in Italy and the precautions that they took were significantly more regulated than here in the US."
Less Restrictions Internationally	International (17%)	"There's is many variations of the preventions countries might have, but I think there is many things such as mask obligation that should be applied, as well to put an obligated quarantine to people that has been expose in the past days. "
	United States (1.7%)	"I have friends in different countries where there are nearly no restrictions at all."

However, medical students internationally and in the United States did believe that their countries generally had good healthcare and good initiatives and policies. 11.1% of international responses and 26.3% of United States responses mentioned the theme "good healthcare" regarding their own countries, while 26.3% of international responses and 38.6% of United States responses mentioned the theme "good initiatives and policies". Respondents primarily mentioned preventative measure messaging and vaccine distribution.

Table 4. Themes and Responses Corresponding to Social Media Presentation of COVID-19.

Theme	Country (% of responses)	Examples
Informative Information	International (27.8%)	"Thanks to the social networks, I have been able to be informed about the development of the modern laboratory vaccine, also including that they published advances on how patients with this contagious disease were being treated."
	United States (16.9%)	"Currently most people are posting to spread awareness about availability of COVID vaccine, or that they got the vaccine. I think it is a good way to communicate to large audiences that the vaccine is safe and helps people see that if their friends are getting the vaccine, they should too."
Mental Health Impact	International (22.2%)	"I think national news outlets have remained true to the facts, so it does get very overwhelming at times. I've had to consciously limit my exposure to the informations shared through these platforms in order to preserve my mental health. Nowadays, I feel like I'm used to it. It's everything and I see and everything I hear. "
	United States (8.5%)	"I personally became very overwhelmed by the death tolls being released everyday on social media, for a period of time I had to step back from social media because it was very sad."
Misinformation	International (25.9%)	"Social media I think it's not 100% accurate, there is a lot of fake news and people trying to convence you with many fake ideas of covid. My grandma for example she always send me many "news" saying wrong things of covid, and this is a common problem in my country because people read and think is always true, and it affects by making people more scared or not interested in covid when is actually a really important disease nowadays."
	United States (30.5%)	"The media construes statistics and blows things way out of proportion in spite of what is actually reality. "
Positive Messaging on COVID-19 Prevention	International (46.3%)	"Salvadorian media has presented COVID-19 with the utmost alert, so people keep following the social distances and biosafety precautions to avoid any sort of exposition to the virus; "
	United States (25.4%)	"I have seen a lot of people posting vaccine photos and encouraging others to get vaccinated as there is still a lot of skepticism there."
Spread of Negative Information and Fear	International (13%)	"In my country there have been many information and news headlines that have been made in order to alarm the population and that is something that has bothered me a lot. An example of this was the vaccination day that the media published images where it was seen that vaccinated people were suffering when they really were not. I feel that there has been a lot of morbid on the part of the mass media with this subject."
	United States (1.7%)	"The news has created a fear of COVID that is completely out of proportion to what it should be."

United States medical students were more likely to express a decrease in the number of academic opportunities and academic performances. The theme "decrease in academic opportunities and performance" was present in 15 of 75 United States

responses (20%) compared to 9 of 67 international responses (13.4%). Only 1 of 75 United States responses mentioned a positive experience of academic opportunity and performance. A United States response containing the theme "decrease in academic opportunities and performance" stated:

"I have had to adjust to a new way of doing school, mainly online, as well as coming to terms with the fact that I am not getting to experience many of the social aspects of medical school that I was looking forward to."

International students were more likely to express views on negative mental health impacts due to their personal beliefs (27.3%) and social media influence (22.2%). The United Sates responses showed less of a mental health impact due to personal beliefs (1.7%) and social media (8.5%), and expressed stronger negative views on how COVID-19 was handled, with 40 of 75 US responses (53.3%) reporting the theme "need better initiatives and policies". The theme "mental health impact" included responses such as: "My anxiety and panic have risen to such levels that it is hard for me to tolerate casual touch and proximity. I don't remember the last time I hugged a friend."

Understanding of COVID-19 and its policies was a major theme reported for both international and United States medical students with the theme "Understanding of COVID-19, Policies, and Preventative Methods" as seen in 45.5% of international responses and 43.3% of United States responses.

Medical students internationally were more likely to believe that social media was informative with 27.8% of responses containing the theme "informative information" while 25.9% of responses contained the theme "misinformation". The opposite was seen in the United States with 16.9% of students believing that social media was informative and 30.5% of students believing that social media spread misinformation. International students were also more likely to report positive messaging on COVID-19 (46.3%) than United States medical students (25.45%). An example of an international student's response containing the theme "informative information" is as follows:

"Thanks to the social networks, I have been able to be informed about the development of the modern laboratory vaccine, including the published advances on how patients with this contagious disease were being treated."

Discussion

The pandemic of COVID-19 has affected medical students' social, emotional, and academic stability and success both domestically and internationally since it began in 2019. The psychological well-being of the medical student is also based on their perception of COVID-19. The results of this study suggest this perception is influenced by restrictions, restriction changes, social media, and personal beliefs.

Mental health was seen to be a common theme among medical students, both from the international schools and the United States, with over 1 out of 4 of the participants reporting the experience of increasing stress and anxiety during the pandemic. As previously mentioned, medical students are an already vulnerable population with one of the highest rates of depression, burnout, and suicidal ideations.[4] This supports the notion that the current pandemic is only worsening an already widespread condition among students. Moreover, students from the international schools reported a much higher effect on their mental health than United States students. In a recent meta-analysis, the pooled prevalence of depression and anxiety among medical students internationally and domestically negatively increased with the progress of the pandemic.[14] The study concluded a prevalence of depression and anxiety, which was 37.9%-33.7% higher than that of the general population and healthcare workers.[14] Supporting our hypothesis, these meta-analysis findings indicated that international students who perceived higher levels of pandemic-related stress may have had a negative impact on their academic performance in medical school.[15] However, even though mental health was a common theme, it was only listed in 27.3% of the responses of the international students and 1.7% of the responses of the United States students. Future studies exploring how the different medical students contributed to the medical care in their countries during the pandemic could further elucidate the difference in mental health.

The stress of having their medical education negatively impacted by the pandemic only added to the overall impact as over 1 out of 3 of the participants reported concerns of delayed graduation, decrease in academic opportunities and performance as well as inability to interact with patients in the clinical setting, and inability to go on rotations. As reported in the current literature, sudden change impacted the traditional training of medical students, with limited access to clinical internships.[16-17] These findings support previous results where students expressed their desire to return to rotations, despite the pandemic, in order to assist as healthcare staff and move forward with their education.[18]

When asked about their perspectives on the national and international COVID-19 interventions, there were contrasting responses between the United States and international medical students. International medical students, generally, reported more restrictions in their country, which was supported by the United States medical students claiming that there were more restrictions internationally. This finding also confirms our hypothesis and current literature, that perceived social support is a protective factor and influences the mental health status of the medical student.[15] It is worth noting that United States medical students had political critiques of how COVID was handled at the beginning of the pandemic, which was not seen in the international responses. As reported, the government plays an important role in reducing mental health disparities with efficient intervention and appropriate policy changes.[14] This may have influenced the United States medical students' personal beliefs at the peak of the pandemic. Since the responses critiquing the political reactions were vague accurate prevalence of the themes were unable to be calculated.

Both international and US responses considered that there were "good responses internationally", 45.3% and 42.4% respectively. These findings could be attributed partially to the fact that, international participants considered that first world countries have better access to medical care, better quality of care, technology, etc. allowing a better response as compared to their own countries.[19] They also mentioned that there was a better enforcement of the regulations by the police and that there was better technology to allow citizens to continue with their daily lives while ensuring social distance and lockdown.

Limitations

All responses were obtained in English. However, 55.9% of the participants were native Spanish-speakers, with English being their second language. For this reason, the data obtained was limited to our participants' English proficiency levels. Limited responses in each week also reduced the accuracy of the study. The international students participating in this study were all of similar cultural backgrounds. A multicentered study with participants from backgrounds in Europe, Asia, and Africa could be of future interest.

Conclusion:

COVID-19 continues to impact the globe, not only through health impacts but also through its impacts on individuals social, emotional, and educational lives. COVID-19, as seen in the responses, affect the mental health and educational opportunities of medical students. These have a direct impact on a medical student's ability to successfully practice medicine, not only in their clinical education, but also as future residents and attending physicians. Further research would evaluate the long-term implications of COVID-19's impact on medical students and its effects on physicians and patient care. Regardless, it must be acknowledged that the medical school experience has changed for both international and the United States medical students and affected them not only academically but mentally, and socially.

Summary – Accelerating Translation

Title: Comparison of Multinational Medical School Students Experiences in the Face of the COVID-19 Pandemic: A Qualitative Analysis

Background: The COVID-19 pandemic has presented unique challenges for countries and governments are the world requiring them to implement different laws, policies, and guidelines to minimize the spread of the virus. The ever-changing landscape of the pandemic required these laws, policies, and guidelines to frequently be revised and new policies and guidelines added. Medical students around the world have been affected by these policies and guidelines as well as their own personal beliefs about the pandemic, and the social media portrayal of the pandemic.

Aim: This study sought to assess medical student's perspectives on how the COVID-19 pandemic was handled within their own country and internationally, with regards to the different policies and guidelines. In addition, it aimed to analyze medical students' attitudes and understanding on the pandemic, and how they have personally been affected in their social and academic lives. Lastlythis study also determined how these views differ between countries.

Methodology: Students who were enrolled in the Global Seminar for Health and Environment elective course in their respective medical school were recruited to participate in the study. Participating students were enrolled in medical schools across four different countries (United States, El Salvador, Dominican Republic, and Honduras). For 6 consecutive weeks, students completed a non-graded journaling assignment by answering open ended questions about their personal beliefs and knowledge of the COVID-19 pandemic, COVID-19 policies and guidelines in their country, COVID-19 policies and guidelines in other countries, and social media presentations of the COVID-19 pandemic. The responses were then analyzed by researchers through the identification of common themes. These themes were then compared across medical schools.

Results: A total of 142 assignment submissions were collected and analyzed. Medical students who attended an international medical school (El Salvador, Dominican Republic, and Honduras) reported more governmental policies and restrictions in their countries, a larger mental health impact, and more individuals within their country showing a lack of regard for the policies and restrictions set by the government. Medical students in the United States were more likely to express a decrease in academic opportunities and academic performance. Compared to United States medical students, international students believed that social media with informative and helpful. Both international and United States medical students reported that they felt as if they had a good understanding of the COVID-19 pandemic.

Conclusion: The COVID-19 pandemic continues to affect medical students globally. The pandemic has changed the medical school experience for both international and United States medical students and affected them not only academically, but mentally, and socially.

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Acknowledgments

We would like to acknowledge the international medical schools who participated in this study: El Instituto Tecnológico de Santo Domingo (INTEC), Universidad Tecnológica Centroamericana (UNITEC), and Universidad Evangélica de El Salvador (UEES).

Conflict of Interest Statement & Funding

The Authors have no funding, financial relationships or conflicts of interest to disclose.

Author Contributions

Conceptualization: HDS, AMS. Data Curation: ACS, PWR. Formal Analysis: ACS, PWR, CO, TH, MVO. Funding Acquisition: HDS, AMS. Investigation: ACS, PWR, HDS, AMS. Methodology: HDS, AMS. Project Administration: ACS, PWR. Resources: ACS, PWR, CO, TH, MVO. Software: ACS. Supervision: HDS, AMS. Validation and Visualization: ACS, PWR. Writing – Original Draft Preparation and Writing – Review & Editing: ACS, PWR, AMS.

Cite as

Skoczek AC, Ruane PW, Onley C, Haydel T, Ortega MV, Sutphin HD, Stoner AM. Comparison of Multinational Medical School Students Experiences in the Face of the COVID-19 Pandemic: A Qualitative Analysis. Int J Med Stud. 2022 Oct-Dec;10(4):353-60.

ISSN 2076-6327

This journal is published by Pitt Open Library Publishing

Supplementary Material

Open ended journal questions:

1. What are your personal beliefs and knowledge of the novel coronavirus and COVID-19? How has it affected you at a personal level?
2. What is your perspective on the interventions and prevention initiatives that have been taken in your country, region, and city? What would you change, if any?
3. What is your perspective for the interventions and prevention initiatives of other countries or regions? What knowledge or information have you received about them?
4. How has social media and news outlets presented the novel coronavirus/COVID-19 in your country, region, city? How has that affected you?

IJMS INTERNATIONAL JOURNAL of MEDICAL STUDENTS

Original Article

Effects of Social Distancing and Lockdown Protocols on Fatality Rates of COVID-19 in the U.S. during the First Year of the Pandemic

Valerie Hardoon,[1] Bryant A. Pierce,[2] Solomon C. Mbanefo,[2] Harin N. Shah,[2] Kanav Markan,[3] Marika L. Forsythe.[2]

Abstract

Background: SARS-CoV-2, the coronavirus strain responsible for the COVID-19 pandemic, can lead to respiratory diseases ranging in severity. In the early stages, each U.S. state implemented a transition or "phasing" policy that included varying degrees of safety protocols. This allowed the states to slowly reopen while controlling transmission. The initial lockdown was observed to help suppress the pandemic, and our study aimed to determine if there was a correlation between fatality rates and the phase transitions across the states. **Methods:** Six states from regions with different caseloads were chosen for this study: Florida, California, New York, Washington, Kansas, and Texas. Incidence and mortality rate of COVID-19 were obtained from their respective government websites, allowing case fatality rates to be calculated and compared using Bayesian logistic mixed models. **Results:** When examining the fatality rates across phases grouped by state, there was a downward trend with each transition except in Texas. However, when the states were combined, the overall downward trend was clear, with a median fatality rate of 0.039 in phase 0 dropping to 0.010 by phase 4. **Conclusion:** Implemented safety protocols and phase transitions were shown to assist in controlling the spread of COVID-19 as the states re-opened. Differences in fatality rates throughout the U.S. can likely be explained by how disciplined each state was with quarantine requirements and social distancing policies. This allowed certain states to control the infectious spread more efficiently than others, thus allowing the states to progress through the phase transitions at different rates.

Key Words: COVID-19; Phase Transition; New York; Washington; Kansas; Texas; California; Florida (Source: MeSH-NLM).

Introduction

Coronaviruses (CoV) are positive-sense, single-stranded RNA viruses surrounded by an envelope made of glycoprotein. They are one of the viruses that can cause acute, mild upper respiratory tract infections. Transmission is generally via airborne droplets on the nasal mucosa, where they replicate in the local ciliated epithelium, resulting in cell damage and inflammation.[1] Following an outbreak of pneumonia from an unknown cause in Wuhan, China in December 2019, a novel coronavirus was isolated and dubbed COVID-19 by the World Health Organization in February 2020.[2] It was initially designated as 2019-nCoV, and later changed to severe acute respiratory syndrome disease (SARS-CoV-2). Over the next few months, the virus spread to different countries across the world resulting in the COVID-19 pandemic.[3]

In an effort to control the spread within the U.S., every state in the nation implemented masking and social distancing protocols. Additional states also initiated a state-wide lockdown to slow the infection rate, which was followed by four "phases" of reopening where each transition between phases resulted in progressively fewer restrictions implemented on the public as the state re-opened all its businesses. This process was to effectively reduce the incidence while slowly returning to a state of normalcy. At the same time several research companies, such as Pfizer,[4] Moderna,[5] and Johnson & Johnson,[6] worked to develop a COVID-19 vaccine to protect individuals against the virus. However during the vaccine development, individuals had to depend on themselves to remain safe. Each state experienced varying success when implementing the protocols as phase transitions occurred by state instead of nationwide, which increased the risk for a state to reopen prematurely and allow a resurgence in incidence rates.

Each phase transition varied between the states, but there were similarities in terms of what reopened and what remained closed. The phase 1 transition typically resulted in reopening of outdoor activities, including state parks and outdoor spots. In addition, retail stores were required to have curbside pick-up for their customers.[7,8] Phase 2 saw reopening of restaurants with outdoor dining, as well as some indoor dining that was typically reduced to 25-50% capacity. In-store shopping was also opened at reduced capacity, as well as salons, barbershops, and offices.[8,9] Phase 3 allowed a continued increase in indoor dining, and

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Editor: Francisco J. Bonilla-Escobar
Student Editors: Brandon Belbeck & Andrew Thomas
Copyeditor: Marcel Chee
Proofreader: Laeeqa Manji
Layout Editor: Ana Maria Morales

Submission: Jul 20, 2022
Revisions: Aug 27, 2022; Sep 28, 2022
Responses: Sep 2, 2022; Oct 05, 2022
Acceptance: Nov 25, 2022
Publication: Dec 2, 2022
Process: Peer-reviewed

reopening of nail salons, massage parlours, and many theme parks, including Disney World and Universal Studios.[8,10] Phase 4 was the final phase transition across the states, but it still included some limitations to aid in preventing the spread of the still-present virus while the pharmaceutical companies finished the development of the vaccines. Entering this phase allowed the reopening of low-risk outdoor and indoor arts and entertainment, including zoos, botanical gardens, museums, and aquariums, as well as fitness centers, bowling alleys, and casinos.[8]

Initial evidence from the early months of the pandemic suggested the implemented lockdown would suppress the spread of the virus.[11] However, creation of the re-opening phases introduced the possibility of resurgence. This study aims to examine the effectiveness of these safety protocols after the initial lockdown on case fatalities across the states, and whether there were any correlations between the rate of case fatalities (number of deaths / number of infections) and the transition between phases as the states re-opened.

Methods

Data Sources

COVID-19 case rates varied across the U.S., as some states observed higher rates of infection than others. The CDC separated the states into six categories to monitor their progression.[12] Currently, these categories were separated in the following way:

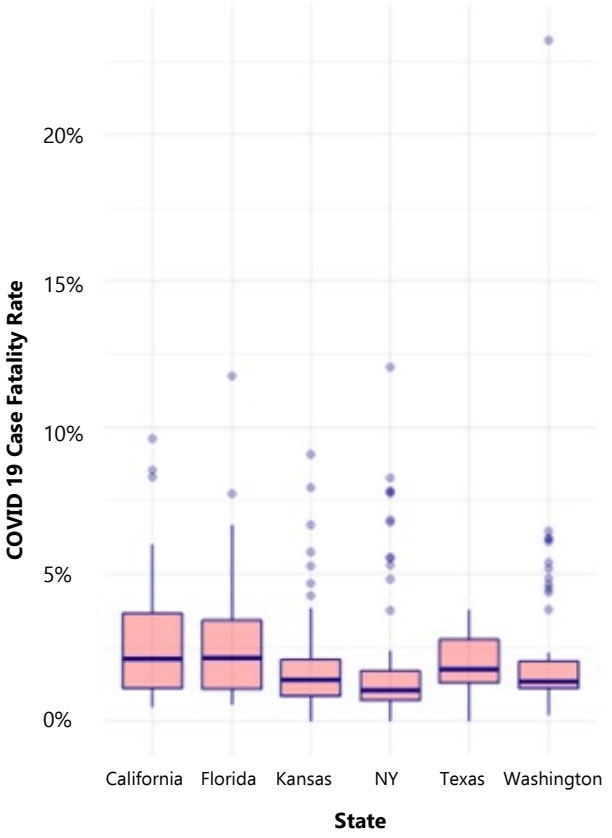
1. 14.0 – 17.8k cases per 100,000
2. 18.3k – 23.1k cases per 100,000
3. 23.5k – 25.5k cases per 100,000
4. 25.5k – 26.7k cases per 100,000
5. 26.9k – 28.9k cases per 100,000
6. 29.2k – 34.7k per 100,000

To account for the variation in case rates across the U.S., one state from each category was chosen for this study: Florida (3), California (6), New York (5), Washington (1), and Kansas (2), and Texas (4). Data obtained for the study concerning new cases and deaths from each state was publicly available on their local government websites.[13-18] The data was grouped weekly, starting from the first week of March 2020 as Week 1 until the second week of April 2021 as Week 58 for each state. It was further divided to indicate when each new phase was implemented in each state. Certain states, including Florida, New York, and Washington, did not initiate each phase transition statewide and instead did it by region or county. This necessitated further division into half phase transitions to indicate when groups of smaller regions or counties had transitioned between phases (i.e., phase 0.5, 1.5, etc.), as it was usually weeks before the larger areas (i.e., NYC, Miami, etc.) had transitioned. Some of these grouped areas transitioned at different dates, therefore the latest date was used to indicate the group's phase transition. Whole phase transitions indicate when the entire state had transitioned to the next phase. ***Table 1*** depicts the areas of each state that transitioned to the next phase and when the transition occurred.

Table 1. Phase transition dates and locations in the states of Florida, California, New York, Washington, Kansas, and Texas.

Phases	Florida	California	New York	Washington	Kansas	Texas
Phase 0.5	*Area:* -	*Area:* -	*Area:* All regions, except NYC	*Area:* -	*Area:* -	*Area:* -
	Date: -	*Date:* -	*Date:* May 29, 2020	*Date:* -	*Date:* -	*Date:* -
Phase 1	*Area:* Statewide	*Area:* Statewide	*Area:* Statewide	*Area:* Statewide	*Area:* Statewide	*Area:* Statewide
	Date: May 20, 2020	*Date:* March 19, 2020	*Date:* June 8, 2020	*Date:* May 5, 2020	*Date:* May 4, 2020	*Date:* April 27, 2020
Phase 1.5	*Area:* All counties, except for Broward, Miami-Dade, and Palm Beach	*Area:* -	*Area:* All regions, except NYC	*Area:* All counties, except Clark, Klickitat, Okanagon, Pierce, Skagit, Snohomish, and Whatcom	*Area:* -	*Area:* -
	Date: June 5, 2020	*Date:* -	*Date:* June 10, 2020	*Date:* May 28, 2020	*Date:* -	*Date:* -
Phase 2	*Area:* Statewide	*Area:* Statewide	*Area:* Statewide	*Area:* Statewide	*Area:* Statewide	*Area:* Statewide
	Date: September 14, 2020	*Date:* May 26, 2020	*Date:* June 22, 2020	*Date:* June 19, 2020	*Date:* May 22, 2020	*Date:* May 18, 2020
Phase 2.5	*Area:* -	*Area:* -	*Area:* All regions, except NYC	*Area:* Asotin, Coumbia, Ferry, Garfield, Grays Habor, Island, Kittitas, Lewis, Lincoln, Mason, Pacific, Pend Oreille, Skamania, Stevens, Thurston, Wahkiakum, and Whitman counties	*Area:* -	*Area:* -
	Date: -	*Date:* -	*Date:* June 24, 2020	*Date:* June 24, 2020	*Date:* -	*Date:* -
Phase 3	*Area:* Statewide	*Area:* Statewide	*Area:* Statewide	*Area:* Statewide	*Area:* Statewide	*Area:* Statewide
	Area: September 25, 2020	*Date:* June 12, 2020	*Date:* July 6, 2020	*Date:* March 22, 2021	*Date:* June 8, 2020	*Date:* June 3, 2020
Phase 3.5	*Area:* -	*Area:* -	*Area:* All regions, except NYC	*Area:* -	*Area:* -	*Area:* -
	Date: -	*Date:* -	*Date:* July 8, 2020	*Date:* -	*Date:* -	*Date:* -
Phase 4	*Area:* -	*Area:* -	*Area:* Statewide	*Area:* -	*Area:* -	*Area:* Statewide
	Date: -	*Date:* -	*Date:* July 20, 2020	*Date:* -	*Date:* -	*Date:* March 2, 2021

Figure 1. Distribution of Fatality Rate Over the First 58 Weeks of the Pandemic in the U.S. by State. New York was Found to Have to Lowest Median Fatality Rate.



Statistical Methods

Statistical analysis was performed using the Goodrich, B. et al (2020)[19] rstanarm R package, with Gaussian distributions as uninformative priors. The rstanarm R package emulates other R model-fitting functions, but uses "Stan", a platform for statistical modeling, for back-end estimation. Bayesian logistic mixed models (estimated using MCMC sampling with 4 chains of 2000 iteration and a warmup of 1000) were used, which are the Bayesian analogous of a logistic mixed model. They are best suited for predicting the fatality rate with phases from the ratio of deaths/infections when data is clustered (i.e., states), first considering all phases and then across each phase transition. The model included the states as random effects, which are parameters that vary at more than one level. Each state had its own regression equation, defined as yij = axij + b + cj, where i was the individual case and j was the state. The equations differed only by the constant term as each slope is assumed to remain fixed for all states. The fatality rate odds were used for the random intercept models due to the assumption that the dependent variable can take any value.

After using the Sequential Effect eXistence and sIgnificance Testing (SEXIT) framework, the median of the posterior distribution and its 95% CI (Highest Density Interval) along the probability of direction (pd), the probability of significance, and the probability of being large were reported. The thresholds beyond which the effect is considered significant and large were |0.09| and |0.54|. The Bayesian sampling was assessed using R̂ (the vector r divided by the magnitude of r), which should be below 1.01, and the Effective Sample Size (ESS; an estimate of the sample size required to achieve the same level of precision if that sample was a simple random sample), which should be greater than 1000, to determine convergence and stability.[20-22]

Prior distribution for the parameters were set as normal, with the SD varying depending on whether it covered all phases or individual phase transitions. The parameters used in each model are as follows:

All Phases: Normal distributions (mean = 0.00, SD = 2.04) were set. The model's intercept, corresponding to phase = 0, is at -2.98 (95% CI [-3.22, -2.75]). The effect of phase (Median = -0.41, 95% CI [-0.41, -0.40]) has a 100.00% probability of being negative (< 0), 100.00% of being significant (< -0.09), and 0.00% of being large (< -0.54). The estimation successfully converged (R̂ = 0.999) and the indices are reliable (ESS = 3528).

Phase 0 to 1/1.5: Normal distributions (mean = 0.00, SD = 3.95) were set. The effect of phase (Median = -0.51, 95% CI [-0.53, -0.47]) has a 100.00% probability of being negative (< 0), 100.00% of being significant (< -0.09), and 0.35% of being large (< -0.54). The estimation successfully converged (R̂ = 1.001) and the indices are reliable (ESS = 3363).

Phase 1.5 to 2: Normal distributions (mean = 0.00, SD = 10.34) were set. The effect of phase (Median = 1.39, 95% CI [1.24, 1.56]) has a 100.00% probability of being positive (> 0), 100.00% of being significant (> 0.09), and 100.00% of being large (> 0.54). The estimation successfully converged (R̂ = 1.000) and the indices are reliable (ESS = 2647).

Phase 2 to 3: Normal distributions (mean = 0.00, SD = 9.09) were set. The effect of phase (Median = -0.59, 95% CI [-0.63, -0.55]) has a 100.00% probability of being negative (< 0), 100.00% of being significant (< -0.09), and 98.08% of being large (< -0.54). The estimation successfully converged (R̂ = 1.000) and the indices are reliable (ESS = 3934).

Phase 3 to 4: Normal distributions (mean = 0.00, SD = 6.07) were set. The effect of phase (Median = 0.68, 95% CI [0.65, 0.70]) has a 100.00% probability of being positive (> 0), 100.00% of being significant (> 0.09), and 100.00% of being large (> 0.54). The estimation successfully converged (R̂ = 1.001) and the indices are reliable (ESS = 3144).

The STROBE checklist was used as an instrument of evaluation for the study.[23]

Figure 2. Distribution of Fatality Rate Over the First 58 Weeks of the Pandemic in the U.S. Across Phases, When Combining the Study States. the Median Fatality Rate Shows a Downward Trend.

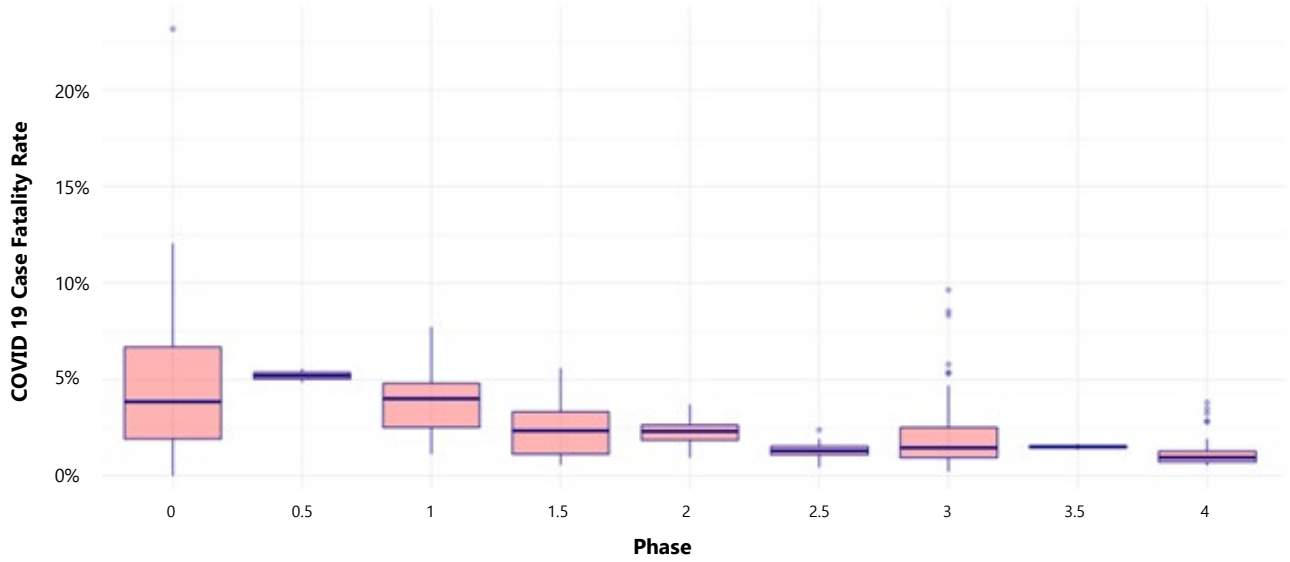
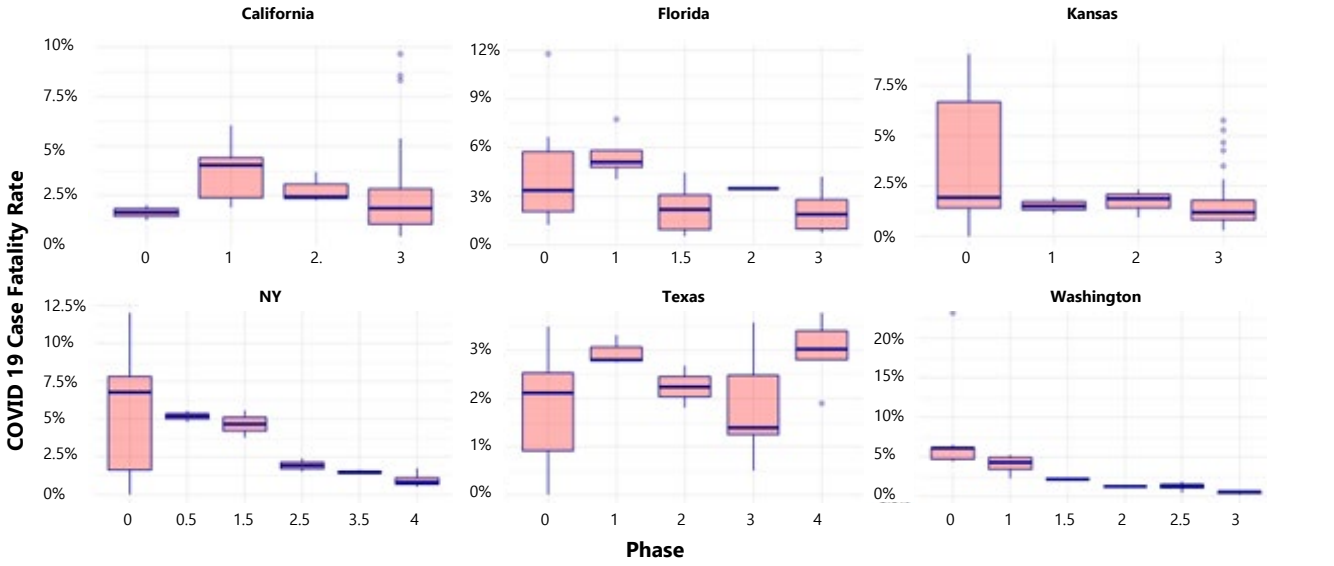


Figure 3. Distribution of Fatality Rate Over the First 58 Weeks of the Pandemic in the U.S. Across Phases, When Combining the Study States. the Median Fatality Rate Shows a Downward Trend.

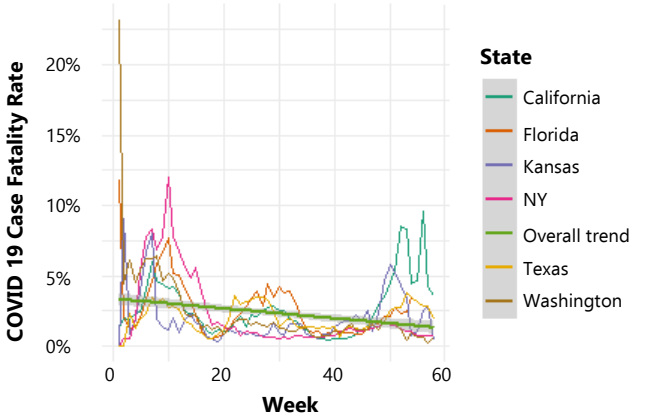


Results

Fatality Rates

When grouped by state across all phases, New York was found to have to lowest median fatality rate (median [IQR]; 0.011 [0.007, 0.017]), followed by Washington (0.014 [0.011, 0.020]), Kansas (0.014 [0.009, 0.021], Texas (0.018 [0.013, 0.028]), California (0.021 [0.011, 0.037]), and Florida (0.022 [0.011, 0.034]) (*Figure 1*). Examining across phases when combing the states, there is a clear downward trend in fatality rate. At the beginning of the lockdown, in phase 0 the median [IQR] is initially 0.039 [0.019, 0.067], and after an increase across phase 0.5 (0.052 [0.050, 0.054]), the trend decreases across phase 1 (0.040 [0.025, 0.048]), phase 1.5 (0.023 [0.011, 0.033]), phase 2 (0.023 [0.018, 0.026]), and phase 2.5 (0.013 [0.011, 0.015]). There is another slight increase across phase 3 (0.015 [0.009, 0.025]) and phase 3.5 (0.015 [0.014, 0.016]), and then finishing with a greater decrease across phase 4 (0.010 [0.007, 0.013]) (*Figure 2*). This downward trend is also evident across phases when grouped by state. It can be observed in all states except Texas, with the pattern being most evident for New York and Washington (*Figure 3*). The variation in fatality rate in all six states over the first 58 weeks of the pandemic is displayed in a linear graph in *Figure 4*, with the overall downward trend over time included over top.

Figure 4. Fatality Rate of the Six Study States in the U.S. Over the First 58 Weeks of the Pandemic. There is an Overall Downward Trend Over Time.



For each phase transition model, there was a big gap between marginal and conditional R^2 that suggested that most of the variation in the fatality rate is explained by the variance within each state. The model for all phases had a small gap between marginal and conditional R^2, also suggesting that most of the variation is due to the variance between each state. When analyzing all phases together, each progression to the next phase had a decrease in fatality rate by about 33.4% (with a 95% probability of falling in the 33.1% - 33.7% range).

The intraclass correlation coefficient (ICC) value of 0.03 indicates that 3% of the observed variance in fatality rate is due to systematic between-state differences compared to the total variance. The phase transition from 0 to 1/1.5 had a decrease by roughly 39.7% (with a 95% probability of falling in the 37.8% - 41.4% range). The ICC value of 0.08 indicates that 8% of the observed variance in fatality rate is due to systematic between-state differences compared to the total variance. The phase transition from 1.5 to 2 had an increase by roughly 303% (with a 95% probability of falling in the 244.7% - 370.2% range). The ICC value of 0.17 indicates that 17% of the observed variance in fatality rate is also due to systematic between-state differences compared to the total variance. The phase transition from 2 to 3 had a decrease in fatality rate odds by roughly 44.7% (with a 95% probability of falling in the 42.4% - 46.8% range). The ICC value of 0.04 indicates that 4% of the observed variance in fatality rate is due to systematic between-state differences compared to the total variance. The phase transition from 3 to 4 had an increase in fatality rate odds by roughly 96.5% (with a 95% probability of falling in the 90.9% - 102.1% range). The ICC value of 0.15 indicates that 15% of the observed variance in fatality rate is due to systematic between-state differences compared to the total variance.

Random Intercepts

Distribution of random intercept across the phases are shown in *Figures 5-9*. When analyzing all phases together, Washington has a significant and negative intercept, corresponding to good management of the COVID-19 cases across the phases. On the

Figure 5. Distribution of the Random Intercepts Over the First 58 Weeks of the Pandemic in the U.S. for Each Study State Across all Phases. Washington has a Significant and Negative Intercept, Corresponding to Good Management of the COVID-19 Cases While New York Has a Positive and Significant Intercept, Indicating Poor Management of the Cases.

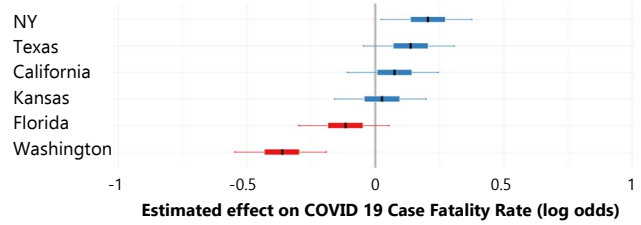


Figure 6. Distribution of the Random Intercepts Over the First 58 Weeks of the Pandemic in the U.S. for Each Study State Across the Phase 0 to Phase 1/1.5 Transition. Kansas and Texas Have Significant and Negative Intercepts, Corresponding to Good Management of the COVID-19 Cases While California and New York Have Positive and Significant Intercepts, Indicating Poor Management of the Cases.

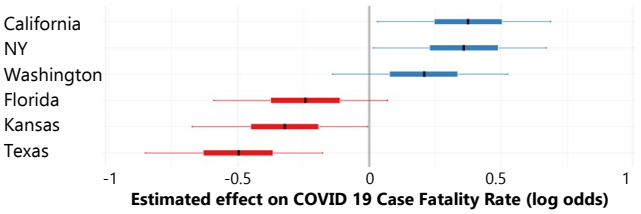


Figure 7. Distribution of the random intercepts over the first 58 weeks of the pandemic in the U.S. for each study state across the phase 1.5 to phase 2 transition. Kansas has a significant and negative intercept, corresponding to good management of the COVID-19 cases while New York has a positive and significant intercept, indicating poor management of the cases.

