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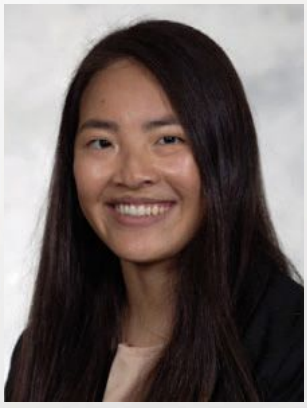
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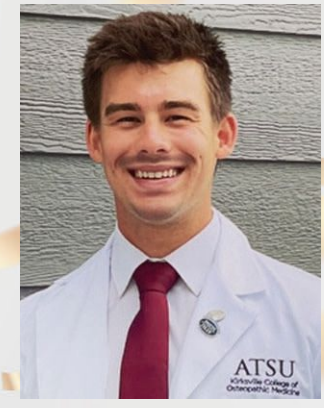
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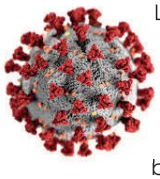


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The Zantac Scare and Junk Science

by The Wall Street Journal Editorial Board

A federal judge exposes the false claims behind a trial-lawyer assault.

The press typically treats lawsuits against business as inherently righteous and amplifies the junk science behind them. So in case you missed it, a federal judge on December 6, 2022, dismissed claims that the once top-selling heartburn medication Zantac causes cancer in a debunking for the ages.

A few years ago, the small lab Valisure generated headlines after purportedly finding astronomical levels of the cancer-causing chemical NDMA in Zantac (ranitidine). The Food and Drug Administration's daily limit for NDMA is 96 nanograms, and Valisure claimed to have found levels exceeding 3,000,000 ng. Talk about causing heartburn.

The same day that Valisure announced a "Citizen Petition" with the FDA urging a recall of ranitidine, numerous lawsuits were filed against drug manufacturers. This suggests coordination between plaintiff attorneys and Valisure. The FDA investigated and initiated a recall after finding NDMA in some pills that exceeded 96 ng.

But as Judge Robin Rosenberg notes in her 341-page ruling, the FDA daily limit is "conservative"—equivalent to a meal of grilled meat. "If one were to consume 96 ng of NDMA every day, for 70 years in succession, the risk of cancer would be 1 in 100,000, or .001%," and "even the highest-tested pill [by the FDA] showed NDMA at a tiny fraction of the level reported by Valisure."

This important context was left out of lawsuits and press reports. Ditto that the FDA found Valisure's lab equipment created NDMA. It gets worse, as Judge Rosenberg details. Valisure heated the ranitidine to 266 degrees Fahrenheit—well above the roughly 98 degree temperature found in the human body—to achieve its test result of 3,000,000 ng.

When Valisure tested ranitidine at 98 degrees, it found no NDMA. The extremely high temperature may have caused ranitidine to degrade into NDMA. Valisure also tested ranitidine's reaction with salt in an artificial stomach, which resulted in NDMA levels exceeding 300,000 ng. But the enormous levels of salt in the test might alone have been enough to kill someone.

When Valisure tested ranitidine with salt concentrations approximating what a human could safely ingest, it detected no NDMA. The

This editorial first appeared in the *Wall Street Journal* on December 8, 2022, and is reprinted with permission.

plaintiffs also relied on a Stanford University study that reported to find NDMA levels in ranitidine exceeding 47,000 ng. That study was later retracted by its authors after the lab equipment was found to have created NDMA.

"There is no scientist outside this litigation who concluded ranitidine causes cancer, and the Plaintiffs' scientists within this litigation systemically utilized unreliable methodologies with a lack of documentation on how experiments were conducted, a lack of substantiation for analytical leaps, a lack of statistically significant data, and a lack of internally consistent, objective, science-based standards for the evenhanded evaluation of data," wrote Judge Rosenberg, who was appointed by Barack Obama.

Share prices of ranitidine manufacturers GSK and Sanofi surged after the judge dismissed some 50,000 lawsuits. Morgan Stanley estimated potential damages against the various drug makers could reach $45 billion if the litigation were successful. Drug makers have had to spend tens of millions of dollars to defend themselves and face tens of thousands of more lawsuits in state courts. And progressives complain about high drug prices?

Valisure's role in the Zantac and other consumer lawsuits deserves more scrutiny. Its report that the diabetes drug metformin contained high levels of NDMA also triggered a blizzard of lawsuits. Valisure made headlines again in recent months after reporting scary-high levels of the carcinogen benzene in sunscreens and dry shampoos.

On December 5, 2022, the FDA sent Valisure an eight-page letter criticizing its data controls, equipment and failure to "establish and document the accuracy, sensitivity, specificity, and reproducibility of its test methods." A spokesperson said Valisure will respond to the FDA letter but offered no comment on the judge's ruling. The Valisure methods and plaintiff attorney suits look like a litigation scam, and congratulations to Judge Rosenberg for exposing it.

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Silence Won't Fix or Prevent Future EHR — Our Voices Still Can

by George P. Hubbell, MD

Last year at my inauguration, outgoing MSMA President Alex Hover, MD, graciously gave me a book, *Big Med*. Written by an economist and a sociologist, the book eloquently demonstrates all the effects physicians have been experiencing via large integrated hospitals, termed 'Megaproviders,' who bear the majority of responsibility for and have an obsession with profit and pricing, now responsible for half to two-third of all health care spending. These large integrated providers can now exploit their marketplace. Prices are demonstrated to be higher where the Megaproviders have more market power and further mergers have been shown to create even larger prices.

In this large-player marketplace, scale and scope of influence have not led to any economies on price and have yet to demonstrate any significant quality gains. For physicians, there have been waves of employment into health systems: HMO integration, ACA, and HITECH act incentives to adopt EHR and join a system, Medicare regulatory requirement changes, and most recently, the impact of the COVID pandemic. An epidemic of burnout and attrition exists in all counties of Missouri, save one, creating a physician workforce shortage.



George P. Hubbell, MS, MD, FACOG, is the Immediate Past President of the Missouri State Medical Association. He is a Obstetrician/Gynecologist from Lake Ozark, Missouri.

As physicians in clinical practice, our communication is face-to-face and, at the speed of sound, vocal. During the pandemic, virtual visits became part of our day-to-day profession, not totally losing but certainly reducing some of the total human interaction and stimulation therein. Removing the human contact and hands-on experience detracted from our professionalism, making some of this IT interaction no more than just addressing a disease process. As Sir William Osler stated over a century ago: "Good physicians treat a disease and great physicians treat the patient," we were undeniably unable to treat the total patient. Suddenly we became beholden to our IT and not our patients. And the pace has been digital, near the speed of light.

I would maintain that the unacceptable 60% burnout rate in our profession is a new crisis in our profession and is related to EHR and IT integration. There has been a further loss of human interaction, something all of us approached clinical medicine for the reward of those relationships we developed in our practices.

We can no longer just take care of our patients—we must fulfill all the EHR duties and documentation, too. No longer can our office staff help us with most of the menial daily duties because we are tasked with coding, billing, and quality mensuration requirements, spending six of our 11-hour days behind computer screens.

We are working to satisfy all the EHR requirements, and it needs to work better and more efficiently for us, especially at the cost of the price-detracting from our allegiance to patient interaction and our social isolation as a result of documentation to create longer notes. The EHR note is on average 60% longer than former written ones, is harder to interpret between users and well over half are repetitious with abundant cut and paste confounders.

The EHR burden is listed as the largest reason for attrition when retiring physicians are polled. One of

five physicians have recently stated they plan to retire in the next two years. While indelible circumstances follow pandemics, new opportunities for response and resolution are now open. The saying that: "dumb stuff pushes hard times and hard times then can kill dumb stuff," hopefully will resonate. Spoken word in our clinical and even casual encounters with colleagues has weight and occurs at the comfortable speed of sound.

I have pleaded in past columns for true interoperability and reduction in IT burden. My father always admonished for me to never complain unless I could offer some solution for change for the better. I think it is time we get involved in meaningful technology that is swiftly becoming available, i.e., artificial intelligence for all our EHR documentation and more widespread use of medical scribes or anything else related to reduce this digital stress our system has created.

There is a small window to still comment on interoperability with the ONC who accredits all the Megaprovider software vendors, registering online and commenting on the inadequacies that are morphing at digital speed. The new VA medical system EHR is continuing release now, and just in a pilot release has been attributed with six catastrophic events and thousands of errors.

Last week, a democratic U.S. Senate bill in Congress will seek to implement reforms for the VA EHR and monitor progress; this bill joins two republican bills in the House of Representatives that were introduced last month. We must hold vendors responsible. Go to HealthIT.gov and click on the proposed rule link to learn more about it. Silence won't fix or prevent future EHR misadventures, but our voices still can.

Sources

1. David Dranove and Lawton R. Burns. *BIG MED; Megaproviders and the High Cost of Healthcare in America.* University of Chicago Press. 2021.
2. Hananah Nelson. "Senate Democrats Plan for EHRM Program Overhaul." EHRIntelligence: March 30, 2023.
3. Jaqueline LaPoint. "Healthcare Has Yet to Feel Full Impact of Physician Retirements." Revcycle Intelligence: March 22, 2023.
4. Sarai Rodriguez. "VA admits Oracle EHRM Issues contributed to 4 Veteran Deaths. "EHRIntelligence: March 21, 2023.

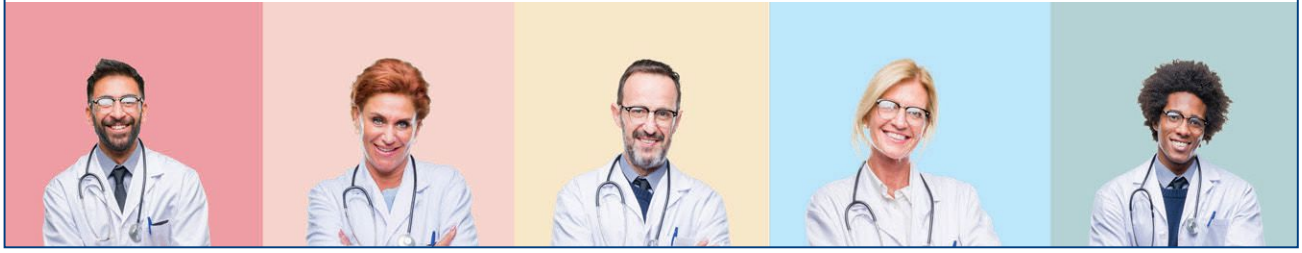
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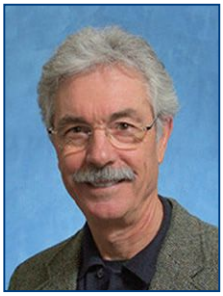


Effect of Retail and Urgent Care Clinics on Primary Care in Missouri

by David Voran, MD

With primary care transforming from care delivered exclusively in a physician's office to care that can be delivered in multiple sites and through different venues such as virtually or in retail settings, we should carefully critique what is gained from this primary care transformation—and what, if anything, is being lost.