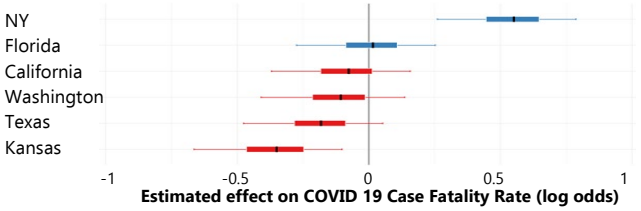


Figure 8. Distribution of the random intercepts over the first 58 weeks of the pandemic in the U.S. for each study state across the phase 2 to phase 3 transition. Washington has a significant and negative intercept, corresponding to good management of the COVID-19 cases.

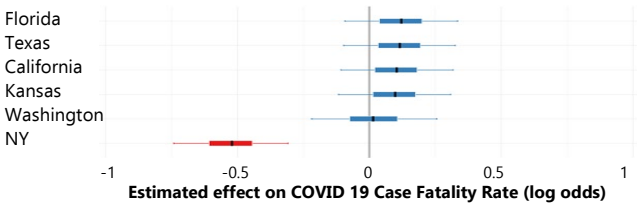
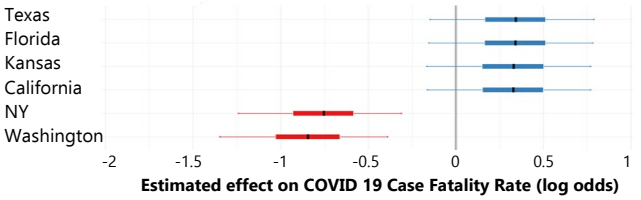


Figure 9. Distribution of the random intercepts over the first 58 weeks of the pandemic in the U.S. for each study state across the phase 3 to phase 4 transition. Washington and New York have significant and negative intercepts, corresponding to good management of the COVID-19 cases.



other hand, New York has a positive and significant intercept, indicating poor management of the cases. From phase 0 to 1/1.5, Kansas and Texas have significant and negative intercepts, corresponding to good management of the COVID-19 cases through this phase transition. On the other hand, California and New York have positive and significant intercepts, indicating poor management of the cases. From phase 1.5 to 2, Kansas has a significant and negative intercept, corresponding to good management of the COVID-19 cases through this phase transition. On the other hand, New York has a positive and significant intercept, indicating poor management of the cases. From phase 2 to 3, Washington has a significant and negative intercept, corresponding to good management of the COVID-19 cases through this phase transition. From phase 3 to 4, Washington and New York have significant and negative intercepts, corresponding to good management of the COVID-19 cases through this phase transition.

Discussion

Differences amongst the States

Based on the statistical models, the implementation of phase systems for reopening is significantly correlated with a decreased fatality rate of COVID-19, when examined across all the states included in this study. It is observed that overall phase progression shows a significant case fatality odds reduction. The case fatality reduction is accompanied by a general reduction in the margin of error from phase 1 through phase 4.

The states selected for this study allowed for the evaluation of different management styles throughout the phase transitions. For instance, Washington is the only state whose management across all phases could be considered effective, even though there was a decrease in fatality rate across all states. Other states also performed well in individual transitions, such as when New York joined Washington in having statistically the best management in transition from phase 3 to phase 4. This occurred despite New York's overall management, which was the poorest from our pool, as it is the only state consistently outside the margin of error in the positive direction. Texas as an individual state did not show the same trend as other states in the study. There is a myriad of potential reasons as to why Texas failed to follow the trend that could warrant an independent study. The trendline for new cases in Texas resembled that of Washington or Kansas, and Texas's population distribution is not significantly different from other study states such as Kansas, however the fatality rate is radically dissimilar. This might be a product of the general culture of these states or the product of the populations' cultures within the states, and as such, show areas where sociological or anthropological studies might be indicated.

Detection and Treatment

It should be noted that the reduction of fatalities in the early stages is likely a secondary effect to the quarantine and could be argued that it is a more direct result of reducing total COVID-19 infection in the overall population. Coupled with the lack of detection means, the early information on the reduction in mortalities is matched against projections and early case fatality estimates. As detection methods became readily available and other advances in treatment emerged, our study could have encountered confounders. Ease of testing and high specificity tests entering the market create the possibility that we incorrectly identified the fatality rate initially. The initial available testing modalities had a sensitivity ranging only from 72-77% in symptomatic patients, with even lower sensitivity in asymptomatic patients, leading to a significant number of false negatives that could impact the data.[24-26] Additionally, lockdown measures could have acted as a stopgap, allowing evolution of treatments that have led to a reduction in fatality. An example of radical treatment transformations can be seen in California, where greater than 40% of treatment courses for hospitalized cases consisted of antimicrobials azithromycin and hydroxychloroquine in March, but by June of 2020, there was a significant reduction in this modality. A decrease from greater than 40% patients to less than 5% of patients receiving hydroxychloroquine was observed.[27] This timetable also correlates with other studies that show a reduction in mortality with increased use of dexamethasone and remdesivir.[28] Another existing possibility is that the most susceptible died early in the pandemic. By the same token, those same individuals are largely the easiest people to isolate in lockdown protocols, including those over the age of 80 who had the highest fatality rate.[29]

Enforcement of Protocols

While efforts were made to keep the public safe, there is the possibility that the study states were not entirely adherent to the protocols. Anecdotal stories and a cursory glance across news sites and police reports indicate that Florida often experienced widespread violation of phase protocols in Miami-Dade, Palm Beach, and Broward counties during the first year of the pandemic. This could account for the spikes in Florida from week 14 onwards, as these counties account for nearly 30% of the population and have the highest population density within Florida. Given the dynamics of the business model for Southern Florida as not only a tourist destination but also as a primarily service-based economy, limiting interactions would place many businesses in situations where violating protocol would be tempting. While this is truly speculative, this possibility is granted further viability by the fact that these counties were the only counties that delayed transitioning to phase 2 with the rest of the state. This same spike is mirrored in New York, where NYC and Long Island account for more than 50% of the state population and the same narrative of violations exist during the lag time between other New York regions reopening and NYC resuming services.

Future Studies

As previously mentioned, this study involved the first year of the pandemic, which was when the first variant of COVID-19, "alpha", was the primary strain in the U.S. This was followed by the "delta" variant, which appeared towards the end of 2020 in India before also spreading worldwide (the "beta" variant, found in South Africa towards the end of 2020, was not commonly seen in the U.S). As each new COVID-19 strain appeared, contagiousness of the virus increased, leading to a higher incidence rate. However, severity of the associated illness potentially decreased with each new variant.[30] Due to the ever-evolving virus, it is possible that

the lockdown protocols and gradual reopening of the states might not have been as effective in controlling fatality rates with the newer variants. Another confounding factor is the introduction of COVID-19 vaccines in late 2020, which slowly became available to all age groups (excluding 0-4 years) by the end of 2021.[31] Certain safety protocols, such as wearing masks and limiting group sizes, continue to change between mandatory to optional across the states. It would be interesting to determine if there is a correlation between the shift in these safety protocols and the fatality rates, considering the newer variants and the availability of the COVID-19 vaccines and boosters, which have different levels of effectiveness against newer strains.

Study Limitations

There are a few potential limitations associated with this study. The first is regarding how the data was originally compiled. As metrics such as incidence and mortality rate of COVID-19 from each state were obtained from their respective government websites, and not a central agency, it is possible that different biases may have influenced how each state classified a "COVID-19-related death" and also how truthful they were when releasing the data. For example, in New York it was discovered that the then Governor had significantly understated the extent of COVID-19 related deaths in nursing homes.[32] This led to a vast overestimation of the success of the state of New York in controlling the spread of infection in the early stages. Unfortunately, COVID-19 had been politicized by both the Democratic and Republican parties, and with the looming 2020 presidential election, it is conceivable that politics played a role in the perception and tracking of COVID-19 across various states. The second limitation observed concerns the sample size. Only 6 U.S. states out of 50 were chosen and acted as surrogates for their respective case rate categories, which could be viewed as too small for an adequate sample size. Various regional and geographic factors of these surrogates could also impact the overall data. For instance, populations of certain states may experience a differing prevalence of illnesses than others, such as cardiomyopathies, coronary heart disease, heart failure, hypertension, obesity, sickle cell anemia, diabetes, etc., all of which have a significant comorbidity with COVID-19. This would result in these states also seeing a higher COVID-19 case fatality rate, causing them to potentially misrepresent their case rate category. Finally, as mentioned previously, it is difficult to gauge the extent to which the enforced protocols were actually effective. Recommendations of the CDC and local and state agencies were not uniformly embraced by the American people, making it difficult to properly gauge the effectiveness of the safety protocols across different states.

Conclusion

This study has shown the effectiveness of the implemented safety protocols and phase transitions in controlling the spread of COVID-19 as the states reopened during the first year of the pandemic. Adherence to the protocols likely played a large role in reducing fatality rates, resulting in different reopening schedules across the states. This could be due to certain counties being more disciplined than others, maintaining better control of the infectious spread than other parts of the state and thus, progressing through the phase transitions quicker. As global efforts continue to fight the COVID-19 pandemic, it may be the case that repeat studies are indicated in the event of additional lockdowns with the added variables of vaccination rates and variant detection causing new spikes in infection rates.

Summary – Accelerating Translation

The COVID-19 pandemic changed virtually everyone's way of life. Out of the nearly 6.52 million deaths worldwide, the U.S. contributed significantly to that count with roughly 1.05 million fatalities to date. While countries such as Australia and New Zealand maintained strict, strenuous COVID restrictions countrywide, in the U.S. each state tackled the crisis independently. After the lockdown was initiated across the country, each U.S. state implemented their own safety protocols or "phase transitions" as businesses were reopened, based on regional data and recommendations from the Center for Disease Control and Prevention (CDC) on how to keep the citizens safe. The plan was that as COVID-19 fatality rates were controlled, states would allow more businesses to reopen with fewer restrictions on group sizes, social distancing, etc. Due to each state acting independently, this created unique reopening schedules with certain states maintaining stricter guidelines for longer than others. Americans, in general, were opposed to strict authoritative quarantining mandates, such as those imposed in China, and state governors often made decisions based on their political party. Accounting for all these variables, this begs the question, how effective were the states in curbing the effects of COVID-19, and was there a correlation between the fatality rates and phase transitions as the states reopened their economy?

This study addresses these points by comparing fatality rates across multiple U.S. states in 2020 to early 2021, each with their own implemented phase transitions as businesses reopened. The CDC separated the states into six categories based on infection rates, and to account for this variation, a surrogate state from each category was chosen for the study: California, Florida, Kansas, New York, Texas, and Washington. Each state has its own unique culture, geography, and distinctive political preferences. Data regarding new cases and new deaths related to COVID-19 was obtained from the respective local government websites, as a centralized database does not exist.

Statistical analysis of the data, when assessed by individual states, demonstrated a downward trend with each transition, with Texas as a notable exception. Thus, most states maintained an overall decrease in fatality rate as restrictions were lifted, presumably due to better social distancing, mask compliance, and quarantine protocols. Because Texas did not exhibit such a trend, its suggests that perhaps this state transitioned too quickly between phases or did not follow the quarantining guidelines properly. There are numerous possibilities as to why fatality rates in Texas fluctuated so widely across the phase transitions, and future studies are warranted. However, when combining the states for the analysis there is an observed decrease in fatality rate from 0.039 [0.019, 0.067] in phase 0 to 0.010 [0.007, 0.013] in phase 4. Thus, this decrease supports an overall effectiveness of the implemented safety protocols in controlling COVID-19 transmission as the states reopened.

Based on this study's results the initiated phase transitions did exhibit success in controlling the spread as the economy reopened, as demonstrated by decreasing fatality rates across the U.S. Future studies that account for the introduction of COVID-19 vaccines and new emerging COVID-19 variants, and their impact on the fatality rates may prove beneficial in determining the next steps in combatting the pandemic.

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Acknowledgments

We thank Sergio Gámez for his assistance with the statistical analysis.

Conflict of Interest Statement & Funding

The Authors have no funding, financial relationships or conflicts of interest to disclose.

Author Contributions

Conceptualization: VH, BAP, SCM, HNS, KM, MLF. Data Curation: VH, BAP, MLF. Formal Analysis: VH, MLF. Investigation, Methodology, Writing – Original Draft Preparation, Writing – Review & Editing: VH, BAP, SCM, HNS, KM, MLF.

Cite as

Hardoon V, Pierce BA, Mbanefo SC, Shah HN, Markan K, Forsythe ML. Effects of Social Distancing and Lockdown Protocols on Fatality Rates of COVID-19 in the U.S. during the First Year of the Pandemic. Int J Med Stud. 2022 Oct-Dec;10(4):361-9.

ISSN 2076-6327

This journal is published by Pitt Open Library Publishing

IJMS INTERNATIONAL JOURNAL of MEDICAL STUDENTS

Original Article

Reddit Users' Questions and Concerns about Anesthesia

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Abstract

Background: Patients utilize social media in search of support networks. Reddit is one of the most popular social media sites and allows users to anonymously connect. Anesthesia patients are actively using Reddit to discuss their treatment options and experiences within the medical system. **Methods:** Posts published on an active Reddit forum on Anesthesia (i.e., /r/Anesthesia) were used. Big Query was used to collect posts from /r/Anesthesia. We collected 3,288 posts published between December 2015 and August 2019. We collected a control group of 3,288 posts from a Reddit forum not related to Anesthesia. Using latent Dirichlet allocation (LDA), we extracted 20 topics from our data set. The LDA topic themes most associated with posts in /r/Anesthesia compared to the control group were determined. **Results:** LDA analysis of posts in /r/Anesthesia relative to a control group produced 6 distinct categories of posts (Table 1). The posts most associated with /r/Anesthesia when compared to a control group belonged to the "Physician-Patient Experience" category (Cohen's d= 0.389) while the posts least associated with /r/Anesthesia were from the "Uncertainties" category of posts (Cohen's d= 0.147). Examples of the experiences from members of the /r/Anesthesia forum highlight subjective experiences of patients undergoing anesthesia. **Conclusions:** The language used on social media can provide insights into an individual's experience with anesthesia and inform physicians about patient concerns. Anesthesiologists are poised to address these concerns and prevent anonymous misinformation by providing verified physician insights on the forum /r/Anesthesia.

Key Words: Social Media; Facebook; Reddit; Twitter; Anesthesia (Source: MeSH-NLM).

Introduction

Annually, there are over 230 million major surgical procedures requiring anesthesia performed globally.[1] Anesthesia is a medical treatment that prevents patients from feeling pain during surgery through the use of drugs called anesthetics.[2] Previous research reports that patients express significant anxiety in the perioperative setting regarding topics such as anesthesiologist error, waking up during surgery, or not waking up from surgery.[3] One study of more than 15,000 patients found that anxiety was the number one response to the question: "What was the worst thing about your operation?," outpacing both 'pain' and an 'inability to carry out usual activities.'[4] Anxiety is especially important because it can impact all aspects of anesthesia such as the preoperative visit and induction.[4] For example, anesthetic complications associated with perioperative anxiety have been reported to extend the length of recovery periods and hospital stays.[5]

With the advent of the Internet, patients now often use online searches to answer their health-related questions. Prior research has shown that 70-80% of Internet users seek health information online about symptoms, treatments, and medications."[6] Asch and colleagues (2018) found that in the seven days prior to an ED visit, 15% of Google searches, a prominent search engine, were health-related.[7] In addition to online search engines, patients also utilize social media platforms to obtain health information and connect with other patients.[8,9] In fact, one study found that more than 40% of patients use social media platforms to obtain health-related information and this proportion is pronounced among 18–24-year-olds.[10,11] Previous research found that patients use and consult the following social media platforms, Facebook, Instagram, Twitter, TikTok, and Reddit, for health-related information gathering and exchange.[10,11].

Facebook and Instagram, both owned and operated by Meta Platforms Inc., are two prominent social media platforms with over nearly 3 billion users and over 1 billion users globally, respectively.[12,13] Both Facebook and Instagram have demonstrated cases of users sharing patient education information and creating supportive communities. One study on breast cancer found over 600 Facebook groups with over a million users that utilized for breast cancer awareness, fundraising, and support-seeking.[14] Wong and colleagues (2019) note that patients use Instagram to review other cases of their medical conditions throughout their patient journey.[15] Health-information exchanges on Twitter, TikTok, and Reddit are garnering research attention. A large body of research found that Twitter and TikTok, a short video-sharing application, are growing

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Proofreader: Laeeqa Manji
Layout Editor: Ana Maria Morales

Submission: Sep 5, 2022
Revisions: Oct 1, 2022, Nov 11, 2022
Responses: Nov 27, 2022
Acceptance: Nov 28, 2022
Publication: Dec 2, 2022
Process: Peer-reviewed

sources of health information dissemination to patients.[16,17] Reddit is among the most popular social media websites, ranking fifth for Internet traffic in the United States in 2018.[18] Reddit has been demonstrated to be an effective source of user-generated information on dermatology-related, mental health, cardiovascular, COVID-19, and cancer questions and issues.[18-23] Despite the Reddit platform being an important online space for health-related information sharing[18-24], there is limited research on how Reddit users discuss anesthesia questions and concerns. Our report specifically analyzes and characterizes Reddit users' questions and concerns about anesthesia.

Methods

We extracted posts published on an active Reddit forum on Anesthesia (i.e., /r/Anesthesia: https://www.reddit.com/r/Anesthesia/). /r/Anesthesia has 3,000 members as of August 2021 and is titled, "All anesthetic topics, all the time." Other forums related to anesthesia exist on Reddit, namely /r/Anesthesiology; however, posts on /r/Anesthesiology are more related to the professional field of Anesthesiology rather than the patient experiences expressed via the forum /r/Anesthesia. The forum /r/AskReddit was selected as a control group because it focuses on discussions around general topics as opposed to /r/Anesthesia which is specifically tailored to discussions focused on patient experiences regarding anesthesia. Big Query25, a data storage that includes posts, comments, and meta-data from Reddit was used to collect posts from /r/Anesthesia and /r/AskReddit. This study was considered exempt under Universtiy of Pennsylvania Institutional Review Board guidelines as it involves the analysis of publicly available data.

We extracted 20 topics from our data set (i.e., posts from /r/Anesthesia and the control group) using the topic modeling algorithm, latent Dirichlet allocation (LDA)26, which groups words in documents that occur in the same context together. LDA makes the assumption that topics are made up of a combination of words and that Reddit posts are made up of a mixture of topics. Based on the words associated with a topic, a label can be assigned. For Example, LDA may cluster the words (January, February, March April, May) as "months of the year." The LDA topic themes most associated with posts in /r/Anesthesia compared to the control group /r/AskReddit were determined.

Results

We collected 3,288 posts published between December 2015 and August 2019 on /r/Anesthesia. We also collected a control group of 3,288 posts from the Reddit forum r/AskReddit. *Table 1* shows the topics most associated with /r/Anesthesia posts and the effect sizes measured using Cohen's D.

LDA analysis of posts in r/Anesthesia relative to a control group produced six distinct post categories (*Table 1*). The categories in order of highest association to lowest from r/Anesthesia posts when compared to a control group belonged to "Patient-Physician Experience" (Cohen's d= 0.389), "Medication" (Cohen's d= 0.385), "Health Care Infrastructure" (Cohen's d= 0.366), "Procedures" (Cohen's d= 0.304), "Personal Inquiries" (Cohen's d= 0.201), and "Uncertainties" (Cohen's d= 0.147).

Table 1 displays themes, correlation values with valence, and illustrative narrative posts. It should be noted that, posts were edited, and any personally identifying information was removed. The category of highest association, "Patient-Physician Experience", included posts surrounding relationships between members of the care team and patients. An illustrative example of a post from this category was "I was still a little on edge, but my amazing and caring anesthesiologist basically informed me that given my health, she wouldn't even bother describing extreme risks".

Discussion

Despite previous research demonstrating that Reddit has become a widely used tool for sharing health information and seeking support for medical concerns, there is limited research on how Reddit users discuss anesthesia questions and concerns.[18]Using latent Dirichlet allocation (LDA) techniques, this study characterized the language used in posts published on an anesthesia forum by users who express and seek support around anesthetic procedures compared to a control group of posts from an unrelated forum. The language differences were found to reflect the questions and concerns from the Reddit community /r/Anesthesia. This study revealed six distinct categories of posts within the subreddit among users: "Patient-Physician Experience" (Cohen's d= 0.389), "Medication" (Cohen's d= 0.385), "Health Care Infrastructure" (Cohen's d= 0.366), "Procedures" (Cohen's d= 0.304), "Personal Inquiries" (Cohen's d= 0.201), and "Uncertainties" (Cohen's d= 0.147), illustrating some of the concerns regarding anesthesia that users tend to seek advice on the Reddit forum /r/Anesthesia (*Table 1*).

Our results show that the topic of "Patient-Physician experience" (Cohen's d= 0.369) was most associated with posts in the subreddit forum /r/Anesthesia (*Table 1*). This demonstrates that the forum is utilized often to address the relationship and communication between patients and members of their care team. A potential explanation for this finding may be related to the poor communication regarding postoperative care.[27] Most patients who undergo surgery do not have the necessary preoperative discussions with the anesthesia team to properly address the recovery experience following surgical procedures.[27] Gleaning from this analysis, we recommend that Reddit be used as a forum for both patients and their health care providers to address specific aspects of care that have not been discussed during the preoperative anesthesia visit. Additionally, while anesthesiologists mostly communicate on the logistical aspects of care, more time and attention are warranted to discuss non-technical information such as patients' values and goals of care.[27] Research has shown that patients want to be more involved with their care and seek emotional support during their care in ambulatory anesthesia.[28] Reddit can serve as a tool to address these types of concerns between the patient and their anesthesia providers.

Table 1. Latent Dirichlet Allocation Topics associated with /r/Anesthesia Posts with Correlated Words Used to Highlight the Topic and Redacted Illustrative Examples.

Category/Theme	Operational Definition	Cohen's D	Correlated Words	Redacted Illustrative Posts
Patient-Physician Experience	Posts surrounding relationships between members of the care team and patients	0.389	Anesthesia, surgery, procedure, sedation, anesthesiologist, patient, anesthetic, surgeon, pain, experience	Hello everybody, I underwent a procedure this morning while sedated. I came and read the pinned post in this subreddit since I had been worrying about it for weeks, and it truly helped me relax. I generally struggle with quite severe anxiety relating to my health. While getting ready this morning, I was still a little on edge, but my amazing and caring anesthesiologist basically informed me that given my health, she wouldn't even bother describing extreme risks; she only said that I might feel nauseous and have a sore throat after. I was asleep with one of the nurses holding my hand, and when I awoke, I was overjoyed. After roughly 4 hours of being awake, I feel great! The fear of the unknown made me worried, but I now get that it is truly okay. Thank you for your help across this forum.
Medication	Posts surrounding medication administration	0.365	Patient, risk, blood, propofol, dose, patients, anesthetics, pressure, drug, higher	Why does the white IV fluid hurt when it is inserted? I'm not sure what it was, but it quickly reached my brain and knocked me out in minutes Too bad it HURT LIKE HELL on my arm. Has Reynaud's been linked to this? I really struggle with that. What was this fluid, and why did they claim that some feel pain with it and others don't?
Health Care Infrastructure	Posts including various members of healthcare industry as a whole	0.336	CRNA, work, practice, school, medical, experience, states, nurse, job, hospital	I am currently completing a respiratory therapy AA program in California. I am very interested in pursuing anesthesia of some kind, and I am deciding between going to medical school to become an anesthesiologist, moving out of state to become an anesthesiology assistant, or returning to nursing school after I graduate from respiratory school and possibly pursuing a CRNA in the future. Can someone please describe the distinctions between the roles in terms of autonomy and the duties of each job?
Procedures	Posts surrounding specific procedures requiring anesthesia administration	0.304	Surgery, pain, block, body, nerve, heart, hospital, hours, spinal, epidural	I'm going to have a tummy tuck, and I read an article about someone who had general anesthesia and woke up, but they were paralyzed from the medication given along with the general anesthetic, so they couldn't tell anyone they were awake. I'm very scared right now! This surgery takes six hours! I hope I don't wake up during any of it, but if I do, I'd like to know how to let someone know so they can put me back to sleep!
Personal Inquiries	Posts including direct questions regarding anesthesia	0.201	Question, future, important, making, fact, learn, true, difficult, situation, personal	I have a cardiac problem and have a procedure tomorrow. I'm seeking feedback before scheduling this sedated procedure. For the last few years, I've experienced a persistent cough, shortness of breath, and periodic chest discomfort that feels like a heart attack (along with pain in my left arm, jaw, and back), as well as irregular heartbeats while lying down.... I'm worried that because I'm unsure of whether I have a problem or not, I won't know whether I should be sedated for the surgery until I get more information. Even though it's a colonoscopy and not surgery, I'm worried.
Uncertainties	User posts regarding patient worries and fears	0.147	I'm, don't, shit, stop, smoking, give, smoke, week, anxiety, die	Help me. I spent three weeks without doing any drugs. A friend of mine invited me out to drinks last Thursday (also something I must stop, but anyway). I let him know that I stopped doing drugs and that I needed to keep clean (especially for two weeks) since I am scheduled to undergo major surgery on April 15... Does anyone here have any information on whether I should be able to have the surgery? Has anyone ever smoked meth and felt sick afterwards?

Our analysis demonstrates that patients utilize Reddit as a resource to discuss highly personal questions and concerns regarding anesthesia. These questions may be stigmatizing and difficult to talk about during the preoperative anesthesia visit. For example, a redacted illustrated post highlighted concerns about methamphetamine use impacting the likelihood of having surgery: "Does anyone here have any information on whether I should be able to have the surgery? Has anyone ever smoked meth and felt sick afterward?" (***Table 1***). The patient-provider discussion of substance use during the preoperative period is paramount so that their anesthesiologists can understand potential drug interactions, predict tolerance to some anesthetics, and recognize drug withdrawal so that they are prepared to manage all these factors in the perioperative period.[29] Since Reddit requires only an email address to sign up, it ensures anonymity to facilitate easier sharing of emotionally sensitive topics such as these which can be beneficial as some studies have shown that patients tend to under-report substance use in the hospital setting.[18,30]

It would be incredibly advantageous for the field of anesthesiology if providers knew more about social media's utility in facilitating conversations that could address patients' concerns that have either not been discussed previously or ones that are more difficult to talk about due to the sensitivity of the topic. We believe this would encourage more anesthesiologists to feel compelled to engage with patients on these platforms including the subreddit /r/Anesthesia. For example, social media sites such as Twitter have already been used by anesthesiologists to converse over research topics. In fact, anesthesiology journals with a "highly performing Twitter account" are more likely to have an increase in impact factor than those who do not.[31] In addition to this, sites like Twitter have been utilized for live interaction during anesthesiology research conferences.[31,32] The easy accessibility and wide usage of social media should poise anesthesiologists to address the concerns and questions of its users, including those demonstrated on the subreddit community /r/Anesthesia.

While Reddit may be helpful in alleviating the anxiety of some patients regarding anesthesia, it still can present a large opportunity for spread of misinformation across the forum. A major concern with crowdsourcing sensitive healthcare information online is the lack of ability to verify information

despite it requiring immense expertise. There often is a lack of editorial responsibility, peer review, and accountability on social media networks which can question the authenticity of information.[33] Despite this, our analysis demonstrates how Reddit can still be of value for health care providers to interact with patients who have questions or concerns regarding anesthesia if appropriate provider disclosures and safeguards are put into place.

limitations

Limitations of this study include retrospective design, selection and responder bias. We identified content on only one subreddit thread, and therefore, other threads might yield different themes and sub-themes. The study sample consists of social media users and is not representative of the general population. We also collected posts only in the English language, and so, non-English posts could yield different themes. Despite these limitations, social media platforms provide an unstructured and accessible venue for users to share their experiences regarding anesthesia procedures.

Summary – Accelerating Translation

Title: Reddit Users' Questions and Concerns about Anesthesia

Main Problem To Solve: Reddit users of the forum r/Anesthesia utilize the forum for anonymous discussion of questions and concerns regarding upcoming procedures requiring anesthesia. Due to the ability to post anonymously, there is risk for misinformation being spread across the platform which may be potentially harmful for patients.

Aim of Study: Our study aims to analyze discussions patients are having across the forum r/Anesthesia in order to better inform anesthesia providers of ways to better serve their patients both online and in the peri-operative setting.

Methodology: Posts published on an active Reddit forum on Anesthesia (i.e., /r/Anesthesia) were used for analysis. Big Query was used to collect posts from /r/Anesthesia. We collected 3,288 posts published between December 2015 and August 2019 across the forum as well as a control group of 3,288 posts from a Reddit forum not related to Anesthesia. Using latent Dirichlet allocation (LDA) we extracted 20 topics from our data set. The LDA topic themes most associated with posts in /r/Anesthesia compared to the control group were determined.

Results. LDA analysis of posts in /r/Anesthesia relative to a control group produced 6 distinct categories of posts (Table 1). The posts most associated with /r/Anesthesia when compared to a control group belonged to the "Physician-Patient Experience" category (Cohen's d= 0.389) while the posts least associated with /r/Anesthesia were from the "Uncertainties" category (Cohen's d= 0.147). Examples of experiences from members of the /r/Anesthesia forum highlight subjective experiences of patients undergoing anesthesia. For example, one user stated, "I was asleep with one of the nurses holding my hand, and when I awoke, I was overjoyed. After roughly 4 hours of being awake, I feel great! The fear of the unknown made me worried, but I now get that it is truly okay. Thank you for your help across this forum." This demonstrates the beneficial aspects of utilizing the community r/Anesthesia for social support.

Conclusions: Our study demonstrates that Reddit data can provide utility for physicians to engage with patients who have concerns regarding anesthetic procedures. Furthermore, data from social media forums such as Reddit may be leveraged to identify ways in which patients lend support to one another in an anonymous social setting. Future research has the potential to expand this methodology to other subspecialties to elucidate patient concerns across the spectrum of medicine.

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Acknowledgments

None.

Conflict of Interest Statement & Funding

The Authors have no funding, financial relationships or conflicts of interest to disclose.

Author Contributions

Conceptualization, Methodology: KE, AA, LS. Validation, Visualization: KE, KH, LS. Investigation : AA. Writing – Original Draft Preparation, Writing - Review & Editing: KE, KH, LS.

Cite as

El-Jack K, Henderson K, Andy AU, Southwick L. Reddit Users' Questions and Concerns about Anesthesia. Int J Med Stud. 2022 Oct-Dec;10(4):370-74.

ISSN 2076-6327

This journal is published by Pitt Open Library Publishing

IJMS INTERNATIONAL JOURNAL of MEDICAL STUDENTS

Original Article

Healthful Practices Among Blood Donors in A Low-Income Setting

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Abstract

Background: Blood donation is sustained by the availability of healthy donors. It does not only require recruiting new healthy donors, but also maintaining existing ones in optimal health. As recruitment of new donors is not guaranteed, it is essential that existing donors are always in good shape. The study therefore assesses the lifestyles and healthy habits of a sample of recurrent blood donors, their demographic characteristics, and motivations for donation. **Methods:** This was a cross-sectional study involving 127 blood donors between the ages of 17 and 60 years in Korle-bu, Ghana. Participants were sampled by the snowball method and were provided with pre-tested electronic questionnaires. The data was summarised using the Numbers software by Apple Inc. and then analysed. **Results:** All were non-smokers and engaged conscientiously in at least one healthy habit, with 60.3% actively following fitness schedules. There were no lifestyle-related health conditions or substance addictions. Up to 94% of the respondents had attained university education. Motivations for donations revolved mostly around altruism and almost half (46.5%) of the respondents conceded that being blood donors had made them live healthier. **Conclusion:** Voluntary blood donors in the selected low-income setting were mostly health conscious, and the donor status significantly affected this way of life, only more indirectly than directly. More indirectly because the healthy habits practised predominantly oriented to personal well-being, reinforced by the desire to donate blood in many situations.

Key Words: Healthy Lifestyle, Blood Donation, Blood Donors (Source: MeSH-NLM).

Introduction

Blood donation is a process described from the 19th century as collecting blood from apparently healthy individuals and infusing into ill individuals.[1] It has undergone several evolutions but maintains its essence. Millions of lives have been saved from this practice–which remains the single most effective way of replacing lost blood.[2] Millions of people all over the world need blood transfusions yearly, majority being pregnant women, and children under 5 years.[3]

The health of blood donors remains paramount to the sustainability of this lifesaving process.[4] The standard questionnaire by the World Health Organisation (WHO) for blood donors, for instance, focuses on the health status of prospective donors, by inquiring symptoms and signs of specific diseases.[3] The healthy donor effect, coined from the healthy worker effect, is a phenomenon largely perceived as a form of membership bias.[5] It describes a kind of top-bottom association between health and donation, in which donation is always a product of good health and that donation by itself can not improve health. The potential bottom-top association between these two is worthy of discussion.

Family replacement donation (FRD) is directly linked to inadequate supply of blood as it is unreliable. In Ghana, for instance, 63% of blood is sourced from FRDs.[6] A survey from 2014 to 2016 revealed a higher incidence of transfusion transmissible diseases (TTDs) such as viral hepatitis in FRDs compared with voluntary donors.[7] For this reason, the WHO advised countries to push for 100% voluntary donations by 2020.[3] Fitness for donation relies on the sustained health of the donors, which is not an expectation from FRD donors. As such, the WHO guidelines for blood donation suggest national policies be put in place to protect the health of blood donors, and proposes continuous haemovigilance by blood transfusion services, in order to get a near-real-time health status of their donors.[8] Donations from voluntary donors reduce by up to 10% when subjects either feel or have been diagnosed with sub-optimal health.[9] Healthy blood comes from healthy donors hence the need to ensure good health of the donor at all times.

To remain as a blood donor, one is required to maintain good health not just for themselves, but also for the safety of the recipients (who must be protected from maliferous blood). This study was therefore necessary for assessing the demographic characteristics, health habits and motivations for donation in recurrent donors.

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Editor: Francisco J. Barrera
Student Editors: Ashwini Patankar & Khabab Abbasher Hussien Mohamed Ahmed
Proofreader: Laeeqa Manji
Layout Editor: Ana Maria Morales

Submission: Mayr 16, 2022
Revisions: Jun 17, 2022, July 13,022, Oct 25, 2022,Oct 31, 2022
Responses: Jun 29, 2022, Nov 17, 2022
Acceptance: Dec 4, 2022
Publication: Dec 6, 2022
Process: Peer-reviewed

Methods

Study design, population and area

This was a cross-sectional study that employed the snowball sampling technique, in which recommendations were received from eligible participants to others of similar characteristics for contacting.

The target population was blood donors who had donated to the National Blood Service Ghana (NBSG) directly or indirectly. Direct donors to the NBSG, are those who visit the facility at Korle-Bu in Accra to donate blood as well as those who donate during mobile blood donor drives. Indirect donors are those who donate at programs supervised by the NBSG. Known blood donors were first contacted, who then shared contacts of other eligible donors—facilitating the snowball sampling.

Participants were aged 17-60 years, and were either voluntary (who had donated multiple times) or FRD donors. For FRD donors, preference was given to those who planned to donate again in the future while those who had donated only once, and did not plan to donate blood in the future were excluded. The sample size was determined by the formula:

$n = z2p\ (100\ p)/d2$

where n= sample size, p= prevalence of voluntary blood donors, and d=margin of error. With prevalence set at 9, margin of error at 5%, and corresponding z score for the error margin at 1.96, the calculated sample size was 126. The study involved 127 subjects. The value of p was estimated as 9% because there were no studies on the prevalence of voluntary donors in Accra (or Korle-bu). However the probability of looking for blood donors in this setting is greater than 5% due to the presence of the hospital and the NBSG. Data was summarised using the Numbers Software by Apple Inc. by exporting from Google forms and then analysed descriptively.

The study area was within Korle-Bu with 3 different settings: the NBSG, Southern area blood bank of the NBSG, and the University of Ghana Medical Student Hostels. The NBSG at Korle-Bu is an agency of the Ministry of Health and head office for blood donation services in Ghana.[10] It organises and supervises blood donation exercises to ensure sustainability of blood donation in Ghana. Donors, here, are always voluntary.

The Southern area of the NBSG runs a smaller blood bank within the Korle-Bu Teaching Hospital, where voluntary as well as FRD donors are able to donate blood safely, under the direct supervision of the NBSG. The student hostels house medical students from 3rd year to 6th year and are also situated close to the hospital.

Data collection instrument

A 40-item electronic questionnaire designed with Google Forms was used and had predominantly closed-ended questions. This was developed by the first author (but not validated) and pretested on 18 subjects. Based on the feedback given by these initial subjects, revisions were made by removing ambiguous questions and eliminating almost all open-ended questions. The links to the questionnaire were thereafter sent to the respondents via the communication media of their preference. It was sectioned: demographics (assessing basic information like sex and occupation), donor and donation history (covering donor details such as blood group and frequency of donation), and health and the donor (which assessed health habits such as exercise frequency and health conditions of the donors such as presence of chronic illnesses and frequency of hospital admissions). Necessary help was given for completing the forms, which totally eliminated partial responses. Contacting the respondents greatly increased the response rate and also helped reduce selection error. Those that were unable to submit their responses within a week were considered non-respondents. The data was collected in July 2020 during a partial lock-down (necessitating the snowball sampling method).

Ethical considerations

All participants gave informed consent. They were assured of anonymity and confidentiality for all information provided. Permit was sought from the National Blood Service Ghana, as well as the Proposal and Ethics Review Committee of the Department of Community Health of the University of Ghana Medical School with clearance number UGMS-CHDRC/49/2020.

Results

127 of 139 eligible donors completed the survey (response rate 91%).

Demography

The sex distribution was 51.2% males to 48.8% females, with 93% being under 31 years. The mean age was 26.6 years with a standard deviation of 4.7. 61.4% were medical students, 18.1% health workers, 7.1% teachers and the remainder had other professions like private business owners. All were educated (about 94% to the university level). The major ethnic groups in Ghana were: Akan-64%, Ewe-13%, Ga-10%, Northern group-9%, Guan and Nzema-4%.

Donor and Donation History

The data included donors from all blood groups, with most being blood group O+ or B+ (44.9% and 29.9% respectively). 91.3% were voluntary donors while 8.7% were family replacement donors (that planned on being voluntary donors).

Most had been donors for at least a year prior to the survey (83%) and 52.4% were registered blood donors at the NBSG. Almost half (49.6%) became donors when aged 18-20 years and 48% at ages 21-30 years.

The majority (91.2%) of the participants were not donors with specific schedules for donating blood. Of the 8.8% scheduled donors (11 respondents), 56% donated at least twice a year and the highest number of donations per year was three times (by 3

respondents). Of the 91.2% unscheduled donors, most (91.8% of 114 respondents) donated only once a year on average, and the remainder donated at most, twice a year on average.