Missouri citizens, especially those living in larger urban centers, have more healthcare choices than they used to when seeking medical care.



David Voran, MD, is an Associate Professor, Community and Family Medicine, University Health KC – Lakewood Campus, University of Missouri - Kansas City School of Medicine, Kansas City, Missouri.

These include 1) walk-in retail clinics staffed by advanced nurse practitioners operating in pharmacies, grocery stores, or other convenient locations; 2) traditional clinics staffed by physicians, nurse practitioners, physician assistants, nurses, and ancillary support staff (whether practitioner-owned or run by nearby hospitals and large independent healthcare networks); 3) urgent care centers (both privately owned and operated and those run by hospitals and networks); 4) emergency rooms operating in and run by local hospitals; and 5) on-demand virtual visits that has grown in popularity recently.

Patients factor in time, expense, urgency, familiarity, and insurance coverage when deciding which of these facilities to visit for their ambulatory healthcare needs. While physician offices and emergency rooms have long been a healthcare

landscape fixture, urgent care centers and retail clinics are relatively recent developments that are changing the nature of ambulatory care provided by physicians in their offices and emergency rooms. To examine the effect of these choices on traditional office settings, a brief history of definition of these settings is necessary.

Retail Clinics

The first retail clinic appeared in Minnesota in 2001, when a frustrated father and future Minute Clinic cofounder, experienced a long wait at an urgent care center for treatment of his son's strep throat.[1] Since then, this type of service has expanded to a market size of $3.49 billion in 2021, spurred on by a 21.5% growth during the first year of the COVID-19 pandemic, and projected to reach $4.22 billion by 2029.[2] Major players in this market include: Walmart, CVS Health, Walgreens Boots Alliance, The Kroger Co., Kaiser Foundation Health, Target Brands, Bellin Health Systems, and Geisinger Health.

Retail clinics are generally located within retail stores, such as pharmacies or "big-box" outlets like Wal-Mart. They offer a limited range of services and staffed by nurse practitioners or physician assistants. Retail clinics are typically open seven days a week, have extended hours in the evenings, and do not require appointments. Retail clinics compete with doctors' offices for basic primary care services by offering lower and more transparent prices, shorter waiting times, and convenience. By-and-large, retail clinics limit their offerings to many low-risks servies, where 10 clinical issues such as sinusitis and immunizations comprise more than 90% of retail clinic visits. These same clinical issues make up only 12% of Emergency Department (ED), 13% of adult Primary Care Physician (PCP) visits, and 30% of pediatric PCP visits.[3] The same study suggested retail clinics appear to be serving a patient population underserved by traditional clinics; young adults (ages 18 to 44) who pay out-of-pocket for their care and less likely to have established a relationship with a PCP. They also appear to be lowering the cost of this type of care. A typical visit cost ($110) is less than similar visits to physician offices ($156) or EDs ($570), while providing the same quality of care.[4] One study in New Jersey demonstrated these clinics reduced nearby ED visits by 3-13% and estimated to generate $70 million savings if they were more readily available across that state.[5]

State regulations governing nurse practitioner scope of practice are one of the factors constraining the growth of Retail Clinics. Missouri is one of the states that limit nurse practitioners' ability to practice medicine without physician supervision. The regulations limit the number of nurse

Table 1. List of Urgent Care Companies

Urgent Care Company	Centers
Concentra Urgent Care	295
Urgent Care Extra	26
Hometown Urgent Care	21
Fast Pace Urgent Care Clinic	15
Urgent Team	11
Premier Urgent Care	11
PhysicianOne Urgent Care	9
Walk In Urgent Care	9
Fast Pace Urgent Care	9
Doctors Urgent Care	8
Cross Keys Urgent Care	7
Excel Urgent Care	7
Night Lite Pediatrics	7
Sherwood Urgent Care	6
St. Luke's Urgent Care	6
Total Access Urgent Care	6
FastMed Urgent Care	6
MASH Urgent Care	6
Advanced Urgent Care	6
Alliance Urgent Care	6
A Plus Walk-In Urgent Care	5
Dusk To Dawn Urgent Care	5
First Med Urgent Care	5
Five Star Urgent Care	5
Greater Mobile Urgent Care	5
Northwest Ohio Urgent Care	5
Nova Medical & Urgent Care Center	4
Optum Clinic + Urgent Care	4
Sisters of Mercy Urgent Care	4
ProHealth Urgent Care	4
Rockwood Urgent Care Center	4
Urgent Doc	4
Glendora Urgent Care Center	4
Lansing Urgent Care	4
Le Bonheur Urgent Care Center	4
Meridian Urgent Care	4
MedPost Urgent Care	4
CityDoc Urgent Care	4
Community Urgent Care	4
Baptist Urgent Care	4
ASAP Urgent Care	3
Action Urgent Care	3
Advance Urgent Care & Walk-In Clinic	3
ERDOX Urgent Care	3
Evening Pediatrics	3
New England Urgent Care	3
Med7 Urgent Care Center	3
Hoag Urgent Care Anaheim Hills	3
Kootenai Urgent Care	3
Good Night Pediatrics	3
	593

practitioners a physician may supervise (six FTE) and requires the collaborative physician practice within a specific distance (30 miles) from the nurse practitioner's site.[6] There is evidence the number of retail clinics increases when states remove these restrictions compared to nearby states who retain restrictions.[7] Studies on the effects of this expansion are still forthcoming. There are many arguments made on both sides of the debate. Recent legislative changes enable the nation to study the long-term effects of increased scope of care vs. continuation of closer supervision.

Urgent Care Centers

The first urgent care centers appeared in the early 1970s and now number over 8,000 across the United States U.S.), according to the American Academy of Urgent Care Medicine (AAUCM). This organization defines urgent care service as "the provision of immediate medical service offering outpatient care for the treatment of acute and chronic illness and injury."[8] In one survey using a 2014 national database or 31,022 communities from the Urgent Care Association of America, identified 6,898 urgent care centers. More than 75% of these centers are in urban communities associated with areas of higher income levels and higher levels of private insurance.

A Microsoft Bing® Excel mashup, (an automatic add-in to Microsoft 356 versions of Excel that adds background queries based on elements in tables being used) lists 51 public urgent care companies with over 590 centers in the U.S. (Table 1). It should be noted this list does not include urgent care centers run by hospitals or independent healthcare networks. The distribution of these centers is concentrated in populous states (Figure 1). Missouri also demonstrates this, where more than 95 of the more than 130 are located in urban metropolitan areas (Figure 2). It should be noted that more than 40 urgent care centers are located in relatively rural areas. Most of these are associated with several of the larger healthcare networks in Missouri. These centers typically offer extended weekday and weekend hours, accept unscheduled visits, and provide low-acuity to mid-acuity episodic care to patients who would otherwise seek care at emergency departments or by primary care clinics.[9] They are usually staffed by family medicine specialists with support from physician extenders such as nurse practitioners and physician assistants.

Figure 1. Distribution of Urgent Care Centers by State
Sourece: Bing

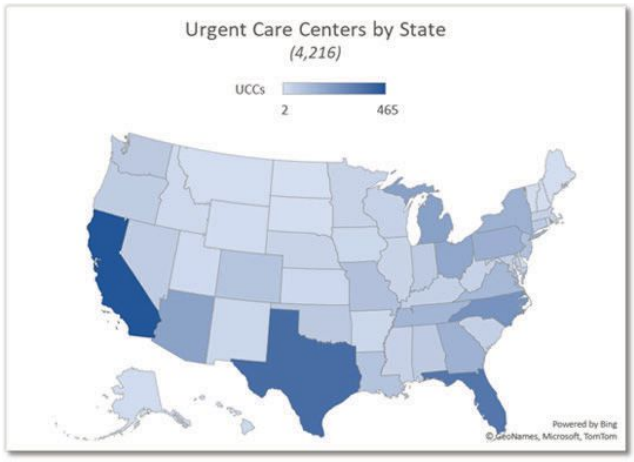
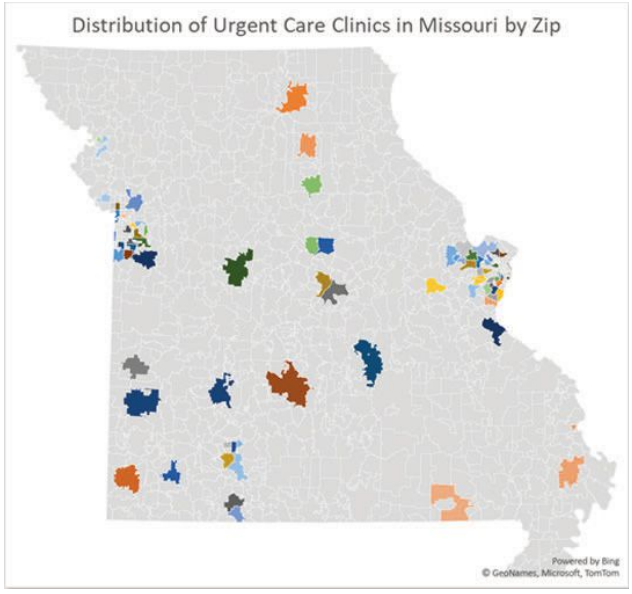


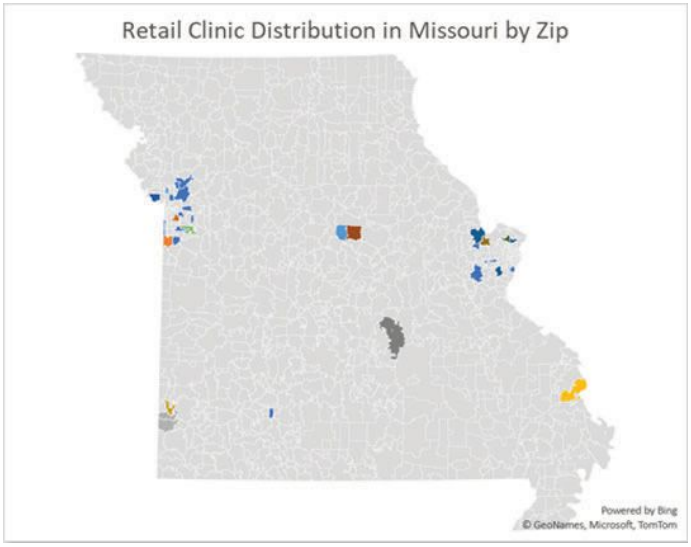
Figure 2. Missouri Urgent Care Distribution



Hard numbers are exceedingly difficult to come by, as there is a gradual continuum of clinic types from traditional clinics with walk-in services to urgent care centers that contain many of the services found in EDs. The number of urgent care facilities increased from 6,400 in 2014 to nearly 10,000 in 2020 according to several internet sources.[10] Some of the largest urgent care operators in the U.S. include American Family Care, City MD, Concentra, Fast Med, GoHealth, HCA CareNow, MedPost, NextCare, Patient First, and US Healthworks.[11]

These urgent care centers are filling the widening gap between primary care and emergency room care and usually include providing unscheduled care,

Figure 3. Retail Clinic Distribution in Missouri



after-hours access, expanded services compared to primary care, all at lower cost than emergency care. These include on-site laboratory, imaging, intravenous medications and fluids, repair of lacerations, foreign body removal, basic fracture care, and treatment of abscesses.[12] Only 8% of urgent care centers offer primary care in addition to urgent care while roughly 3% are "hybrid" urgent care/PCP centers.[13]

There is data to show the rate of urgent care utilization does not seem to impact the rate of primary care visits, despite the increasing number of urgent care visits over time.[14] This may reflect that most urgent care clinics are staffed by physicians who do not want to interfere with a patient's primary care relationship and as many as half of these are run by the same healthcare systems that employ many of the physicians in their own clinics.

Discussion

The increase in options for patients has anecdotally reduced simple visits from primary care clinic visits and subsequently increased the complexity of patients. With primary care transforming from care delivered exclusively in a physician's office to care that can be delivered in multiple sites and through different venues such as virtually or in retail settings, we should carefully critique what is gained from this primary care transformation—and what, if anything, is being lost. For instance, entrepreneurs, policymakers, pharmacy and hospital chains, focused on perpetual growth, may believe that the retail clinic model of primary care must expand to include complex service delivery. However, the current body of research does not tell us nearly enough about whether this belief is founded in reality.[15] Minute Clinic, as an example, with its Health Hubs, has been trying to move into comprehensive primary care and chronic condition management. Now, combined with Aetna, it has rolled out a nationwide virtual primary care practice that promises a broad scope of care with access to board-certified physicians and coordinated care from a consistent team of specialists.[16]

UnitedHealth and Blue Cross Blue Shield are also aggressively entering primary care. UnitedHealth is building a network around physicians who work for its Optum arm. This unit has acquired a sprawling network of physician practices, surgery centers and urgent care clinics.[17] Blue Cross Blue Shield is following step with its SpiraCare clinics.

It is difficult to imagine how these convenience sites of care would be able to participate in many of the activities supporting longitudinal care aligned with Patient Centered Medical Home goals and alternative payment systems like Primary Care First. This is especially so as the distribution of clinics is severely restricted to only urban areas and are far fewer in number than urgent care centers (Figure 3). The American Academy of Pediatrics is but one professional society that has concluded retail clinics are not appropriate venues for primary care for children due the fragmented, episodic nature of their care.[18]

In a study of retail clinic utilization by traditional fee-for-service Medicare beneficiaries in the greater Houston area, patients without chronic conditions were more likely to use retail clinics compared with those beneficiaries with existing chronic conditions and those with established PCP relationships.[19] The same study showed most of these visits were for vaccinations and simple acute infections, often when PCP clinics were closed. The study did find that 10% of the visits by Medicare beneficiaries were for management of chronic conditions. What is concerning is the study showed there was minimal PCP follow-up visits raising concerns about quality, coordination, and outcome of care among elderly retail clinic users. This lack of coordination and close follow-up raise questions as to the overall efficacy of this fragmentation of primary care despite studies showing nurse practitioners

can provide the same quality of care for low acuity conditions and complaints seen in the retail clinics.[20] The primary difference lies in the tendency for advance nurse practitioners to limit their decision-making to the presenting problems where physicians were more likely to also address underlying comorbidities.[21]

Anecdotal evidence exists the presence of retail clinics has reduced the volume of minor acute care visits conditions that used to be the "bread and butter" of traditional family practice clinic and replaced these visits with complicated patients. Current CPT coding paradigms are not keeping up with the time required to adequately treat and manage these complicated patients and meet many quality standards required by third-party payers. These trends put increased competitive pressure on traditional clinics that face an uphill battle with little or no resources compared to retail clinics backed by large, corporate entities.[22]

One approach is to integrate an urgent care clinic within a family medicine practice as done by the University of North Carolina's Family Medicine Center. They allowed the practice to offer extended hours and enabled them to welcome more people into primary care and provide them with a comprehensive approach that would otherwise be lacking in a regular non-affiliated urgent care center.[23] While this approach may be possible for larger centers with adequate staffing, it is probably beyond the scope and capabilities of most family practice clinics.

Another approach available to primary care clinics in urban areas is to participate and enter collaborative relationships with nearby retail clinics' nurse practitioners who are seeing many patients without a PCP relationship who do need follow-up beyond their scope of care. These type of relationships have the potential to expand access to their patients by cross-referring them after hours to the retail clinic in return for being a place where nurse practitioners can refer patients needing care that is more complex.

Reimbursement and poor attribution cause major problems as care choices expand. Nationally, there is an inexorable attempt to move away from traditional fee-for-service to value-based reimbursements. Value-based reimbursements hinge on the ability of practices to meet an ever-expanding set of quality metrics for their attributed patients to qualify for incentives. If outside nurse practitioners and urgent care physicians see patients for minor problems but do not address the patient's comorbidities, the practice may suffer in their quality metrics. It is unlikely the retail clinic provider will see these patients enough to be the attributed provider, nor allowed to be the attributed provider of record by covering entities. Even if allowed, it is hard to image these retail clinics will willingly enter value-based contracts with third party payers. The same is-true for urgent care clinics, especially public ones. The business model limits them to episodic care and chronic care seems incompatible with that type of care.

There are hints of this changing in Missouri and the entire United States as acquisitions and mergers increase in both private and public health venues. When pharmaceutical companies acquire insurers who then acquire or expand their healthcare footprint their ownership and responsibility to the patients seen will increase proportionately.

Israel is a nation whose health care is highly managed with-emphasis solutions that reduce cost, improve efficiency while reducing unnecessary utilization. The convergence of managed and consumer-driven care has led to a rapid growth of urgent care centers in Israel.[24] Lee Resnik, MD, in his commentary thinks the American urgent care model will eventually resemble the Israeli model, where a wide assortment of retail and urgent care centers are integrated and aligned with health systems and insurance companies. The entry of insured-owned clinics and networks supports this evolution.

It's easy to imagine this happening within large independent Missouri healthcare systems like Mercy Health, SSM, St. Luke's, and Cox Health who have a growing combination of retail, convenient clinics, urgent care centers, out-patient primary care clinics, emergency rooms, and hospitals. Most of these share a common electronic record system to provide continuity of across multiple venues. As insurers enter primary care and begin offering their own networks of care combined with their contracts with healthcare systems, we could begin to see some cooperation, if not integration happening to achieve cost savings and improve the convenience for their enrollees.

Recent legislative efforts are beginning to get serious about interoperability. Over the last couple of years, clinicians are beginning to witness record availability across platforms and among traditional competitors. This could lead to better shared chronic and complex care management while providing local and accessible convenient urgent care.

Summary

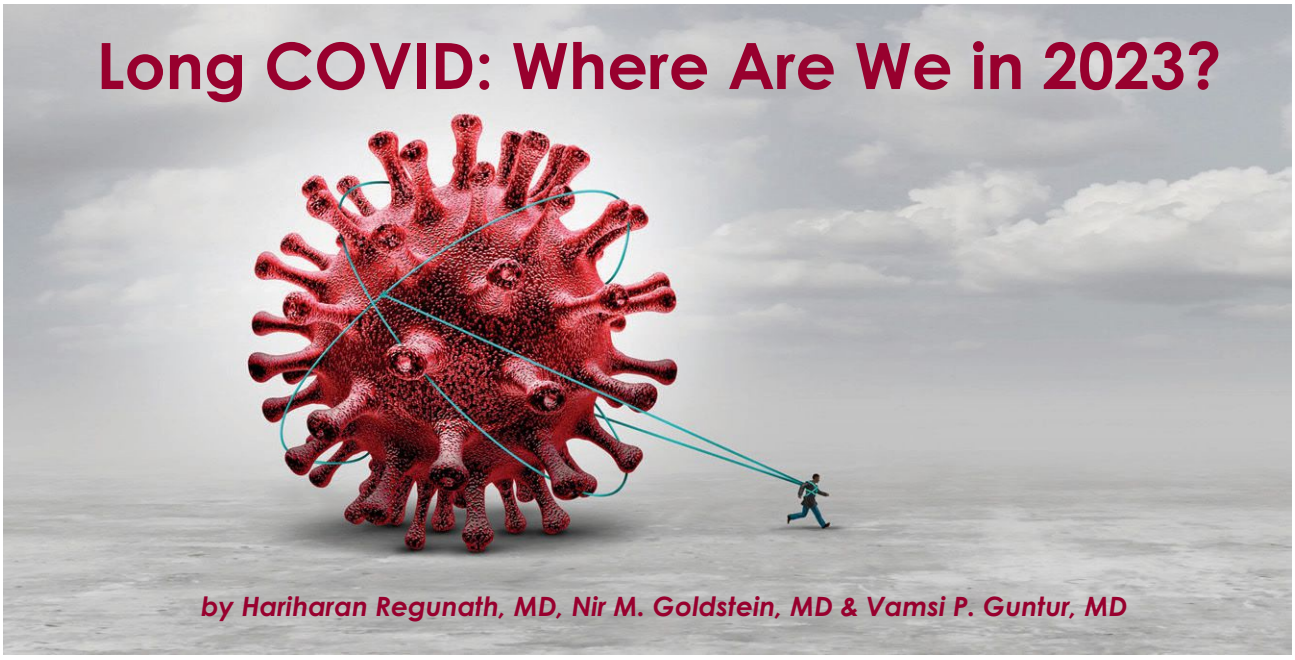
Patients have an increasing number of choices to receive medical care. The COVID pandemic has dramatically driven this trend. These medical venues include on-demand virtual visits, conveniently located retail clinics, urgent care centers that offer extended hours, in-house lab, and imaging leading to prompt care and diagnoses. Planned and scheduled physician-lead primary care or specialists can lead to effective longitudinal care. Traditional hospital emergency room services for true emergencies will expand. Ideally, patients will have choices of hospitals with care and insurance integration for a higher standard of care. Presently, insurance coverage and patient's recognition of various scopes of care is problematic and can lead to unexpected, and sometimes devastating, financial burdens. These choices are not equitable along wealth and location axis. Ideally, the trends we have outlined here will lead to the highest possible level of medical care for all patients in all urban, suburban and rural locals.