Motivations for donation included altruism and desire to be part of a lifesaving team (64.8% and 53.3% respectively), conscience (17.2%), promotions from media, health workers or other sources (18%), incentives such as free food (4.9%), and positive impact on personal health (9%).

Health and The Donor

A little over 20% (21.3%; 27 responses in all) had ever deferred donating blood for various reasons such as anaemia (55.6%), and low weight (18.5%)

None (0%) had any chronic diseases such as hypertension or diabetes and almost all (98.4%) had never received blood transfusions themselves.

Table 1. Summarises the Demography and Various Practices Engaged in by the Donors.

Demography	
Mean ages[a]	%(SD)
18.5	6.0(7.7)
25.5	87.4(0.7)
35.5	4.7(9.3)
51.8	2.3(31.8)
Gender[b]	No(%)
Male	61(48.4)
Female	66(51.2)
Occupation[c]	n(%)
Student	78(61.4)
Health worker	23(18.1)
Teacher	9(7.1)
Others	17(13.4)
Practices	No(%)
1. Special preparation before a donation[d]:	28(23.0)
Increasing food intake	21 (80.0)
Healthier food choices	14 (53.8)
Food supplementation	8 (30.8)
Exercising	8(30.8)
2. Weekly Fruit consumption[e]	105 (82.7)
3. Fitness schedule[f]:	78 (60.3)
Aerobics	48 (60.0)
Jogging	31 (38.8)
Sports	27 (33.6)
Brisk walking	29 (36.3)
Yoga	10 (12.5)
Others	9 (11.7)
4. Alcohol intake[g]	29 (22.8)
5. Smoking[h]	0 (0.0)
6. Over the counter drug usage[i]	85 (67.5)
7. Caffeine[j]	52 (42.6)
8. Multiple sexual partners[k]	11 (8.7)

Legend: a,b,c,e,g,h,I,j,k All used a common denominator of 127 representing all respondents. dSpecial preparations such as increasing food intake, food supplementation and healthier food choices all used a common demoninator of 28, representing those that made special preparations fFitness schedules such as aerobics, jogging, sports, etc used a common denominator of 80

24 respondents (18.6%) had ever experienced adverse reactions and the commonest was dizziness or faintness (69.6%). Others included nausea (39.1%), headaches (30.4%), passing out (26.1%), and bleeding (4.3%).

For those that followed fitness schedules, about 3.5% attributed the discipline directly to the responsibility of being donors. Most (87.1%) just wanted to be in good shape, while 34.1% specifically wanted to prevent chronic lifestyle diseases. These fitness activities were simply hobbies to 3.6% of them.

The majority (81.1%) had never had hospital admissions over the antecedent 2 years and 18.1% did routine medical checkups.

Most over the counter (OTC) drugs such as analgesics (61.1%). Cough mixtures, antibiotics, lozenges, and antihistamines were routinely used by 12.7%, 13.5%, 11.1%, and 11.9% respectively; 15.7% of them took herbal medications. There were no substance addictions.

Nearly half (46.5%) of the respondents admitted that the donor status had influenced their health choices in one way or the other. The setbacks to implementing multiple good health practices related mainly with time (35.4%), a feeling of satisfaction (complacency) with what was already practised (40.9%), funds (10.2%), lack of exploratory will (12.6%), and lack of proper scheduling in those without time constraints (18.1%).

Discussion

The sex distribution is close to that of the 2021 population census of Ghana which revealed 97 males for every 100 females or 49.3% to 50.7%.[10] Some studies suggest that health workers are not likely to donate blood than the general population, despite their adequate knowledge of the exercise. [11-12] The converse finding in this research could be explained in part by the regular donation exercises organised by various health associations found in Korle-bu as well as the proximity of the NBSG, which makes donation convenient. This is to say that the opportunity to donate is always very close to those that are willing.

All donors sampled were educated with many in the health sector. This prospect, though inconclusive, opens doors to the question of whether or not educated people are more likely to be voluntary donors. Even though the level of knowledge of donation may not be proportional to the donation rates, informed or educated people record higher voluntary donation numbers.[3,13] However, a study in China found no significant association between educational level and blood donation.[13]

Of the 114 (91.2% of the respondents) that were unscheduled donors, almost 92% donated blood just once a year, while up to 56% of the regular, scheduled donors (11 respondents) donated blood at least twice every year. This is consistent with studies by the WHO and another in England, which mentioned that self-motivated donors are more likely to donate frequently. [3,15]

Motivation for donation among the respondents mainly revolved around humanitarian values such as altruism, desire to save lives and conscience—corroborating various studies.[16-18] The altruistic drive is in itself linked with good mental and overall well-being according to the mental health foundation.19 These motivations need to be maintained because most blood donors, at least from this study (98.4%), had never needed transfusion themselves.

Few (21.7%) of the respondents had ever deferred blood donations and their reasons were all from relatively benign conditions such as anaemia and low weight, which could in no way harm the recipients. It is remarkable that none of the participants had lifestyle-related diseases. Though inconclusive, the engaging in good health practices (discussed later) probably contributes to this finding. Other studies also posit that blood donation potentially lowers risk and improves lifestyle-related conditions like hypertension and dyslipidemia.[20-21] This could be a potential reason for this observation in the recurrent donors.

Common adverse reactions, such as dizziness, nausea and headaches [21-23] reported by 18.6% of the respondents suggests that such donors should be in optimal states of health, because combining such adverse reactions with chronic infirmities could be debilitating and potentially interrupt subsequent donations. Therefore, donors should have a lot of 'fitness reserves' to be able to tolerate these potentially debilitating adverse reactions. The 23% of respondents that prepared for donations in ways such as modifying food intake, or by food supplementation may be practicing in these to abate the possibility of experiencing adverse reactions, as the numbers closely match.

60.3% of the donors followed fitness schedules such as jogging, suggesting a high level of health discipline. This point is ratified by other trends of healthy living such as regular fruit consumption (up to 82.7% did at least weekly), and avoiding alcohol and smoking (in 75.6% and 100% respectively). Again, there was no substance addiction and those that took addictive substances such as caffeine-based products were not addicted. While 32% did not need OTCs, majority of those that needed, took painkillers (61.1%). Hospital admissions over the antecedent 2 years was less than 20%. These statistics, all of which suggest good shape, are attributable to healthy lifestyles.

Even though only 3.5% of the motivations of fitness schedules were directly attributable to the responsibility of being blood donors, 46.5% conceded that the prospect of being blood donors had made them live healthier. Following a fitness schedule is indeed just one aspect of a healthy lifestyle (as practised by 60.3% of the respondents). This shows that the responsibility of being blood donors makes a significant percentage live more healthily, and less riskily. Most of the respondents had low risk sex lives, with only 8.7% having more than one sexual partner. This implies that the risk of transfusion transmissible diseases [24-26] would be minimal in this population. These observations tend to corroborate a study that concluded that frequent blood donations are associated with lower morbidity and mortality even though not perceived as a consequential health effect.[27] Since the entire exercise requires some health screening, it could help with early detection and treatment of certain health conditions. In this sample population, there is adequate awareness of blood donation as a result of high levels of education, especially by those in the health sector.

The survey shows laudable lifestyle in the sampled donors. Further cross-sectional studies across different population groups would be necessary for comparing outcomes. Voluntary blood donation could become a competitive practice if studies confirm improved longevity, effectively decreasing the shortage of safe blood supply in most health facilities.

Strengths and limitations

The survey is novel as there are not many studies that cover this aspect of blood donors and donation. It therefore delivers a perspective on the lifestyle trends of blood donors as well as the impact of blood donation on health habits. However, it is limited by snowballing technique that may have introduced selection bias. This is evident in areas such as the age groups captured (youthful) and that majority were in the health sector. Furthermore, the questionnaire was not validated and there was a small sample size resulting in lack of generalisability to other populations. Finally, being a cross-sectional study limits the understanding between the temporality of the measured variables and the practice of donating blood.

Conclusion

Voluntary blood donors from the selected low-income setting were youthful and displayed laudable degrees of health consciousness. The responsibility of being voluntary donors influenced their lifestyles, only more indirectly than directly. Motivations for healthful practices were primarily personal well-being oriented and the donor status appeared to augment these motivations, wherein lies the indirect association. Even though the healthy donor effect[5] has a bearing on the instantaneous health of donors in that healthy people are more likely to donate, the reverse could as well be a significant phenomenon, in the sense that blood donors are likely to live healthier (a hypothesis requiring further studies). This becomes a point of interest because nearly half of the respondents conceded that being blood donors makes them opt for healthier life choices. The association between health and donation therefore remains noteworthy, since healthy lifestyles among blood donors provide the triple advantage of improving quality of life of donors, ensuring sustainability of blood donation and ensuring safety of blood received by patients.

Summary – Accelerating Translation

Blood donation is a lifesaving process that requires the availability of blood donors for sustainability. Voluntary blood donors are a more reliable source of blood, especially in terms of blood safety as proven by a number of researches. This article assesses the lifestyle of a sample of voluntary blood donors from a low income setting with regards to healthy living as well as their overall wellbeing.

The findings were that blood donors from the chosen low-income setting were health-conscious and engaged in good health practices. It was also found that the donor status had a significant influence on the healthy lifestyles they lived. None of the donors assessed had chronic health conditions related to lifestyle.

The conclusion from these findings was that blood donation has the potential to improve the lifestyle of donors which in turn ensures their availability for subsequent donations as well as ensuring blood safety for recipients.

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Acknowledgments

The authors wish to thank the department of Community Health of the University of Ghana Medical School for facilitating efficient data collection during the Covid-19 pandemic.

Conflict of Interest Statement & Funding

The Authors have no funding, financial relationships or conflicts of interest to disclose.

Author Contributions

Conceptualization, Formal Analysis, Methodology, Project Administration, Validation, Visualization, Writing – Original Draft Preparation, Writing -Review & Editing SAT, YDA. Data curation, Investigation, Software: SAT. Supervision: YDA.

Cite as

Amo-Tachie S, Adomokoh YD. Healthful Practices Among Blood Donors in A Low-Income Setting. Int J Med Stud. 2022 Oct-Dec;10(4):375-80.

ISSN 2076-6327

This journal is published by Pitt Open Library Publishing

IJMS INTERNATIONAL JOURNAL of MEDICAL STUDENTS

Original Article

Traumatic Brain Injury in Honduras: The Use of a Paper-based Surveillance System to Characterize Injuries Patterns

Erica Johnson,[1] Cristina Rodriguez,[2] Juan C. Puyana,[3] Francisco J. Bonilla-Escobar.[4]

Abstract

Background: Traumatic brain injuries (TBI) are a leading cause of death and disability worldwide. Violence is the leading cause of mortality in Honduras. However, the incidence and impact of TBI in this low-middle income country (LMIC) is unknown. The aim of this study is to describe the epidemiology of TBI in Honduras, as captured by an injury surveillance tool in the country's major referral center. **Methods:** A cross sectional review of all TBI-related emergency department visits at the main referral hospital in Honduras from January to December 2013 was conducted. The calculation of descriptive statistics from Injury Surveillance System (InSS) data was performed. **Results:** Of 17,971 total injuries seen in 2013, 20% were traumatic brain injuries (n=3,588). The main mechanisms of injury were falls (41.11%), road traffic accidents (23.91%), blunt trauma (20.82%), penetrating knife injuries (5.85%), and firearm injuries (2.26%). Most TBI were classified as mild; 99.69% (Glasgow Coma Scale=15). Emergency room mortality was low (1.11%). The modified Kampala Trauma Score median was 8 (interquartile range 7-8). **Conclusion:** Mild TBI accounts for a significant percentage of all injuries presenting to a high-volume referral center in Honduras in 2013. Despite the high incidence of violence in this country, most TBI were accidental, secondary to road traffic accidents and falls. Further research is required with more recent data as well as with prospective data collection methods.

Key Words: Wounds and Injuries; Nervous System Trauma; Trauma Centers; Violence; Honduras; Traumatic Brain Injuries (Source: MeSH-NLM).

Introduction

Traumatic brain injury (TBI) causes death and significant disability worldwide.[1-3] Estimates of the global incidence of TBI are as high as 69 million per year.[4] The impact is especially high in low- and middle-income countries, where the population is at risk for injury due to epidemiological and environmental factors, and have three-times the incidence rate of high-income countries. The affected populations are often younger and live below the poverty line.[5] In addition, most countries in Latin America experience high rates of road traffic collisions and exceedingly high rates of interpersonal violence.[6]

Results from the WHO Global Burden of Disease Study suggests that Latin American countries have the highest incidence of intracranial injury in the world.[7,8] TBI age-standardized prevalence has increased from 1990 to 2016 by 8.4% and is responsible for 8.1 million years of life lived with disability. The most common causes of TBI have been reported as falls and road injuries.[9] There is a need of information regarding TBI in Latin American countries to inform public health policies and implement trauma protocols to reduce this burden.[10]

The Central American country of Honduras, a low-middle income country (LMIC), has a high rate of violence.[11] In 2014, the United Nations ranked Honduras as the world's most violent country, with homicide rates of 85.5 per 100,000 inhabitants. Males were mainly affected (91.6%) and were most often injured with firearms (83%).[12,13] Despite the high rate of violence, there are few published studies that have assessed the impact of traumatic injury in Honduras.[2,14] It is difficult to obtain data on injury patterns in Honduras due to the lack of a formal trauma registry.[15] Recently, an incidence of 279 TBIs and a prevalence of 567 per 100,000 inhabitants were reported in Honduras, with an increasing trend of 30% in both indicators when comparing the year 1990 to 2016.[9]

The Injury Surveillance System (InSS) is a paper-based injury surveillance system used to capture epidemiological data on injury-related visits to the University's Medical School Hospital (UMSH) in Tegucigalpa, Honduras. The goal of the InSS is to measure and study injury epidemiology and trauma-related outcomes in the absence of a trauma registry. The InSS was established in 2005 through initiatives and funding from the United States Center for Disease Control (CDC), the Pan-American Health Organization (PAHO), and the United Nations Development Programe (UNDP). Paper-based trauma surveillance systems have been successfully used to collect injury data in emergency departments in other low- and middle-

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Editor: Mihnea-A. Gaman
Student Editors: Leah Komer & Duha Shellah
Copyeditor: Johnmark Boachie
Proofreader: Laeeqa Manji
Layout Editor: Ana Maria Morales

Submission: Feb 1, 2022
Revisions: Feb 28, 2022, Aug 15, 2022
Responses: Mar 29, 2022, Aug 25, 2022
Acceptance: Sep 7, 2022
Publication: Dec 2, 2022
Process: Peer-reviewed

income countries, such as Colombia, El Salvador, Peru, and Jamaica.[16] The InSS was last validated in 2013 and therefore, well suited for this study. To the best of our knowledge, there is no recent data available from any hospital-based surveillance systems on TBI in the country.

The aim of this research was to use data from the InSS to describe the patients with traumatic brain injuries, the characteristics of the injuries, and the patients' outcomes in a major referral center in Tegucigalpa, the capital of Honduras. This research could help establish a baseline of TBI in the city, as well as provide more information on patient characteristics towards the promotion of novel assessments of this issue and future improvement of healthcare provision and prevention.

Methods

A cross-sectional review of all injury-related Emergency Department visits to the University's Medical School Hospital (UMSH) in Tegucigalpa from January 1st, 2013 to December 31st, 2013 was conducted. The UMSH is the main referral center for 64 primary care health centers and five hospitals in the Central District of Honduras, home to 1.8 million inhabitants. The hospital recorded an estimated 87,000 patients visits a year, with approximately 15% of admissions due to trauma. Injury data from the injury surveillance system (InSS), a paper-based instrument that was first implemented in 2005 to register all injury-related visits to the UMSH emergency room, was obtained. The goal of the InSS is to obtain basic epidemiological information on traumatic injuries.[16-18]

A hospital worker at the UMSH completed an InSS document for every patient that arrived at the Emergency Department by interviewing the patient and/or the family. The paper-based form captures demographic information (age, date of birth, and marital status), descriptions of injury mechanism, injury type and severity, and circumstances of injury. Specific information on injury intentionality, the presence of drug or alcohol use at the time of injury, and on road traffic collisions is included in the form. The InSS also includes some basic outcomes measures, such as the patient's treatment plan, clinical evaluations, disposition, and mortality.[17] This information is included in each patient's chart and later transferred to an electronic record.[18]

A physician evaluated each patient at the emergency room and filled the medical, diagnosis, and treatment sections of the InSS. All patients with TBIs described in the InSS in the diagnosis section of the form were included. TBI was considered as a sudden trauma to the head that could have affected the brain, with different grades of severity from transitory symptoms such as blurry vision, confusion, and loss of consciousness to severe loss of cognitive and motor responses. Exclusion criteria included not having at least 20% of the specifications; however, all prospective subjects met the inclusion criteria and were used in this study.

For the purposes of this study, all InSS data were transferred to Stata 14® (StataCorp, TX, USA) for review and analysis. The quantitative variables were described using central tendency and dispersion measures while categorical variables were described with frequencies and percentages. Chi-squared tests were performed to compare groups for categorical variables. Injury rates per 100,000 inhabitants and 95% exact confidence intervals (95%CI) were calculated based on a binomial distribution (N=8,303,771 inhabitants, National Institute of Statistics of Honduras). The mortality risk was assessed using the modified Kampala Trauma Score, a validated tool to assess injury severity. The modified Kampala Trauma Score, calculated using age, systolic blood pressure, respiratory rate, neurologic status, and number of injuries, is used for risk stratification of patients in resource-limited settings.[22]

Injuries were either classified as intentional or unintentional. Intentional injuries were either violent interpersonal injuries or self-inflicted. Unintentional injuries included both falls and road traffic collisions.

This study was approved by the Institutional Review Board of the University of Pittsburgh (PRO17080111) as a part of a wider study assessing trauma in Honduras.

Results

In 2013, a total of 17,971 patients were registered in the InSS over the period of January 1st, 2013 to December 31st, 2013, resulting in an injury rate of 216.42 per 100,000 inhabitants (95% CI: 213.27-219.60). There were 3,588 TBIs captured in the InSS, accounting for 19.97% of all injuries over the study period (3,588 /17,971 injuries in 2013, ***Table 1***). Most patients were treated and discharged on the same day of arrival (54.9%, 9,855 patients), and 44.7% of patients were hospitalized (8,021).

Among the recorded traumatic brain injuries, 14.88% were open injuries. The male-to-female injury rate was 2:1 (***Table 2***). The average age of injury was 23±19 years, with the majority occurring between 0-17 years of age (46.42%, ***Figure 1***).

The main mechanisms of injury were falls (41.11%), road traffic (23.91%), and blunt trauma (20.82%, ***Figure 2***). Most injuries occurred at home or in the streets (***Figure 3***). Overall, the vast majority of injuries were non-intentional (83.39% of patients). Only 16.58% of injuries were intentional, with 16.05% of these due to interpersonal violence and 0.53% due to self-inflected injuries (***Table 1***). Intentional injuries were more likely among men ($p<0.001$) and patients aged 18-45 ($p<0.001$, ***Table 3***).

Most traumatic brain injuries seen at the UMSH were mild. Most patients had a Glasgow Coma Scale (GCS) of 15 on arrival (99.69%). Almost half (43.2%) of the patients were hospitalized, with higher injury rates in males in general (74.7%, $p<0.001$), individuals aged 0-17 years (51.9%, $p<0.001$), and more injuries occurring at home or in the streets (33.3% or 48.6%, respectively,

Table 1. Characteristics of Traumatic Brain Injuries in Honduras, 2013.

Factor	Frequency (n=3588)
Sex, n (%)	
Female	1028 (28.7%)
Male	2554 (71.3%)
Age, median (IQR)	19 (7 - 33)
Age categories in years, n (%)	
0-17	1659 (46.4%)
18-45	1415 (39.6%)
46-65	322 (9.0%)
66-95	178 (5.0%)
Pregnancy, n (%)	12 (1.2%)
TBI severity based on Glasgow coma scale, n (%)	
Mild	3582 (99.9%)
Moderate	3 (0.1%)
Severe	2 (0.1%)
Other affected anatomical sites, n (%)	
Eyes	46 (1.3%)
Nose	28 (0.8%)
Neck	22 (0.6%)
Others	69 (1.9%)
Place of injury, n (%)	
Street	1478 (43.9%)
Home	1255 (37.3%)
Workplace	194 (5.8%)
Vehicle	151 (4.5%)
School	132 (3.9%)
Sport arena	84 (2.5%)
Other	74 (2.1%)
Main mechanism of injury, n (%)	
Fall	1475 (42.2%)
Road traffic collision	858 (24.5%)
Blunt force	747 (21.3%)
Sharpe object injury	210 (6.0%)
Gunshot	81 (2.3%)
Other	128 (3.6%)
Activity, n (%)	
Recreation	1302 (40.2%)
Traveling	1007 (31.1%)
Working	472 (13.2%)
Drinking alcohol	152 (4.7%)
Working/cleaning the house	110 (3.4%)
Practicing sport	106 (3.3%)
Other	86 (2.4%)
Intentionality	
Unintentional	2991 (83.4%)
Intentional	576 (16.1%)
Self-inflicted	20 (0.6%)
Outcome at Emergency	
Discharged	1997 (55.7%)
Hospitalized	1549 (43.2%)
Dead	40 (1.1%)

Legend: SD: Standard deviation. ♀ GCS is categorized as mild (13-15), moderate (9-12) and severe (≤ 8). ¥ Calculated only for women (n=1,028).

Figure 1. Age Distribution of Patients with Traumatic Brain Injury in Honduras, 2013.

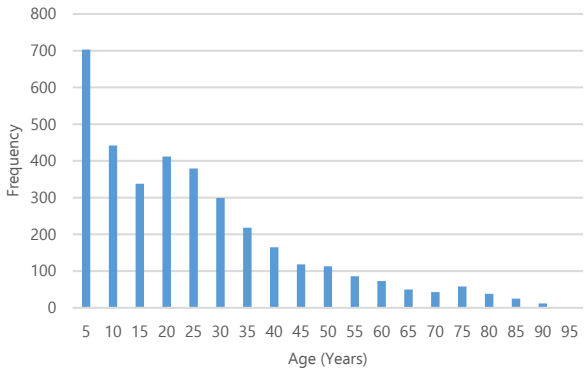


Table 2. Patients with Traumatic Brain Injury Characteristics by Intention of the Injury in Honduras.

Characteristics	Intentional TBI (n=576)	Unintentional TBI (n=3,012)	p-value
Sex*			p<0.001
Male	485	2,069	
Female	91	937	
Age*			p<0.001
0-17 years, n	96	1,563	
18-45 years, n	396	1,019	
46-98 years, n	82	418	
Pregnancy ♀			p=0.291
Pregnant	2	10	
Not pregnant	90	929	
Glasgow Coma Scale ¥			p=0.583
Mild, n	575	3,008	
Moderate, n	0	2	
Severe, n	1	2	

Legend: * Significant at p=0.05. ♀ Calculated only for women (n=1,028). ¥ GCS is categorized as mild (13-15), moderate (9-12) and severe (≤ 8)

p<0.001), caused by falls (40.3%, p<0.001), and during recreational activities or travelling (39.8% or 33.2%, respectively, p<0.001, ***Table 3***).

Only 1.11% of the patients with a TBI died in the emergency room (***Table 2***). They had multiple traumas including cervical (5%), thoracic (7.5%), abdominal (7.5%), and muscle/bone(15%). These patients also had severe injuries that required surgery in 80% of the cases. Death at emergency room was significant in males (87.5%, p=0.02) and individuals with ages between 18 and 45 years (66.7%, p<0.001), and caused by non-intentional injuries (67.5%, p=0.007), in road traffic collisions (50%, p<0.001), working or travelling (45% and 40%, respectively, p<0.001), and in the streets (73.1%, p=0.005, ***Table 3***). The modified Kampala Trauma Score median was 8 (interquartile range 7-8).

Table 3. Patients with Traumatic Brain Injuries Characteristics Based on Status at Discharge (Hospitalization or Death) from the Emergency Room.

Characteristics	Status			Hospitalized		
	Alive (n=3,548)	Died (n=40)	p-value	No (n=2,039)	Yes (n=1,549)	p-value
Sex, n (%)			0.023			<0.001
Female	1,023 (28.9%)	5 (12.5%)		636 (31.3%)	392 (25.3%)	
Male	2,519 (71.1%)	35 (87.5%)		1,398 (68.7%)	1,156 (74.7%)	
Age, median (IQR)	19 (7-33)	27 (20-44)	<0.001	21 (7-34)	17 (8-31)	0.006
Age groups, n (%)			<0.001			<0.001
0-17	1,654 (46.8%)	5 (12.8%)		859 (42.2%)	800 (51.9%)	
18-45	1,389 (39.3%)	26 (66.7%)		863 (42.4%)	552 (35.8%)	
46-65	320 (9.1%)	2 (5.1%)		199 (9.8%)	123 (8.0%)	
66-95	172 (4.9%)	6 (15.4%)		113 (5.6%)	65 (4.2%)	
Place of injury, n (%)			0.005			<0.001
Home	1,253 (37.5%)	2 (7.7%)		781 (40.2%)	474 (33.3%)	
School	132 (3.9%)	0 (0.0%)		84 (4.3%)	48 (3.4%)	
Street	1,459 (43.7%)	19 (73.1%)		787 (40.5%)	691 (48.6%)	
Workplace	192 (5.7%)	2 (7.7%)		114 (5.9%)	80 (5.6%)	
Vehicle	148 (4.4%)	3 (11.5%)		68 (3.5%)	83 (5.8%)	
Other	158 (4.7%)	0 (0.0%)		111 (5.7%)	47 (3.3%)	
Main Mechanism of Injury, n (%)			<0.001			<0.001
Road traffic collision	839 (24.2%)	19 (50.0%)		368 (18.4%)	490 (32.7%)	
Fall	1,469 (42.4%)	6 (15.8%)		872 (43.6%)	603 (40.3%)	
Blunt force	744 (21.5%)	3 (7.9%)		570 (28.5%)	177 (11.8%)	
Sharpe object injury	208 (6.0%)	2 (5.3%)		108 (5.4%)	102 (6.8%)	
Gunshot	73 (2.1%)	8 (21.1%)		29 (1.4%)	52 (3.5%)	
Other	128 (3.7%)	0 (0.0%)		54 (2.7%)	74 (4.9%)	
Activity, n (%)			<0.001			<0.001
Working	463 (14.4%)	9 (45.0%)		253 (13.3%)	219 (16.4%)	
Recreation	1,301 (40.5%)	1 (5.0%)		771 (40.6%)	531 (39.8%)	
Traveling	999 (31.1%)	8 (40.0%)		564 (29.7%)	443 (33.2%)	
Drinking alcohol	151 (4.7%)	1 (5.0%)		90 (4.7%)	62 (4.6%)	
Other	301 (9.4%)	1 (5.0%)		222 (11.7%)	80 (6.0%)	
Intentionality			0.007			0.06
No-intentional	2,964 (83.6%)	27 (67.5%)		1,721 (84.4%)	1,270 (82.0%)	
Intentional	583 (16.4%)	13 (32.5%)		318 (15.6%)	278 (18.0%)	

Discussion

Traumatic Brain Injury in Honduras

In general, traumatic brain injury accounted for a significant proportion of emergency department visits during the study period. This is similar to incidence rates in other Caribbean countries. An evaluation of Emergency Department admissions in Haiti demonstrated that neurotrauma, including both brain and spinal cord injuries, accounted for 28% of visits.[19] At UMSH in Honduras, a majority of the injuries were mild, as assessed by the Glasgow Coma Scale, and with a low risk of mortality, as measured by modified Kampala Trauma Score.

The burden of TBI in Honduras is mainly in the youth and children. The average age of patients seen at the UMSH was 23, and the largest proportion of injuries occurred in children aged 0-17. This is in contrast to epidemiological data in the United States and Europe, where both the young and the elderly are affected by TBI. A recent systematic review of the epidemiology of traumatic brain

Figure 2. Primary Mechanism of Injury for Patients with Traumatic Injury, 2013.

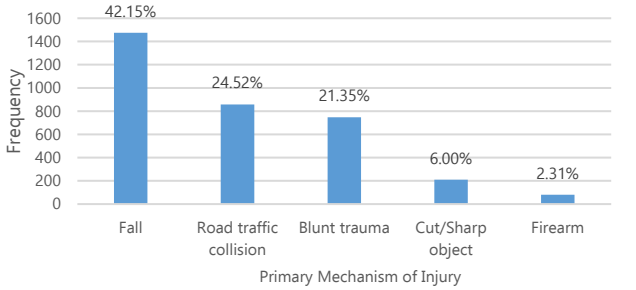
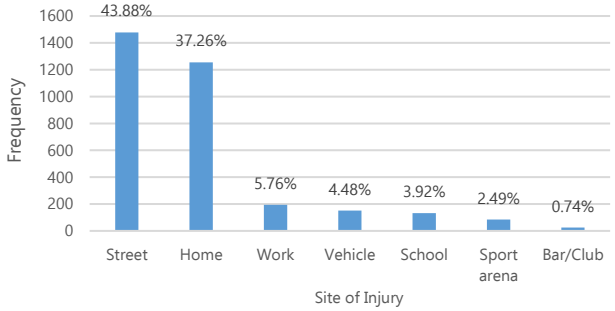


Figure 3. Location at Time of Injury for Patients with Traumatic Brain Injury.



injury in Europe found that TBI showed a bimodal distribution, predominantly affecting those younger than 25 years or older than 75 years.[20] Males were disproportionately affected by TBI, consistent with existing epidemiological studies of these injuries in low- and middle- income countries. The main mechanisms of injury were falls and road traffic collisions. This data is similar to that obtained from traumatic brain injury emergency department admissions in the United States, where the common causes of TBI were falls (47%), being struck by/against an object (15%), and motor vehicle collisions (14%).[21] In contrast, Latin America and the Caribbean have higher rates of TBI due to road traffic incidents.[7]

Overall, this study effectively used the InSS data to characterize TBI and potential risk factors for hospitalization, and common mechanisms of injury and outcomes using the best available information on injuries in Honduras. This data could be used to develop targeted measures to inform the development of preventive strategies, optimization of treatment, and reallocation of scarce healthcare resources. For example, public health strategies targeting motor vehicle accidents and falls could decrease the occurrence of TBI in Honduras. The introduction of trauma registry systems has been shown to improve outcomes, and even to decrease mortality.[22] Data from injury surveillance systems and trauma registries may be used to develop standardized trauma protocols (STP), which have been shown to improve outcomes in traumatic brain injury. One retrospective cohort study investigating the use of an STP at a Level 1 trauma center in Colombia found improved outcomes after STP implementation: in-hospital mortality decreased ($p = 0.024$) and discharge GCS increased from a median of 10 to a median of 14 ($p = 0.034$).[23,24]

In addition, improving triage and diverting mild TBI to other facilities could allow a more efficient use of limited resources in managing trauma. In this study, most TBI seen at the UMSH were mild with a low risk of mortality; these injuries could potentially be managed at other facilities, freeing resources for the management of higher acuity trauma.

Limitations

There are several limitations of this study. Firstly, the InSS only captures injuries in those stable enough for emergency department admission or transfer, thus providing a limited view of overall injury patterns. However, in the absence of a codified trauma registry, the InSS does provide the best available data for characterizing injuries in Honduras. Secondly, the use of a paper-based system could also contribute to variability and error in the way injury data is recorded and coded. We did seek to minimize this error by providing clear instructions on the use of the InSS to those recording this data. Additional studies are necessary to determine the nature of these findings. Finally, the InSS does not describe injuries based on the International Classification of Disease (ICD) coding system, making it difficult to categorize Honduras' injuries and make comparisons with other countries. However, the InSS contains sufficient data to record a Kampala Trauma Score, a measure used in resource limited settings to characterize injury severity. Finally, the last validation of the InSS was conducted in 2013, therefore, this is the last available data for research that we had access to. A further research updating our data as well as with prospective data collection methods could provide a bigger picture of the situation towards preventive strategies.

Conclusion

The paper-based Injury Surveillance System provided sufficient data on traumatic brain injury in Honduras to characterize risk factors, mechanism of injury, and injury severity. Trauma registries provide an important tool to improve understanding of epidemiology of injury, treatment regimens, and practice patterns in LIMCs. Trauma surveillance systems have the potential to transform trauma care in LMICs by identifying the specific challenges and opportunities unique to the region, as evidenced by registries instituted in Paraguay, Jamaica and Cali-Colombia.[16] The InSS provides an important first step in characterizing injury patterns in Honduras, and further research in injuries is required to promote better patient-care and trauma surveillance.

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Acknowledgments

None.

Conflict of Interest Statement & Funding

The Authors have no funding, financial relationships or conflicts of interest to disclose. Dr. Juan C. Puyana work is partially funded by the National Institute of Health (NIH) of the United States with the grant R21TW011151. The opinions expressed in this article are the author's own and do not reflect the view of the National Institutes of Health, the Department of Health and Human Services, or the United States government.

Author Contributions

Conceptualization: CR, FJBE. Methodology: EJ, JCP, FJBE. Formal Analysis: FJBE. Investigation, Writing – Original Draft: EJ, FJBE. Resources: CR, JCP. Funding Acquisition: JCP. Supervision: JCP, FJBE. Data Curation: FJBE. Writing – Review & Editing: EJ, CR, JCP, FJBE.

Cite as

Johnson E, Rodriguez C, Puyana JC, Bonilla-Escobar FJ. Traumatic Brain Injury in Honduras: The Use of a Paper-based Surveillance System to Characterize Injuries Patterns. Int J Med Stud. 2022 Oct-Dec;10(4):381-386

ISSN 2076-6327

This journal is published by Pitt Open Library Publishing

IJMS INTERNATIONAL JOURNAL of MEDICAL STUDENTS

Original Article

A Cross-Sectional Study of p66Shc Gene Expression in Liquid Biopsy of Diabetic Patients. Is It Possible to Predict the Onset of Renal Disease?

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Abstract

Background: Diabetic nephropathy (DN) is a disorder affecting glomerular function that, histologically, is due to the presence of glomerulosclerosis accompanied with endothelial dysfunction of the afferent and efferent renal arterioles. Insulin resistance in diabetic patients is known to be one of the causes of endothelial dysfunction because it increases oxidative stress, and one of the main genes regulating the production pathways of reactive oxygen species is p66Shc. The aim of this study was to evaluate the p66Shc gene expression as a precocious biomarker of renal dysfunction in diabetic patients, using liquids samples of urine sediment and peripheral blood. **Methods:** 29 diabetic patients and 37 healthy donors were recruited from the Centro Universitário FMABC outpatient clinic. The RT-gPCR technique was applied to evaluate p66Shc gene expression in urine and peripheral blood samples from diabetic patients, which were compared with healthy donors. **Results:** There was no significant expression of p66Shc gene in samples from diabetic patients compared with healthy donors. However, p66Shc expression in the blood samples of diabetics (0.02417±0.078652- ΔCT, n=29) was 3.6 times higher than in healthy participants (0.00689±0.01758, n=37) while in the urine samples, it was 1.48 times higher in diabetics group (0.02761±0.05412- ΔCT) than in CTL group (0.0186±0.02199). **Conclusion:** There was no significant p66Shc gene expression in peripheral blood and urine samples of diabetic patients without kidney injury compared with healthy donors, although there is a tendency for this gene to participate in the oxidative imbalance present in diabetes.

Key Words: Diabetes Mellitus; p66Shc; Biomarker; Liquid biopsy (Source: MeSH-NLM).

Introduction

Type II diabetes mellitus (T2DM) is a heterogeneous disorder defined by the presence of hyperglycemia due to the functional insufficiency of insulin's action on its receptor.[1,2] Currently, there has been an improved survival rate of diabetic patients and, in parallel, increased chances of developing chronic complications due to the long periods of exposure to hyperglycemia- among these complications is nephropathy, the main reason for the admission of patients to dialysis and transplantation programs.[3,4]

Diabetic nephropathy (DN) consists of a disorder that affects glomerular function, which, histologically, occurs due to the presence of glomerulosclerosis, a condition in which the basal membranes of the glomerular capillaries are thickened, and the mesangium, which surrounds the glomerular vessels, is increased due to the deposition of extra cellular matrix (ECM).[5,6] This is an asymptomatic disease that is rarely identified in the early stages and is therefore considered potentially serious. It is detected between the moderate and late phases. This disease usually presents with three clinical phases that allow the classification of patients according to its progress.[7,8]

Endothelial nitric oxide synthase (eNOS) synthesis is impaired in patients with T2DM, due to factors such as hyperglycemia, hyperinsulinemia, and insulin resistance, which leads to one of the main factors involved in the pathophysiology of DN: a dysfunction of endothelial glomerular capillaries and afferent and efferent arterioles due to the increased production of reactive

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Editor: Mohammad Amin Khazeei Tabari
Student Editors: Rahul Abraham & Hooman Khoshhal
Copyeditor: Sebastian Diebel
Proofreader: Laeeqa Manji
Layout Editor: Ana Maria Morales

Submission: Dec 9, 2021
Revisions: Jul 7, 2022, Sep 24, 2022
Responses: Ago 16, 2022
Acceptance: Sep 26, 2022
Publication: Dec 2, 2022
Process: Peer-reviewed

oxygen species (ROS) and reduced production of nitric oxide (NO). This condition results in vasoconstriction and endothelial oxidative stress that causes significant cell death and worsening of the condition of the patient with DN.[9,10]

The modulation of the oxidative stress process is performed by the p66Shc protein, which is an isoform of the SHC1 gene, located in the first chromosome. p66Shc acts on the endothelial cell by increasing the production of ROS through three different mechanisms, in the cell nucleus, in the cell membrane, and in the mitochondria, In the nucleus, p66Shc is mediated by Forkhead Box Sub-Group O (FOXO), resulting in decreased expression of the enzymes ROS-scavenging catalase (CAT) and manganese superoxide dismutase (MnSOD), both responsible for regulating ROS levels during cellular oxidative stress. In the mitochondria, p66Shc moves from the cytosol to the intermembrane space of the mitochondria, binding to cytochrome C, and becoming an oxidoreductase that catalyzes the production of hydrogen peroxide (H2O2).

The ROS generated by these mechanisms will activate mitochondrial permeability transition pores, culminating in organelle dysfunction, release of mitochondrial apoptotic factors (caspases), in cell apoptosis and finally in the generation of glomerular endothelial dysfunction and sclerosis.[11,12] Considering the information mentioned above, this study evaluated the potential use of p66Shc gene expression in liquid biopsy using urine sediment and peripheral blood, before changes in classic biomarkers, such as creatinine or microalbuminuria. For this, a biomarker of oxidative stress pathway, which had already been studied by protein expression, was used.

Methods

Design

The present study is a cross-sectional study. It was conducted in 2018 and early 2019, and the patients were treated at the medical specialties' outpatient clinic of the Centro Universitário FMABC/FMABC. Patients who agreed to participate in the study were given a free and informed consent form (FICF). Blood samples were not stored and were discarded after the measurements were made. We conducted an interview to collect the volunteers' personal data, as well as to measure height, body weight, and verify any and all medications used to treat diabetes and its comorbidities.

Participants

The studied groups were as follows: healthy individuals (CTL), healthy non-diabetic individuals without a family history of diabetes or kidney disease, and diabetic patients. The individuals who participated as healthy individuals or healthy non-diabetic individuals without a family history of diabetes or kidney disease were at least 21 years old, and non-smokers or users of illicit drugs. Diabetic patients (T2DM) group composed of patients diagnosed with type II diabetes mellitus (fasting glucose ≥140mg/dL and glycated hemoglobin greater than 7%) for at least five years, and preserved renal function (serum creatinine <1.3mg/dL and microalbuminuria <30mg/dL) with a minimum age of 21 years and undergoing treatment for T2DM. The inclusion criteria for T2DM group was expressed will to participate by the patient and diagnosed kidney disease (GFR <60mL/min/1.73m2 or GFR> 60mL/min/1.73m2) associated with at least one marker of parenchymal kidney damage (e.g. proteinuria> 15.0 mg/dL) present for at least three months. The exclusion criteria for the T2DM group was insulin dependent patient; hospitalization for any reason in the last 30 days; and patient with a history of chronic liver disease.

This study was approved by the Ethics Committee of the Centro Universitário FMABC (no. 2.302.284). The informed consent forms were given to the volunteers for completion prior to their participation. The present study was conducted in accordance with the relevant guidelines and regulations/ethical principles of the Declaration of Helsinki.

Assessment of glycemic levels in patients with T2DM:

Determination of fasting plasma glucose was performed by assessing the concentration of glucose in the blood after a nocturnal fasting period. The automated enzymatic method was performed using fluoride serum. Evaluation of glycemic control was conducted with the values of fasting glucose, values above 140 mg/dL for glucose were considered altered.

Assessment of glycated hemoglobin (HbA1c) levels in patients with T2DM by LPLC:

Glycated hemoglobin (HbA1c) was determined using the low pressure liquid chromatography (LPLC) technique, using a DiaStat – Bio-Rad analyzer, which expressed the percentage of the total hemoglobin and evaluated the average blood glucose level, during a 3-month period. The collected material was 5 ml of whole blood with 1 ml of hemolyzed reagent. Values above 7% for HbA1c were considered altered.

Evaluation of kidney function in patients with DM2:

Serum creatinine was measured by the ELISA method to assess the kidney function of patients. The standard methodology of the Clinical Analysis Laboratory of the Faculdade de Medicina do ABC was followed. The estimated GFR was calculated using the Modification of Diet in Renal Disease (MDRD) formula.

Microalbuminuria determination

Determination of microalbuminuria in isolated urine samples was performed by the Biosystems® immunoturbidimetry method (BioSystems S.A. Costa Brava, Barcelona - Spain). The reference value was up to 15 mg/L for normoalbuminuric and between 30mg and 300 mg/24h for microalbuminuria.

Homocysteine quantification

Determination of total plasma homocysteine was performed by the Abbott Diagnostics fluorescence polarization immunoassay. Plasma concentrations of total homocysteine were calculated by Abbott Axsym® and high values were considered to be those greater than 15 µmol/L, according to values proposed in a recent meta-analysis.

Cystatin C Quantification

Quantification of cystatin C was performed using the Enzyme Linked Immunosorbent Assay (ELISA) method, Cystatin C Kit (Human), catalog ALX-850-292, and brand Enzo Life Sciences. This test was based on the identification of antigens by antibodies marked with an enzyme, which acted on its substrate and caused the color of the chromogen (colorless substance that when oxidized by the enzyme causes a change in its color) to change.

p66Shc gene expression in peripheral blood cells and urinary sediment cells

The total RNA in peripheral blood cells was extracted using the following method: total RNA was isolated from leukocytes contained in peripheral blood obtained through hemolysis by centrifugation at 2500 RPM for 15 minutes, using the TRIzol method (TRIzol LS Reagent, Thermo Fisher cat. no. 10296-010), and according to the manufacturer's protocol. To extract total RNA from the urine sediment, samples (15 mL) were initially centrifuged at 2500 revolutions per minute (RPM) for 10 minutes at 4ºC to obtain the urine sediment. The supernatant was then discarded and 1 ml of TRIzol was added to the cell pellet. The extraction process followed the standard protocol instructions for TRIzol. Total RNA concentration was estimated by spectrophotometric reading using a NanoDrop equipment (ThermoFisher Scientific - Waltham, Massachusetts, USA). Samples of total RNA (starting amount 1 μ g) obtained from peripheral blood and urine sediment were converted into cDNA using SSIII First Strand qPCR Supermix (Invitrogen, cat. no. 11752050), according to the manufacturer's protocol. RT-qPCR, p66Shc gene expression was evaluated by real-time PCR (RT-qPCR). The specific primers for each selected gene were designed with the aid of the Primer3 Input 0.4.0 software program, available at http://frodo.wi.mit.edu/primer3/. The designed primer sequences were then checked for specificity by the Primer-BLAST program, available at http://www.ncbi.nlm.nih.gov/tools/primer-blast. To normalize the relative expression of the target genes, expression values of the reference gene RPL13A were used.

Sequence of specific primers and their amplicons: p66Shc, *Forward*: GCTGCATCCCAACGACAAAG, *Reverse*: GAGTCCGGGTGTTGAAGTCC, *pb*: 113

Statistical analysis

The results were expressed as mean ± standard deviation (SD). These were compared using unpaired student's t-test and Mann-Whitney for non-parametric data. These analyses were performed with the aid of the computer program GraphPad Prism (GraphPad, version 7.0, USA). The significance level was set at 5% (descriptive p <0.05). The sample size was determined by calculations performed in the computer program GPower 3.1.

Results

A total of 66 volunteers were evaluated, of which 37 healthy participants - CTL and 29 patients with T2DM. Within the CTL group, there were 55% female participants and 45% male participants. The mean age was 45±14 years with a predominance of Caucasian ethnicity (89%), and 5% of the total were hypertensive (***Table 1***).

Table 1. Anthropometric Data of Participants in the Healthy Group (CTL)

Parameters	
Gender (%)	
Female	55
Male	45
Age (mean±SD) years	45±14
Ethnicity (%)	
Black/Brown	11
Caucasian	89
Arterial Hypertension (%)	
Yes	5
No	95
Don't know	0

Legend: Standard Deviation (SD).

In the T2DM group, 60% of the participants were females and 40% were males. The mean age was 63±8 years and the predominant ethnicity was Caucasian (75%). The majority of the participants in this group reported having arterial hypertension (60%), 20% were not hypertensive and another 20% reported not knowing this information. When the time since T2DM diagnosis was evaluated, was found that 80% of the participants had been diabetic for at least 5 years, 5% for 5 to 10 years and 15% for more than 10 years (***Table 2***).

To characterize the studied sample, blood glucose measurements of the CTL and T2DM groups (87±11 vs. 152±71 mg/dL, *p<0.05) as well as Hb1Ac (5.5±0.4 vs. 7.5±1.9%, *p<0.05) were performed. A statistical difference between the groups, due to high values of these biochemical markers, was expected and observed. BMI values were compared between groups (CTL: 27±5 vs. T2DM: 28±5 Kg/m2) (***Figure 1***).

Table 2. Anthropometric Data of Participants in the Diabetic Group (T2DM)

Parameters	
Gender (%)	
Female	60
Male	40
Age (mean±SD) years	63±8
Ethnicity (%)	
Black/Brown	25
Caucasian	75
Arterial Hypertension(%)	
Yes	60
No	20
Don't know	20
Time of disease (%)	
0-5 years	80
5-10 years	5
>10 years	15

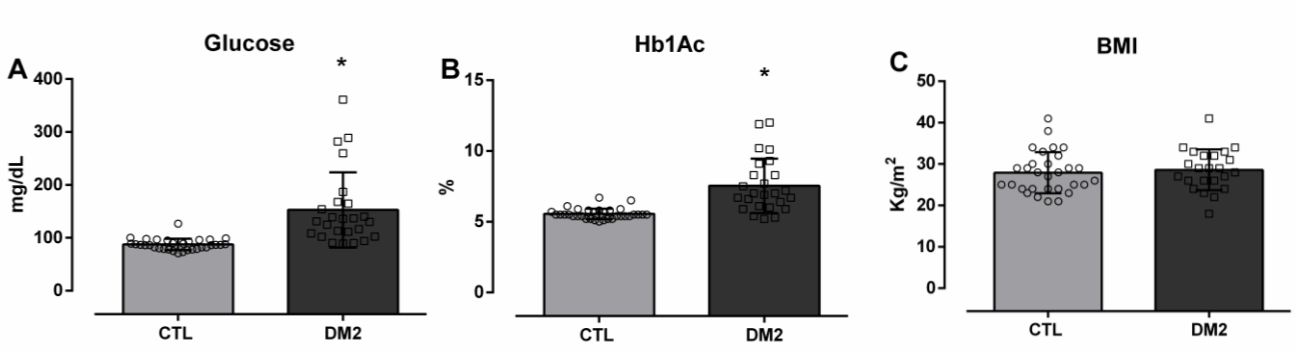
Legend: Standard Deviation (SD).

Figure 2 shows the evaluations of classic biochemical markers of renal function. Alterations in the values of plasma creatinine (A) (CTL 0.80±0.20 vs. T2DM 0.87±0.29 mg/dL), urinary creatinine (B) (CTL 134±85 vs. 130±69 mg/dL), urea (C) (CTL 32±12 vs. T2DM 53±83 mg/dL), proteinuria (D) (CTL 12.2±10.2 vs. 23.1±48.1 mg/dL) and GFR (F) data were not observed. We only verified alterations in the values of microalbuminuria (D) (CTL 20.3±37.0 vs. T2DM 23.4±24.7 mg/L, *p<0.05).

Figure 3 illustrates p66Shc gene expression in blood (A) and urine (B) samples. It was observed that there was no statistical difference in the expression of this gene between the CTL group and T2DM group. However, p66Shc expression in blood was 3.6 times higher in diabetics (T2DM 0.024±0.079) than in healthy participants (CTL 0.0069±0.0176 $2^{-\Delta CT}$). In urine, p66Shc expression was 1.48 times higher in diabetics (0.0276±0.0541) than in CTL (0.0186±0.0219 $2^{-\Delta CT}$).

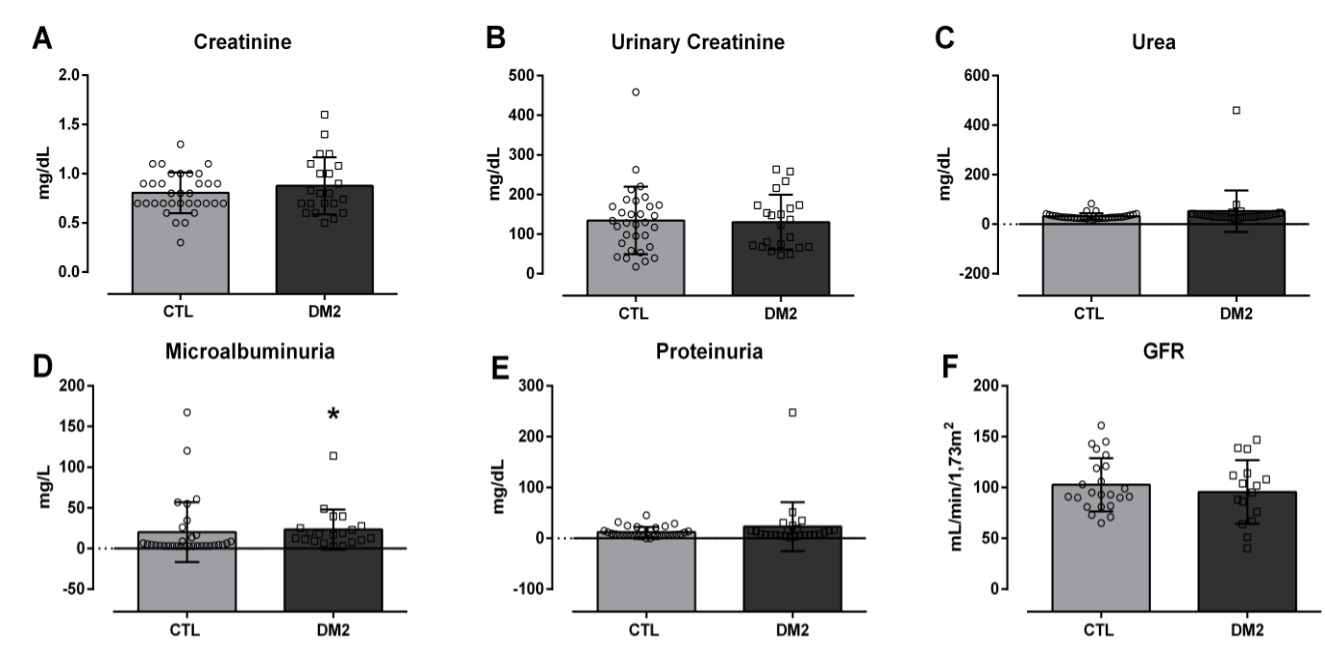
When measuring Hcy and cystatin C concentrations, no significant alterations between groups were identified: Hcy T2DM (22.20±4.15 µmol/L) and CTL (19.90±5.61 µmol/L), cystatin C (T2DM 1.05±0.15 vs. CTL 1.02±0.14 mg/dL) **(*Figure 4*).**

Figure 1. Values of Blood Glucose (A), Glycated Hemoglobin (Hb1Ac) (B) and Body Mass Index (BMI) (C) of Healthy Participants (CTL) versus Diabetic Participants (T2DM).



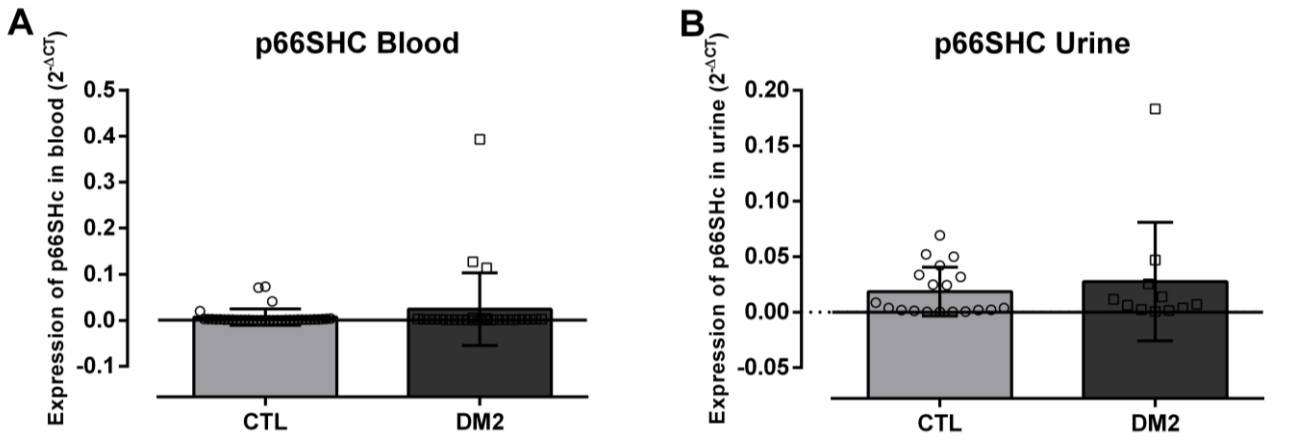
Legend: Values Expressed as mean±SD. *p<0.05 vs. CTL. Unpaired Student's t-test.

Figure 2. Values for Plasma Creatinine (A), Urinary Creatinine (B), Urea (C), Microalbuminuria (D), Proteinuria (E) and Glomerular Filtration Rate (GFR) (F) of Healthy Participants (CTL) versus Diabetic Participants (T2DM).



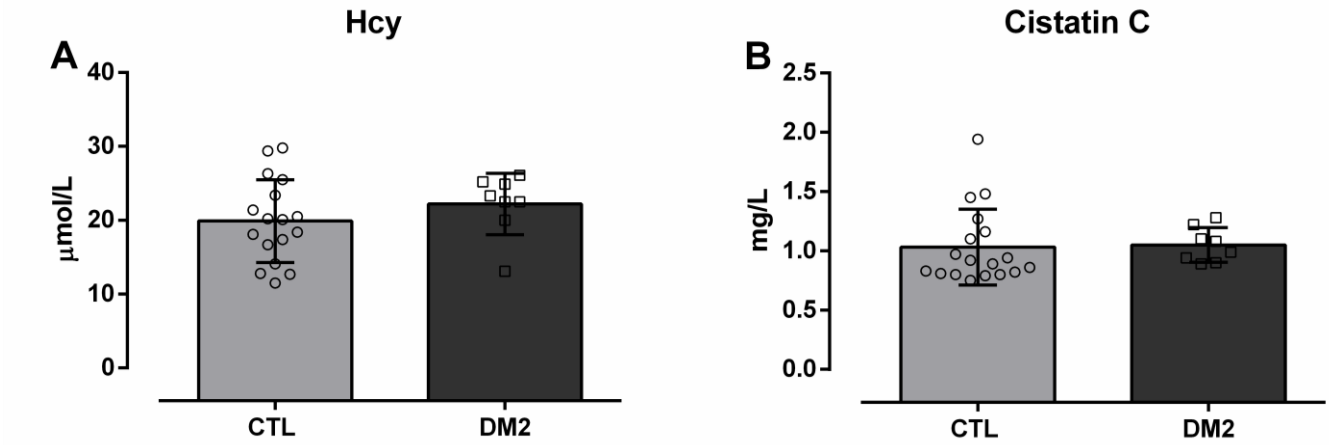
Legend: Values Expressed as mean±SD. *p<0.05 vs. CTL. Unpaired Student's t-test.

Figure 3. p66Shc Gene Expression Values (2- Δ CT) in Healthy Participants (CTL) Compared to Diabetic Participants (T2DM) in Blood (A) and Urine (B) Samples.



Legend: Mann-Whitney test.

Figure 4. Representative Graphs Referring to the Measurement of Homocysteine (A) and Cystatin C (B) of Healthy Participants (CTL) versus Diabetic Participants (T2DM).



Legend: Values Expressed as mean±SD. *p<0.05 vs. CTL. Mann-Whitney test.

Discussion

The concept of liquid biopsy is based on the use of liquid/fluid samples (especially from peripheral blood or urine) to detect early changes in the expression of a gene of choice, through the evaluation of cell-free nucleic acids. This is a new approach that has already been studied in cancer and is able to indirectly reflect the future expression of proteins involved in the formation of tumors or changes in tissue function. Furthermore, the fundamental idea of this method is to be less invasive than traditional disease probing methods. This method still needs to be standardized for the consolidation of its diagnostic and/or prognostic use, and therefore, the efforts for this elucidation are valid. This study evaluated a biomarker that actively participates in the oxidative stress pathway, to propose an early marker of renal changes in diabetics patients.[13-15]

Oxidative stress in diabetic patients is higher when compared to healthy patients, since the formation of intracellular ROS - considered a common route in renal injury induced by hyperglycemia - is greater in these patients and increases proportionally with the development of the disease.[16] As previously described, p66Shc is a protein responsible for modulating the production of mitochondrial ROS, causing the stressed cell to produce more ROS, providing positive feedback that results in cell apoptosis. Despite the studies identifying this activation of p66Shc associated with the pathophysiology of DN in endothelial cells, this study evaluated whether this alteration also occurred in peripheral blood leukocytes and urinary sediment cells, in view of the ease and importance of using liquid biopsy for monitoring of patients. Liquid biopsy, originally studied in oncology, consists of isolating circulating cells as a source of genomic and proteomic information.[17]

The increase in p66Shc gene expression in this study was not significant. However, further analysis of the research showed that the p66Shc gene expression in the blood was 3.6 times higher in

diabetics compared to healthy individuals, and in urine, this difference was 1.48 times greater under the same comparison. This suggests that in as number of patients increases, a significant increase in this gene expression would be seen. The study of p66Shc gene expression in diabetic patients without diagnosed kidney injury had not been explored, at least to our knowledge.

The data of this study showed that all diabetic patients had high glucose and glycated hemoglobin levels, adequately supporting the purpose of this research. At the same time, classic markers of the onset of kidney disease, creatinine, proteinuria, and microalbuminuria were evaluated, and GFR was calculated. In all these measurements, it was observed that the patients did not have kidney disease prior to the evaluations.

As known, cystatin C is a current and accurate marker of the assessment of initial renal function loss, as it is freely filtered by the glomerulus and subsequently reabsorbed in the proximal tubule. So, the serum cystatin C levels reflect glomerular filtration- its increase in serum means a reduction in GFR.[18] The patients in this study did not show any increase in the measurement of this marker, confirming that the diabetic group did not have nephropathy.

The participants with T2DM did not show an increase in Hcy measurements, which indicated the absence of endothelial injury. In this study, there was a subtle alteration in p66Shc gene expression, without significant changes in Hcy levels. The relationship between p66Shc overexpression and increased Hcy levels has been previously described in patients with confirmed endothelial dysfunction. The main cause of this relationship is closely linked to DNA methylation, promoted by p66Shc.[19, 20] Our data suggest that the increase in p66Shc expression is the mechanism responsible for the initiation of the deregulation of Hcy synthesis. We believe that the consolidation of the over-expression of this gene increases DNA methylation and causes, in later stages of T2DM, irreversible endothelial changes, followed by kidney damage. On the other hand, when there are high levels of the Hcy precursor, S-Adenosilhomocysteine (SAH), there is an increase in the production of ROS and in the expression of p66Shc in endothelial cells, that is, there is self-regulation between the expulsion of this gene and the increase in Hcy.[21]

The relationship between p66Shc expression and diabetic nephropathy is evident, as shown in studies in mice. These studies have shown that the deletion of this gene prevents endothelial dysfunction induced by hyperglycemia, in addition to reducing the oxidative stress of cells, which prevented the alteration of renal structure and function in these animals.[22-24] The endothelial and myoblastic cells of p66Shc knockout mice demonstrated a lower rate of apoptosis in ischemic conditions, thus proving the role of p66Shc in cell survival in response to hypoxia.[25] Another protein involved in renal damage to DN is the hypoxia-inducible factor (HIF-1 α). The relationship between p66Shc and HIF-1 α has been described by proposing a pathway in which HIF-1 α, stimulated by T-cell hypoxia, activates p66Shc, which contributes to the release of extracellular vascular endothelial growth factor (VEGF) and, is one of the responses to low oxygenation mediated by HIF-1 α. In addition, p66Shc itself is stimulated by oxidative stress induced by hypoxia, and triggers cell apoptosis.[26] Our study identified the subtle elevation of p66Shc gene expression in diabetic patients who, as previously described, are in oxidative imbalance due to hyperglycemia, hyperinsulinemia, and insulin resistance. Therefore, it can be suggested that the pathway explained above is activated.[9]

Expression of the p66Shc protein in peripheral blood and in renal tissue of diabetic patients had already been studied, under conditions of already established kidney injury. The authors found an increase in the expression of the p66Shc protein and suggested that the evaluation of its expression in peripheral blood could be used as a potential biomarker of the progression of kidney injury mediated by increased oxidative stress.[27]

Considering that the oxidative stress pathway is activated by hyperglycemia, we suggest that in our patients there is a synergism between the hyperexpression of markers against decapentaplegic homolog 1 (SMAD1), which are intracellular proteins capable of regulating transcription factors and expression of target genes, associated with that of p66Shc, with the first promoting mesangial expansion and the second mediating oxidative imbalance. Positive feedback between these two pathways may be responsible for the gradual and silent loss of kidney function. Therefore, we suggest that minor changes in p66Shc gene expression may signal the dysregulation of the oxidative system and, thus, lead to late kidney damage.[21, 23, 28, 29]

This study showed that there was no significant p66Shc gene expression in peripheral blood and urine samples of diabetic patients without kidney injury in comparison with healthy donors. However, in our experimental conditions p66Shc gene expression is slightly elevated in T2DM group. There was no association between increased gene expression and the other laboratory variables that were studied. We believe that increasing the number of patients may elucidate the viability of the data.

The limitation of this study was the small sample size and the difficulty in assessing gene expression in urine samples. We are certain that the use of specific extraction kits for samples of low cellularity, such as urine samples, will facilitate this type of study in this biological matrix.

Summary – Accelerating Translation

Título: Estudo transversal da expressão do gene p66Shc em biópsia líquida de pacientes diabéticos. É possível prever o início da doença renal? O objetivo deste estudo foi avaliar a expressão do gene p66Shc como um possível biomarcador precoce de disfunção renal em pacientes com diabetes, utilizando amostras líquidas de sedimento urinário e sangue periférico. Foram avaliados 29 pacientes diabéticos e 37 doadores saudáveis, estes foram recrutados no ambulatório do Centro Universitário FMABC. Foi avaliada a expressão do gene p66Shc pela técnica de RT-qPCR em amostras de urina e sangue periférico de pacientes diabéticos e foram comparadas com doadores saudáveis. Não foi observado alteração da expressão do gene p66Shc em amostras de pacientes diabéticos em comparação com doadores saudáveis. No entanto, a expressão de p66Shc no sangue de diabéticos foi 3,6 vezes maior em diabéticos (0,02417±0,078652- ΔCT, n=29) do que em participantes saudáveis

(0,00689±0,01758, n=37) e na urina foi 1,48 vezes maior no grupo de diabéticos (0,02761±0,05412- ΔCT) do que no grupo CTL (0,0186±0,02199). Portanto, não houve expressão significativa do gene p66Shc em amostras de sangue periférico e urina de pacientes diabéticos sem lesão renal em comparação com doadores saudáveis, embora haja uma tendência desse gene participar do desequilíbrio oxidativo presente no diabetes.

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Acknowledgments

We thank the Fundação de Amparo a Pesquisa do Estado de São Paulo (FAPESP), for financial support in this study

Conflict of Interest Statement & Funding

The Authors have no funding, financial relationships or conflicts of interest to disclose.

Author Contributions

Conceptualization: DPS, FLAF, GLV. Data Curation: MMP, BCAA, FLAF, GLV. Formal Analysis: GLV. Funding Acquisition: DPS, FLAF, GLV. Investigation: DPS, MMP, BCAA, JFAE, JRSR, CGCA, VLM, MISM, LAMM, NM. Methodology: MMP, BCAA, JFAE, JRSR, CGCA, VLM. Project Administration: DPS, FLAF, GLV. Resources: MMP, FLAF, GLV. Software: BCAA, GLV. Supervision: FLAF, GLV. Validation: MMP, BCAA, FLAF, GLV. Visualization: DPS, MMP, BCAA, JFAE, JRSR, CGCA, VLM, MISM, LAMM, NM, FLAF, GLV. Writing – Original Draft Preparation: DPS, FLAF, GLV. Writing – Review & Editing: DPS, MMP, FLAF, GLV.

Cite as

Simões DP, Perez MM, Alves BCA, Encinas JFA, Raimundo JRS, Arcia CGC, et al. A Cross-Sectional Study of p66Shc Gene Expression in Liquid Biopsy of Diabetic Patients. Is It Possible to Predict the Onset of Renal Disease?. Int J Med Stud. 2022 Oct-Dec;10(4):387-94.

ISSN 2076-6327

This journal is published by Pitt Open Library Publishing

IJMS INTERNATIONAL JOURNAL of MEDICAL STUDENTS

Review

Elective Courses in Global Surgery for Undergraduate Medical Students: A Narrative Review and a Proposal for European Universities

Giovanni Rossi,[1] Gioele Fusato,[1] Tindara Scirocco,[1] Paolo Rodi,[2] Simone Villa,[3] Mario C. B. Raviglione.[4]

Abstract

Global surgery (GS) is the discipline of improving health by expanding universal access to surgical care. GS is an essential part of the global health (GH) concept, but it is almost invariably neglected in academic settings. This review assesses the engagement of undergraduate medical students in the field of GS. PubMed, Embase, and Web of Science were searched with focus on electives organized by universities and only eight results were found. The scientific literature on this topic is scarce and uneven, and the number of students involved in these experiences is considerably low. Although few, the existing electives prove that building sustainable and useful GS projects is possible and that both students from high-income countries (HICs) and low-income and middle-income countries (LMICs) can extensively benefit from these experiences. Given the currently low involvement of European universities and medical schools, of which the authors are part, this review aims at encouraging European universities to organize GS electives for their students. In addition, this review suggests key activities to undertake in such electives including theoretical sections, research projects, and bilateral international rotations between HICs and LMICs.

Key Words: Medical Student; General Surgery/education; Global Health; International Cooperation; Curriculum (Source: MeSH-NLM).

Introduction

Global surgery (GS) is an area of study, research, practice, and advocacy that places priority on reducing surgical inequities and on addressing surgical conditions, which constitute a third of the global burden of disease worldwide.[1,2] GS aims to ensure adequate, quality, safe, timely, and affordable surgical care universally, with a special emphasis on underserved populations and populations in crisis.[1] These are often those living in low-income and middle-income countries (LMICs), although high-income countries (HICs) are also hosting marginalized populations that can benefit from equitable access to surgery.[3,4] Aligned with the principles of global health (GH), GS is a multidisciplinary approach incorporating obstetrics and gynecology, perioperative care, anesthesia, palliative care, rehabilitation, emergency medicine, nursing, and other health-related practices, such as public health, population-level preventive strategies, economics, data sciences, digital technology, social sciences, and pharmacy.[1]

No one had ever considered surgery as a major international health issue until 1980,[5] when World Health Organization (WHO) General Director defined it as the "most serious manifestation of social inequity in health care".[6] However, surgery remained "the neglected stepchild of global public health",[7] at least until 2006, when it was first included in the second edition of the Disease Control Priorities Project.[8] A key turning point was the establishment of the Lancet Commission on Global Surgery (LCoGS) in 2014,[9] which drew up guidelines and goals to be achieved by 2030 to reduce the global surgical burden. These were soon adopted within the World Health Assembly (WHA) resolution no. 68.15,[10] and were later revised and updated.[11,12] Since the report of the LCoGS, GS has extensively grown in consensus within the GH community.[13] Nevertheless, the goal of ensuring universal access to surgical care is yet to be achieved.[14]

To increase the specialist surgical workforce density and the surgical volume in every country by 2030, as advocated by the LCoGS,[9] it is essential to engage future surgeons. They are none other than the current undergraduate medical students.[15] This paper assesses the role that European students can play in GS and how they can already contribute to addressing GS challenges. The lack of exposure to GS during the standard medical student curriculum is common around the world,[16] and especially among European students as the authors' experiences show. Literature on this topic is scarce and disorganized.

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Editor: Francisco J. Bonilla-Escobar
Student Editors: Andrew Thomas, Nikoleta Tellios & David Ulrich Dalle
Copyeditor: L V Simhachalam Kutikuppala
Proofreader: Laeeqa Manji
Layout Editor: Ana Maria Morales

Submission: Jul 2, 2022
Revisions: Aug 30; Nov 21; Nov 22, 202
Responses: Sep 5; Nov 27, 2022
Acceptance: Aug 25, 2022
Publication: Dec 2, 2022
Process: Peer-reviewed

The purpose of this paper is to review existing GS initiatives undertaken by medical schools that support the practical involvement of undergraduate students. Ultimately, the article aims to create opportunities for European universities and to encourage them to engage in such a way that European students can be exposed to – and consider – GS as one career option, thereby contributing to the universal access goal promoted by GH.

Methods

This review adheres to the Scale for the Assessment of Narrative Review Articles (SANRA) for IJMS guidelines.

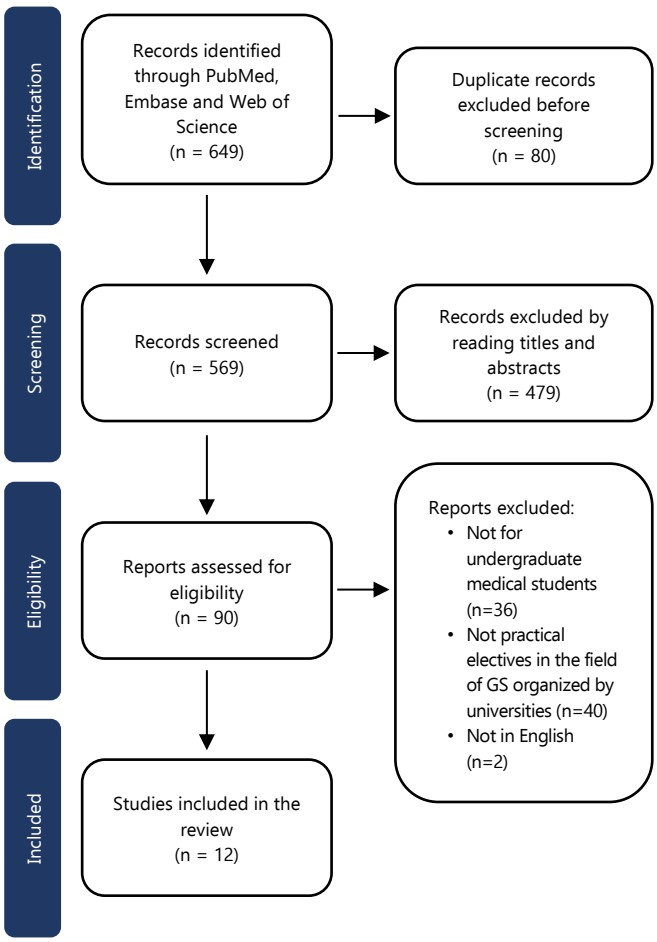
We designed a search strategy to identify peer-reviewed articles focused on electives for undergraduate medical students in the field of GS, which included practical involvement and that were organized by universities. We included articles written in the English language only. We searched PubMed, Embase, and Web of Science, to identify articles published from 1950 to 2022. Additional articles were identified from the retrieved articles' references. The literature was last checked on 30th June 2022.

The search strategy and keywords are as follow. PubMed search strategy: (general surgery[MeSH Terms]) AND ((education, medical, undergraduate[MeSH Terms]) OR (faculty, medical[MeSH Terms]) OR (schools, medical[MeSH Terms]) OR (students, medical[MeSH Terms]) OR (curriculum[MeSH Terms])) AND ((Global Health[MeSH Terms]) OR (international cooperation[MeSH Terms]) OR (international educational exchange[MeSH Terms]) OR (medical missions[MeSH Terms])). Embase search strategy: ('general surgery'/de OR 'surgery'/de) AND ('medical student'/de OR 'medical school'/de OR 'medical education'/de OR 'clinical education'/de) AND ('global health'/de OR 'international cooperation'/de OR 'rural health care'/de OR 'middle income country'/de OR 'low income country'/de OR 'developing country'/de). Web of Science search strategy: ("global surgery" OR "general surgery" OR "surgery") AND ("medical student" OR "medical school" OR "medical education" OR "clinical education" OR "undergraduate medical students") AND ("global health" OR "global surgery" OR "international cooperation" OR "rural health care" OR "middle income country" OR "low income country" OR "developing country" OR "high income country").

GR and GF independently read titles and abstracts to identify eligible and appropriate articles. Disagreements were solved by TS. Data extraction from the assessed articles was performed by GR, GF, and TS independently in their entirety.

Data extracted focused on the practical organization of projects described in said articles. Categories of analysis include location and setting, participants, program structure, formative objectives, and costs and funding. The outcome of these projects is also highlighted, and both positive results, as well as limitations, are assessed.

Figure 1. Flow Diagram of the Articles' Screening and Inclusion Process.



Results

The search strategy retrieved 649 results, of which 12 studies were included in this review (***Figure 1***).[17-28] In total there were eight projects – labeled alphabetically from A to H – in GS were been offered worldwide by universities to undergraduate medical students (***Table 1***), as five articles referred to project A.[17-21] While five projects (from A to E) were explained in detail, information on the remaining three was superficial and fragmented (projects from F to H).

Organization of the Projects

Location and Settings

All electives included were organized by a university in a HIC of the "Global North": four in the United States of America (projects A, B, D, and F), two in Sweden (projects D and E), two in the United Kingdom (projects G and H), and one in Canada (project C). Sister institutions involved in these courses were either universities (n=5), hospitals (n=6), and/or non-governmental organizations (NGOs) (n=2). Academic institutions from LMICs were in Haiti (one in project C), Rwanda (one in project C), Zimbabwe (one in project D), and Colombia (two in project F). Hospitals directly involved were in Haiti (one in project A), India (one in project B), Rwanda (one in project H), Tanzania (one in project H), and

Table 1. Characteristics of Elective Courses in Global Surgery for Undergraduate Medical Students Organized by Universities Available in the Literature.