References

1. Burkle CM. The advance of the retail health clinic market: the liability risk physicians may potentially face when supervising or collaborating with other professionals. Mayo Clin Proc. 2011 Nov;86(11):1086-91. doi: 10.4065/mcp.2011.0291. PMID: 22033253; PMCID: PMC3202999.
2. The U.S. retail clinics market is projected to grow from $2.05 billion in 2022 to $4.22 billion by 2029, at a CAGR of 10.8% in forecast period, 2022-2029... Read More at:- https://www.fortunebusinessinsights.com/u-s-retail-clinics-market-106419
3. Ateev Mehrota, Margarat Wang, Judith Lave, John Adams, Elizabeth McGlynn. A Comparison of Patient Visits to Retail Clinics, Primary Care Physicians, and Emergency Departments. Health Aff (Milwood). 2008; 27(5); 1272-1282. Doi:10.1377/hlthaff.27.5.1272.
4. Katherine Knapp, Keith Yoshizuka, Debra Sasaki-Hill, Rory Caygill-Walsh. Co-located Retail Clinics and Pharmacies: An Opportunity to Provide More Primary Care. Pharmacy, 2019, 7, 74; doi:10.3390/pharmacy7030074
5. Diane Alexander, Janet Currie, Molly Schnell, Check up before you check out: Retail clinics and emergency room use, Journal of Public Economics, Volume 178, 2019, 104050, ISSN 0047-2727, https://doi.org/10.1016/j.jpubeco.2019.104050.
6. https://pr.mo.gov/nursing-advanced-practice-nursing-collaborative.asp. Last accessed 1/18/2023
7. J Margo Brooks Carthon, Therese Sammarco, Darcy Pancir, Jesse Chittams, Kelly Wiltse Nicely. Growth in retail-based clinics after nurse practitioner scope of practice reform. Nursing Outlook. 2017 65(2); 195- 201. Doi.10.1016/j.outlook.2016.11.001
8. AAUCM (2023) American Academy of Urgent Care Medicine. https://aaucm.org/what-is-urgent-care-medicine/. Last accessed 1/16/2023.
9. Sidney T Le, Renee Y Hsia. Community characteristics associated with where urgent care centers are located: a cross-sectional analysis. BMJ Open 2016;6:e010663. Doi:10.1136/bmjopen-2015-010663.
10. United States Urgent Care Centers Markets, 2020-2025: What is the Market for Urgent Care Centers? What Services are they Selling? Who is Selling Testing and Vaccine Products to Urgent Care? December 9, 2020 Source Research and Markets. https://www.globenewswire.com/en/news-release/2020/12/09/2142221/28124/en/United-States-Urgent-Care-Centers-Markets-2020-2025-What-is-the-Market-for-Urgent-Care-Centers-What-Services-are-they-Selling-Who-is-Selling-Testing-and-Vaccine-Products-to-Urgent-.html last accessed 1/16/2023
11. Shelagh Dolan. How the growth of the urgent care industry business model is changing the healthcare market in 2022. eMarketer - Insider Intelligence. April 15, 2022. https://www.insiderintelligence.com/insights/urgent-care-industry-trends/. Last accessed 1/18/2023.
12. Sean McNeeley. Urgent Care Centers: An Overview. American Journal of Clinical Medicine. 2012 9(2): 80-81.
13. Alan A Ayers. Pros and Cons of Urgent Care vs Primary Care Billing for Urgent Care Services. Journal of Urgent Care Medicine. https://www.jucm.com/pros-and-cons-of-urgent-care-vs-primary-care-billing-for-urgent-care-services. Last accessed 11/26/2022
14. Trudy Millard Krause, Cecilia Ganduglia-Cazaba, Linda B Piller, Vidya Venkataraman. Comparison of. Utilization of urgent care and primary care 2011-2015. Family Medicine and Care. 2017. Doi: 10.15761/FMC.1000102
15. Timothy Hoff, Kathryn Prout. Comparing Retail Clinics With Other Sites of Care: A Systematic Review of Cost, Quality, and Patient Satisfaction. Medical Care 2019; 57 (9): 734-741
16. CVS Health launches first nationwide virtual primary care solution. https://www.cvshealth.com/news/virtual-care/cvs-health-launches-first-nationwide-virtual-primary-care-soluti.html. Last accessed 1/18/2023.
17. Anna Wilde Mathews. Physicians, Hospitals Meet Their New Competitor: Insurer-Owned Clinics. Wall Street Journal. February 24, 2020. https://www.wsj.com/articles/physicians-hospitals-meet-their-new-competitor-insurer-owned-clinics-11582473600. Last accessed 1/18/2023
18. Weltmer K, Talib N, Mann K. Retail-based clinics & the patient-centered medical home. Mo Med. 2014 Jul-Aug;111(4):316-8. PMID: 25211860; PMCID: PMC6179463.
19. N Ogechi Abara, Nicole Huang, Mukaila A Raji, Young-Fang Kuo. Effect of Retail Clinic Use on Continuity of Care Among Medicare Beneficiaries. J Am Board Fam Med. 2019; 32:531-538. Doi: 10.3122/jabfm.2019.04.180349
20. Angela Nash, Ashley N. Carranza, Pamela J. Munoz. Comparing quality of care in medical specialties between nurse practitioners and physicians. Journal of the American Association of Nurse Practitioners. 2020;33:184-193. Accessed February 3, 2023. https://search.ebscohost.com/login.aspx?
21. Jessica Holman, Aditi Patel, Parth Parikh, Michael Rothberg. Comparing Encounter Characteristics Among Advanced Practice Clinicians and Physicians for Adult Same-Day Visits in Primary and Urgent Care J Gen Intern Med 37(3):689–91
DOI: 10.1007/s11606-021-06669-w © Society of General Internal Medicine 2021
22. Ken Terry. How to compete with retail clinics. Medical Economics Journal. August 25, 2019 96 (16). https://www.medicaleconomics.com/view/how-compete-retail-clinics last accessed 1/18/2023
23. Amir Barzin, Olivia C Seybold, Cristy Page. Integrating an Urgent Care Clinic Into an Academic Family Medicine Practice. Fam Med. 2020 52(6):440-443. Doi: 10.22454/FamMed.2020.933051.
24. Lee A Resnik. Urgent Care: the evolution of a revolution. Isr J Health Policy Res. 2013; 2: 39. Doi:10.1186/2045-4015-2-39.

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Long COVID: Where Are We in 2023?



by Hariharan Regunath, MD, Nir M. Goldstein, MD & Vamsi P. Guntur, MD

The term "COVID Long-Hauler" or "Long-Haul COVID" was first created by patients within few months of the onset of the pandemic.[1, 2] The first publication of persistent symptoms following acute COVID-19 was from Italy in July 2020, where-in, 143 hospitalized patients with acute COVID-19 between April and May 2020, who eventually tested negative by polymerase chain reaction (PCR), were followed for two months as out-patient and 87.4% had at least one persistent symptom.[3] The database study from the United States (U.S.) Department of Veterans Affairs (VA) was the first largest study to show that beyond a month of illness, there existed a higher risk for death and healthcare utilization because of a variety of incident respiratory, cardiovascular, neurological, musculoskeletal, gastrointestinal and metabolic disorders.[4] Subsequently, multiple other observational studies have been published.[5-10] The systematic reviews that followed, were limited by the low quality of such studies, lack of standardized definition and representative biologic markers for the different organ systems involved as a part of this syndrome.

To date, "long COVID" remains loosely defined by the Centers for Disease Control and Prevention (CDC) as new-onset, persistent or evolving symptoms that linger beyond four weeks following recovery from a documented acute COVID illness or diagnosis, and characterized by persistent physical or mental health issues.[11] The World Health Organization (WHO) uses a longer interval of 12 weeks in the absence of an alternative explanation or diagnosis.[12, 13] Consensus continues to be lacking for a unified definition due to wide variations in study criteria, measures, and quality.[14] Long COVID, post-COVID conditions, post-acute sequelae of SARS CoV-2 (PASC), chronic COVID-19, ongoing symptomatic COVID-19, post-COVD-19 persistent symptoms, and post COVID-19 syndrome are all merely different terms for a set of continued symptoms that linger after recovery from



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acute illness. Table 1 displays the different terms, definitions still in use as proposed by organizations and website references.[14, 15] Clinically useful and meaningful definitions based on the organ system of greatest involvement, or prolonged manifestations from initial illness (e.g. post-ARDS, lack of pulmonary involvement, minimal URI involvement) are yet to be sorted out.

Recent estimates from the CDC, report a wide range of 5-30% for the incidence of post-COVID conditions, attributed to the variability in reported symptoms, follow-up duration, study settings (inpatient or outpatient) and whether data is generated by self-report or health records database.[16] The wide variety of symptoms (an increasing list of >200 symptoms) in the long COVID studies have been classified by two systematic reviews into three common clusters, ongoing respiratory issues; fatigue with bodily pain or mood swings; and cognitive problems.[17, 18] Another data-driven study used a machine learning approach to analyse two large electronic health databases (INSIGHT comprising 20,881 patients out of 12 million in New York City and OneFlorida+ with 13,724 out of 19 million patients from Florida, Alabama, and Georgia). They abstracted and refined a list of 137 diagnosis categories listed by the VA study and evaluated their incidence after 30-180 days of a documented SARS CoV-2 infection. They reported four sub-phenotypes that differed in their demographics, comorbidities, and severity of the preceding acute COVID illness: cardiac and renal; respiratory, sleep and anxiety; musculoskeletal and nervous system; and digestive and respiratory system sequelae.[19] The first two sub-phenotypes predominated over the latter two.