	Institutions involved	Reported period	Students involved	Structure of the elective
Project A[17-21]	- Emory University School of Medicine (USA). - Project Medishare for Haiti (NGO). - Hôpital St. Thérèse in Hinche (Haiti).	2008-2013, every year. From 2013, until unspecified data.	Each year, a team of 10 3rd year HICs' students is selected. 2nd, 3rd, and 4th year students.	Pre-departure part: Suture labs. Basic surgical skills. Sterile technique. Abroad part: - An elective week of the mandatory surgical clerkship. - Students can evaluate patients, propose a treatment plan to the attending surgeon, order the necessary laboratory tests and imaging studies for the potential surgical operation, and take care of patients' postoperative care. Pre-departure part: - 4th year students are involved in peer-tutoring activities and support younger students in raising funds and materials. Abroad part: - 4th year students spend 3-4 weeks in Haiti; during the first week, they are involved in setting up the operating rooms and other logistical issues of the elective. - 2nd and 3rd year students spend 1-week of practical internship in Haiti (as before 2013). Back home: - Students must examine clinical cases observed in Haiti and elaborate reviews, supporting their work with references to the scientific literature.
Project B[22]	- Oregon Health and Science University (USA). - Sanjay Gandhi Postgraduate Institute of Medical Sciences (India).	2009-2015, every year.	Multi-year project (only HICs' students): - 1st and 2nd year: junior seminar course (open to all students of the course). - 3rd year: senior clinical lecture (open to all students of the medical school). - 4th year: global clinical elective in India (open to a selected few).	Theoretical part (pre-departure): - Lectures, lessons, and seminars. - Topics: global burden of surgical disease, financial and societal costs, ethics of international volunteerism and research, disaster response, logistical challenges of building emergency, surgical and obstetrical capacity in developing world. Practical part (abroad): - 1-3 months of internship in general surgery in India. - Students participated in morning rounds, and in scheduled and emergency operations.
Project C[23]	- McGill University (Canada). - Université Quisqueya (Haiti). - University of Kigali (Rwanda). - Medical student 4 Haiti (no-profit).	2012-2016, every year.	Multi-year project: - Near-peer teaching approach. - Rwandan and Haitian students in Canada for 3 weeks.	Activities for LMICs' students in Canada: - Structured near-peer teaching sessions: lectures and lab demonstrations. - Research methodology. - Anatomy dissection. - Clinical simulation activities. - Clinical shadowing with pathologists and trauma surgeons. Since 2016 the project has expanded: - Extended theoretical-educational curriculum. - Involvement of French students (which French university is not specified).
Project D[24]	- Lund University (Sweden). - Harvard University (USA). - University of Zimbabwe.	2015-2017, every year.	- Final year medical students. - Total of 50 students in 3 years (14-18 students each year): 42 from Sweden, 4 from the USA, and 4 from Zimbabwe.	Theoretical part: - 2 initial weeks of didactic coursework: lectures, case studies, and small group discussions, held by international guests. - HICs' and LMICs' students all together in Sweden. Practical part: 2 weeks. - Swedish and American students traveled to Zimbabwe, where they joined surgical, Ob/Gyn, anesthesia, and pediatric (only in the 2nd and 3rd editions) teams; there was 1 accompanying faculty member for every 4 international students. - Zimbabwean students had a clinical experience in a Swedish hospital. Capstone project: 1 final week. - Only for American and Swedish students. - In order to synthesize practical experience and expand knowledge on a specific topic in GS.
Project E[25]	- Karolinska Insitutet (Sweden). - Soroti Hospital (Uganda). - Mulago National Referral Hospital (Uganda).	2016-2020, biannually.	- 4th year medical students. - Only from Sweden.	Theoretical part (pre-departure): Lectures and seminars in Sweden. Practical part (abroad): - 2-week clinical rotation in Uganda. - Supervision and tutoring from both Swedish and Ugandan surgeons. - Observation and, possibly, assistance in ward rounds, in ward duties and in OR of general surgery, obstetrics, surgical oncology, cardiothoracic surgery, burns and plastic surgery, pediatric surgery, and orthopedic surgery.
Project F[26]	- Rutgers Robert Wood Johnson Medical School – RWJMS (USA). - Universidad del Valle Medical School (Colombia). - Universidad de Antioquia (Colombia).	2015-2016.	- Students interested in GS in two general programs on GH. - Over 2 years, 6 out of 16 selected students have chosen to investigate issues related to GS. - 1st program: "Distinction in Global Health" (DGH): 1st year students, no previous GH experience required (only 1 GS student). - 2nd program: "Chancellor's Global Scholars" (CGS): accepted medical students, prior to matriculation, with previous GH experience required (the remaining 5 GS students).	- One local or transnational practical experience in the DGH program, or two transnational practical experiences, during the first and graduating years of medical school, in the CGS program. - American students collaborate with Colombian students, faculty tutors, and international teachers (RWJMS assistant professors of surgery and Colombian university surgeons) in identifying areas of GS research implementation need. - Field research, together with local partners, takes place in the summer, for one month. - Upon their return to the USA, students have to carry out their research through abstracts, posters, podium presentations at national/international conferences, and manuscripts.
Project G[27]	- Cambridge University (UK). - National Institute for Health Research Global Health Research Group for Neurotrauma (UK). - LMICs' partners not defined.	Before 2018 (not better specified).	- HICs' students travel to LMICs, where they can work with local students. - Students' university year not specified.	Online "Research for Publication" courses: - In collaboration with the British Medical Journal. Open to both HIC and LMIC students. Research project on neurotrauma: - Active involvement in the planning and management of the project. - HICs' and LMICs' students learn to manage the different stages of the development of a research project.
Project H[28]	- Oxford University (UK). - Hospitals in Tanzania and Rwanda.	2017-now.	- HICs' students travel to LMICs, where they can work with local students. - Students' university year not specified.	Participation in research projects on pediatric surgery epidemiology (Oxford Paediatrics Linking Oncology Research with Electives – OxPLORE): - Cross-sectional observational study. - Analysis of the variation, in contexts with different resources, of incidence, management and postoperative outcomes of pediatric patients with Wilms tumor, neuroblastoma, or rhabdomyosarcoma. - Scientific publications,[29,30] and presentation of results at international conferences.

Uganda (two in project E). Projects A and C had NGOs involved, of which the one operating in project C was a non-profit student association.

Participants

Five projects had detailed information on the year of attendance of participants (projects from A to E). Projects B, C, and F involved the same students in multi-year projects; projects A, D, and E involved students attending one of the last years of their education for only one year. Students from the "Global North" were participating in all projects and a field trip to LMICs was always planned except for project C. Only in projects C, D, and G, students from the "Global South" were offered to attend field trips to the "Global North"; project G lacked clarity on the role and activities performed by said students.

Program Structure

Electives from A to E were structured in an academic module, organized at HIC's institutions, followed by a period on the field. The first learning module consisted of either lectures or seminars held by GS experts (projects A, B, D, and E) and a practical course on basic surgical skills (project A). In projects C and, partially, A, this module was organized following a near-peer teaching model. The on-field module was organized as a rotation of students in hospitals either in LMICs (projects A, B, D, and E) or HICs (electives C and D) with roles ranging from simple observation to surgeon assistance. Electives from F to H focused on GS research, where students were actively involved in the design and management of a research project (elective G) and in the production of scientific literature (projects F and H).

Formative Objectives

With regards to projects A to E, formative objectives for students from HICs were aimed to improve their clinical skills, to educate them in the context of GS, to expose them to the possibility of pursuing a career in this field, and to raise awareness of the social, cultural, and economic aspects underlying healthcare. Formative objectives for students from LMICs were only reported for projects C and D and they were limited to involving students during university lessons and clinical rotations in HICs' facilities. In project A, attention was paid to the assessment of the needs and possible benefits that HICs' medical students could bring in LMICs' context, thanks to a preliminary inspection at the LMICs' institutions carried out by physicians with proven experience in the GH field.

Electives from F to H focused their objectives on research to allow both LMICs' and HICs' students to acquire the ability to organize and manage research projects (especially in the GH field), produce scientific literature, and present it at international contests, thereby improving their communication and public speaking skills. In addition, these electives intended to provide students with the opportunity to start a career in the context of GS and to weave international relations. Only project H had the objective to implement and support research in LMICs.

Costs and Funding

Data about costs and their coverage is provided only for projects A, D, and F. Transport accounted for the largest share of the costs, e.g., 24,000 USD corresponding to 2/3 of the total budget of project A. Expenses were, generally, covered by funds obtained through donations, independent fundraising, and/or solicitation of family and friends. For example, for elective D, costs were covered by grants from the Swedish Foundation for International Cooperation in Research and Higher Education and by reimbursements from Lund and Harvard University (also for Zimbabwean students). Instead, elective F yielded two inner projects, the Chancellor's Global Scholars (CGS) program and the Distinction in Global Health (DGH) program. For the CGS program, institutional funding support of 5,000 USD was provided for each student, derived from a 40:60 split between the Health Sciences Chancellor's Office, and the United States Agency for International Development – Research and Innovation Fellowship Program. For the DGH program, no funds were earmarked, and students were guided in applying for grants from external and intramural sources and were ultimately awarded a total of 1,000 USD through the Rutgers Intelligence Community Center for Academic Excellence Scholarship.

Outcomes of the Projects

Positive Results

Data regarding the benefits acquired by students from these experiences are available only for electives A to E. Even if all participants declared to be satisfied, the evaluation of the impact on the students' careers is relatively complex. Regarding influence on career, project B suggested that this experience was a determining factor in the choice of participating students' careers. Instead, project D stated that the data obtained are not yet sufficient to declare the role of the elective in the career choices of the students involved. In terms of the evaluation of theoretical learning, project C proposed a test to evaluate theoretical training. Electives D and E proposed a test before the elective and one thereafter, with the aim of comparing the results. Project A reported considerable difficulties in acquiring data on students' learning. In general, evaluation outcomes were positive. In the assessment of relational and practical skills acquired, electives A and B reported major improvements in interpersonal skills acquired by participating students. Study C investigated these improvements through an interview, while projects D and E did the same through questionnaires. In addition, positive results of elective H can be found directly in the literature, as this project led to the publication of a few papers.[29,30]

Limitations

The main limitations recognized were poor or incomplete experience-based data in projects from A to D, and difficulties in raising funds in project D. In addition, the existence of negative implications related to the decision to involve students and non-doctors for the host countries should be evaluated, i.e., projects A, D, and E.

Discussion

This review shows that projects dedicated to medical students in the field of GS are few and uneven, with a small number of HICs' students involved, especially from Europe, and even fewer LMICs' students. Nonetheless, these electives can be strategic starting points to develop new and more effective ones. Upon these instances, European institutions should promote similar projects and should foster European students' involvement in GS, which is now particularly scarce.

European Universities

While in the reviewed electives, NGOs and single hospitals occasionally took part in organizing the projects. We propose that universities and related academic institutions should be the ones to develop electives in GS, in close collaboration with LMICs' institutions. In Europe, student associations, which are active in the field of GS and organize initiatives for medical students, such as the American InciSioN,[31,32] and GSSA,[33] are less common. At the same time, both European students and universities are already familiar with, and inclined to, international collaboration as a result of the decennary Erasmus+ project.[34,35] Therefore, universities are the institutions that could better define uniform educational objectives for these electives and appropriate training paths for both HICs' and LMICs' students.[19,36,37]

Benefits for HICs' students

There seems to be a favorable consensus in the general GH literature regarding the usefulness of these electives for students from the "Global North".[38-40] First, students participating in international electives in the field of GH show improvements in clinical skills and knowledge, reporting greater self-confidence in their ability to collect medical history and in conducting physical examinations.[38,39] Furthermore, the electives help to bring about significant attitudinal changes in the participants, such as the acquisition of a human approach to the patient and his illness, a greater sensitivity to cultural differences, and an awareness of the impact of surgery on the patient's private and social life, as "the most profound lessons of a surgical trip abroad [...] come less from within the walls of the operating room and more from the patients themselves".[40] Finally, these electives are crucial in influencing and directing the career of doctors and surgeons of the future towards GH and GS.[4,39] This would mean not only having surgeons trained to support projects in LMICs, but also having professionals sensitive to the realities of the poorest people in HICs' societies, who do not access the same healthcare as their fellow citizens.[41,42] In conclusion, there will be no future global surgeons suited to the challenges that LCoGS has highlighted without adequate exposure of undergraduate students to GS.

Benefits for LMICs' Students

Unlike the case of HICs' students, the advantages described for the students of the "Global South" appear more uncertain. Although the learning methods proposed to LMICs' students during their stay in the "Global North" were adequate, there was a definite numerical disparity between HICs' and LMICs' participating students. In general, LMICs' students claim to have benefited from the project as far as it concerns their personal and professional growth. This includes the acquisition of new skills, the creation of an international network of relationships, and increased motivation to help their own community.[23] However, only two of the projects assessed involve LMICs' students, and they do so in a limited way. For instance, only 4 out of 50 total participants of project D came from LMICs. The limited engagement of LMICs' students is a fundamental problem in the whole sphere of GH electives.[43-45] There are significant impediments, such as costs,[24,44] the brain drain from rural areas to richer ones (be they in HICs or in the more affluent centers of the LMICs),[46,47] and the limited applicability of the knowledge acquired in resource-rich settings in resource-poor ones.[44] However, "offering opportunities for students and trainees from institutions that are commonly on the receiving end of such collaborations is a necessary step in the achievement of equitable and mutually beneficial institutional partnerships".[48] Doing the opposite means contradicting "the spirit of training in global health".[48]

Global Surgery and Decolonization

Rejecting a heritage of colonialism among the causes of the unbalanced involvement of LMICs' students in GS programs would not do justice to the spirit of GH. Indeed, one needs to acknowledge the frequent persistence of a paternalistic attitude that leads to power imbalances with benefits to individuals at HICs' institutions at the expense of their LMICs' partners.[49] Several proposals have been formulated in the literature on how to decolonize GH.[50,51] In the reviewed electives, there are both positive and negative elements in this sense. Among the latter, there is the lack of long-term planning. Instead, longer-term electives, less scarce and more continuous over time, would sound less like an "honorable vacation" for HICs' students,[52] because they would guarantee useful collaborations within the realities of the "Global South".[53]

In elective D, the staff of the host structure reported a significant increase in work burden due to the presence of HICs' students, while at the same time claiming to be in favor of repeating the experience. This suggests that these electives are not intrinsically perceived as colonialist or paternalistic in attitude; rather the problem lies in the lack of strategies to make them sustainable and mutually helpful. Sustainability can be obtained through shared, continuous, and harmonized planning between involved institutions. In this sense, the experience of project A is significant as HIC's physicians with proven experience in GH have carried out an inspection at the LMIC's institutions (involving the hospital and the ministry of health), to probe their real needs and to plan adequate measures of intervention. This allowed a clear definition of the students' role and adequate training prior to the visit, thereby avoiding unnecessary or harmful activities, or activities they would not otherwise have permission or possibility to practice in their home country.[54] Other positive examples were electives F, G, and H, which involved LMICs' students in research activities, thus enabling them to overcome challenges caused by a lack of infrastructure and resources.

Proposed Structure of the Electives

Based on the results of this review and the need to make GS projects equitable, a GS elective should focus on the following key-points (***Table 2***).

A multi-year approach should be encouraged, such as the one adopted by electives from A to C, as it allows a deeper and a more organic training. This would also guarantee a constant generational change among students, thereby enabling long-lasting bilateral exchanges. In addition to the concrete surgical practice, studying theory and research plays a major role to give a truly global meaning to the surgical elective. They can guarantee a more complete and contextualized education from a socio-cultural, epidemiological, and economic point of view, more than in terms of clinical skills. Therefore, gradual training courses that start from the preclinical years of university should be evaluated.

To introduce the students to the subject, we strongly support the widespread model of lectures and seminars held by experts in the sector, both from LMICs and HICs. Possible topics for a comprehensive curriculum should include the global burden of surgical disease, associated financial and social costs, barriers to access to surgical care, inequality of access to care, essential surgical care, Bellwether procedures and basket of essential procedures, ethics and decolonization of international collaborations, application contexts (e.g., civil trauma, assistance in times of war, disasters response), National Surgical Obstetric Anesthesia Planning, logistical challenges to build emergency surgical and obstetric skills in disadvantaged countries, surgical assistance for marginalized/migrant/poor populations in EU, climate change, and emerging infectious diseases. Theoretical lectures should be delivered via videoconferences and webinars to ensure mutual benefits and sharing of knowledge.[45]

Thereafter, students should be introduced to GS research (as in electives from F to H) by working in groups at their own institution. Each year, they should focus on a specific aspect of the surgical epidemiology of their country of origin. This increases the chances of future strengthening of the scientific workforce and enriches the scientific literature about GS, it teaches students how to conduct research in this field, and it allows them to start building a career in GS and to advocate for greater and more equitable access to essential surgery in their specific region. Moreover, the knowledge obtained can then be transmitted to students of sister institutions during their visits and rotations, according to a near-peer tutoring model (as shown by electives C and, partially, A). This model has been already adopted in various fields of medical education.[55] In particular, it has been shown to be useful in the transmission of socio-cultural issues in medicine,[56] an aspect that makes this choice even more significant in this context.

Concerning rotations at sister institutions, students – both from HICs and LMICs – should have acquired some clinical competence prior to traveling and be exposed to pre-rotation testing to help identify the acquired skills justifying a GS rotation. They should also be attending the last years of university training. On site,

Table 2. Key Points of Proposed Structure of Possible Electives in Global Surgery for Undergraduate Medical Students Organized by Universities.

Multi-year elective	**Pre-clinical years**	**Lectures and seminars** (1st year of university)	- Held by experts in the sector, both from LMICs and HICs. - Via videoconference, so that all students both from LMICs and HICs can participate at the same time. - Possible topics: • Global burden of surgical disease; • Financial and social costs associated; • Barriers to access to surgical care; • Inequality of access to care; • Essential surgical care; • Bellwether procedures and basket of essential procedures; • Ethics and decolonization of international collaborations; • Application contexts (civil trauma, assistance in times of war, disasters response); • National Surgical Obstetric Anesthesia Planning; • Logistical challenges to build emergency surgical and obstetric skills in disadvantaged countries; • Surgical assistance for marginalized/migrant/poor populations in the EU; • Climate change; • Emerging infectious diseases.
		GS research (2nd year)	- Conducted by students working in groups at their own institution. - Each year, focus on a specific aspect of the surgical epidemiology of the home country.
		Near-peer tutoring (3rd year)	- Lectures given by students at this point in the elective to visiting students of the sister institution. - Topic: the research they themselves conducted in accordance with the previous point.
	Clinical years	**Abroad at the sister institution** (4th or 5th year)	Near-peer tutoring - According to the previous point. - One session per week. **Rotation in the surgical ward** - 1-3 months. - Possible tasks of the students: • Medical history, physical examination, and case presentation; • Compilation of medical, hospitalization, and discharge records; • Proposal and discussion of adequate drug therapies; • Preparation of the sterile field; • Assistance at the operating room; • Monitoring of parameters; • Change of dressings in the postoperative period; venous sampling; • Placing catheters in arteries; • Care and suture of small wounds; • Removal of drains and sutures; • Assistance in the non-bloody reduction of fractures and in the placement of plaster casts; • Quality control (review of complications and mortality).
		GS publication (5th or 6th year)	- Ponder on the experience. - Detailed description of all acquisitions and inform the evolution and improvement of future electives.

students can be foremost taught local surgical epidemiology by native colleagues still in the early stages of the elective, through their own research, according to the near-peer model previously described. These classes could be held once a week throughout the rotation. This will allow visiting students to have a complete and in-depth understanding of the situation in the host country, in order to conduct their work with appropriate knowledge.

Students' roles in the ward must be clear and well-defined. Based on this study, students should take up the following tasks at host institutions: medical history, physical examination, and case presentation, individually; compilation of medical, hospitalization and discharge records, individually; proposal and discussion of adequate drug therapies; preparation of the sterile field, and assistance at the operating room; monitoring of parameters, and change of dressings in the postoperative period, individually; venous sampling, individually; placing catheters in arteries, under supervision; care and suture of small wounds, under supervision; removal of drains and sutures, individually; assisting in the non-bloody reduction of fractures and in the placement of plaster casts; and quality control (review of complications and mortality). The assumption of these responsibilities can only be gradual and contextual to the student's integration into the ward. An adequate length of stay, i.e., one to three months, can ensure that students undertake all set-out tasks while also learning how a LMIC's surgical ward operates and how it is different from an HIC's one, and vice versa. This duration is in principle sustainable also considering the private life and academic record of the student, but it still depends on the specific projects.

The experience does not end after returning from the host institution. Upon returning to their respective countries, students can ponder on the experience and, perhaps, contribute to filling scientific literature gaps on GS. This could produce in a detailed report of all acquisitions and inform the evolution and improvement of future electives (similar to the capstone project in elective D). It will also help to address those shortcomings in the literature that justified this article. It goes without saying that in any paper produced thanks to these electives, co-authorship by all contributors, professors and students coming from both HICs and LMICs, will consolidate and sustain collaboration among institutions.

Conclusion

Global surgery is an intrinsic component of GH and a fundamental discipline aimed to alleviate the global burden of disease. Developing undergraduate courses to educate and train those who will become health professionals, medical doctors, and surgeons is strategic to further address the global surgical health challenges. However, only some are exposed to this topic during medical school, and even fewer are directly involved in GS. Although positive experiences exist, they require extensive enhancement both quantitatively and qualitatively.

The goal of this review was to collect existing examples of projects on GS designed by universities and dedicated to undergraduate students with the ultimate aim of identifying best practices and issuing a call to intensify didactic efforts addressing GS. We, therefore, call upon European universities to engage assertively in GS by organizing electives and exposing students to this multidisciplinary field, together with institutions of LMICs so that equitable access to these courses and to corresponding benefits is fully shared. In the same way, we appeal to all students worldwide to read, learn, and engage in GS projects. The hope is that our review is a starting point to encourage universities and students to responsibly contribute to the further development of the field, thus allowing all to approach and appreciate the benefits of GS.

Summary – Accelerating Translation

Title: Perché le università europee dovrebbero organizzare corsi elettivi di Chirurgia Globale per i loro studenti

Qual è il problema

Per Chirurgia Globale, o meglio Global Surgery (GS), si intende una branca della Salute Globale con la priorità di ridurre le disuguaglianze nell'accesso alle cure chirurgiche a livello mondiale. Si stima infatti che un terzo del Global Burden of Disease – che è una descrizione dello stato di malattia della popolazione mondiale – sia dovuto all'impossibilità di accedere a trattamenti chirurgici adeguati, sicuri e tempestivi. Ciò è particolarmente vero per le popolazioni svantaggiate, specialmente nei Paesi a basso e medio reddito (LMICs), ma anche in alcuni contesti dei Paesi ad alto reddito (HICs).

Si tratta di una problematica di rilievo mondiale, ma se si chiedesse a uno studente di medicina di un'università europea che cosa sia la GS, probabilmente non saprebbe rispondere. Questo perché, nel campo della Salute Globale, la GS è sempre stata messa in secondo piano e solo dal 2014 è stata veramente portata al centro del dibattito grazie al lavoro e alle proposte della Lancet Commission on Global Surgery. Tuttavia, ancor oggi, la GS viene citata raramente nelle università. La vera conseguenza? Che, se nessuno parla di GS ai futuri medici, nessuno di loro potrà scegliere di impegnarsi in questo campo e non sarà possibile ridurre il peso globale delle malattie chirurgiche.

Però esistono alcune università che riconoscono l'importanza di formare gli studenti in questa disciplina e che hanno così organizzato dei corsi elettivi in GS. Gli autori di questo articolo, studenti di medicina europei, hanno analizzato la letteratura scientifica su tali elettivi, per creare una recensione approfondita delle esperienze esistenti, mettendo in luce punti di forza e di debolezza e stilando le caratteristiche che un corso elettivo di GS dovrebbe avere. L'obiettivo finale è un appello alle università europee perché realizzino un'offerta di esperienze di GS per i propri studenti.

I risultati della ricerca

Gli autori hanno messo a punto una strategia di ricerca per identificare la letteratura scientifica in lingua inglese riguardante corsi elettivi di GS, per studenti di medicina non ancora laureati, con coinvolgimento pratico e organizzati dalle università. I database utilizzati sono stati PubMed, Embase e Web of Science. Alla fine, sono stati selezionati 12 articoli, per un totale di 8 progetti riscontrabili nell'intera letteratura scientifica.

L'analisi di questi risultati ha mostrato che i corsi elettivi in questione sono pochi e frammentari, con la partecipazione di un basso numero di studenti provenienti da HICs ed uno ancora più basso da LMICs. Pochi corsi esistenti significa pochi dati basati sull'esperienza da cui trarre conclusioni. Nonostante questo, sono presenti svariati elementi che consentono di riconoscere che gli elettivi in GS sono esperienze valide e significative.

Degli 8 elettivi, 5 sono organizzati in due fasi distinte: una prima parte, didattica, svolta nelle università dei paesi HICs tramite lezioni frontali, esercitazioni pratiche e/o peer-tutoring; e una seconda parte, basata sulla mobilità internazionale in un contesto svantaggiato e/o diverso da quello di appartenenza, che porta gli studenti sul campo con ruoli osservazionali o di assistenza chirurgica. I restanti 3 elettivi, invece, si sono focalizzati sulla ricerca scientifica su tematiche di GS: gli studenti hanno realizzato collaborazioni internazionali con altri studenti e/o medici, al fine di produrre nuova letteratura.

In generale, i partecipanti da HICs sono stati soddisfatti e hanno tratto benefici sia in termini di apprendimento clinico che di formazione personale e relazionale; spesso, questo si è tradotto in scelte di carriera orientate a un impegno nelle discipline associate alla GS. Più limitati sono invece i dati riguardo i benefici tratti dagli studenti provenienti dai LMICs, tra cui la creazione di una rete di relazioni internazionali e un'intensificata motivazione ad aiutare la propria comunità.

Bisogna però considerare anche i lati negativi, per cercare di migliorarli. Tra questi, anzitutto i costi, specialmente per i trasporti, cui alcuni degli elettivi hanno fatto fronte grazie a donazioni, raccolta fondi a carico dei singoli studenti e fondi istituzionali. Poi, la fuga di cervelli dalle aree rurali verso quelle più ricche. Infine, il colonialismo, ossia un atteggiamento paternalistico in cui le istituzioni HICs rischiano di incorrere, con squilibri di potere a scapito dei loro partner LMICs: in parte anche a questo va ascritta la squilibrata partecipazione di studenti HICs e LMICs. Risolvere questo fenomeno è di primaria importanza per la Salute Globale e, per quanto riguarda questo articolo, è certamente fondamentale una partecipazione continua e condivisa tra le istituzioni in gioco nel definire scopi e organizzazione degli elettivi.

La nostra proposta

Le università europee, da anni coinvolte nel progetto Erasmus+, poiché riconoscono l'importanza formativa degli scambi studenteschi, sono istituzioni privilegiate per attuare corsi elettivi in GS con solide ed autentiche partnership internazionali. L'analisi dei risultati ha portato gli autori a formulare una proposta completa di elettivo, che coinvolga equamente studenti da paesi HICs e LMICs durante l'intero arco della loro carriera universitaria, con obiettivi specifici per ogni anno.

Durante il primo anno, gli studenti seguono seminari e lezioni, in videoconferenza, su temi legati alla GS. Al secondo anno, fanno ricerca su uno specifico tema di epidemiologia chirurgica del proprio Paese. Al terzo, diventano peer-tutor per gli studenti partner in visita (i quali sono già ad uno step successivo del percorso), illustrando proprio i risultati delle loro ricerche dell'anno precedente. Al quarto/quinto anno, avviene l'esperienza di scambio internazionale, di 1-3 mesi, durante i quali gli studenti sono sotto la supervisione di medici dell'istituzione partner, che aiutano e da cui sono formati su compiti specifici e definiti, come l'assistenza in sala operatoria, la confezione di piccole suture, medicazioni e gessi... Infine, l'ultimo anno è dedicato alla verifica dell'esperienza vissuta e alla produzione di letteratura scientifica sui risultati di ricerca derivati dall'esperienza di collaborazione internazionale..

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Acknowledgments

University of Milan.

Conflict of Interest Statement & Funding

The Authors have no funding, financial relationships or conflicts of interest to disclose.

Author Contributions

Conceptualization: GR, GF, TS, and MCR. Methodology: GR, GF, TS, PR, and SV. Validation: SV. Data Curation: GR, GF, and TS. Investigation: GR, GF, and TS. Resources: GR, GF, and TS. Writing – Original Draft: GR, GF, and TS. Writing – Review & Editing: GR, GF, TS, PR, SV, and MCR. Visualization: GR, GF, and TS. Supervision: PR, SV, and MCR. Project Administration: GR.

Cite as

Rossi G, Fusato G, Scirocco T, Rodi P, Villa S, Raviglione MCB. Elective Courses in Global Surgery for Undergraduate Medical Students: a Narrative Review and a Proposal for European Universities. Int J Med Stud. 2022 Oct-Dec;10(4):395-404.

ISSN 2076-6327

This journal is published by Pitt Open Library Publishing

IJMS INTERNATIONAL JOURNAL of MEDICAL STUDENTS

Review

Biomedical Engineering Advancements after Management of Myelomeningocele Study (MOMS): A Narrative Review

Natalie C. Campbell,[1] Stephen B. Trippel,[2] Eric A. Nauman.[3]

Abstract

Spina bifida is a neural tube defect resulting from an incomplete closure of the caudal neuropore. The most debilitating form of spina bifida, myelomeningocele (MMC), can present with Chiari II malformation with concomitant hydrocephalus, bowel and bladder abnormalities, and impaired motor function of the lower limbs. The incidence rate of spina bifida is 3.4 per 10,000 live births reported within the US. Advancements in the standard therapy, namely prenatal intervention pioneered by the Management of Myelomeningocele Study (MOMS), have aimed to reduce maternal and fetal complications, and yet complications were increased, calling for the need of further improvements. Beyond current standard interventions for MMC, the most promising developments have employed various biomedical methods ranging from isolated stem cell injections to biodegradable scaffold patches. These scaffolds can be biologic or synthetic and are often incorporated with bioactive proteins or stem cells. This review discusses the benefits and limitations of post-MOMS era biomedical engineering intervention articles found in 3 medical and biomedical databases consisting of systematic reviews, meta-analyses, randomized control trials, and experimental studies. After analysis of the advancements and limitations of these studies, an engineered synthetic biodegradable scaffold seeded with bioactive proteins and stem cells create a superior scaffold possessing watertight impermeability and cytocompatibility for successful coverage and host integration with minimal inflammation. Coupled with minimally invasive intra-amniotic injection delivery, an earlier mitigation could further prevent progression of poor neurologic outcomes, and possibly even regenerate neuronal tissue in patients with MMC.

Key Words: Myelomeningocele, Fetoscopic Surgery; Tissue Engineering; Tissue Scaffolds; Neural Tube Defect (Source: MeSH-NLM).

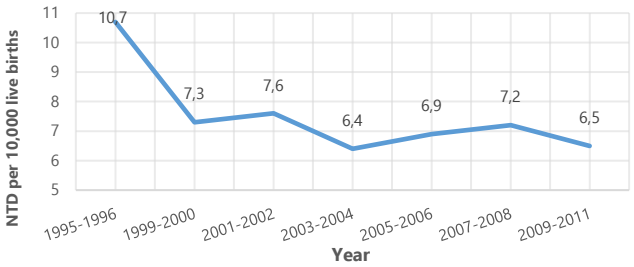
Introduction

Spina bifida is a type of neural tube defect (NTD) caused by the failure of the caudal neuropore to close prior to day 27 of gestation.[1] Failure of neural tube closure results in incomplete fusion of the vertebral arches, most commonly in the lumbar and sacral regions, allowing various amounts of central nervous system contents to expand beyond the vertebral canal.[1] The incidence rate of all neural tube defects is 3.4 per 10,000 live births reported within the United States, with a 1-year survival rate of 88-96% and a survival rate into adulthood of 75%.[2] The worldwide incidence rate of neural tube defects is 140,000 annually.[3]

The most debilitating form of spina bifida is myelomeningocele (MMC), characterized by the presence of both meninges and spinal cord outside of the vertebral canal. MMC can often present with Chiari II malformation and accompanying hydrocephalus, bowel and bladder abnormalities, and lower extremity motor function deficits. These sequelae are due to the spinal cord's unnatural exposure to fetal waste products in amniotic fluid as well as leakage of cerebrospinal fluid (CSF).[4] MMC has severe impacts on several aspects of quality of life, such as physical, psychological, social, and neurocognitive functioning. The average lifetime cost for a general MMC patients is $560,000 in 2007, estimated in 2021 to be around $722,400, highlighting the financial burden on a person living with MMC for lifelong services such as skilled caretakers and loss of ability for employment.[3]

Although the prevalence has decreased through prenatal folic acid supplementation and fortification of foods, preventative measures have not eradicated neural tube defects (*Figure 1*).[5]

Figure 1. Prevalence of Neural Tube Defects (NTD) per 10,000 Live Births in the United States from 1995-2011.



Legend: Neural tube defects defined as both spina bifida and anencephaly. Mandatory folic acid fortification introduced in 1998.[5]

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Copyeditor: Sebastian Diebel
Proofreader: Michael Tavolieri
Layout Editor: Fatma Monib

Submission: Jul 26, 2021
Revisions: Aug 8, 2021; Feb 13, 2022
Responses: Sep 9, 2021; Apr 2, 2022
Acceptance: Apr 11, 2022
Publication: Apr 14, 2022
Process: Peer-reviewed

The current treatment of MMC was established through a well-known clinical trial titled "Management for Myelomeningocele Study" (MOMS), which spanned from 2003-2010.[6] This interventional randomized study compared the previous standard treatment of 48-hour postnatal repair surgery to the then novel prenatal surgery using open surgical interventions with the placement of either an autologous dura mater graft or synthetically derived collagen matrix (DuraGen)[6] during weeks 19-25 of gestation.[6] The trial found that the prenatal open surgical intervention reduced neonatal death or the need for ventricle shunt placement, and improved motor function as well as quality of life outcomes of fetuses with MMC (*Table 1*).[6]

Table 1. MOMS Statistically Significant Outcomes Comparison between the Prenatal and Postnatal (control) Cohorts at 12 Months Postnatal for Primary Outcomes and 30 Months for Secondary Outcomes.

	Prenatal Surgery	Postnatal Surgery (Control)	p-value
Primary Infant Outcomes at 12 Months			
Shunt criteria met	65%	92%	0.001*
Placement of shunt	40%	82%	0.001
Any hindbrain herniation	64%	96%	0.001
Any brainstem kinking	20%	48%	0.001
Abnormal location of fourth ventricle	46%	72%	0.002
Syringomyelia	39%	58%	0.03
Difference between motor function and anatomical level	0.58±1.94	-0.69±1.99	0.001†
Secondary Outcomes of Children at 30 Months			
Mean Bayley Psychomotor Development Index	64.0±17.4	58.3±14.8	0.03‡
Peabody stationary score	7.4±1.1	7.0±1.2	0.04§
Peabody locomotion score	3.0±1.8	2.1±1.5	0.002§
Peabody object manipulation score	5.1±2.6	3.7±2.1	0.001§
Walking independently on examination	42%	21%	0.01
Walking status			0.03
No walking ability	29%	43%	
Walking with orthotics/devices	29%	36%	
Walking without orthotics/devices	42%	21%	
WeeFIM self-care score	20.5±4.2	19.0±2.4	0.02¶
WeeFIM mobility score	19.9±6.4	16.5±5.9	0.003¶

Legend: Statistically significant defined as ($p<0.05$).[6]

* Criteria for shunt placement criteria included patients to meet at least 2 of the following: (Increase in greatest occipital-frontal circumference, adjusted by gestational age, crossing designated percentiles. Patients with bulging fontanelle, or split sutures, or sunsetting sign. Increasing hydrocephalus on consecutive imaging studies. Head circumference >95th percentile for gestational age.) OR presence of syringomyelia with ventriculomegaly OR ventriculomegaly with Chiari malformation symptoms OR persistent CSF leak from repair site

† Regarding the difference between motor function and anatomical level= positive values indicate function that is better than expected on the basis of the anatomic level of hindbrain herniation via brain and spine MRI analysis and motor function determined by motorsensory and somatosensory function.

‡ Higher numeric values indicate better performances, ranging from a minimum score of 50 and maximum score of 150.

§ Higher numeric values indicate better performances, ranging from a minimum score of 0 and maximum score of 20.

¶ Self-care measurements range from minimum of 8 to maximum of 56 and mobility measurements range from minimum of 5 to maximum of 35 with higher scores indicating a greater level of independence.

Based on this data, open surgical intervention has become the standard treatment of MMC. Open fetal surgery did not come without its cost of significantly increased fetal and maternal adverse outcomes. (*Table 2*)[6] Statistically significant maternal outcomes included oligohydramnios, pulmonary edema, blood transfusion, chorionic membrane rupture, spontaneous membrane rupture, and spontaneous preterm labor. Statistically significant fetal outcomes included bradycardia during intervention, gestational age at birth, mean birth weight, and respiratory distress syndrome.[6]

Table 2. Comparing Both Statistically Significant Maternal and Fetal Outcomes Arising from Prenatal vs Postnatal Surgery.

Outcomes	Prenatal Surgery	Postnatal Surgery (control)	p-value
Maternal Outcomes			
Blood transfusion at delivery	9%	1%	0.03
Chorionic membrane separation	26%	0%	0.001
Spontaneous membrane rupture	46%	8%	0.001
Spontaneous labor	38%	14%	0.001
Oligohydramnios	21%	4%	0.001
Placental abruption	6%	0%	0.03
Pulmonary edema	6%	0%	0.03
Fetal outcomes			
Gestation age at birth, weeks	34.1±3.1	37.3±1.1	0.001
Bradycardia during fetal or neonatal repair	10%	0%	0.003
Mean birth weight, grams	2383±688	3039±469	0.001
Respiratory distress syndrome	21%	6%	0.008

Legend: Statistically significant defined as ($p<0.05$).[6]

In response to these adverse outcomes, engineered scaffold patches have been proposed to serve as advanced treatment for replacement of lost tissue and an earlier alternative for wound closure as fetal tissues cannot easily be manipulated before 19 weeks.[7] Additionally, minimally invasive methods have been proposed to lower surgical complications in both the fetus and mother when compared to open fetal surgery.[8]

The purpose of this narrative review is to provide a clinical perspective in the various methods (*Table 3*), results, limitations, and future implications of research in the post-MOMS era, and how it has progressed the prenatal intervention of MMC to provide earlier intervention in MMC repair while minimizing both maternal and fetal peri-operative complications. More specifically, this narrative review serves as a novel approach to compare not only scaffold compositions, but also effects of various bioactive proteins seeded scaffolds, and method of administration.

Table 3. Summary of the Biomedical Engineering Study Methods Used by Various Groups to Improve Upon Standard Treatment of Myelomeningocele in the Post-MOMs Era.

Literature	Subjects	Method of MMC creation	Nature vs Synthetic scaffold	Scaffold material	Seeded with bioactive proteins	Seeded with stem cells	Method of intervention
Biologic scaffolds seeded with bioactive proteins							
Watanabe et al.[9]	Rats	RA induction	Natural	Gelatin	bFGF	-	Open fetal surgery
Watanabe et al.[10]	Rats	RA induction	Natural	Gelatin microspheres	-	-	Intra-amniotic injections
Watanabe et al.[11]	Sheep	Surgical creation	Natural	Gelatin sponge	bFGF	-	Open fetal surgery
Biologic scaffolds seeded with stem cells							
Brown et al.[13]	Sheep	Surgical creation	Natural	Amniotic membrane	-	Early and late gestational pMSCs	Open fetal surgery
Li et al.[15]	Rats	RA induction	Natural	Chitosan-gelatin	-	BMSCs	Open fetal surgery
Isolated stem cell intervention							
Dionigi et al.[16]	Rats	RA induction	-	-	-	afMSCs	Intra-amniotic injections
Feng et al.[17]	Rats	RA induction	-	-	-	afMSCs, pMSCs	Intra-amniotic injection
Synthetic biodegradable scaffolds							
Oria et al.[19]	Rats	-	Synthetic	PLA, PCL	-	-	Subcutaneous and dural implantation
Tatu et al.[21]	-	-	Synthetic	PLA, PCL	-	-	-

Legend: **RA**= retinoic acid, **bFGF**= basic fibroblast growth factor, **BMSCs** = bone marrow mesenchymal stem cells , **afMSCs**= amniotic fluid-derived mesenchymal stem cells, **pMSCs**= placenta-derived stem cells , **PLA**= poly l-lactic acid, **PCL**= poly ε-caprolactone.

Methods

Search Strategy and Selection Criteria

Articles for this narrative review were selected from 1 June 2019 – 31 July 2020 utilizing a key word search via PubMed, Science Direct, Online Wiley Library, Via Medica. Key words included: "Myelomeningocele", "Fetal Surgery", and "Tissue Engineering". Articles included ranged from publication in 2010-2019.

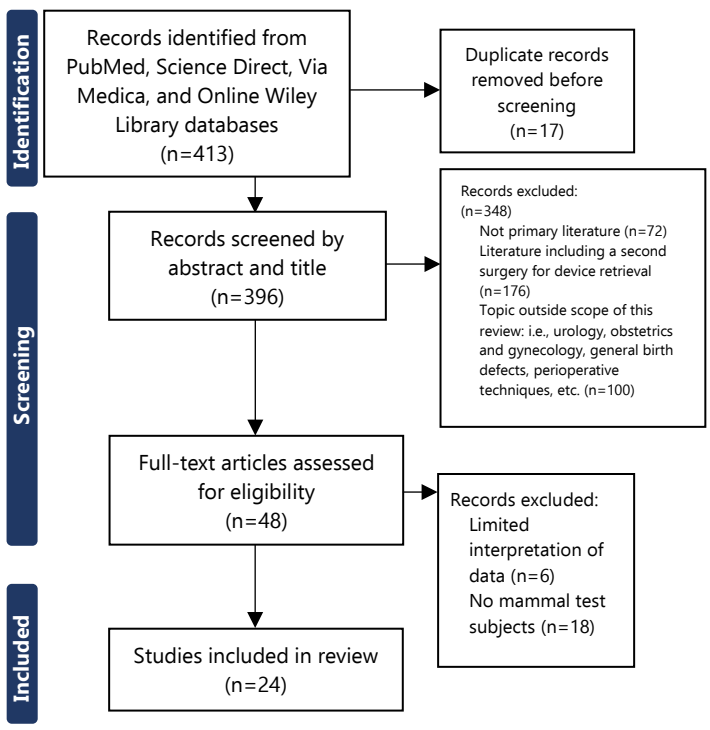
Inclusion criteria included articles published in the last 10 years; specific types of literature: review articles, clinical trials, meta-analyses, randomized control trials systematic reviews, and book chapters; *in-vivo and in-vitro* techniques, surgical or chemical creation of MMC.

Exclusion criteria included specific type of literature: conference abstracts, correspondences, encyclopedias, discussions, editorials, news, short communications, and literature categorized as "other"; literature describing a second surgery for device retrieval; literature largely discussing broad techniques in fetal surgery; literature largely discussing topics outside scope of this review: i.e., urology, urodynamics, obstetrics and gynecology, general birth defects, and perioperative techniques.

Results

Since the MOMS trial, tissue engineering studies have been conducted through various avenues. A total of 413 pieces of literature were identified with ultimately 24 meeting the inclusion criteria (*Figure 2*).

Figure 2. PRISMA Study Flowchart.



Biologic scaffolds seeded with bioactive proteins

A natural biological scaffold is uniquely derived from an existing organic source. Popular organic sources have included bovine, ovine, and porcine bone that researchers have ultimately transformed into gelatin, collagen, or a hybrid of the two.[9-14,17-19] The porous nature of the scaffold materials allows for scaffold-host integration via cellular differentiation and neovascularization, resulting in defect coverage as well as similar innate mechanical properties of native tissue. [9-14,17-19] A natural biological scaffold benefits from being biodegradable, and thus, not requiring a future surgery for its removal. Scaffolds can also serve as vessels to deliver bioactive proteins, stem cells, and other small molecules.

Watanabe et al. conducted a series of 3 studies exploring the utility of natural biological scaffolds seeded with bioactive proteins.[9-11] They tested gelatin-based sponges seeded with basic fibroblast growth factor (bFGF) using chemically induced (via retinoic acid) MMC fetal rats in their 2010 and 2011 studies, and then, surgically induced MMC fetal sheep in their 2016 study. The group chose bGFG for its ability to induce both epithelization and neovascularization, and gelatin for its porosity together promoting host integration. The methods of scaffold placement differed: 2010 study via open fetal surgery, 2011 via ultrasound-guided intra-amniotic injections, and 2016 via open fetal surgery.

In 2010, Watanabe et al. showed enhanced incorporated epithelialization and neovascularization, with the seeded bFGF gelatin scaffolds compared to the untreated control subjects.[9] A total of 32 surviving fetal rats were analyzed, showing that both epidermal ingrowth and neovascularization were significantly greater in bFGF seeded cohort compared to non-seeded cohort, ($p<0.05$) highlighting the clear benefit of bFGF.[9] One limitation in this study included early degradation of the sponges resulting in partial defect coverage. This study improved upon the MOMS trial as it exemplifies that a porous patch can support neovascularization and epithelialization, enhanced by bFGF in place of suture closure.

In 2011, Watanabe et al. continued their study using biologic scaffolds (via gelatin microspheres) with a shift in focus on using intra-amniotic injection therapy.[10] This method highlighted a major benefit to treatment intervention as injection therapy does not rely on tissue strength as much as suture, thus allowing for earlier gestational intervention. A total of 52 surviving fetal rats were analyzed with the injectable microsphere cohort measuring significantly greater epidermal thickness compared to group without intervention ($p < 0.05$).[10] One limitation was using rats as they have relatively short gestations. This study improved upon the MOMS trial by offering injectable therapy as a potential method for earlier intervention compared to the standard open surgical approach.

In 2016, Watanabe et al. applied their biologic scaffold to a large animal study.[11] This sheep model allowed the group to observe the subjects longer (average gestation of sheep: 20-22 weeks) and allowed for better theorized application to the human counterpart. Additional analysis in this 2016 study measured preservation of spinal cord material and the degree of hindbrain herniation in the 5 surviving fetal sheep separated into unique cohorts, with varying component-seeded gelatin scaffolds. Results showed the experimental groups, with preserved spinal cord material through significantly greater tissue thickness overlying the spinal cord, compared to group without intervention ($p < 0.0001$).[11] Additionally, hindbrain herniation in the experimental groups was significantly less when compared to the control group ($p <0.01$).[11] Limitations of this study included inconsistent surgical MMC creations with unknown effects of innate epithelial healing vs scaffold-mediated neoepithelialization. This large animal study allowed Watanabe et al. to get closer to translational human studies and applying the post-MOMs trial advancements discussed in their 2010 and 2011 studies.

Biologic Scaffolds Seeded with Stem Cells

One unique utility of stem cells is their pluripotency, the capacity to become several cell derivatives. Stem cells have the potential to influence MMC coverage not only with spinal cord protection via epithelization, but also with an additional role in neuron regeneration. Due to the prolonged spinal cord exposure to the harmful fetal waste products in amniotic fluid, motor neuronal death leads to the observed lower motor extremity deficits seen in postnatal subjects.[12] The idea behind seeding natural biological scaffolds with stem cells has the potential to serve two important functions: cover the MMC defect reducing further neurological damage, while also promoting regeneration of motor neurons in the spinal cord.

In 2016, a study by Brown et al., compared the utility of autologous amniotic membrane patches seeded with early gestational placenta-derived mesenchymal stem cells (pMSCs) vs late gestational pMSCs in surgically created MMC fetal sheep.[12] The authors noted that early gestational pMSCs has been found to produce factors associated with neural protection.[13] The cohorts were compared using histological analysis of the lambs' spinal cords after birth and neurological testing focusing on limb movement, stance, hindlimb weight bearing, standing, stepping, and hindlimb clearance.[14] The early gestation pMSC seeded cohort showed the greatest proportion of defect coverage, as well as normal ambulation compared to the lower motor neuron dysfunction in late gestation pMSCs.[12] Limitations of this study included limited statistical analyses, as well as the subjective use of the motor function scale. Brown et al.'s study illustrates the potential benefit of incorporation of early gestational pMSCs, highlighting its convenient autologous nature as well as adjunct immunomodulating cytokines and neuronal protection.

In 2016, Li et al. engineered a chitosan-gelatin scaffold seeded with bone marrow mesenchymal stems cells (BMSCs) applied using microsurgery technology to analyze its efficacy in patching

defects and regenerating neurons in chemically created MMC in fetal rats.[15] The authors chose chitosan-gelatin scaffolds for its high composition of collagen, lack of antigenicity, and large pore size of 300μm, all important qualities to facilitate cell growth and metabolism.[15] BMSCs were chosen for their angiogenesis and ability to prevent fibrosis.[15] The study found that the transplanted BMSCs seeded chitosan-gelatin scaffolds lessened MMC defects as well as expressed markers of neural stem cell and neurons.[15] Some notable limitations to this study were the absence of statistical analysis, as well as the late treatment application. The results from Li et al.'s study show successful alternative materials for tissue scaffolds, highlighting high porosity of gelatin being able to support both tissue repair and regeneration aided with adjunct BMSCs seeding.

Isolated Stem Cell Intervention

Isolated stem cell injections do not have the same size and space occupations as biological scaffolds and consequently they can be administered by tools as small as needles. Some of the benefits of injectable therapy with stem cells not only includes the already mentioned pluripotency of stem cell and its autologous nature, but this type of therapy also opens the opportunity for earlier therapy, and lower surgical complications.[16,17]

In 2015, Dionigi et al. tested the effect of trans-amniotic stem cell therapy (TRASCET) with amniotic fluid mesenchymal stem cells (afMSCs) on chemically induced MMC fetal rats.[16] This study measured the degree of brainstem and cerebellar herniation using histology and high-resolution magnetic resonance imaging in 62 fetal rats. They found that the intra-amniotic injected afMSCs cohort showed less brainstem and cerebellar herniation as well as more MMC coverage on histological analysis when compared to the cohort without intervention ($p<0.001$).[16] A notable limitation of this study was the small window (1 week) between induced MMC and therapeutic intervention.[16] The results from this study showed the potential of using TRASCET to benefit subjects with MMC utilizing a minimally invasive technique, earlier intervention, and use of autologous afMSCs in reducing neurological sequelae.

In 2016, Feng et al. compared autologous placenta-derived mesenchymal stem cells (pMSCs) and amniotic fluid-derived mesenchymal stem cells (afMSCs) via TRASCET to evaluate defect coverage in chemically induced in MMC fetal rats.[17] The selection of pMSCs to compare against afMSCs was influenced by availability of prenatal testing via chorionic villus sampling (CVS) for pMSCs (10 weeks gestation) vs amniocentesis to acquire afMSCs (15 weeks gestation). The amount of coverage was compared using histological analysis of 238 fetal rats. There was no significant difference in complete defect coverage between the afMCSs and pMSCs cohorts or when both were compared to the cohort without intervention.[17] A limitation of this study was the lack of analysis apart from reporting the amount of defect coverage. The results from this study illustrate that earlier acquirement of pMSCs via CVS vs afMSCs via amniocentesis do not appear to aid in earlier MMC defect coverage.

Synthetic Biodegradable Scaffolds

Most synthetic biodegradable scaffolds are broadly characterized as non-toxic, biodegradable, easily reproducible, and resist early destructive enzymatic breakdown.[18] Synthetic scaffolds can have a self-expanding quality in body temperature, ideal for achieving complete coverage of the MMC defect starting with a small injectable product.[19-21]

In 2019, Oria et al. studied the in-vivo effects of a blended PLA (poly l-lactic acid) and PCL (poly ε-caprolactone) biodegradable synthetic scaffold via subcutaneous and dural implantation in anatomically normal rats.[19] Tissue analysis of the PLA-PCL group revealed no signs of neural inflammation via absence of astrocytic reaction or glial scar formation.[19] A limitation of this study was that the patch was not directly tested using animal MMC models and its effect in prenatal treatment. The biocompatible results from this study support integration of biodegradable synthetic scaffolds for MMC interventions.

In 2019, Tatu et al. also studied biodegradable PLA and PCL blended synthetic scaffolds with focus on its characteristics; namely the scaffold's in-vitro self-expansion, permeability, and biodegradable abilities.[21] The patch was observed in-vitro to self-expand at body temperature (37° C), impermeable to water, and did not degrade while studied in amniotic fluid.[21] One limitation of the study was the properties of their biodegradable synthetic patch were not tested in-vivo, limiting application to MMC treatment. Based on their in-vitro studies, synthetic scaffolds have several favorable properties that could make it a useful alternative in MMC repair.

Discussion

Currently, there are sparse systematic reviews or meta-analyses that consider the material of scaffolds as well as any seeded materials for earlier and safer intervention for MMC therapy. One meta-analysis by Kunpalin et al. focuses on the efficacy of stem cell injections as well as stem cell seeded biologic scaffolds but does not include discussion of synthetic scaffolds or the use of bioactive proteins.[22] This narrative review serves as a novel approach to compare not only scaffold compositions, but also effects of various bioactive proteins seeded scaffolds, and method of administration.

After analyzing the contributions and limitations of these studies, a combination of different materials and methods could theoretically produce a patch that can successfully prevent and potentially reverse poor neurological outcomes in patients with MMC. It is unclear which source of stem cells and selection of bioactive proteins would be most beneficial to serve this role as no existing study compares them directly. However, the successes in the various studies mentioned in this review suggest there could be multiple solutions.

When comparing biological versus synthetic scaffolds, synthetic scaffolds are superior for several reasons. Biodegradable synthetic scaffolds could mitigate some limitations of biologic scaffolds. Biologic scaffolds have the potential to initiate an immune response, due to its antigenicity, which in turn could interfere with other biological processes, such as general development, tissue healing and tissue regeneration.[23] Synthetic biodegradable materials lack antigenicity, and thus have less risk of producing an immune reaction. Synthetic scaffolds also have greater mechanical strength compared to biological scaffolds as synthetic materials are less susceptible to early degradation via host enzymatic reactions, thus preserving tensile strength to support tissue remodeling.[21] Additionally, synthetic scaffolds can be designed to have large enough pores for neovascularization and epithelialization without having an open connection through the scaffold, thus prohibiting further neurologic degradation via amniotic fluid and preventing progressive CSF loss.[19] The self-expansion characteristic of the synthetic patch can decrease operative time, potentially decreasing fetal and maternal operative-related complications.[21]

Regarding selection of bioactive protein seeding, it is clear from the studies discussed in this paper that bFGF has a favorable effect on epithelialization and neovascularization ultimately providing host integration and neurologic protection.[9] Additionally, selection for early placenta-derived mesenchymal stem cells has also shown to aid in MMC defect coverage and hopeful neural regenerative properties, as demonstrated in the study conducted by Brown et al.[13] The benefit of its autologous nature and early retrieval through chorionic villus sampling beginning at 10 weeks' gestation allow pMSCs to be a convenient and a potential restorative seeding material.

Upon analyzing the various delivery methods used in these studies, an in-utero injectable approach could be superior as it allows for less invasive and earlier intervention compared to the current treatment of open fetal surgery.[24] It is unclear how early an injectable delivery method could be implemented in humans, and future research into this area is required, but the goal of intervention should be as close to MMC diagnosis (typically gestational week 16-18) as possible.

Finally, it is important to consider the limitations of the discussed studies to help avoid future pitfalls. Some suggestions for future studies using the methods proposed in this discussion should include larger cohorts, use of large animals with gestation lengths closer to humans, and measurement of outcomes like that of the MOMS trial for greater assessment of a study's advancements on current treatment of MMC.

Conclusion

Since the MOMS era spanning from 2003-2010, great emphasis has been placed on engineering a scaffold that can preserve and possibly reverse the neurological deficits seen in patients with myelomeningocele in a way that poses minimal risk to the health of the mother and baby. Scientists have gone down several unique avenues to offer therapeutic solutions for earlier and safer intervention, yet there is no clear superior intervention at this time. Upon analysis of the advancements and limitations of several studies, patients with MMC defects could benefit from an engineered synthetic biodegradable scaffold seeded with bFGF and placenta-derived mesenchymal stem cells. This combination would aim to incorporate the qualities that many studies have highlighted as crucial for an MMC scaffold to possess. Delivery of this scaffold would ideally be placed via intra-uterine injection(s) shortly after diagnosis of MMC. Not only could this solution serve to prevent poor neurological outcomes caused by MMC, but it could reduce the healthcare cost of multiple surgeries, hospitalizations, and lifestyle adjustments associated with the current MMC therapies.

Summary - Accelerating Translation

Biomedical Engineering Advancements after Management of Myelomeningocele Study (MOMS): A Narrative Review

Spina Bifida is birth defect in the spine that can cause damage to the spinal cord before a baby is born. There are several types of spinal bifida, each with varying degrees of spinal cord damage. There is also a range of complications from damaging the spinal cord including hydrocephalus (water on the brain), bowel and bladder incontinence, and impaired leg mobility. Historically, the standard of care to treat myelomeningocele (one of the more severe types of spina bifida) involved surgery shortly after birth. As science has advanced, a large study called MOMS "Management of Myelomeningocele Study" spanning from 2003-2010 compared the number of complications between repairing spina bifida defects while the baby was still in the womb with the standard method of postnatal repair. The MOMS trial found less complications in both the moms and the babies in the prenatal group when compared to the postnatal group, resulting in the new prenatal standard of care for myelomeningocele standard of care. Our group chose to research studies from 2010-2019 that aimed to further improve upon the MOMS trial with emphasis on using biomedical engineered patches that could be used to repair spina bifida defects even earlier and with less invasive methods.

Our group searched through 413 pieces of literature, using the following inclusion criteria: primary literature published within the last 10 years, with key words of 'myelomeningocele', 'fetal surgery', and 'tissue engineering', and using animals with lab-inflicted myelomeningocele. Studies that were excluded were certain types of primary literature such as abstracts, correspondence, encyclopedias, discussions, editorials, news, short communications, and literature categorized as 'other', studies that had a second prenatal surgery to remove the engineered spinal patch, as well as literature that was outside the scope of this narrative review such as studies with a primary focus on urology, obstetrics and gynecology, general birth defects, and various operative techniques. In the end, 24 studies were included in this narrative review.

Some of the differences found between the studies included method of inducing spina bifida (either chemically or surgically), the type of animal (rats vs sheep), material used for the scaffold, seeded material (proteins and or stem cells), the method of introducing the scaffold, and finally the week of gestation the scaffold was placed.

Retinoic acid was used to chemically induce some of the test subjects, while a surgical incision was used to induce spina bifida in others.

Rats were used in some studies as a more convenient and cost-effective animal subject compared to sheep; however, the consequence of using rats included shorter gestational periods compared to sheep and shorter time between induction of spina bifida and implementing the engineered scaffold. Conversely in sheep with longer gestational periods, studies were able to make stronger conclusions to human implications.

Several studies experimented with reverse engineering scaffold patches made from cow, pig, or sheep bone into a more malleable/ porous collagen material. Other studies derived a similar product using synthetic materials, like PLA (poly l-lactic acid) and PCL (poly- ε caprolactone). Both biological and synthetic materials were able to serve as vessels to carry signaling proteins, naturally found in the body, to enhance incorporation of the engineered patch to the fetus prevent further damage to the spinal cord. Largely, these signaling proteins enhanced growth of nerve cells and connective tissue cells. Some studies also incorporated stem cells into their scaffolds, allowing the potential of multiple cell types to grow. All patches discussed in this review were biodegradable preventing a second surgery to retrieve the device.

The various methods of scaffold placement used were open surgery and intra-amniotic injections. The choice of method depended on several factors including gestational age, as early fetuses do not have the structural integrity to undergo open surgery and patch fixation.

Since the MOMS era spanning from 2003-2010, great emphasis has been placed on engineering a scaffold that can preserve and possibly reverse the complications seen in patients with myelomeningocele in a way that poses minimal risk to the health of the mother and baby. Scientists have gone down several avenues to offer earlier and safer intervention, yet there is no clear superior intervention at this time. Upon analysis of studies included in this narrative review, patients with myelomeningocele could benefit from an engineered synthetic biodegradable scaffold seeded with both proteins and stems cells to promote scaffold incorporation and structural integrity. Delivery of this scaffold would ideally be placed via intra-uterine injection(s) shortly after diagnosis of spina bifida. Not only could this solution serve to prevent common complications of spina bifida, but it could reduce the healthcare cost of multiple surgeries, hospitalizations, and lifestyle adjustments associated with the current therapies.

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Acknowledgments

None.

Conflict of Interest Statement & Funding

The Authors have no funding, financial relationships, or conflicts of interest to disclose.

Author Contributions

Conceptualization: NC & EN. Data Curation: NC. Formal Analysis: NC. Funding Acquisition: NC. Investigation: NC. Methodology: NC. Project Administration: NC. Resources: NC. Software: NC. Supervision: NC & ST. Validation: NC & ST. Visualization: NC. Writing - Original Draft Preparation: NC. Writing- Review and Editing: NC & ST.

Cite as

Campbell NC, Trippel SB, Nauman EA. Biomedical Engineering Advancements after Management of Myelomeningocele Study (MOMS): A Narrative Review. Int J Med Stud. 2022 Oct-Dec;10(3):405-12.

ISSN 2076-6327

This journal is published by Pitt Open Library Publishing

IJMS INTERNATIONAL JOURNAL of MEDICAL STUDENTS

Case Report

Aberrant Right Subclavian Artery: Cadaver Case Report

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Abstract

Different aortic arch branching patterns exist in the general population. These branching patterns can be benign or can cause a variety of symptoms in patients. In the case of a more benign branching pattern, anomalies often go undiagnosed until discovered postmortem. Case: While examining the anatomy of a cadaver in a medical school gross anatomy course, an aortic arch anomaly was discovered. This variant is consistent with an aberrant right subclavian artery (ARSA). In this variant, the right subclavian artery branches from the most distal part of the aortic arch and runs both retrotracheal and retroesophageal as it courses to the right shoulder. This variant is a result of aberrant development of the aortic arch and may present with symptoms such as dysphagia and shortness of breath, if any at all. In addition to the ARSA, there exist a common bicarotid trunk and a direct branching of the left vertebral artery from the aortic arch, both of which are rare anomalies. The cadaver's medical history includes dysphagia and stretched esophagus, although the severity is unknown. Conclusion: this case report draws attention to these rare anatomical anomalies and includes a discussion of the most common clinical presentation, and surgical implications of an aberrant right subclavian artery anomaly

Key Words: Aberrant Right Subclavian Artery; Case Reports; Aortic Arch; Dysphagia (Source: MeSH-NLM).

Introduction

The aortic arch is a critical structure in the cardiovascular system, as it is the beginning of the systemic arterial circulatory system. Formation of the aortic arch begins during the fourth week of embryonic development and is ultimately derived from multiple structures. At this time, a structure called the aortic sac starts to develop. During the fifth week of development, the aortic sac begins to grow and branch off into the two dorsal aortas and the ventral aorta. Six paired pharyngeal aortic arches develop, which connect the ventral and dorsal aortae.[1] Some of these arches completely regress while portions of the other persist as the mature aorta develops.[1] The primary origins of the aortic arch, from proximal to distal, are the aortic sac, the left fourth aortic arch, and the dorsal aorta.[2]

An aberrant right subclavian artery (ARSA) affects approximately 1% of the population.[2] ARSA develops as a result of the abnormal regression of the right fourth aortic arch and right dorsal aorta distal to the right common carotid artery.[1] In this case, the aberrant right subclavian develops from the right seventh segmental artery of the descending aorta and becomes the most distal branch of the aortic arch.[1,2] The aberrant right subclavian artery passes retrotracheal and retroesophageal in 80% of the cases.[2] Alternatively, it courses between the trachea and the esophagus in 15% of the cases, and anterior to the trachea in 5% of the cases.[2] In addition to an aberrant right subclavian artery, there can also be the occurrence of a bicarotid trunk. The coexistence of both ARSA and the bicarotid trunk has an estimated prevalence of <0.05%.[3]

Highlights:

- A cadaver case was discovered to have an aberrant right subclavian artery.
- There are many variants in the branching patterns of the aortic arch and highlighted here is one of those specific patterns.
- Disruption in the embryonic development of the aortic arch leads to a wide variety of branching patterns in the general population.
- Most patients are asymptomatic, but dysphasia lusoria is the most common presenting symptom.

A majority of individuals with an aberrant right subclavian artery are asymptomatic,[4] and it is estimated that 60-80% of individuals with this anomaly will never develop any symptoms.[4] For those who do develop symptoms, it is more common for them to have dysphagia, caused by mechanical compression of the esophagus by the aberrant artery. This is referred to as dysphagia lusoria.[5] Dysphagia lusoria is seen in 71.2% of symptomatic individuals, but can range from only mild intermittent dysphagia to a potentially severe, and continuous dysphagia of both solids and liquids.[6] These symptoms usually appear in the middle to older age groups. However, the exact reason for this is unclear.[5] Other

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Editor: Francisco J. Bonilla-Escobar
Student Editors: Hang-Long (Ron) Li & Muhammad Romail Manan
Proofreader: Laeeqa Manji
Layout Editor: Ana Maria Morales

Submission: Sep 9, 2022
Revisions: Sep 30, 2022
Responses: Nov 17, 2022
Acceptance: Nov 30, 2022
Publication: Dec 3, 2022
Process: Peer-reviewed

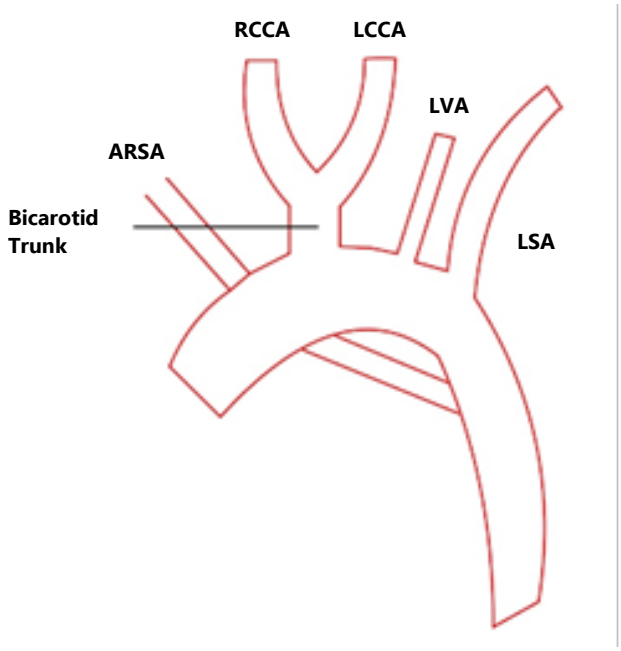
symptoms and their prevalence in symptomatic individuals include dyspnea (18.7%), retrosternal pain (17.0%), cough (7.6%), and weight loss (5.9%).[5] This case report highlights a patient with a right aberrant subclavian artery and a bicarotid trunk who experienced dysphagia. Uniquely, our report includes gross anatomical imaging and discusses the clinical implications of such an anomaly.

The Case

While examining cadavers as part of a medical school gross anatomy course, an anomalous origin of the right subclavian was discovered. The variant was consistent with the aberrant right subclavian artery, as previously described. In this case, the right subclavian artery originates from the aortic isthmus rather than the brachiocephalic trunk.

Figure 1 depicts the presentation of the aortic arch and its branches in our cadaver. The left subclavian artery and left vertebral artery branch separately travel to the left shoulder and head, respectively. The right and left common carotid arteries arise from a common bicarotid trunk prior to coursing up the lateral portion of each side of the neck.

Figure 1. Schematic Depiction of the Aortic Arch and its Branches in the Cadaver.

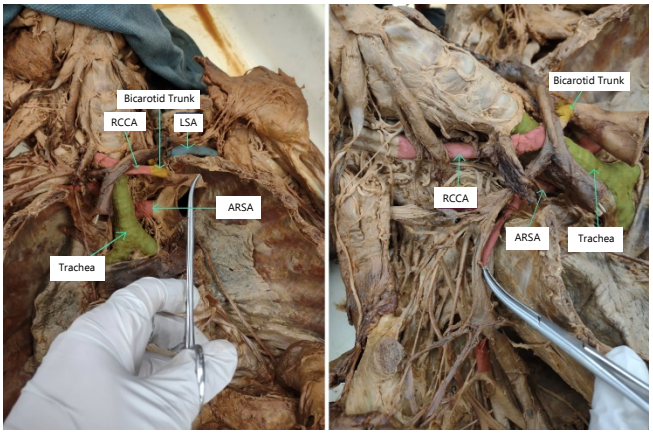


Legend: ARSA = Aberrant Right Subclavian Artery; LCCA = Left Common Carotid Artery; LSA = Left Subclavian Artery; LVA = Left Vertebral Artery; RCCA = Right Common Carotid Artery.

Figure 2 are photographs taken of the cadaver's ARSA. The cadaver's ARSA courses are posterior to the trachea and esophagus. This is the most common ARSA variant, occurring in nearly 80% of cases.[7]

Dissection of the cadaver was performed as part of a prosection course at the Michigan State University College of Human Medicine. The cadaver was dissected to reveal neurovascular structures of the mediastinum and deep thorax, to include the subclavian vessels. Our patient is an 81 year old male of unknown ethnicity with a past medical history of aspiration pneumonia, diabetes, and Alzheimer's disease. The causes of death noted for the cadaver are cardiac arrest, acute respiratory failure, acute kidney injury, and congestive heart failure. In addition to many other comorbidities, additional medical information includes a history of stretched esophagus and dysphagia. Although the severity of these medical conditions is unknown in the cadaver's history, dysphagia is often one of the sole symptomatic indicators of an ARSA.

Figure 2. Schematic Depiction of the Aortic Arch and its Branches in the Cadaver.



Legend: Left: Overhead View of the Cadaver Shows the Aberrant Origin of the Right Subclavian Artery. The Proximal Aortic Arch is Being Reflected to the Left in Order to Display the Very Posterior Origin. Right: A Lateral View of the Right Side of the Cadaver Shows the Right Subclavian Artery Exiting Retrotracheal and Retroesophageal.

Discussion

During a routine examination of cadavers as part of a gross anatomy course, an aberrant right subclavian artery was discovered. This specific aortic arch anomaly is only present in about 1% of people.[2] However, in addition to the aberrant right subclavian artery, there was also the occurrence of a bicarotid trunk, which is an extremely rare variant. The coexistence of both ARSA and the bicarotid has an estimated prevalence of <0.05%.[3] Lastly, the left vertebral artery arises from the aortic arch, which is estimated to occur in around 4% of all individuals. Nevertheless, the combination of all three has not been well documented.[8] Therefore, the incidence cannot be determined in this report.

ARSA variations have been reported in the literature and Adachi-Williams have classified them into three types based on the branches coming off of the aortic arch. Type I (Type-G) has four branches: the right common carotid artery (RCCA), left common carotid artery (LCCA), left subclavian artery (LSA), and aberrant right subclavian artery (ARSA). Type II (Type CG) is the same as type I along with the addition of a branch for left vertebral artery (LVA). Lastly, type III (type H) is seen with a bicarotid trunk, LSA,

and ARSA branches coming from the aorta.[9] The case seen here is a combination of type II and type III variations due to the presence of four branches: the LVA (seen in type II) and the bicarotid trunk (seen in type III), along with LSA, and ARSA.

A recent systematic review, aimed at categorizing left sided aortic arch variants, classified the variants based on the number of emerging branches into type 1b (one branch), 2b, 3b, 4b, 5b and further subclassified based on prevalence.10 The systemic review concluded that a typical branching pattern had a prevalence of 78% with a 22% prevalence for all other branching patterns. The most common variant was 2b, with bovine arch (LCCA originating from the brachiocephalic arch) being the most common subtype of the 2b variant.

This case report is especially useful for examining an aortic arch anomaly and uniquely presents gross anatomical findings as evidence of the anomaly. This report also includes rare evidence of an ARSA coexisting with a bicarotid trunk. An associated history of dysphagia in the cadaver helps demonstrate possible clinical findings of a patient with an aortic arch anomaly. Due to the nature of the case report, we were unable to examine the patient while they were still living and experiencing symptoms. The findings of the case report were limited to the patient's brief medical history reported to the anatomy lab. Other cadaver case reports have reported similar findings of an ARSA, and included more information on the clinical severity of the patient's anomaly.[11,12] However, future cadaver case reports should include thorough and complete clinical descriptions of patients' dysphagia as well as record of physician assessments and surgical recommendations made during the clinical course. Diagnosing an ARSA in a living patient is rare and is usually accidently discovered on a coronary angiogram. Surgery may be implicated in extreme cases of dysphagia but is usually foregone in favor of supportive treatment due to the risks of the procedure.

Individuals with ARSA variations can be asymptomatic and those with symptoms often do not present until later in life, which makes a clinical diagnosis challenging. Despite this, it is important that physicians consider an ARSA anomaly when a patient presents with dysphagia, shortness of breath, and/or stridor. Other concerning symptoms for a suspected ARSA include worsening retrosternal pain, cough, and acute limb ischemia.[5] Although a surgical intervention is unlikely except for in rare and severe cases, this case report raises clinical awareness of the possibility of such a condition and can guide more specific intervention and treatment.

Summary – Accelerating Translation

The title of this case report is Aberrant Right Subclavian Artery: Cadaver Case Report. The aorta is the major blood vessel leaving the heart and provides oxygenated blood to the tissues. The aortic arch gives off 3 branches in 78% of the population. Normal and pathological variation in the branching patterns and in the number of branches exists in the general population. This case presentation discusses an aberrant right subclavian artery (ARSA) in a cadaver. In the normal variant, the right subclavian artery branches off the brachiocephalic artery, the most proximal branch of the aortic arch. In our case, the right subclavian artery is the most distal branch of the aortic arch and branches directly off of it as it courses behind the trachea and esophagus to the right shoulder.

Most patients with this anomaly are generally asymptomatic, and the few that develop symptoms tend to develop them later in life. Trouble swallowing, also called dysphagia lusoria, is the most common symptom associated with ARSA. The abnormal position and path of the right subclavian artery mechanically compresses the esophagus causing the dysphagia. Other less common symptoms include shortness of breath, chest pain, cough, and weight loss. Although interventions are generally rare, it's important for physicians to consider ARSA when working up a patient with dysphagia, and to be aware of the variation in the branching patterns of the aortic arch when planning for cardiothoracic interventions.

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Acknowledgments

None.

Conflict of Interest Statement & Funding

The Authors have no funding, financial relationships or conflicts of interest to disclose.

Author Contributions

Conceptualization: JK, AI, JB, JF, JCL; Data Curation: JF; Formal Analysis: JK, AI, JB, JF, JCL; Investigation: JK, AI, JB, JF; Project Administration: JF, JCL; Supervision: JF, JCL; Writing- Original Draft Preparation: JK, AI, JB; Writing- Review & Editing: JK, AI, JB, JF, JCL.

Cite as

Kopp J, Irshaid A, Baker J, Fitzsimmons J, Lin JC. Aberrant Right Subclavian Artery: Cadaver Case Report. Int J Med Stud. 2022 Oct-Dec;10(4):413-16.

ISSN 2076-6327

This journal is published by Pitt Open Library Publishing

IJMS INTERNATIONAL JOURNAL of MEDICAL STUDENTS

Case Report

Primary Cough Headache Associated with Jugular Insufficiency: Report of Two Cases

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Abstract

Background: Insufficiency of the internal jugular valve is a scarcely found etiology in the literature for the cough headache, which can be associated with other vascular disorders. The objective of this study is to report, through clinical and imaging findings, the rarely described association between cough headache and jugular insufficiency. **Cases:** Two male patients, ages 79 and 70-years respectively, were evaluated with episodes of headache associated with the Valsalva Maneuver. The first patient presented with a holocranial headache and two episodes of associated syncope after cough, while the other patient reported headaches after use of an abdominal belt, as a preventive measure to contain abdominal hernia. In both cases, the insufficiency was proved upon jugular reflux on Doppler sonography. **Conclusion:** The two case reports help to broaden the discussion on the possible association between primary cough headache and insufficiency of the internal jugular vein system, although the correlation between those two pathologies is still being debated.

Key Words: Primary cough headache; Valsalva Maneuver; Jugular Vein; Venous Insufficiency; Doppler Ultrasound (Source: MeSH-NLM).

Introduction

Primary cough headache (PCH) has a prevalence in the general population of 1%, more frequent in males, usually self-limited and with prolonged remissions.[1] The pain has a sudden onset (<10 seconds), reaches a plateau, and lasts for seconds to minutes until it completely disappears after 120 minutes. The cough headache syndrome may be associated with intracranial structural changes: Chiari type I malformation, vascular disorders of the carotid and vertebral arteries; tumors of the middle and posterior fossa; basilar impression; platybasia; reversible cerebral vasospasm syndrome, among others. Cases with undefined etiology are classified as probable PCH. This type of primary headache usually does not present with associated symptoms such as nausea, vomiting, photophobia, phonophobia or autonomic manifestations.[2]

A functional jugular valve prevents retrograde flow into the internal jugular vein.[3] In opposition, vein reflux has been associated with events of transient global amnesia,[3] physical exertion headache,[4] idiopathic intracranial hypertension associated with transverse sinus stenosis,[3] cough headache when related to uremia and deep vein thrombosis,[5] and a single report of cough headache without other associated pathologies.[6]

The association of insufficiency of the internal jugular valve with PCH is rarely described. In this work, we report two cases, present their clinical aspects, and discuss the proposed mechanisms of this association. Jugular insufficiency was considered as the presence of venous reflux flow lasting >0.88 seconds in the Doppler sonography as done previously in the literature.[7] This case report was approved by the Ethics Committee of the Federal University of Paraná General Hospital (registration 4.523.357; Certificate of Presentation of Ethical Appreciation number: 42357721.8.0000.0096) and written informed consent was obtained from both patients prior to data collection.

Highlights:

- We report two cases presenting insufficiency of the internal jugular valve with Primary cough headache discussing the proposed mechanisms of this association.
- Both patients had symptoms consistent with Primary cough headache who also had jugular venous insufficiency induced by Valsalva Maneuver verified in Doppler sonography.
- These findings may relate jugular venous insufficiency to Primary cough headache, but further studies are needed to confirm.