An elusive variety of direct (viral) and indirect pathophysiological hypotheses for long COVID, included viral persistence/reservoir in different tissues, mitochondrial dysfunction, immune dysregulation as a continuation from the initial infection, persistent vascular endothelial or other organ injury, triggering or exacerbation of auto-immunity, gut dysbiosis and certain co-morbidities that increase the risk for long COVID.[20-24] The most interesting of these mechanisms is evidence for persistent SARS CoV-2 in the human body from a few small studies predating the omicron period, purporting a potential target for treatment or surrogate marker for clinical trials.

One study from the University of California San Francisco, showed higher levels of plasma neuronal exosomes (extracellular vesicles released by neuronal cells[25]) containing nucleocapsid and spike protein levels in long COVID patients with neuropsychiatric symptoms.[26] Another retrospective study measured plasma SARS CoV-2 antigens (S1, spike or N) in samples gathered from a biorepository (two or more samples gathered up to 12 months) and noted that antigens were detected in >70% of those who reported cardiovascular, systemic, head-eye-ear-nose-throat and musculoskeletal symptoms.[27] Spike protein was most often detected in 60% of those with long COVID at multiple time points. The authors concluded by indicating that a reservoir of active virus may endure in the body, as an explanation for the continued antigenemia (not viremia).[27] An autopsy study from the NIH has also demonstrated that SARS CoV-2 can be widely distributed in different extra-pulmonary tissues of the body and can persist for months, providing further rationale for more research to decipher mechanisms of viral persistence in contributing to long COVID.[28] Yet, these findings require confirmation by larger studies. Hence, a unifying pathophysiology remains enigmatic, because persistent symptoms could represent various other disease processes as well.

Designing clinical trials for long COVID has been difficult because it is still a syndrome (and not a disease) with many symptoms that differ between patients and within the same patient (waxing and waning or new symptoms), many long COVID symptoms are akin to myalgic encephalomyelitis (ME)/chronic fatigue syndrome (CFS). The lack of a diagnostic confirmatory marker (lab test) is another major impediment. Eventually, surrogate biomarkers whose levels, correlate with disease activity, are also essential for conducting trials on treatment. Our treatment approaches to Human Immunodeficiency Virus (HIV) and Hepatitis C Virus (HCV) diseases took decades to evolve, revolutionized by molecular diagnostics that provided reliable surrogate markers, namely HIV and HCV RNA levels, most of those spurring from concerted efforts by the CDC, National Institutes of Health, and the global community of translational and clinical research. Similar combined efforts are pacing towards the goal of testing and ultimately identifying effective candidates for surrogate biomarkers (lab tests) in long COVID.

The CDC's Household Pulse survey and the RECOVER [Researching COVID to Enhance Recovery] initiative by the NIH have been laying the foundations for clinical trials on long COVID, several of which started in early 2023, including the testing of various biomarkers and possible interventions

Table 1. Proposed Long COVID Definitions

Terms	Developed or proposed	Definition	Suggested website references
Long COVID*	Patients and people with lived experience; patient-researchers	Can be broadly defined as signs, symptoms, and sequelae that continue or develop after acute COVID-19 or SARS-CoV-2 infection for any period; are generally multisystemic; might present with a relapsing–remitting pattern and a progression or worsening over time, with the possibility of severe and life-threatening events even months or years after infection.	https://www.sciencedirect.com/science/article/pii/S0277953620306456?via%3Dihub
Persistent symptoms or COVID-19 consequences	Commonly used research term	Persistent signs and symptoms that continue or develop after acute COVID-19 for any period.	https://www.sciencedirect.com/science/article/pii/S0163445321005557; https://gh.bmj.com/content/6/9/e005427.long
Post-COVID-19 condition	WHO	Post-COVID-19 condition occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis; common symptoms include fatigue, shortness of breath, and cognitive dysfunction, and generally have an impact on everyday functioning; symptoms might be new onset after initial recovery from an acute COVID-19 episode or persist from the initial illness; symptoms might also fluctuate or relapse over time; a separate definition might be applicable for children	https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00703-9/fulltext
Ongoing symptomatic COVID-19	NICE†	Signs and symptoms of COVID-19 from 4 weeks up to 12 weeks.	https://www.nice.org.uk/guidance/ng188/resources/covid19-rapid-guideline-managing-the-longterm-effects-of-covid19-pdf-51035515742
Post-COVID-19 syndrome	NICE†	Signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis; it usually presents with clusters of symptoms, often overlapping, which can fluctuate and change over time and can affect any system in the body; post-COVID-19 syndrome might be considered before 12 weeks while the possibility of an alternative underlying disease is also being assessed.	https://www.nice.org.uk/guidance/ng188/resources/covid19-rapid-guideline-managing-the-longterm-effects-of-covid19-pdf-51035515742
Post-COVID conditions	CDC	An umbrella term for the wide range of physical and mental health consequences experienced by some patients that are present four or more weeks after SARS-CoV-2 infection, including by patients who had initial mild or asymptomatic acute infection.	https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/index.html
Post-acute sequelae of SARS CoV-2 infection*	NIH	Persistent or new symptoms after COVID-19 infection; the definition will be revised in an iterative manner based on existing data, medical literature, and feedback from patient representatives, patients, and the scientific community; updated definitions might be used to implement a strategy to modify deeper phenotyping.	https://recovercovid.org/docs/RECOVER-Adult-Protocol_02-02-2022.pdf

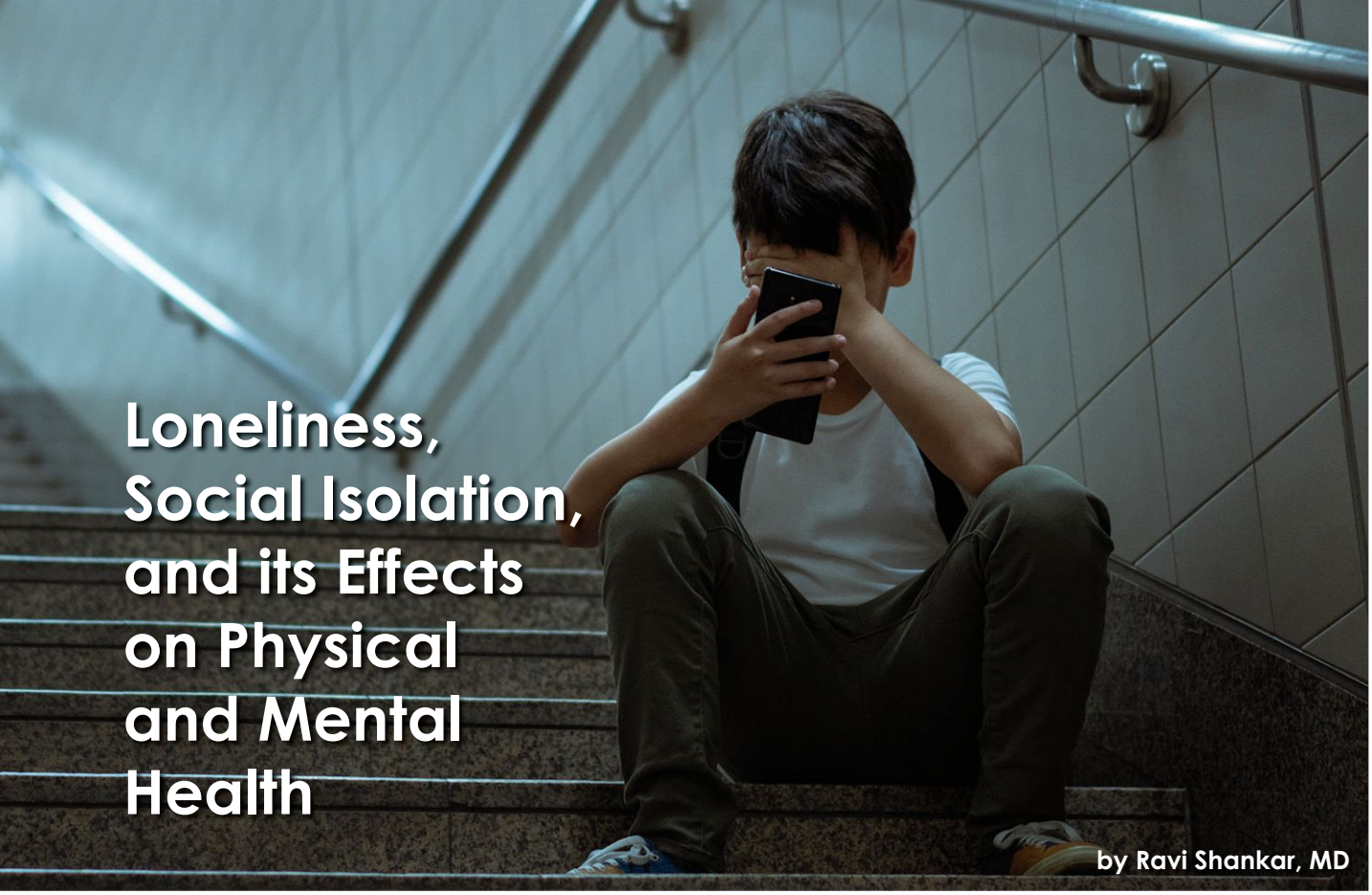
CDC – Centers for Disease Control and Prevention; NIH – National Institutes of Health; COVID – Coronavirus disease; SARS CoV 2 – Severe acute respiratory syndrome coronavirus 2; NICE=National Institute for Health and Care Excellence (UK). †NICE also states that: "In addition to the clinical case definitions, the term 'long COVID' is commonly used to describe signs and symptoms that continue or develop after acute COVID-19. It includes both ongoing symptomatic COVID-19 (from 4 to 12 weeks) and post-COVID-19 syndrome (12 weeks or more)." [Reproduced from *The Lancet Respiratory Medicine*, Vol 10, Issue 7, Daniel Munbit et al, "Long COVID: aiming for a consensus", p 632-634, July 2022, with permission from Elsevier©2022]

including the use of antiviral therapy.[29] This has become possible because of their continued efforts to support observational studies, pathobiology studies, evaluation of potential biomarkers and analyses of millions of electronic health records in the National COVID Cohort Collaborative (N3C) data using machine learning approach, which have now informed endpoints and enabled trial designs.[30, 31] The Research Review (R3) Seminar Series from the RECOVER initiative, provides useful periodic updates by experts researching on the different aspects of long COVID, to promote a shared understanding of the continued progress in long COVID research.[30]