Case #1

A 79-year-old man of Portuguese heritage, Body Mass Index (BMI) of 25.9 kg/m², reported headaches with initial onset eight months ago associated exclusively with Valsalva Maneuver (VM) such as when coughing or sneezing. He denied previous history of headaches. The headache manifested as high intensity pain in

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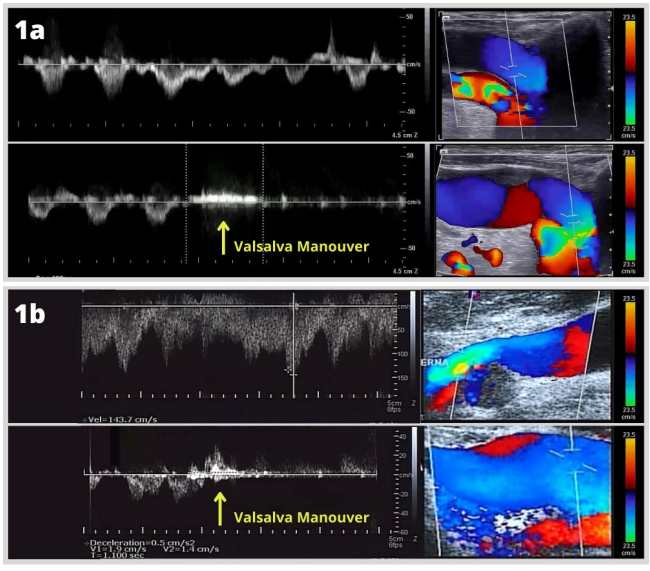
Layout Editor: Ana Maria Morales

Submission: Jul 21, 2022
Revisions: Oct 18, 2022
Responses: Nov 21, 2022
Acceptance: Nov 30, 2022
Publication: Dec 3, 2022
Process: Peer-reviewed

the right temporoparietal region with immediate holocranial distribution, of sudden onset, reaching peak intensity in 10 seconds, maintaining the same characteristics for 60 seconds, and easing within 10 minutes. No associated symptoms were described, and no abnormalities were detected on neurological examination. Brain Magnetic Resonance Imaging (MRI) showed moderate signs of supratentorial microangiopathy and small foci of hemosiderin deposition by micro-hemorrhages. Brain Magnetic Resonance Angiography (MRA) with both arterial and venous phases only showed signs of atheromatosis with irregularities in the vertebro-basilar system. The venous phase did not show any type of alterations suggestive of venous congestion such as arteriovenous malformations. Doppler sonography of the jugulars showed insufficiency of the Right Internal Jugular Vein (RIJV) with a reflux of 0.9 seconds during VM (*Figure 1A*). The left vein had a reflux of 0.7 seconds. Being clinically classified as having PCH, the patient was treated with 10 mg of propranolol and 1 capsule of horse chestnut (Aesculus hippocastanum), every 12 hours, with an improvement of 70% in pain intensity and frequency. Indomethacin, the first choice for PCH, could not be used because the patient had gastritis with consequent intolerance to the drug.

Figure 1a. Blood flow in the right internal jugular vein (RIJV) at rest (above) and in the Valsalva Maneuver (below). ***Figure 1b.*** Blood flow in the right internal jugular vein (RIJV) at rest (above) and in the Valsalva Maneuver (below).

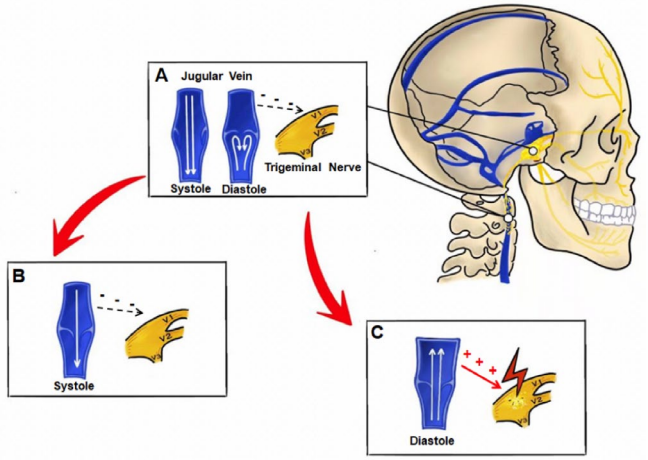


Legend: Figure 1a - The reflux confirms the insufficiency of the RIJV (below) in case #1. Figure 1b - In the second patient (case #2), blood reflux is noticed after the Maneuver, which reinforces the insufficiency of the RIJV (below).

Case #2

A 70-year-old man of Germanic heritage, BMI of 29.1 kg/m^2, reported onset of headaches one year ago after starting the use of a belt to control abdominal hernia post-cholecystectomy. He presented with two distinct headache pain patterns. The first was continuous, located on the right occipital region; of moderate intensity, radiating to the cervical region and aggravated by head extension, cough, and digital compression on the ipsilateral major occipital nerve. It was diagnosed as major occipital nerve neuralgia and controlled with an anesthetic block of the respective nerve. The second pain pattern was explosive, localized to the right temporoparietal region, with subsequent holocranial distribution, triggered by cough, reaching maximum intensity in 8 seconds and lasting up to 3 minutes, with improvement and pain resolution in 15 minutes. No associated symptoms were described and neurological examination was within normal range. It was diagnosed as PCH. Previously, he only had episodes of migraine without aura, becoming asymptomatic after 50 years of age. Brain MRI and MRA (arterial and venous phases) only showed diffuse cerebral atrophy and discrete atherosclerosis, respectively. The venous phase of the MRA also did not show any type of alterations suggestive of venous congestion. Doppler sonography demonstrated the presence of insufficiency of the RIJV with a reflux of 1.1 seconds with re-production of pain symptoms (similar to the PCH) during the VM (*Figure 1B*). The left vein had a reflux of 0.5 seconds. The patient was treated with the same therapeutic combination used in the first patient, with an improvement of 40% in pain. Indomethacin could not be used because the patient, coincidentally, also had gastritis. However, once the belt was removed, the patient became totally asymptomatic from the second headache pain pattern.

Figure 2. Internal Jugular Valve in Function.



Legend: A. System in normal function during diastole and systole without triggering nociceptive trigeminal fibers. B - Jugular valve insufficiency during systole and without Valsalva Maneuver. C - Jugular valve insufficiency during diastole, associated with Valsalva Maneuver and pre-valvular ingurgitation subsequent to nociceptive trigeminal trigger.

Discussion

We describe two cases of PCH, and specifically in the second case, the patient re-presented with his headache symptoms during the VM on the Doppler sonography that identified the presence of an associated right jugular insufficiency. The diagnosis of this primary headache entity is established according to the criteria of the International Classification of Headache Disorders 3rd edition

(ICHD-3), which are cited as follows: A - minimum of two headache episodes satisfying criteria B to D; B - caused by and taking place only in association with coughing, straining and/or other VM; C - sudden start; D - duration between one second and two hours; E - not better explained by another ICHD-3 diagnosis.[2] All the above mentioned factors were observed in our patients.

According to some authors, the associated jugular venous insufficiency could be a factor related to the pathogenesis of PCH, although some also have suggested that this entity could be considered a secondary headache when venous insufficiency is demonstrated.[6] The classification of these patients is complex, since it is not possible to directly relate the headache with jugular insufficiency, which is found in healthy individuals, with a prevalence of about 20–40% and increasing with age and obesity.[3]

Headache associated with the reflux of the internal jugular vein during diastole can be justified by increased intracranial pressure; cerebral edema; venous infarction, and stimulation of trigeminocervical nociceptors located on the surface of the venous system.[8, 9] Doepp et al. found that the retrograde flow of the jugular vein may play an important role in the pathophysiology of primary exertional headache, showing a 70% prevalence of jugular failure in symptomatic patients versus 20% in the asymptomatic control group.[4]

In a letter, Knappertz first hypothesized that patients with cough headaches had incompetence and/or a lack of functionality of the internal jugular valve, accentuated during VM, due to the increase in intrathoracic and intra-abdominal pressures.[10] The retrograde venous flow, due to insufficiency, produces an intravenous swelling with dilation of the plexus in the pre-valvular region, a site innervated by nociceptors from the trigeminal system, commencing with pain and resulting in trigeminal stimulation (*Figure 2*).[5] This effect is not only in the pre-valve region, but also having fluctuations in pressure causes an equidistant change from this location, as shown by a study that evaluated the pressure inside the sigmoid sinus at rest (160 mmH2O) and during the VM (425 mmH2O) in a patient with PCH and internal jugular valve failure.[6]

The VM is a controlled method for a better understanding of how the cough acts in the human body, since both produce similar physiological effects in increasing the venous pressure within the chest and abdomen.[11] This system is richly formed by veins that anastomose without the presence of a suitable valve system, mainly around the spinal canal. The transmission of the dilation of this venous system over the dura mater produces a collapse (pressure) on the neuraxis, increasing the pressure of the cerebrospinal fluid (lumbar pressure > cisternal pressure), which produces an upward wave in the lumbar cisternal direction, followed by a pressure balance and a subsequent reduction of lumbar pressure by inverting this wave from descending (cisternal - lumbar) and returning to the normal resting state.[11] This is one of the reasons why VM can result in an increase or appearance of headache due to increased intracranial pressure.

After VM, the blood withdrawn in the venous system returns to the heart, producing an immediate cardiac output, thereby leading to peripheral vasoconstriction with a transient increase in blood pressure and heart rate, and a subsequent compensatory bradycardia.[11] The more intense or persistent these autonomic changes, the more it can alter the control of the intracerebral neurovascular unit, reducing pain thresholds. Due to the physiology involved in VM and its compensatory responses and the consequences of a jugular insufficiency, the occurrence of headache in both reported cases shows a possible causal association between those factors. However, evidence demonstrating this direct etiological correlation is lacking in the literature. Therefore, our article brings a favorable occurrence to the association of a headache caused by VM and jugular venous insufficiency.

According to the current literature, Indomethacin is the recommended therapy for patients with PCH.[12] Both patients had clinical contraindications for the use of this medication, being prescribed propranolol in these cases.[13] Horse chestnut is occasionally used in the treatment of chronic venous insufficiency,[14] although not directly associated with benefits in jugular vein insufficiency. The report of these two cases is not able to prove the efficacy of the therapy with horse chestnut on the patients' symptoms, and therefore, more studies are required on the drug therapy of this specific condition. On the other hand, the subjective outcome was satisfactory according to both patients and the removal of the abdominal belt resulted in a complete resolution of the headache in the second case, strongly suggesting the correct diagnosis and treatment of this patient. That said, the clinical outcome of these cases can be summarized in good prognosis and control of the PCH in the long term, even if an ideal treatment is still unclear.

Conclusion

Two patients are described with symptoms consistent with PCH, who also had jugular venous insufficiencies verified in Doppler sonography, which may or may not favor the occurrence of this primary headache. Although this association was clinically observed, it is not yet possible to determine a correlation between these two pathologies, hence reinforcing the necessity of further clinical studies.

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Acknowledgments

We are grateful for the images provided by Ana Luiza Dias Valiente Engelhorn, MD.

Conflict of Interest Statement & Funding

The Authors have no funding, financial relationships or conflicts of interest to disclose.

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Cite as

Zhen F, Yamaguto GE, Yamaguto TT, Bochnia Küster JG, Piovesan EJ. Primary Cough Headache Associated with Jugular Insufficiency: Report of Two Cases. Int J Med Stud. 2022 Oct-Dec;10(4):417-420.

ISSN 2076-6327

This journal is published by Pitt Open Library Publishing

IJMS INTERNATIONAL JOURNAL of MEDICAL STUDENTS

Interview

Addressing Adversities in Caring for Mental Health in Rural Settings: A Conversation with Rural Mental Healthcare Practice Co-founder Dr. Taryn S. Van Gilder-Pierce

Ahmed Nahian,[1] Jewel Shepherd,[2] Taryn S. Van Gilder-Pierce.[3]

Abstract

Due to lack of mental healthcare facilities in rural areas, the population often resorts to private practice practitioners to address their need for mental health services. Dr. Taryn S. Van Gilder-Pierce and her husband, Dr. William D. Pierce founded their private practice in Yankton, SD in 2001. She has more than 25 years of training and experience treating individuals, married couples, families, and groups in rural South Dakota. The interview delves into the challenges faced by early career professionals in building a practice in remote areas and extends into the room for expansion within the field of rural mental health provision of services.

Key Words: Rural; Mental; Psychology; Telemedicine; Telerehabilitation (Source: MeSH-NLM).

Introduction

The disparities between prevalence of mental health needs and access to healthcare in the rural and urban areas of South Dakota is concretely visible.[1, 2] The rural areas are 1.6 times more likely to be impoverished than the urban areas of the state.[3] With only 24 publicly funded outpatient community mental health center clinics across the state, the rural population often resorts to private practice professionals for treatment.[4] Taryn S. Van Gilder-Pierce, Ph.D. received her education in San Diego, California, and currently maintains a group private practice in Yankton, South Dakota (Figure 1). She co-founded the practice in Yankton in 2001 with her husband, William D. Pierce, Ph.D. Her 2.5 decades of experience offers a wide spectrum of expertise with competence in individual, couples, family, and group settings that provide a concrete picture of mental healthcare as it plays out in rural underserved areas. Diagnostic assessment and psychological evaluations are provided as diagnostic services facilitate therapy planning. Forensic services offered include child custody evaluations and various criminally related evaluations. Her group serves people of all ages, from infants to the elderly, and offers therapeutic intervention that is direct, active, and collaborative to maximize long-lasting effects.

Ahmed Nahian (AN): Good afternoon, Dr. Van Gilder-Pierce. I really appreciate you taking the time to meet with me. As part of the Summer Program for Undergraduate Research in Addiction (SPURA) here at the University of South Dakota, our team looked at the role of rurality and rural settings on substance use disorders (Figure 2). However, I am interested in mapping out caring for mental health in rural settings, in general. To start, can you tell us a bit about your career till now, your journey into caring for mental health, and why South Dakota as a practice location?

Dr. Taryn S. Van Gilder-Pierce (TSVGP): My husband and I were educated in California and did predoctoral internships in Little Rock and Cabot, Arkansas, respectively from where we were recruited into a small group practice headed by a psychiatrist in southern Arkansas. We spent about five years in that non-metropolitan setting with a practice radius of about 90 miles, which is common for practitioners in rural areas. While servicing a dynamic cohort of patients, I became more expansive in my practice serving most needs of individuals ranging from the child and adolescent years to geriatrics as well as custody evaluations, while my husband expanded his expertise in substance abuse and prison practice. When my husband received a psychologist position in Yankton with the federal prison system, we were able to start a private practice in an area of need with the security his job offered. Despite knowing no one, the practice grew rapidly, given the great need for services.

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Layout Editor: Ana Maria Morales

Submission: Aug 2, 2022
Revisions: Sep 24, 2022
Responses: Oct 2, 2022
Acceptance: Nov 16, 2022
Publication: Dec 3, 2022
Process: Peer-reviewed

AN: What do you feel differentiates practicing in a rural setting as opposed to a setting in a metropolitan area?

TSVGP: You become a jack-of-all-trades when you practice in a rural setting. People want to be served locally. It is inconvenient for individuals seeking treatment or testing to drive to cities. I learned how to treat across the lifespan by practicing locally and expanding my areas of practice. Compared to my colleagues in the cities, who tend to be more specialized on their focus of care, I learned how to be more general while maintaining competency.

Figure 1. Dr. Taryn S. Van Gilder-Pierce's professional picture provided by her practice.

AN: What are the biggest challenges and rewards of practicing in a rural setting for you so far?

TSVGP: There would be different versions of experience depending on your role or mode of employment. I am an employer who also is an employee. As a self-employed private practice rural practitioner, I get to choose the array of services and who I serve while running a business. In my experience, rural providers get to see the benefit of their work in rural communities. People value your help and accessibility as there are so few practitioners to meet the tremendous amount of need. We, however, are on our own, which can be a disadvantage, especially in expanding to meet ever rising needs. Government grants are virtually impossible to acquire for private groups like ours, and we must self-fund a recruitment budget. We have less mobility for expanding our service provider team and overhead needs.

AN: In your perspective, what are the major features of a successful mental health caregiver in a rural setting?

TSVGP: I think one of the biggest factors would be resiliency. According to current research, practicing as a self-employed practitioner opens you up to more room for burnout.[5] Those of us who have been in this format of practice for a long time have been able to do so mainly for our resiliency; instead of feeling the need to work, you have the desire to work. Being truly engaged in the work feeds you rather than depletes you. It is not that the work is without stress but being energized by my work helps to preserve my personal mental health and secure my longevity of practice.

AN: What is the future of mental health in rural care? Do you think the government will take the initiative to provide opportunities for rural populations to have mental health support?

TSVGP: The government is trying, especially in South Dakota. The state has provided and is expanding mental health centers. In my experience, however, there are a lot of people who do not want a community setting and many prefer a private setting. The big push is to provide more private services offered by psychiatrists and psychologists by supporting and attracting them to rural areas. For example, in my field, the pre-doctoral internship offers a springboard into your career. It offers exposure to the location in which that internship is located and from where you may receive job leads. Although many states have an abundance of APA accredited pre-doctoral internships, South Dakota has only two internship placements at VA hospitals. In my understanding, pre-doctoral students who attend VA placements intend to remain working in the VA system. However, given that the VA system only serves veterans, attracting pre-doctoral students to South Dakota through the VA does not serve the nonveteran population. APA accredited internships are time-consuming for those institutions that offer them. Therefore, unless a large institutions with resources, such as a private hospital, begin offering pre-doctoral accredited internships, we must seek alternate avenues to recruit psychologists as well as psychiatrists to our state.

Figure 1. Ahmed Nahian, Recipient of the Summer Program for Undergraduate Research in Addiction (SPURA) Grant at the University of South Dakota, with His Mentor, Dr. Jewel Shepherd, After the Completion of His Summer Project Presentation in Lee Medical Building, Sanford School of Medicine, Vermillion, SD.

We were lucky enough to recruit an interested candidate, Alexandra Pagel, PsyD, to our team due to her desire to be closer to her family in North Dakota and Minnesota. Unless funding for training opportunities is provided in the private industry, we will not have an abundance of psychologists and psychiatrists interested in moving to rural communities.

AN: Can you tell us about the history of your practice and what led to its longevity?

TSVGP: We started in 2001 without any connection in the local area. As we planned to start the practice in January 2002, we listed our telephone landline at home under our business heading. We began getting calls for services shortly after listing it in summer 2001 and started the practice in November 2001 in advance of our previously planned opening. Starting from the scratch has its own benefits in that we could develop the practice in a manner that we felt best served community needs. The word-of-mouth strategy played a key role as did building strong referral relationships with area medical providers, other mental health providers, and attorneys. People want to be served locally and when you demonstrate competence, word spreads quickly.

AN: Do you think rural populations do not want to receive or do not have the means to reach out for mental health support?

TSVGP: We often talk about stigma in mental health, which is something that stands in the way of individuals seeking care. But, we forget to see the arial view of seeking mental health support. As a group of private practice psychologists, we do not see a large segment of indigent cases that are typically serviced for free or a greatly reduced rate through the local community mental health centers. Most people we serve therapeutically have private insurance, Medicaid, or Medicare. Legally related services are a cash product. For individuals who do not have some type of insurance, cash services are prohibitive, resulting in long waitlists at the community mental health centers. People who want services, sometimes, cannot get them due to a limited number of mental health professionals, in addition to a lack of financial resources. South Dakota developed a program to meet the needs of uninsured individuals in the state recently. However, we were willing to provide services through the program, because by history, individuals with no insurance and a lack of finances often sought services at our local community mental health center, and we had very few individuals seeking services through the program with our group. Although we were serving those who presented through the voucher system, we were discontinued as providers because our numbers were not high enough. The program was there, and we were willing to participate to meet needs of those without insurance population, but that opportunity ended for us.

AN: We recently underwent a global pandemic, and statistics indicate that more people reached out for mental health support. Can you tell us a bit about how the pandemic changed how you delivered mental health support to a rural population?

TSVGP: I have been practicing since the 90s, so the pandemic was a big learning experience for me as a practitioner. I had not previously utilized telehealth platforms to provide services. However, Dr. Pagel, who came from and trained at a metropolitan area, had experience with telehealth. Seeing what we were soon to face and having an experienced telehealth platform provider, we quickly made a smooth transition to a telehealth practice using Doxy.me, where you and I are meeting today. Patients were one click away from accessing care for their mental health, which is so fascinating now that I have experienced it. As the pandemic began subsiding, however, most people returned to in-person meetings.

AN: Our research found that adolescents living in rural areas are more likely to fall into substance-use disorders. Do you see this trend coming up in your practice?

TSVGP: Prior to my husband actively joining the practice following his retirement from the Department of Justice, we saw few treatment requests specifically for individuals with substance use disorders. Most of those needs are met through the community mental health center that has an extensive drug and alcohol treatment program and serves legally required substance evaluations. However, since establishing a caseload, my husband's expertise in substance abuse is being sought with a large segment being adolescents. In our group, we are seeing referrals for youth resorting to chronic marijuana use.

AN: While psychiatry and psychology are clinically proven and revered in the medical field, there is still a stigma in seeking care for mental health. What is the current state of people's trust in mental healthcare professionals?

TSVGP: When someone reaches out for treatment, despite the stigma that remains a clear part of the rural community, the biggest hurdle is trust. People who fear being ridiculed for their mental health conditions want utmost privacy. Although, in the mental health field confidentiality is a given, being in a setting that does not suggest exposure by being seen by people they may know is sometimes hard to navigate in a small town. Some individuals are not as affected by stigma and own their mental health whereas others are more challenged to seek help. Privacy beyond confidentially is vital.

AN: Why should aspiring psychiatrists and psychologists consider practicing in rural settings?

TSVGP: As a career, rural healthcare can be fruitful. In the private sector, compensation is competitive. The setting is very peaceful. Rural settings are also engaging because you can become actively involved in the locality. It is a meaningful life.

AN: What are ways interested students can get involved with mental healthcare professionals in rural settings?

TSVGP: Students can reach out to volunteer most times with any practice setting. We have seen a rising demand for paid experiences, however. For those needs, I would suggest that students look to their university programs to contract with local entities. In the past, we have employed Ph.D. students as testing technicians to help with our heavy testing caseload. Although not a full training experience, it gave them hours needed in test administration. With that connection, we recently have been designated as a testing practicum training site for the University of South Dakota. With insurance-based testing services, we can bill for a certain amount of the student's time and thus, offer a paid position with the supervision required for a full training experience, something we did not have the luxury to do in the past. Also, as another example, you have funding from SPURA to conduct this project.

Living with unfulfilled or inadequately treated mental health needs has detrimental repercussions that are disproportionately felt by rural Americans. This long-standing issue's characteristics are clearly described by the need for care highlighted in Dr. Van Gilder-Pierce's story. Starting a practice from the scratch brought along many obstacles that initially challenged the flow of her practice, but she saw that areas of need should have the necessary help they deserve. The anticipated effects on rural mental health will be achieved through research that examines novel treatment systems for rural populations, evaluates suicide prevention techniques, and advocates for better access to mental health practitioners. It is also necessary for researchers to examine the effects of innovative techniques on behavior and patient outcomes to generate larger government funds to shed light on mental health services in rural areas.

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Acknowledgments

This interview was conducted as part of the Summer Program for Undergraduate Research in Addiction (SPURA), hosted by the University of South Dakota (USD). Thanks to Diep Tran, M.S. for helping with data analysis that helped in setting the background for this project. Utmost appreciation for Brian Burrell, Ph.D. and Lisa McFadden, Ph.D. for aiding the students through the facilitation of the research program.

Conflict of Interest Statement & Funding

The Authors have no financial relationships or conflicts of interest to disclose. This research was funded by the National Institute on Drug Abuse (NIDA) of the National Institute of Health (NIH) grant R25-DA033674. The content is solely the responsibility of the authors and does not necessarily represent the official views of the previously mentioned institution.

Author Contributions

Conceptualization: AN, JS. Methodology: AN. Software: AN. Validation: JS. Formal Analysis: AN. Data Curation: AN. Investigation: AN. Resources: JS. Writing — Original Draft: AN, JS. Writing — Reviewing & Editing: TSVGP. Visualization: AN. Supervision: JS. Project Administration: JS. Funding Acquisition: JS.

Cite as

Nahian A, Shepherd J, Gilder-Pierce TSV. Addressing Adversities in Caring for Mental Health in Rural Settings: A Conversation with Rural Mental Healthcare Practice Co-founder Dr. Taryn S. Van Gilder-Pierce. Int J Med Stud. 2022 Oct-Dec;10(4):421-424.

ISSN 2076-6327

This journal is published by Pitt Open Library Publishing

IJMS INTERNATIONAL JOURNAL of MEDICAL STUDENTS

Experience

The Importance of Incorporating Service-Learning Projects into the Medical School Curriculum

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Abstract

The incorporation of Service-Learning Projects (SLPs) into the medical school curriculum is an effective way for students to adopt the leadership skills necessary to apply to their traditional education on social determinants of health into targeted action. For our SLP, our team of second-year medical students organized an after-school science program to address the concerns of academically at-risk K-5th grade students at a local Non-Profit Organization (NPO). The goal was to increase interest in Science, Technology, Engineering, and Mathematics (STEM) subjects and careers. Our weekly lesson plans always utilized experimental learning models in an effort to foster engagement. Throughout the duration of the project, student participation grew to three-fold of the initial cohort. Through this SLP, we identified a disparity within our local community and developed a targeted solution to address this issue. We honed our skills that were not traditionally covered in a medical school curriculum, including program planning, fundraising, marketing, etc., and thus, feel more capable of to take on significant leadership roles in the future. Additionally, our specific SLP provided us with an invaluable lesson in fostering communication skills that will benefit patient education.

Key Words: Medical Students, Medical Education, Mentorship, Leadership (Source: MeSH-NLM).

Introduction

Physicians have a unique authority to lead projects addressing healthcare disparities due to their extensive knowledge and training, as well as the inherent high status associated with their occupation.[1] While traditional medical training prepares students to recognize socioeconomic status, ethnicity, and insurance coverage as social determinants of health,[2] there is a shortage of physicians graduating with the leadership skills necessary to influence these frameworks.[3]

Many studies have called for the incorporation of leadership competencies in community service into the medical school curriculum.[3,4,5] A study at the University of Colorado Denver School of Medicine showed that medical school curriculums that incorporate community-based service projects are "effective at increasing student empowerment and disposition toward community service".[3] Students participating in community-based service projects learn to identify problems in their community, formulate a project to directly mitigate it, and actively implement a solutions-based approach. Nationally, these programs have shown an "increase [...] students' self-efficacy around multiple dimensions of leadership skills (e.g., fundraising, networking, motivating others)".[4]

Florida Atlantic University's (FAU's) College of Medicine has established a SLP requirement for all second-year medical students. Here, students work in small groups with local NPOs, assessing any challenges (medical and non-medical) they may face and designing targeted interventions.

For example, our group was assigned to an NPO that serves academically at-risk K-5th grade students. During our introductory session, we asked the students to create dream boards; this allowed us to understand the students' aspirations, which included dreams of becoming rich, models, teachers, and Whole Foods employees. We were surprised that no students had interests in pursuing medical careers, and almost none chose science. When probed, the students commented that their disinterest in higher education originated from repetitive textbook lessons and homework assignments, in addition to labelling science as "boring". Their concern was that we would use our sessions to make them study. Reflecting on our own journeys to medicine, we realized that our greatest motivators and points of inspiration were experiences that helped us conceptualize "boring" textbooks topics. For this reason, we created an after-school science program that used hands-on projects as the centerpiece of each weekly lesson.

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Copyeditor: Marina Shatskikh
Proofreader: Laeeqa Manji
Layout Editor: Ana Maria Morales

Submission: Apr 26, 2022
Revisions: May 14, 2022
Responses: May 24, 2022
Acceptance: Jul 11, 2022
Publication: Dec 3, 2022
Process: Peer-reviewed

While our school's SLP initiative is not funded, we were able to execute our plans thanks to generous donations from FAU's faculty of medicine.

The goal of our project was to make learning fun and in so doing, improve student engagement and interest in science topics. Through our SLP, we aimed to inspire the next generation of learners to pursue STEM careers

Figure 1. An Example of One of The Formal Lesson Plans We Created for Each Session.

SLP Lesson Plan

Title: What Do Plants Need to Grow?
Date: Tuesday, September 28, 2021 (semester-long project)
Learning Objectives:

- Students will think critically as to what distinguishes animals and plants and what plants need to grow
- Students will learn the parts of a plant and their function
- Students will understand the importance of plants to the environment and animals
- Students will each learn to care for their own seed/plant by applying what they've learned today. They will follow their plants longitudinally throughout the semester

Students Should Understand:

- Plants are living things that make their own food
- Plants grow from seeds
- All plants need sunlight and water to grow
- Plants grow best in soil, but some can grow without it
- Most plants have roots (for water absorption), stems (to stand tall and support their leaves), and leaves (to collect sunlight). Many also have flowers (to grow new seeds)
- Plants provide oxygen to the environment
- Plants are food for many animals

Lesson Plan/Guiding Questions (3:00-3:30PM):

1. "What kinds of plants have you seen before?" *flowers, trees, bushes, etc.*

2. "What makes an animal different from a plant?" *plants can make their own food using sunlight, while animals must eat plants or other animals (who eat plants) to survive*

3. "What do plants need to grow?" *all plants need sunlight and water to grow (different ones need different amounts). Plants grow best in soil, but some can grow without it*

4. "What are the parts of plant? What is each of their function?" ***use printed image***

   *Plants grow upwards from **seeds***
   *They grow **roots** downwards into the soil that absorb water and nutrients*
   *They have **stems** that support **leaves** that soak up sunlight to make food*

*Many plants have **flowers** that can grow more seeds*

Discussion

Each session took several hours of preparation to choose a topic, research language to properly convey these topics, and design a project that was stimulating, but also within budget. For example, when creating our lesson on electricity, traditional "circuit kits" that we found online were expensive. However, we came up with a cheaper alternative: batteries, lightbulbs, foil, and a variety of household conductors and insulators for students to experiment with. This method truly cemented nuances, like the difference between "conductors" and "insulators", to students who were otherwise struggling to grasp the concept of varying flow of electrons through different materials.

We took on the role of teachers, creating lesson plans with objectives, guiding questions, whiteboard interaction, and stepwise directions for the accompanying project. Throughout the weeks, students communicated a greater degree of enthusiasm, not only for our sessions, but for science in general. By the end of the semester, students' interest in our program increased to the point where our NPO added an additional classroom of students to our sessions. We believe that these enriching projects have positively impacted the students and inspired them to further explore STEM subjects.

Figure 2. A Student Using his Knowledge of Circuits and Conductors to Turn on a Lightbulb.

As future physicians, we must actively garner the tools necessary to bridge gaps in medicine. This begins with recognizing the importance of education- a key component of the patient-physician relationship. Our SLP gave us the opportunity to practice communication and simplification of complex scientific topics to a wide audience. Furthermore, our commitment to fostering engagement in learning translates to our future duty to encourage active discussions and patients' participation in maintaining their own health. These are skills we hope to continue to expand throughout our medical education.

On a small-scale, advocating for the establishment of similar SLPs across all medical school curriculums would minimize the negative mindset to being successful that medical students tend to develop regarding their impact on the social determinants of health.[4] Although medical students can be taught how to identify social determinants of health such as literacy, accessibility, and income, it is important to instill in them the drive to amend these disparities in healthcare. SLPs serve as a microcosm for the complex, real-world problems that medical students will face in practice. They allow students to build the critical thinking skills necessary to not only identify socioeconomic obstacles in patient care, but also the forethought to take initiative and enact a functional plan that will address them. Through SLPs, students are able to see their direct impact on the community and be empowered to advocate for their future patients' health. Without this, students may feel discouraged when they are able to identify social determinants of health but lack the basic foundational tools to help fix them.

On a larger scale, these experiences prepare medical students to take on more significant leadership roles in the healthcare field as they progress through their training.[5] Students develop a breadth of skills not traditionally taught, including networking, program planning, fundraising, marketing, motivating, etc.[4] Though our SLP experience was required of all FAU medical students, we are eager to pursue and create similar projects in the future, and are confident that we will be successful.

As the COVID-19 pandemic further exacerbates challenges, both healthcare-related and non-healthcare-related, faced by underserved populations in our communities (access to education, medical care, food, and other resources), medical students would benefit from the formalized incorporation of SLPs into their medical curriculum. These SLPs should be entirely student-led and should be continued until the identified challenge has been addressed and resolved in a cohesive manner.

Summary – Accelerating Translation

Title: The Importance of Incorporating Service-Learning Projects into the Medical School Curriculum

Florida Atlantic University's Schmidt College of Medicine's requirement that all second-year medical students complete a Service-Learning Project (SLP) afforded us the opportunity to become leaders in our community and gain invaluable skills, such as simplification of complex topics and communication to a wide audience that will benefit our future careers as physicians. We present our experience in hopes of inspiring additional medical schools throughout the country to incorporate SLPs into their curriculum. In doing so, we believe it is possible to cultivate physicians with leadership competencies and motivation to tangibly influence barriers to health within their community.

Our group of 4 medical students worked with academically at-risk K-5th grade students, with the goal of generating interest in Science, Technology, Engineering and Mathematics (STEM) subjects. At our first session, we asked the students about their interests and inquired about their future goals and aspirations. We quickly realized that a lack of interest in STEM fields was due to traditional textbook and homework teaching styles, and decided to target this disinterest as the goal of our SLP. To increase student engagement, we designed weekly hands-on lessons and projects that would teach students STEM topics through experiential learning. For example, one week's lesson focused on electrical circuits and the basics of electricity. In order to accomplish this, we brought in batteries, lightbulbs, and other simple materials needed to create a circuit. We had the students experiment with the materials to figure out how to light the lightbulb. As they slowly discovered that aluminum foil worked better than yarn, we were able to explain the difference between conductors, insulators, and other electricity basics.

Implementation of our SLP required creating weekly interactive lesson plans, fundraising money for materials, and purchasing necessary materials. Our school faculty graciously donated money for us to purchase the materials needed for each lesson.

Every week, we saw enthusiasm for learning increase. This was evident in the smiles we received as soon as we walked in the door, in the increased participation from lesson to lesson, and in the various questions crafted by our students who were curious about topics they previously dismissed. We believe that our time with this academically at-risk community has changed their viewpoint not only on STEM, but also on learning, and hopefully inspired them to pursue careers in STEM.

While the community could benefit from formal SLP programs in all medical schools, medical students such as ourselves could also benefit tremendously. For example, we learned how to work with community partners to identify problems and address them directly. We also learned how to leverage our positions as medical students to positively influence our community. Additionally, we gained first-hand experience simplifying complex topics in a way that primary school students could understand; a skill that will become necessary in our future careers as physicians who must explain complicated medical diagnoses and pathophysiology to patients with varying educational backgrounds.

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Acknowledgments

We would like to thank Dr. Peter Averkiou, our faculty mentor who helped create the Service Learning Project initiative at FAU College of Medicine.

Conflict of Interest Statement & Funding

The Authors have no funding, financial relationships or conflicts of interest to disclose.

Author Contributions

Conceptualization, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Supervision, Visualization, Writing – Original Draft Preparation: SL, RA, AE, SSM. Writing – Review & Editing: SL, RA, AE, SSM, PA.

Cite as

Lahiri S, Abdin R, Elimelech A, Massimilian SS, Averkiou P. The Importance of Incorporating Service-Learning Projects into the Medical School Curriculum. Int J Med Stud. 2022 Oct-Dec;10(4):425-428.

ISSN 2076-6327

This journal is published by Pitt Open Library Publishing

IJMS INTERNATIONAL JOURNAL of MEDICAL STUDENTS

Experience

Why the Furor about Polio?

Samuel Amo-Tachie.[1]

Abstract

Poliomyelitis is one of such diseases as measles and dracunculiasis that can be eradicated, because it meets the criteria for eradicable diseases: being infectious, having humans as major host, effective vaccines or treatment available for their control, and the availability of political and financial support for the eradication efforts. Ghana, with the rest of the world has already come far in the fight against polio, by reducing its incidence drastically (to zero as of now). The disease can only be prevented but not reversible, once infection results in paralysis and leaves victims permanently maimed, almost invariably reducing their quality of life. The recent outbreak (caused by a circulating vaccine-derived virus of the type 2 strain) was a call to pay more attention to the disease in order to realize the global aim of its elimination. All the attention needed by the disease is center around vaccination, which indeed was the tool used in combating the outbreak that ensued in Ghana.

Key Words: Poliomyelitis; Vaccine; Poliovirus (Source: MeSH-NLM).

The Experience

As final year medical students, we were privileged to visit less privileged districts in the country, to observe the health management systems there. I happened to be in one such district (Tarkwa in the Western Region of Ghana) with a colleague during which time some cases of polio were recorded during our community outreach. Coming so close to such cases of public health importance involving children caused me heartbreak, disappointment and frustration. Even though we were not privy to the details of the affected children, the atmosphere felt like that of a lost major battle whenever we met with the District Health Management Team (***Figure 1***).

Figure 1. Meeting with the District Health Management Team at Tarkwa.

Poliomyelitis is a highly contagious, disabling, and potentially life-threatening disease of the nervous system.[1] It has several manifestations, most common of which is paralysis, when it affects the spinal cord. Affecting mainly children under 5, it usually results in irreversible paralysis. The associated paralysis and limb deformities have made it a deplorable morbidity. Researches necessitated by this epidemic in developed countries led to the development of the polio vaccines, which have dramatically decreased its incidence.[2] This disease has neared eradication, as active transmission persists in just a couple of countries—Afghanistan and Pakistan.[3] Ghana follows the Global Polio Eradication Initiative (GPEI) and had been polio-free for about a decade, until August 2019 when a case involving a 2-year old girl was confirmed in the North-East Region.[4] About 30 more cases were confirmed and investigations revealed it was a circulating vaccine-derived poliovirus (cVDPV). Three of these 30 national cases were registered in the region I visited.

Significance

Poliomyelitis meets the criteria for eradicable diseases: being infectious, having humans as major hosts, effective vaccines or treatment available for their control, and the availability of political and financial support for eradication efforts.[5-6] The disease can only be prevented but not reversible, once infection results in paralysis and leaves victims permanently injured, almost invariably reducing their quality of life. Given that most cases occur in low socioeconomic settings as the one I visited,[7] these unfortunate children are unable to achieve their full potentials because they do not have access to rehabilitation facilities.