References

1. Callard F, Perego E. How and why patients made Long Covid. Social Science & Medicine. 2021/01/01/ 2021;268:113426. doi:https://doi.org/10.1016/j.socscimed.2020.113426
2. Davis HE, Assaf GS, McCorkell L, et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. eClinicalMedicine. 2021/08/01/ 2021;38:101019. doi:https://doi.org/10.1016/j.eclinm.2021.101019
3. Carfì A, Bernabei R, Landi F, Group ftGAC-P-ACS. Persistent Symptoms in Patients After Acute COVID-19. JAMA. 2020;324(6):603-605. doi:10.1001/jama.2020.12603
4. Al-Aly Z, Xie Y, Bowe B. High-dimensional characterization of post-acute sequelae of COVID-19. Nature. Jun 2021;594(7862):259-264. doi:10.1038/s41586-021-03553-9
5. Halpin SJ, McIvor C, Whyatt G, et al. Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: A cross-sectional evaluation. Journal of Medical Virology. 2021;93(2):1013-1022. doi:https://doi.org/10.1002/jmv.26368
6. Carvalho-Schneider C, Laurent E, Lemaignen A, et al. Follow-up of adults with noncritical COVID-19 two months after symptom onset. Clinical Microbiology and Infection. 2021/02/01/ 2021;27(2):258-263. doi:https://doi.org/10.1016/j.cmi.2020.09.052
7. Chopra V, Flanders SA, O'Malley M, Malani AN, Prescott HC. Sixty-Day Outcomes Among Patients Hospitalized With COVID-19. Annals of Internal Medicine. 2021/04/20 2020;174(4):576-578. doi:10.7326/M20-5661
8. Arnold DT, Hamilton FW, Milne A, et al. Patient outcomes after hospitalisation with COVID-19 and implications for follow-up: results from a prospective UK cohort. Thorax. 2021;76(4):399. doi:10.1136/thoraxjnl-2020-216086
9. Moreno-Pérez O, Merino E, Leon-Ramirez J-M, et al. Post-acute COVID-19 syndrome. Incidence and risk factors: A Mediterranean cohort study. Journal of Infection. 2021;82(3):378-383. doi:10.1016/j.jinf.2021.01.004
10. Garrigues E, Janvier P, Kherabi Y, et al. Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19. Journal of Infection. 2020/12/01/ 2020;81(6):e4-e6. doi:https://doi.org/10.1016/j.jinf.2020.08.029
11. Nalbandian A, Sehgal K, Gupta A, et al. Post-acute COVID-19 syndrome. Nature Medicine. 2021/04/01 2021;27(4):601-615. doi:10.1038/s41591-021-01283-z
12. Post-COVID Conditions: Information for Healthcare Providers. The Centers for Disease Control and Prevention. Updated September 22, 2022. Accessed October 12, 2022. https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/post-covid-conditions.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fhcp%2Fclinical-care%2Flate-sequelae.html
13. A clinical case definition of post COVID-19 condition by a Delphi consensus, 6 October 2021. World Health Organization. Updated October 6, 2021. Accessed October 12, 2022. https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1
14. Munblit D, O'Hara ME, Akrami A, Perego E, Olliaro P, Needham DM. Long COVID: aiming for a consensus. Lancet Respir Med. Jul 2022;10(7):632-634. doi:10.1016/s2213-2600(22)00135-7
15. National Institute for Health and Care Excellence: Clinical Guidelines. COVID-19 rapid guideline: managing the long-term effects of COVID-19. National Institute for Health and Care Excellence (NICE) Copyright © NICE 2020.; 2020.
16. Post-COVID Conditions: Information for Healthcare Providers. Centers for Disease Control and Prevention. Updated Dec 16. 2022. Accessed Jan 1, 2023, 2023. https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/post-covid-conditions.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fhcp%2Fclinical-care%2Flate-sequelae.html
17. Nasserie T, Hittle M, Goodman SN. Assessment of the Frequency and Variety of Persistent Symptoms Among Patients With COVID-19: A Systematic Review. JAMA Netw Open. May 3 2021;4(5):e2111417. doi:10.1001/jamanetworkopen.2021.11417
18. Collaborators GBoDLC. Estimated Global Proportions of Individuals With Persistent Fatigue, Cognitive, and Respiratory Symptom Clusters Following Symptomatic COVID-19 in 2020 and 2021. JAMA. 2022;328(16):1604-1615. doi:10.1001/jama.2022.18931
19. Zhang H, Zang C, Xu Z, et al. Data-driven identification of post-acute SARS-CoV-2 infection subphenotypes. Nat Med. Dec 1 2022;doi:10.1038/s41591-022-02116-3
20. Haque A, Pant AB. Long Covid: Untangling the Complex Syndrome and the Search for Therapeutics. Viruses. 2022;15(1):42.
21. Su Y, Yuan D, Chen DG, et al. Multiple early factors anticipate post-acute COVID-19 sequelae. Cell. 2022;185(5):881-895.e20. doi:10.1016/j.cell.2022.01.014
22. Peluso MJ, Deeks SG. Early clues regarding the pathogenesis of long-COVID. Trends Immunol. Apr 2022;43(4):268-270. doi:10.1016/j.it.2022.02.008
23. Boer Ed, Petrache I, Goldstein NM, et al. Decreased Fatty Acid Oxidation and Altered Lactate Production during Exercise in Patients with Post-acute COVID-19 Syndrome. American Journal of Respiratory and Critical Care Medicine. 2022;205(1):126-129. doi:10.1164/rccm.202108-1903LE
24. Guntur VP, Nemkov T, de Boer E, et al. Signatures of Mitochondrial Dysfunction and Impaired Fatty Acid Metabolism in Plasma of Patients with Post-Acute Sequelae of COVID-19 (PASC). Metabolites. Oct 26 2022;12(11)doi:10.3390/metabo12111026
25. Kalluri R, LeBleu VS. The biology, function, and biomedical applications of exosomes. Science. 2020;367(6478):eaau6977. doi:doi:10.1126/science.aau6977
26. Peluso MJ, Deeks SG, Mustapic M, et al. SARS-CoV-2 and Mitochondrial Proteins in Neural-Derived Exosomes of COVID-19. Annals of Neurology. 2022;91(6):772-781. doi:https://doi.org/10.1002/ana.26350
27. Swank Z, Senussi Y, Manickas-Hill Z, et al. Persistent circulating SARS-CoV-2 spike is associated with post-acute COVID-19 sequelae. Clin Infect Dis. Sep 2 2022;doi:10.1093/cid/ciac722
28. Stein SR, Ramelli SC, Grazioli A, et al. SARS-CoV-2 infection and persistence in the human body and brain at autopsy. Nature. 2022/12/01 2022;612(7941):758-763. doi:10.1038/s41586-022-05542-y
29. Long COVID - Household Pulse Survey. Centers for Disease Control and Prevention. Updated Nov 29, 2022. Accessed Jan 1, 2023, 2023. https://www.cdc.gov/nchs/covid19/pulse/long-covid.htm
30. Understanding the Biomarkers of PASC. National Institutes of Health. Updated Nov 8, 2022. Accessed Jan 1, 2023, 2023. https://recovercovid.org/r3-seminar-series
31. Pfaff ER, Girvin AT, Bennett TD, et al. Identifying who has long COVID in the USA: a machine learning approach using N3C data. The Lancet Digital Health. 2022;4(7):e532-e541. doi:10.1016/S2589-7500(22)00048-6

MM



Loneliness, Social Isolation, and its Effects on Physical and Mental Health

by Ravi Shankar, MD

Recognition of loneliness and social isolation is of paramount significance so that interventions can be done to prevent further deterioration of physical and mental health and decrease morbidity and mortality.

Loneliness is defined in the *Merriam-Webster Dictionary* as being without company, separated from others. It is an unpleasant emotional response to perceived isolation. Social isolation, on the other hand, is an apparent (objective isolation) or perceived (subjective isolation) lack of contact between an individual and society.[1–3]



Ravi Shankar, MD, is Associate Professor of Psychiatry, Director for Psychiatry Residency, Department of Psychiatry, University of Missouri - Columbia, Columbia, Missouri.

Previous estimates of adult social isolation ranges from 15-40%.[4] The National Academies of Sciences, Engineering, and Medicine (NASEM) asserts that more than one-third of adults aged 45 and older are lonely. Nearly one-fourth of adults aged 65 and older are socially isolated.[5] Demographic data on social isolation and loneliness in children and adolescents are unfortunately scarce.

The COVID-19 pandemic led to physical distancing to minimize spread of infection. This unfortunately created social distancing and increased social isolation. In young individuals subject to social isolation, higher levels of cortisol occur causing an increase in BMI. Social isolation can also lead to a sedentary lifestyle and the associated adverse health consequences.[6] Social isolation for infection control of COVID-19 needs to be differentiated from generic social isolation. The latter is more patient-driven among those not wanting to be around people.

While the use of electronics, such as social media, increased during the pandemic in an effort to stay connected and cope, it created additional youth problems such as phone addiction, excessive usage, and decreased physical activity.

Understanding loneliness and social isolation is important considering that these conditions have been associated with poor health. Research demonstrates adverse effects on the cardiovascular, immune, and neuroendocrine systems.[7–10] This is even more common in the elderly, minorities, and the poor.[11]

There is evidence indicating that robust social support may lower the risk of cardiovascular disease.[12] One of the proposed mechanisms underlying this association is the "reactivity hypothesis of disease."[13] According to this hypothesis, individuals with high reactivity are at an increased risk for cardiovascular disease. Social support acts as "buffer" for stress-induced cardiovascular reactivity[14] and promotes healthy behaviors such as exercise which also reduces stress.[15]

The multi-site Enhancing Recovery in Coronary Heart Disease (ENRICHD) study incorporated comprehensive social support interventions. There was no difference in long-term survival between the intervention and control groups. Participants in the intervention group reported benefits of increased social supports at six months. Another potential pathway studied the role of social supports in behavioral processes including health behaviors and medical regimen compliance.[16,17] Social support was posited as health-promoting, facilitating healthy behaviors such as diet, exercise, abstinence from smoking, and increased adherence to medical regimens. The psychological processes linked to mood, assessment, feeling of control[18–20] and practice of health behaviors[21] seem the mechanisms underlying the positive association between social support and cardiovascular health.