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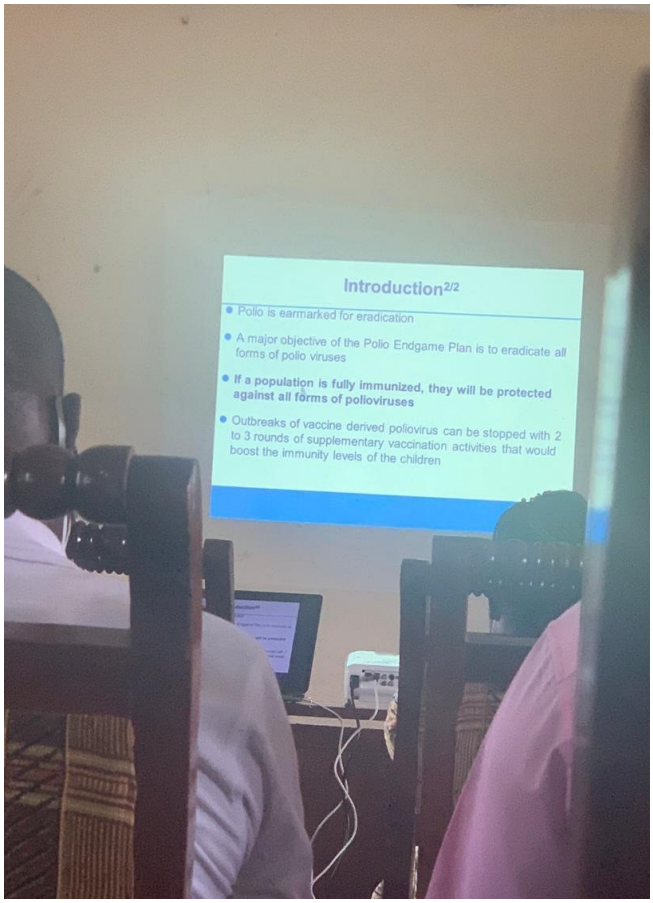
Proofreader: Joseph Tonge
Layout Editor: Anna-Maria Chantaliyska

Submission: Apr 4, 2022
Revisions: May 5; May 12, 2022
Responses: May 12; Jul 13, 2022
Acceptance: Jul 15, 2022
Publication: Jul 19, 2022
Process: Peer-reviewed

Unchecked outbreaks could abate decades of expenditure channeled into its eradication—a major reason for furor in the public health world. Again, immunity to one strain of the virus does not confer immunity to another.[8] This is what gave room for the emergence of the cVDPV (in Ghana) as we shifted from the use of the trivalent oral polio vaccine (OPV) to the bivalent one, which excluded the type 2 strain. There is history that should neither be relived nor forgotten—when up to 75,000 children were paralyzed from this infection all across the continent by 1996.[7]

The GPEI guidelines stipulate minimum response standards following notification of a new poliovirus, or the spread of poliovirus to a new geographic area or population. These include: detailed investigation and risk assessment, enhanced surveillance to increase sensitivity and confidence that any ongoing person-to-person spread of poliovirus is quickly detected, and vaccination response.[9] These steps are effective and comprehensive; following them has saved many countries including Ghana. During my stay at Tarkwa, a mop-up vaccination exercise was being conducted to help curb the outbreak (this was a nationwide program) for which my colleague and I attended orientation programs organized for vaccination volunteers (***Figure 2***).

Figure 2. At the Orientation for Vaccination Volunteers.



About the Virus and the Outbreak

The poliovirus is an enterovirus surrounded by a protein coat and no lipid envelope (making it resistant to harsh gastrointestinal conditions) with 3 strains: types 1, 2 and 3; with type 1 accounting for most cases. It is termed wild-type when acquired naturally and vaccine-derived when related to vaccinations. Administration of the OPV allows polioviruses to replicate for a while in the gut of the recipients and shed in stool, which is normal. Following eradication of the type 2 strain (and its removal from successive vaccines in 2016),[10] the subsequent generation of children benefited from the herd immunity generated by the previous generation (who had received trivalent OPV) against type 2. With time however, the efficacy of this herd immunity was lost, while some of those who had received the trivalent oral vaccine still shed the type 2 strain in their stool. Furthermore, some of the children had not received any polio vaccination. Children who were immunologically naive to this strain got exposed via the faecal-oral route resulting in some developing severe polio, which could also be spread (resulting in the cVDPV). Successful spread of the cVDPV was facilitated by its mutability[13] and insanitary practices, such as improper hand washing. Environmental sanitation officers performed laboratory testing on the sewage of some of the affected communities and found traces of the type 2 strain in the sewage (indicating active shed in faces). This explained the mechanism of the outbreak which was followed by mass immunization with OPV for Type 2. Following this exercise, there have been no new recorded cases, proving the effectiveness of vaccination.

I was amazed at the sort of stir a disease like polio could cause given the timing of this outbreak (which was in the 3rd quarter of 2020 shortly after lockdown restrictions for Covid-19 were eased). This is because for that period of time it felt like even the much feared and relatively novel COVID-19 had been muffled amid the stir. We had just been allowed back to school but at that moment paid less attention to the pandemic and focused on protecting the children endangered by the epidemic through the vaccination exercises. It was a breath of fresh air getting our minds off daily news on the pandemic while actually imparting the lives of children.

Conclusion

Polio is a global menace that has taken lives and maimed children for life. The worldwide effort that has culminated in its near-elimination could be annulled by even a hint of negligence to the threatening epidemic. Many other African countries having experienced this cVDPV tragedy, polio threatens to leave another dent in history. The furor about polio is not just a minor battle but a potential global crisis. Vaccination is a simple but concrete means of its complete eradication. Amendments to regular vaccination schemes in the face of such crises as well as implementation of all indicated regulations of the GPEI are all it takes to end it all. We are near the pinnacle of a global achievement and need not rest now to climax our fight.

Summary – Accelerating Translation

Polio is a disease that causes paralysis of children especially below age 5. It is uncommon these days because of mass immunisations done by various countries against the poliovirus which indeed is a global effort to eradicate the disease. An outbreak happened in a number of countries, including Ghana, which was caused indirectly by vaccines. It was an indirect cause of the outbreak because administration of the vaccines did not cause disease, but the resurgence of and old strain of the virus which existed in older versions of the vaccine. This old strain was being shed by people who had received the older vaccines living in unhygienic conditions which facilitated the spread (as the virus is spread from stool to mouth). This outbreak caused reason for concern because polio is a devastating disease that is very preventable and even near eradication. This article addressed the depth of seriousness of the situation and why this disease should not be neglected but fought to eradication.

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Acknowledgments

The author wishes to commend the Head of Department of the Department of Community Health of the University of Ghana Medical School (Prof Alfred Yawson) for ensuring his safe transportation to the community where he got to have such a life-changing experience.

Conflict of Interest Statement & Funding

The Authors have no funding, financial relationships or conflicts of interest to disclose.

Author Contributions

Conceptualization: SAT; Data Curation: SAT; Formal Analysis: SAT; Investigation: SAT; Methodology: SAT; Project Administration: SAT; Resources: SAT; Software: SAT; Supervision: SAT; Validation: SAT; Visualization: SAT; Writing – Original Draft Preparation: SAT; Writing – Review & Editing: SAT.

Cite as

Amo-Tachie S. Why the Furor about Polio?. Int J Med Stud. 2022 Oct-Dec;10(4):429-31.

ISSN 2076-6327

This journal is published by Pitt Open Library Publishing

IJMS INTERNATIONAL JOURNAL of MEDICAL STUDENTS

Experience

Research Experience of Medical Students Collaborating in an International Peer Research Mentorship Program

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Abstract

In the past decade, research and research mentorship have undergone significant changes with advancements. Since students are actively seeking research opportunities and participating in research workshops, a new era of mentor-mentee programs have emerged by necessity. The peer research mentorship program (PRMP) organized by the International Society for Chronic Illnesses (ISCI) facilitates a global collaboration that does not only improve the quality of research, but also encourages interpersonal relationships and incorporates expertise from different fields. In this article, medical students and early graduates share their experience of participating in a cross-country peer-to-peer mentorship and comment on their learnings and observations. This is an experience report of mentors and mentees in the ISCI-sponsored PRMP. Mentees learnt about metabolic syndrome, alternative medicine, and narrative reviews, and the mentor became more confident in scientific writing and leadership while gaining an in-depth knowledge about the integrative management of metabolic syndromes.

Key Words: International educational exchange; Medical students; Collaboration; Networking; Research (Source: MeSH-NLM).

Introduction

Physicians practicing in tertiary-level hospitals in low- and middle-income countries (LMICs), such as Pakistan and India, spend more time treating and managing patients, and less time engaging in medical research. Few professors or academic physicians at these hospitals concurrently conduct good quality, authentic research and mentor medical students. Insufficient government funds and inadequate state-of-the-art research infrastructure further aggravate this challenge in the medical field.[1,2]

International research collaborations exist among researchers from different areas of expertise with geographical and cultural differences. Such collaborations provide opportunities for learning, skill development, scientific knowledge exchange, and communicative skill improvement to facilitate growth and development, both professionally and personally. They are cost-effective and sustainable solutions for stimulating the development of soft and scientific skills and promoting health-related research in LMICs.[3] Furthermore, papers produced by international research collaborations are more likely to be cited than others by domestic collaborations.[4] At a national level, such projects increase scientific and technological capacity and boost economic performance.[5] However, several challenges, such as credit and responsibility sharing, meeting time scheduling according to different time zones, disagreement among researchers, and research team member attrition, may hinder a smooth and progressive collaboration. Social and geopolitical tensions, such as the recent China-USA rift, have reduced research alliances between China and the USA.[6]

In this article, we describe the experiences of medical students and early graduates who participated in a cross-country peer-to-peer mentorship.

Experience Report

Organization and Research Program

Interventions are needed globally to provide guidance and strategies on peer-research mentorship. One such research program is the Peer Research Mentorship Program (PRMP) launched by the International Society for Chronic Illnesses (ISCI), a non-profit venture with the vision of improving the quality of life of people living with chronic conditions, in August 2021 to guide new researchers in an organized manner.[7] PRMP leadership consists of the project head, national and regional project heads

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Editor: Francisco J. Bonilla-Escobar
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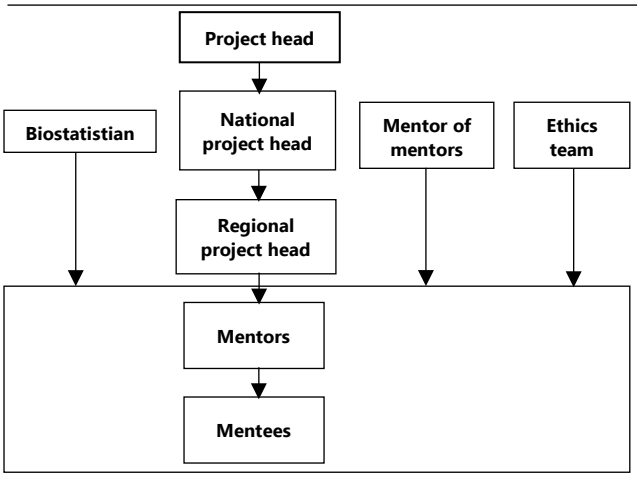
Copyeditor: Johnmark Boachie
Proofreader: xx
Layout Editor: Ana Maria Morales

Submission: Mar 25, 2022
Revisions: Apr 18, 2022; Jul 21, 2022
Responses: Jun 23, 2022; Jul 28, 2022
Acceptance: Aug 9, 2022
Publication: Dec 11, 2022
Process: Peer-reviewed

(NPH/RPH), mentor of mentors, mentors, and mentees (*Figure 1*). Teams are created by the leaders of PRMP based on the topic of interest and study design selected by each researcher in the PRMP Application Form available on ISCI's website, simultaneously making an effort to promote diversity, in terms of geography and designation (*Figure 2*). Mentor-to-mentee ratio is maintained at 1:5 in most teams. Hence, depending on the availability of mentors, the program enrolled medical students as mentees at the beginning of each rotation. As of July 2022, 70 research groups were active in PRMP, with 70 mentors and >450 mentees, consisting of medical students, interns, resident doctors, recent medical graduates, biomedical engineering students and fresh graduates, and PhD students from >15 countries in Asia, North America, Europe, and Africa.

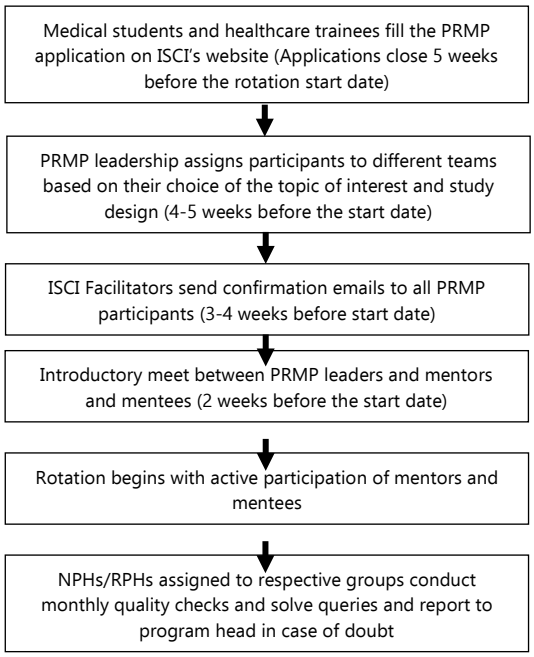
Figure 1. Hierarchical Representation of the Members of Peer Research Mentorship Program.



Pre-requisites for mentees, if they wished to conduct original studies (OS) and case reports (CR), were access to institutional ethics committee (IEC) oversight at home affiliation and permission to share de-identified patient data with researchers from other institutions. These pre-requisites did not apply if a mentee wished to learn systematic review (SR), meta-analysis (MA), or short communication (SC). To participate in SR/MA, mentees needed to have prior research experience and at least one original study publication. Since several medical postgraduates waiting to join a residency program were not affiliated to any institute, the ISCI did not require university affiliation for participation in PRMP. Pre-requisites for mentors consisted of at least one publication in the study design that the mentor wished to teach and could commit for the duration of that rotation. Mentees needed to dedicate 5–7 hours per week for all study designs, whereas mentees were required to dedicate 5–7 hours per week for SR/MA and 2–3 hours per week for OS, CR, and SC.

Mentees could contact respective mentors via WhatsApp messenger and email. All researchers were required to respond to texts and emails within 1 week. Mentors arranged biweekly group meetings to receive updates on mentee activities and resolved issues (*Figure 3*). This format of peer-to-peer mentorship made it easier for mentees in PRMP to seek guidance and actively participate in group discussions, thus, reinforcing the Socratic method of teaching. From case reports to meta-analyses, mentees could choose any type of study design of their preference. Participation in this program was without any monetary cost; therefore, research groups submitted their manuscripts to journals with low processing charges. Each rotation of PRMP was 6 months long, and peer researchers were expected to complete their studies in a time-bound fashion. The quality of research work was maintained by regular quality checks conducted by NPHs/RPHs during which respective groups were checked to ensure compliance with their timelines with their timelines and inactive members were identified and reported back to the Project Head. Authors needed to submit only to PubMed indexed, and peer-reviewed journals to uphold the quality of publications. The end goal of PRMP was to create a network of experienced and trustworthy group of early-career researchers. This workforce would increase the possibility of conducting large-scale and long-term studies of high impact. Results from these studies would then be reported to policy makers, clinicians, and patients.

Figure 2. Process of Team Allotment by PRMP Leadership.



Legend: RMP: Peer Research Mentorship Program. ISCI: International Society For Chronic Illnesses. NPH: National Project Head. RPH: Regional Project Head

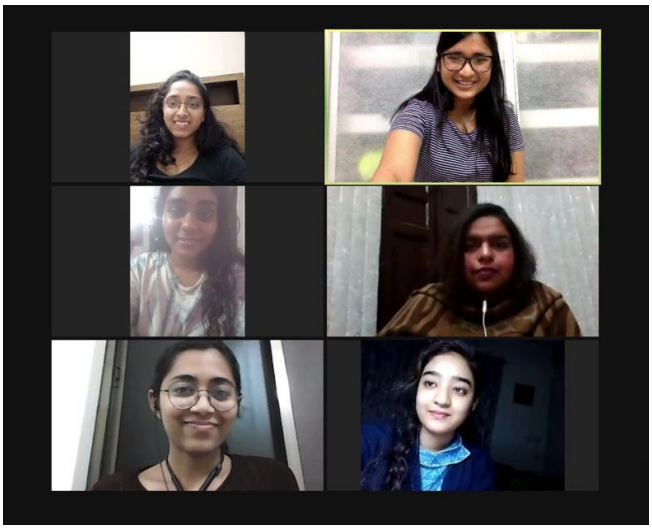
Mentees

We signed up for the PRMP in the August–December 2021 rotation, and our group included five dedicated mentees who were medical students and intern doctors from Karachi Medical and Dental College and Xinxiang Medical University in Pakistan, and JSS Medical College, Baroda Medical College, and Government Medical College of Miraj in India. Our mentor was a research scholar at Harvard Medical School of Postgraduate Medical Education with >10 publications (h-index =

2). Team members had had no previous interactions prior to signing up for the program. After conducting a thorough literature search, we chose to perform a narrative review on metabolic syndromes. As mentees, we received mentorship on literature search, research methodologies, scientific writing, editing, journal selection, and reviewing according to the Scale for Quality Assessment of Narrative Review Articles (SANRA) guidelines. Throughout the project, we were encouraged to share our ideas and express our opinions, which enabled critical questioning of the literature and drawing appropriate conclusions from the data. In some instances, we were asked to teach and guide our fellow mentees, thereby instilling a leadership attitude and fostering an alliances. We were guided through every step in the process, from framing research questions to corresponding with the journal editor.

Unlike most professors who only guide students in research projects, our mentor made the extra effort to guide us in resolving issues. Mostly, we had a huge footfall of patients to cater to in our set-up; hence, professors were preoccupied with clinical duty, sparing minimal time for research. Furthermore, our medical school curriculum does not include research, and more importance is given to enhancing medical knowledge than conducting research studies.

Figure 3. Snapshot from a Zoom Meeting During a PRMP Informative Session.



Legend: PRMP - Peer Research Mentorship Program
Top right corner – mentor

Working with team members from other countries taught us more about our cultural differences while also honing our communicative skills. Since we were at different stages of our medical careers and sometimes preoccupied with other commitments, our mentor was lenient with deadlines and task allocation. For example, if a mentee was not able to meet the deadline for a literature search, others would help in completing that task. Working on this project has boosted our confidence in scientific writing and presentation abilities. We had no ethical issues to deal with and had a pleasant work environment. For example, in November and December, due to imminent medical school examinations, we struggled to balance studies with research. Hence, our mentor guided us on time management and extended the deadline for our research tasks in order to help us to prioritize medical education at that time. In a short period, PRMP enabled us to gain exposure to various aspects of scientific writing and provided us with a valuable research opportunity. We improved our understanding of metabolic syndrome, alternative medicine, and narrative reviews. For medical students in tertiary care institutions in LMICs with limited research aptitude, it was a wonderful opportunity and a valuable learning experience.

Mentor

The mentor screened several articles and videos available on the internet and used past experiences to provide the most factually correct information for mentees. The mentor thoroughly researched the steps of conducting a narrative review and created a timeline for fellow researchers. The mentor consulted the PRMP MoM and gathered information from online journals, videos, and blogs, as and when required. Considering the availability of mentees, the mentor understood the importance of making efficient timelines. In teaching the narrative review steps, including the creation of a research question using the Population, Intervention, Control, and Outcomes (PICO) model, robust literature search on various databases, manuscript drafting using the SANRA guidelines, and article submission to a medical journal, the mentor understood the significance of maintaining deadlines and ensuring flexibility. Delegation and automation of the research process are important in a mentor-mentee relationship.[10] Good mentor-mentee relationship can be nurtured by humility and teachability. The mentor emerged from this research mentorship experience more confident in scientific writing skills and leadership qualities, and gained in-depth knowledge about the integrative management of metabolic syndrome. With this experience, the mentor will manage three more research groups in the July–December 2023 rotation; two mentees of this group are currently mentors in this rotation.

Discussion

Over the last decade, several mentor-mentee research programs have emerged worldwide, especially in low- and middle-income countries. Although such programs are advantageous and fill a significant gap in medical student education, the quality and impact of these programs on medical students and healthcare trainees, and mentor satisfaction should be assessed. Evaluating the efficacy of mentor-mentee research programs is challenging due to the presence of several confounding factors, such as participation of mentees in multiple research programs, difference in interests of mentees and mentors, and variability of skill and knowledge of mentors.

A mentored student project (MSP) program started by Manipal University in India reported that their mentees experienced improvement in their research skills while research knowledge was not much affected.[8] Ssemata et al. found that lack of a formal mentorship structure, low skill and knowledge level of mentors, and unclear roles and expectations were some barriers in these programs. Additionally, the authors asserted the need for measurable outcomes of research projects, creation of shared mentor-mentee expectations, and adaptation of mentoring models to local contexts.[9] According to a review by Atlas et al.[10], these research programs had extensive benefits to mentees, including research development, psychosocial support, confidence building, and improved residency program admission chances. Mentors, on the other hand, enjoyed their relationships

with students, enhanced teaching skills, and refined their curriculum vitae. Due to time constraints of senior mentors, peer mentors were seen as highly approachable.[12] Altonji et al. suggested that mentor training sessions should be incorporated in these programs to enhance their research and communicative skills.[11]

Due to the increasing number of mentor-mentee research programs, the need for creating a structured and formal mentorship increases. Inculcating these extra-curricular research programs into the medical curriculum through collaboration between independent organizations and medical universities may create a path for uniform distribution of research knowledge and skills. This will ensure that only skilled and dedicated researchers are given the responsibility of mentorship. A multi-organizational study may suggest and explore the impacts of the different mentorship styles and program structures on mentee satisfaction and quality of scientific literature produced.

Conclusion

Peer research mentoring is necessary and justified. Universities should organize such programs to expose their students to research early on in their medical careers. Such initiatives will reduce the disparity of opportunities in LMICs.

Summary – Accelerating Translation

In the past decade, research and research mentorship have undergone significant changes with advancements. Since students are actively seeking research opportunities and participating in research workshops, a new era of mentor-mentee programs have emerged by necessity. The peer research mentorship program (PRMP) organized by the International Society for Chronic Illnesses (ISCI) facilitates a global collaboration that does not only improve the quality of research but also encourages interpersonal relationships and incorporates expertise from different fields. In this article, medical students and early graduates share their experience of participating in a cross-country peer-to-peer mentorship and comment on their learnings and observations. This is an experience report of mentors and mentees in the ISCI-sponsored PRMP. Mentees learnt about metabolic syndrome, alternative medicine, and narrative reviews, and the mentor became more confident in scientific writing and leadership while gaining in-depth knowledge about the integrative management of metabolic syndrome.

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Acknowledgments

None.

Conflict of Interest Statement & Funding

The Authors have no funding, financial relationships or conflicts of interest to disclose.

Author Contributions

Conceptualization; Data Curation; Investigation; Visualization; Writing – Original Draft Preparation; Writing – Review & Editing: PCS, KP, AKS, AZ, TA, AS. Project Administration; Supervision: PCS.

Cite as

Shah PC, Patel K, Suvarna AK, Zulfiqar A, Ashok T, Siddiqui A. Research Experience of Medical Students Collaborating in an International Peer Research Mentorship Program, Int J Med Stud. 2022 Oct-Dec;10(4):432-35.

ISSN 2076-6327

This journal is published by Pitt Open Library Publishing

IJMS INTERNATIONAL JOURNAL of MEDICAL STUDENTS

Experience

Barriers for Junior Doctors to Specialize in Rural Generalism – A Medical Student Experience

Madeleine J. Cox.[1]

Abstract

Australia is a large country, with significant healthcare issues affecting its regional country towns. These issues include isolation, poor access to resources, and shortages of doctors. Unique to Australia, is the specialization program of rural generalism, which is in urgent need of increased recruitment rates of junior doctors. Through a medical student experience reflection of my placement in Deniliquin, a small country town in Australia, I explore the facilitators and barriers associated with junior doctors entering the rural generalist pathway. Through the recognition of the current barriers associated with a rural generalist career, I aim to promote change in the developmental strategies for the rural generalist training program and thus, promote the implementation of adequate healthcare resources within rural Australia.

Key Words: Family medicine; General practitioner; Rural health (Source: MeSH-NLM).

The experience

Australia is an exceptional country, with most of its population living on the Eastern Seaboard in highly urbanized, developed capital cities such as Sydney, Melbourne, and Brisbane. However, more than seven million Australian's live inland in some of the flattest, driest, and inhabitable regions on Earth.[1] This poses unique challenges to Australia's regional country towns, as they battle issues such as isolation, substandard health resources, and poor welfare. Despite Australia's world-class healthcare system, unfortunately individuals living in regional Australia, have health comparable to that of low- and middle-income countries.[2] Government strategies have aimed to improve this through lackluster funding, empty promises, and ill-considered pathway strategies.[3,4]

The Australian Government is desperate to train more rural generalists. Through a reflection of my time, experiences, and observations during my placement in the small regional town of Deniliquin, I discuss the facilitators and barriers preventing junior doctors from entering this highly needed career pathway. Through recognition of these challenges, perhaps it will initiate change in the way we implement healthcare strategies for regional Australians.

To contextualize, Deniliquin is a small regional town of 8000 people in New South Wales (***Figure 1***), with a dozen primary care physicians and a single 41-bed hospital facility, which includes general medical, day surgery and maternity beds, as well as a 24-hour Emergency Department.

Facilitators to Specialize in Rural Generalism

Through a medical student experience of rural generalism, I have been enlightened on numerous facilitators to enter a rural generalist career pathway. Firstly, working as a rural generalist enables experiences in interesting and diverse medical cases that present to both clinic and emergency departments in a rural center.

For many junior doctors, this is a very attractive component of the job and can persuade an individual to initiate a career in rural

Figure 1. Map of Australia depicting the location of Deniliquin in relation to the large metropolitan capital cities. *Legend:* Source, Google Maps ©.

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Copyeditor: Sebastian Diebel
Proofreader: Leah Komer
Layout Editor: Cesare Mercalli

Submission: May 5, 2022
Revisions: May 9, 2022
Responses: Aug 16, 2022
Acceptance: Aug 31, 2022
Publication: Sep 09, 2022
Process: Peer-reviewed

generalism. The rural generalist career is also adaptable to any stage of life, allowing doctors even mid-way through their career to easily switch to this medical pathway. Another strong facilitator for a career in rural healthcare is the high demand for doctors *'out bush'*, which enables easy employment in any desired location.

During my own experience in Deniliquin, it was evident that the rural Australian landscape is a strong motive for many junior doctors to move from the busy urbanized cities to the lush green expanses of the countryside.

The perfect tranquil scenes that I experienced in Deniliquin was mesmerizing to wake up to. Dozens of kangaroos would sit outside my window at breakfast, the calm Edward River flowing during my drive to work, and the tall scribbly gumtrees towering above me during my walk to the clinic (***Figure 2***). Most Importantly, the charisma of every rural community was unique and vivacious. During my stay in Deniliquin, I attended street fairs, the country show, and even a salami festival. At every event everyone in the town attended and knew each other. It was a humbling and wonderful experience. The strong community spirit of small country towns is the reason as to way many junior doctors endeavor to work in rural healthcare.

Barriers to Specialize in Rural Generalism

Despite the desperate need to employ more doctors in a rural healthcare setting, there are significant drawbacks preventing junior doctors from committing to a career in rural generalism. Even though the many marketing strategies promote rural generalism as a highly accommodating and adaptable career, during my placement I came to discover that this is not the case. As described above, rural generalist days are long, with most days being double- and triple- booked. One may think that, most doctors have this issue. However, '*out in the sticks*', if you are not in clinic, you are either rounding on hospital patients, assessing patients in emergency, or on-call for emergency obstetrics and trauma. Rural generalists do more than work overtime- they work a dangerous amount. With days, weeks, and months like these, I have learnt that, for rural generalists, planning a personal life outside of work is almost impossible – no matter the seniority. Rural generalist doctors moving to the regional communities would have to give up any personal time due to high levels of workload and uncertainty of working hours. These doctors take up a great responsibility, placing the healthcare of the community above their own lives and their own families. From my experience, work-life balance in rural generalism does not exist and is becoming increasingly more obvious.

Packing your bags and starting your new life in a beautiful town like Deniliquin may sound ideal, how, but, these beautiful landscapes come at a great cost. This cost is the isolation faced by living hundreds-to-thousands of kilometers away from family, friends, transportation, and healthcare resources. Everyone considering a career path in rural generalism must consider if all these barriers and costs are suitable to their current lifestyle. More importantly, the main consideration that a junior doctor must make upon deciding a career in rural healthcare is the health and wellbeing of themselves and their household dependents.

Figure 2. Deniliquin – the Dirt Road I Took Each Day from My Accommodation to the Hospital.

As described earlier, small country-towns are tight knit with a strong sense of community. Nevertheless , this comes with the crucial issue of a lack of privacy. This is exceptionally challenging as a healthcare professional. The predominant issue is separating a privately bound patient-doctor relationships from personal friendships. This is difficult in small country-towns and leads to many clinicians becoming exhausted and lonely. Hence, another barrier preventing junior doctors from entering a rural generalist career.

Conclusion

My placement in Deniliquin has made me realize the reality of the rural generalist pathway. It is one of the most rewarding, yet challenging careers available, and different from any other specialty in medicine. Through a medical student experience, I was able to appreciate the facilitators and barriers for junior doctors considering to specialize in rural generalism. Strategies to overcome these barriers include greater support for interested doctors through flexible rotations, structured training schemes, housing packages, monetary bonuses, and improved healthcare infrastructure in these regions. Using management frameworks like overseas expatriate modelling, may make rural generalism more desirable, and encourage many junior doctors to begin a career in rural medicine.

Summary – Accelerating Translation

Australia is one of the largest countries in the world, with many of its residents living in regional and remote towns. Healthcare services and resources across most of Australia are phenomenal due to well thought

out government led funding. However, there is difficulty accessing these services in rural towns. There is a critical need to provide more healthcare staff rurally, this includes a specialty of rural generalism. A specialized career in rural generalism is one that includes family medicine with added skills to care for regional and remote communities. Unfortunately, there are several barriers that prevent many junior doctors from deciding to continue a career in rural medicine. Through my experience in a small country town called Deniliquin, I discuss the facilitators and barriers including work-life balance, isolation, and privacy concerns. This reflective article exposes the need to improve Australian rural healthcare networks and provide solutions to overcome these barriers to encourage more doctors to specialize in rural healthcare.

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Acknowledgments

I would like to thank Dr. Rachel James and the team at Deniliquin Medical Clinic for their generosity, warmth and hospitality.

Conflict of Interest Statement & Funding

The Authors have no funding, financial relationships or conflicts of interest to disclose.

Author Contributions

Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Software, Supervision, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing: MJC.

Cite as

Cox MJ. Barriers for Junior Doctors to Specialize in Rural Generalism – A Medical Student Experience. Int J Med Stud. 2022 Oct-Dec; 10(4):436-38.

ISSN 2076-6327

This journal is published by Pitt Open Library Publishing

IJMS INTERNATIONAL JOURNAL of MEDICAL STUDENTS

Letter to the Editor

'First, Do No Harm'… A Call to Re-evaluate the Wellbeing of Healthcare Staff

Kyriaki-Barbara Papalois.[1]

Abstract

'Primum non nocere' or 'Do no harm' is the timeless Hippocratic mantra instilled in every healthcare professional at the beginning of their career. It is the ethical compass which guides all decision-making in healthcare, working in the best interests of patients- to give them the best possible treatment and quality of life. This vocation of course does not come without its challenges: long working hours, stress, time constraints and demands, which affect the professional and personal lives of healthcare workers and in some instances, their own health and wellbeing. It is time to raise the profile of this truth and call for ways to practically encourage healthcare professionals to make their wellbeing a priority too.

Key Words: Sars-CoV-2, 'Ethics', 'Health promotion' (Source: MeSH-NLM).

Letter

Dear Editor,

'Primum non nocere' is the key principle which underpins all medical decisions and guides clinicians through ethical dilemmas and uncertainty. The Hippocratic mantra has been instilled in every healthcare practitioner ensuring that the safety of patients is paramount, and action is always in their best interest.

However, even as a medical student, it is quite obvious that although healthcare professionals place all their efforts in realizing this doctrine for the good of their patients, they do not always apply it to themselves. Healthcare staff are exposed to difficult and distressing situations daily. Simultaneously, they are required to work overtime in understaffed and high- pressured environments, where errors due to exhaustion could determine life or death.[1] This reality, although many accept it as default in the medical field, is fundamentally wrong.

This saddening reality has been precipitated by the COVID-19 pandemic. As described by Kapri. And Gadgile, 2020, the novel virus placed an unprecedented stress in the health sector with staff working overtime, re-deployed to intensive care units, and undertaking additional duties to cope with increasing admissions.[2] The pair described this as 'Corona anxiety,' with increased levels of burnout and depression leading to psychiatrists rightly advocating for better mental health support for health workers.[2] This psychosocial impact was also identified by Jenkins and Grasso., 2021, as medical students in the US, reporting adverse pandemic-related experiences (lower physical activity levels, increased substance use) as high as 37.5% in the sample population and deteriorating mental health amongst students.[3]

As future 'frontline workers' many of us started clinical placement at the epicenter of the COVID-19 pandemic, whilst the rest of the world was in lockdown and any reservations that we had when entering the placements in these unprecedented circumstances had to be subverted in order to gain the competences needed to progress in our medical course. As described by Ibrahimli, 2021, disruption to in-person teaching and transition to online formats led to reduced clinical exposure,[4] whilst redeployment of many junior doctors resulted in various personal and professional setbacks. Many medical students, including myself, worked in community care as healthcare assistants and tried to play our part to aid health care professionals during the pandemic. These actions may be as a result of resilience and adaptability of the medical profession. However, it begs the question: does this instilled sense of duty compel us to put ourselves in danger to help in crises as accounted by the humbling experience of Ibrahimli, 2021., as a volunteer in the Nagorno-Karabakh conflict, during the pandemic?[4] Would we, and should we all, have the courage to respond as such? In my placement during the pandemic, many staff in tears confided that they had reached their limits and questioned the limits of goodwill and where their duty was- to themselves or wholly to patients. These moments, seeing healthcare staff who are venerated at their most vulnerable, has stayed with me even today as I write this letter entering my final year in medical school.

So what do we do about it? Undoubtedly, people recognize the challenges that come with the profession and respect the

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Layout Editor: Ana Maria Morales

Submission: Aug 31, 2022
Revisions: Sep 24, 2022
Responses: Oct 10, 2022
Acceptance: Nov 12, 2022
Publication: Dec 3, 2022
Process: Peer-reviewed

healthcare staff, even clapped for them in the UK during the pandemic, which was sentimental, but is it enough? We acknowledge the hardships, but choose to ignore the core problem, especially when doctors are at risk of harming themselves to help others.

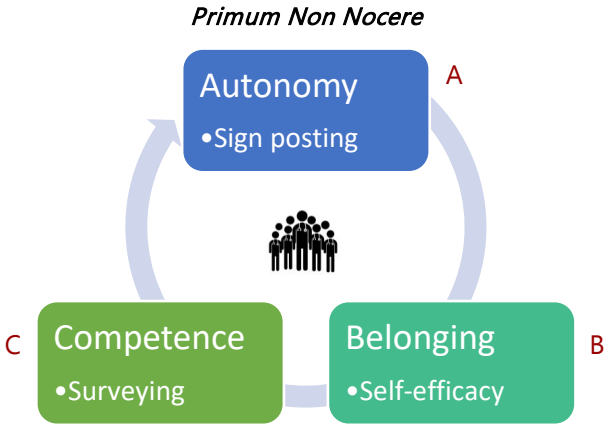
Many have quit the service, re-live distressing and traumatic experiences, and harm their health irreversibly.[1] In 2016, a scene that I vividly recall is junior doctors on strike, protesting in the streets of London for the changes in their contracts- to work on weekends with negligible increase in pay. This decision of junior doctors to strike sparked debates regarding the duties of physicians, with a failure from the UK government and media to understand the already low morale of healthcare staff and reality of medicine as highlighted by the British Medical Association, which was one of the few organizations justifying the strikes in 2016.[1]

Over 35% of respondents in the NHS 2018 Staff Survey reported that they were unwell due to burnout, and many health practitioners especially GPs, reported that they would like to quit the service in the near future. The 2019, GMC 'Caring for doctors, Caring for patients' Report stated that over 50% of those who report burnout are at risk of making a major medical error.[1] Most importantly, is there not also a risk to themselves and their wellbeing?

The 'Physician's Pledge,' a revised version of the Hippocratic Oath adopted by the World Medical Association in 1948, encompasses the notion of newly qualified doctors pledging "I WILL ATTEND TO my own health, well-being, and abilities in order to provide care of the highest standard".[5] This modern public pledge that clinicians make prioritizes their own wellbeing alongside patient safety in order to provide the best standard of care. Furthermore, health infrastructure and workplaces need to adopt uniformity in guidelines and allocation of resources to help all healthcare workers fulfill this pledge.

The UK General Medical Council has proposed some strategies to help combat burnout and advocate for the wellbeing of their staff through the 'ABC' recommendation of 'Autonomy, Belonging and Competence.'[1] These advocate for better control of working hours and conditions, as well as signposting resources to aid staff wellbeing and build a more inclusive workplace. 'Signposting' resources, empowering staff through 'self- efficacy' to seek help, and regularly 'surveying' staff to recognize problems early are to help reinforce the GMC 'ABC' recommendations (*Figure 1*).

Figure 1. A Call to Review Healthcare Worker's Wellbeing. Schematic Proposing Approached to Supplement the GMC's ABC Approach and Uphold the Wellbeing of Healthcare Staff.



Future directions should build on the aforementioned recommendations, whilst listening to healthcare staff when they voice their opinion, which is the first and necessary step to inspire and initiate change.

Primum non nocere': it is not just for the care of patients, it is a universal law for all, a humbling reminder of the dangers of the extremes, and valuing one life over another. Healthcare staff have a duty to their patients as well as to themselves...

Summary – Accelerating Translation

Healthcare staff always place the patient at the center of all decisions they make to improve their overall health and wellbeing. This priority as well as the demands of the work mean that they do not always take care of themselves. It is important to recognize this and look for solutions to support staff to take care of themselves as well.

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Acknowledgments

None.

Conflict of Interest Statement & Funding

The Authors have no funding, financial relationships or conflicts of interest to disclose.

Author Contributions

The authors declare that there are no potential conflicts of interest and no competing financial interests associated with this study that could have appeared to influence the data reported in this paper

Cite as

Papalois KB. 'First, Do No Harm'... A Call to Re-evaluate the Wellbeing of Healthcare Staff. Int J Med Stud. 2022 Oct-Dec;10(4):439-441.

ISSN 2076-6327

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