Apart from the physiological negative effects outlined above, social isolation has harmful effects on mental health. These include worsening of depression, anxiety, and suicidal ideation. Studies have shown a greater prevalence of depressive symptoms and suicidal ideation due to social isolation in adolescence than in adulthood.[22, 23] A systematic review of 63 studies of more than 50,000 children and adolescents found a significant association between loneliness and mental health problems. Loneliness was additionally associated with future mental health problems up to nine years later.[24] Qualter, P., et al. (2010),[25] reported that length of loneliness predicted future mental health problems. As a consequence of pandemic-related increases in social isolation, parents and children have reported worsening of child mental health.[26]

For example, cases of suicidal ideation in March and July 2020, and suicidal attempts in February through July 2020 were found to be significantly higher in comparison to data from 2019.[27] An increased use of emergency room services was also observed during the pandemic.[28] Mental health concerns noted in children during this period varied from excessive clinginess, fear of safety, worrying to increased depressive anxiety, and difficulty in academics.[24] Sexual minority youth were found to be most vulnerable to the mental health effects of social isolation.[29] While the use of electronics, such as social media, increased during the period in an effort to stay connected and cope, it created additional youth problems such as phone addiction, excessive usage, and decreased physical activity.

In summary, both loneliness and social isolation are concepts that have existed for a long time. The consequences of the COVID-19 pandemic have exacerbated loneliness and social isolation. The immersion individuals of all age, especially children, in digital devices and electronics such as cell phones, the internet, computer gaming, and solitary social media that will endure even as COVID-19 wanes.

Loneliness and social isolation can present across the life span and cause troubling physical and mental significant sequala. Recognition of loneliness and social isolation is of paramount significance so that interventions can be done to prevent further deterioration of physical and mental health and decrease morbidity and mortality. This may be done as screening assessments for loneliness, social isolation and depression across several venues including educational, work force, and healthcare to prevent. Digital technology which was extremely helpful during the pandemic to help connecting people. However, it is also difficult to gauge the level of engagement in activities on a digital platform compared to traditional in person activity or club. An ideal approach would be to encourage students to get involved in more in-person activities when available and appropriate. New paradigms are need to identify loneliness and social isolation across all populations.

References

1. Cornwell EY, Waite LJ. Social disconnectedness, perceived isolation, and health among older adults. J Health Soc Behav. 2009;50(1). doi:10.1177/002214650905000103
2. Coyle CE, Dugan E. Social isolation, loneliness and health among older adults. J Aging Health. 2012;24(8). doi:10.1177/0898264312460275
3. Valtorta N, Hanratty B. P36 Loneliness, social isolation and health: 'What's the problem represented to be?' in the United Kingdom? J Epidemiol Community Health (1978). 2016;70(Suppl 1). doi:10.1136/jech-2016-208064.135
4. Elder K, & RJ. Framework for isolation in adults over 50 (Revised edition). . Washington, DC: AARP Foundation. Published online 2012.
5. Donovan NJ, Blazer D. Social Isolation and Loneliness in Older Adults: Review and Commentary of a National Academies Report. American Journal of Geriatric Psychiatry. 2020;28(12). doi:10.1016/j.jagp.2020.08.005
6. Almeida IL de L, Rego JF, Teixeira ACG, Moreira MR. Social isolation and its impact on child and adolescent development: a systematic review. Rev Paul Pediatr. 2021;40. doi:10.1590/1984-0462/2022/40/2020385
7. Cacioppo JT, Hawkley LC, Berntson GG, et al. Do lonely days invade the nights? Potential social modulation of sleep efficiency. Psychol Sci. 2002;13(4). doi:10.1111/j.0956-7976.2002.00469.x
8. Heffner KL, Waring ME, Roberts MB, Eaton CB, Gramling R. Social isolation, C-reactive protein, and coronary heart disease mortality among community-dwelling adults. Soc Sci Med. 2011;72(9). doi:10.1016/j.socscimed.2011.03.016
9. Uchino BN, Cacioppo JT, Kiecolt-Glaser JK. The relationship between social support and physiological processes: A review with emphasis on underlying mechanisms and implications for health. Psychol Bull. 1996;119(3). doi:10.1037/0033-2909.119.3.488
10. Cacioppo JT, Hawkley LC. Social Isolation and Health, with an Emphasis on Underlying Mechanisms. Perspect Biol Med. 2003;46(3). doi:10.1353/pbm.2003.0049
11. House JS, Landis KR, Umberson D. Social relationships and health. Science (1979). 1988;241(4865). doi:10.1126/science.3399889
12. Uchino BN. Social Support and Physical Health: Understanding the Health Consequences of Relationships.; 2004. doi:10.1093/aje/kwi036
13. Lepore SJ. Problems and prospects for the social support-reactivity hypothesis. Annals of Behavioral Medicine. 1998;20(4). doi:10.1007/BF02886375
14. Cohen S, Wills TA. Stress, Social Support, and the Buffering Hypothesis. Psychol Bull. 1985;98(2). doi:10.1037/0033-2909.98.2.310
15. Rejeski WJ, Thompson A, Brubaker PH, Miller HS. Acute exercise: buffering psychosocial stress responses in women. Health Psychol. 1992;11(6). doi:10.1037/0278-6133.11.6.355
16. Umberson D. Family status and health behaviors: social control as a dimension of social integration. J Health Soc Behav. 1987;28(3). doi:10.2307/2136848
17. Lewis MA, Rook KS. Social control in personal relationships: Impact on health behaviors and psychological distress. Health Psychology. 1999;18(1). doi:10.1037/0278-6133.18.1.63
18. Cohen S. Psychosocial models of the role of social support in the etiology of physical disease. Health Psychol. 1988;7(3). doi:10.1037/0278-6133.7.3.269
19. Gore S. Stress-buffering functions of social supports: An appraisal and clarification of research models. Stressful life events and their context. Published online 1981.
20. LIN N. Modeling the Effects of Social Support. In: Social Support, Life Events, and Depression. ; 1986. doi:10.1016/b978-0-12-450660-2.50019-7
21. Ng DM, Jeffery RW. Relationships between Perceived Stress and Health Behaviors in a Sample of Working Adults. Health Psychology. 2003;22(6). doi:10.1037/0278-6133.22.6.638
22. Fichter MM, Kohlboeck G, Quadflieg N, Wyschkon A, Esser G. From childhood to adult age: 18-year longitudinal results and prediction of the course of mental disorders in the community. Soc Psychiatry Psychiatr Epidemiol. 2009;44(9). doi:10.1007/s00127-009-0501-y
23. Nock MK, Borges G, Bromet EJ, et al. Cross-national prevalence and risk factors for suicidal ideation, plans and attempts. British Journal of Psychiatry. 2008;192(2). doi:10.1192/bjp.bp.107.040113
24. Loades ME, Chatburn E, Higson-Sweeney N, et al. Rapid Systematic Review: The Impact of Social Isolation and Loneliness on the Mental Health of Children and Adolescents in the Context of COVID-19. J Am Acad Child Adolesc Psychiatry. 2020;59(11). doi:10.1016/j.jaac.2020.05.009
25. Qualter P, Brown SL, Munn P, Rotenberg KJ. Childhood loneliness as a predictor of adolescent depressive symptoms: An 8-year longitudinal study. Eur Child Adolesc Psychiatry. 2010;19(6). doi:10.1007/s00787-009-0059-y
26. Patrick SW, Henkhaus LE, Zickafoose JS, et al. Well-being of Parents and Children During the COVID-19 Pandemic: A National Survey. Pediatrics. 2020;146(4). doi:10.1542/peds.2020-016824
27. Isumi A, Doi S, Yamaoka Y, Takahashi K, Fujiwara T. Do suicide rates in children and adolescents change during school closure in Japan? The acute effect of the first wave of COVID-19 pandemic on child and adolescent mental health. Child Abuse Negl. 2020;110. doi:10.1016/j.chiabu.2020.104680
28. AAP, AACAP, CHA declare national emergency in children's mental health. AAP news. Published online October 19, 2021.
29. McDanal R, Schleider JL, Fox KR, Eaton NR. Loneliness in Gender-Diverse and Sexual Orientation–Diverse Adolescents: Measurement Invariance Analyses and Between-Group Comparisons. Assessment. Published online 2021. doi:10.1177/10731911211065167

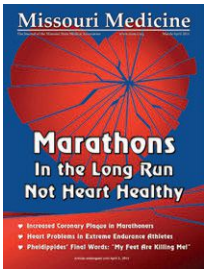
MM

In the News

Did you make the news? Submit your success story and photo to lfleenor@msma.org.

1 PICTURE = 1,000 WORDS

2023 Study in *Circulation* Confirms *Missouri Medicine* Research Published in 2014



Missouri Medicine March/April 2014; 111:2 89-94 "Increased Coronary Artery Plaque Volume Among Male Marathon Runners."

CONCLUSION: Long-term training for and competing in marathons may in men be paradoxically associated with accelerated coronary artery plaque formation.

American Heart Association *Circulation* March 28 2023; 147:13 "Exercise Volume Versus Intensity and the Progression of Coronary Atherosclerosis in Middle-Aged and Older Athletes: Findings From the MARC-2 Study."

American Heart Association. Learn and Live.
Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

CONCLUSION: Exercise intensity but not volume was associated with progression of coronary atherosclerosis during six-year follow-up. It is intriguing that very vigorous intensity exercise was associated with greater CAC and calcified plaque progression, whereas less vigorous exercise was associated with less CAC progression.

[See page 155 in this issue on latest research on "Training Strategies to Optimize Cardiovascular Durability and Life Expectancy" by O'Keefe et. al.]

Missouri Medicine Announces New Editorial Board Member

Missouri Medicine announces new Editorial Board members. Board members are selected on the basis of exceptional professional accomplishment and expertise in their specialty.



Kent K. Huston, MD, is the new Editorial Board member for Rheumatology. Dr. Huston is a Clinical Assistant Professor at the University of Missouri - Kansas City and practices at Saint Luke's Hospital in Kansas City, Missouri. He is board certified in Rheumatology and Internal Medicine. Dr. Huston replaces **Anne Winkler, MD,** who is retiring after 15 years in this position. *Missouri Medicine* has awarded her the Distinguished Service Award, and we wish the best for Dr. Winkler.

Podcast: Recognizing, Caring for Dementia Patients in the Emergency Department

The January 31, 2023, episode of 'Show Me the Science' podcast produced by the Washington University School of Medicine looked at steps being taken to make it easier for people with dementia to navigate emergency room visits.



Missouri Medicine past Editorial Board member **Christopher Carpenter, MD**, Professor of Emergency Medicine, had a bad emergency department experience involving his grandfather, who was suffering from dementia at the time. For over two decades since then, Carpenter has looked for ways to make the emergency department experience easier for those who are living with dementia and their family members and caregivers. He is part of a national effort known as the GEAR Network,



NEW MSMA MEMBERS!

* = Medical Student ** = Resident/Fellow

Elijah Alcorn*
Daniel Arias, MD** – OB/GYN – Chesterfield
Kimberley Beier*
Hannah Bergman, MD – Plastic Surgery – Nixa
Sumeet Bhardwaj*
Sarah Blank*
Samantha Bunk*
Jsoeph Burris, MD – PMR – Columbia
Hannah Caplan*
Pearl Carrillo, DO – Family Practice – Marshall
Ginger Chant*
Zachary Dampier*
Jordan De la Rosa*
Alisha Dhallan*
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David Gibson, MD – Rheumatology – Sikeston
Sydney Gibson*
Michael Hilzendeger*
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Kris Humphreys, MD – Internal Medicine – Kansas City
Quinn Jackson, MD – Family Practice
David Kanarowski*
Ricky Kellenberger, DO – Family Practice – Nevada
Erica Korbel*
Hayley Lange*
Adam Lechner*
Nick Leonard*
Angela Lewis, MD – Neonatal-Perinatal – University City
Emmanuel Madu*
Sreya Mandava*
Sino Mehrmal, DO** – Dermatoloty
Johana Mejias-Beck, MD** – Internal Med/Ped
Samiha Mohammed*
Collin Nadarajah*
Mustafa Naveed*
Sean Nguyen*
Natalie Powell*
Alice Pulsipher*
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Jorge Saucedo*
Riley Short*
Muaaz Tariq*
Denise Taylor*
Rohan Tipnis*
Carmen Tong*
Paula Valiño Ramos*
Lauren Van Winkle*
Vivek Velagapudi*
Aishani Vengala*
Madelyn Ward*
Julie Whitten*

In the News, continued

which stands for Geriatric Emergency Care Applied Research Network, and studies ways to identify and serve older patients with dementia. Carpenter says it's essential to improve emergency care for people living with dementia because as the U.S. population continues to age, the number of such people seeking treatment in emergency departments will continue to increase. Scan code at left to listen to the podcast.

Washington Post Taps *Missouri Medicine* Author for Article on Pickleball Injuries

The *Washington Post* newspaper ran an article on November 11, 2022, on the prevention of pickleball injuries. The primary source quoted by the reporter was a *Missouri Medicine* author Nicholas Greiner, DO, that appeared in the November/December issue. Scan code at right to read the article

MSMA Members in the News



Alexander Garza, MD, was honored with the 2022 St. Louis Metropolitan Medical Society President's Award, which recognizes a SLMMS member who has provided outstanding service to the medical community. Dr. Garza, who serves as the chief community health officer for SSM Health, received the award at SLMMS' Annual Meeting on February 11. **MM**

ATSU | A.T. Still University
FIRST IN WHOLE PERSON HEALTHCARE

Preserving the History and Future of Osteopathic Medicine

by Margaret Wilson, DO

Our alumni have successful careers spanning all disciplines and settings from the White House and NASA to rural America, all while providing patients with compassionate care.

For over 10 years, I have had the privilege to serve as dean of my alma mater, and I am honored by the opportunity to report on the founding school of osteopathic medicine as it celebrates its 130th anniversary. A.T. Still University's Kirksville College of Osteopathic Medicine (ATSU-KCOM) has always been committed to producing the best osteopathic physicians to meet the needs of patients. As a student, I experienced this commitment firsthand, and as dean, my goal has been to carry that commitment forward.

Although ATSU-KCOM has consistently demonstrated exceptional board pass rates, graduate medical education placement, and accreditation outcomes, I believe its greatest success is reflected in our graduates. Our alumni have successful careers spanning all disciplines and settings from the White House and NASA to rural America, all while providing patients with compassionate care. Our faculty and staff are very committed to student success and work collegially to provide a wonderful work environment. Our students are outstanding individuals who are hardworking and dedicated to becoming the best possible professionals.



Margaret A. Wilson, DO, is Dean, Kirksville College of Osteopathic Medicine, and Professor, Department of Family Medicine, A.T. Still University, Kirksville College of Osteopathic Medicine, Kirksville, Missouri.

Each year adds another chapter to the ATSU-KCOM story. This year, as we celebrated a milestone anniversary, we also celebrated the Museum of Osteopathic Medicine's accreditation by the American Alliance of Museums (AAM), the gold standard for museum excellence. The Museum of Osteopathic Medicine is special to ATSU-KCOM because it encapsulates the complete history of the College and the osteopathic profession.

The museum attracts visitors from around the world, and its collections include more than 100,000 objects, photographs, documents, and books dating from the early 1800s to the present. The core of the collection consists of artifacts from the professional and private life of A.T. Still, DO, the founder of osteopathic medicine and ATSU-KCOM. Most of these items were donated by Dr. Still's daughter, Blanche Laughlin, and members of the family. Items continue to be donated to the museum today, and each piece allows the staff to gain more information and a better understanding of the history and growth of the osteopathic profession.

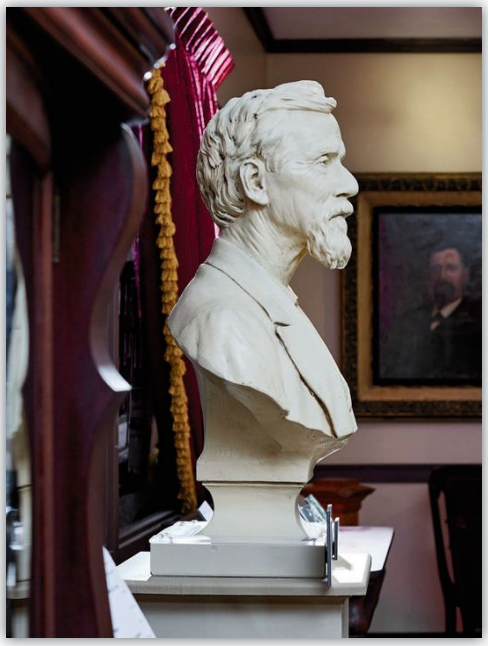
Museum Accreditation

Because AAM is the premier accrediting body for museums in the United States, this accreditation brings national recognition to the museum for its commitment to excellence, accountability, high professional standards, and continued institutional improvement. Of the nation's estimated 33,000 museums, fewer than 1,100 are currently accredited. In Missouri, the Museum of Osteopathic Medicine is one of only 20 accredited museums, including the Nelson-



Still Family Cabin

The Still Family Cabin was built in Lee County, Virginia, in the 1820s and was moved to its current location in Heritage Hall in 1994.



Dr. A.T. Still Bust

Created in 1897, sculptor Howard Kretschmar made a white plaster bust of Dr. Still, which is currently on display in the Grayson Smith Period Room.
Museum of Osteopathic Medicine, Kirksville, Missouri [1975.110.02]

Atkins Museum of Art in Kansas City and the Saint Louis Art Museum.

Led by Museum Director Jason Haxton, MA, the museum's dedicated team completed a long, rigorous process that examined all aspects of their operations. This process included a year of self-study followed by a site visit from a team of peer reviewers. After consideration of the self-study and site visit review, AAM granted accreditation to the museum in summer 2022.

With AAM recognition, the museum team looks forward to new opportunities in growth, outreach, and funding for their work. The Museum of Osteopathic Medicine has demonstrated its credibility and value to funders, policymakers, insurers, community members, and peer institutions. In addition, the accreditation designation helps facilitate loans between AAM member museums, which will allow more osteopathic artifacts to be studied and exhibited at the museum.

Popular Museum Attractions

Originally, ATSU-KCOM was named the American School of Osteopathy, a fitting title for its role in American history. Early patients and supporters of osteopathic medicine included popular American figures like Buffalo Bill, Helen Keller, Teddy Roosevelt, and Mark Twain, who helped push a bill to license osteopathic physicians in New York. As osteopathic medicine has grown and influenced healthcare worldwide, the work of the Museum of Osteopathic Medicine has become increasingly important because it preserves and promotes the history and tenets of osteopathy to a global audience through collections and research.

The history we get to see and experience every day on our campus is inspiring. I encourage anyone who is interested in learning more about osteopathic medicine or the life of Dr. Still to visit Kirksville and tour the museum. Among the many items on display are some popular attractions, including the first school building of the American School of Osteopathy, the Still Family Cabin, a bust of Dr. Still, a dissected nervous system, and a historical medicinal garden.



First Osteopathic School

This two-room building was the first school building of the American School of Osteopathy. It was used from 1892-1894 and was moved to its current location in Heritage Hall in 1994.



Nervous System

From 1925-1926, medical students M.A. Schalck and L.P. Ramsdell, both from the class of 1928, dissected an entire human nervous system. This nervous system is currently on display and is one of four such dissections in the world.

Museum of Osteopathic Medicine, Kirksville, Missouri [1999.08.01]



Historic Medicinal plant Garden

Elsie's Medicinal Garden is located just outside Heritage Hall, next to ATSU Gutensohn Clinic, and features a wide range of native perennials, shrubs, and trees that were grown and used by early medical practitioners. **MM**

Connect to Osteopathic History

Visit the Museum of Osteopathic Medicine in person or virtually to discover photographs, artifacts, books, journals, manuscripts, and more from the earliest days of osteopathic medicine to the modern profession. Guided tours are available by appointment.

Museum of Osteopathic Medicine
800 W. Jefferson St., Kirksville, MO 63501
www.atsu.edu/museum

A Critical Appraisal of AHRQ's "Diagnostic Errors" Report

by Christopher R. Carpenter, MD, Randall Jotte, MD, Evan Schwarz, MD & Richard T. Griffey, MD

While we applaud those seeking to define and quantify EM diagnostic error rates, we are disappointed in this incomplete selection of studies, the authors' illogical extrapolation of outcomes, and underdeveloped contemplation of consequences or productive next steps.



Christopher R. Carpenter, MD, MSC, FACEP, FAAEM, AGSF, (above), **Randall Jotte, MD**, and Richard T. Griffey, MD, MPH, are Professors, and Evan Schwarz, MD, is an Associate Professor in the Department of Emergency Medicine, Washington University School of Medicine, St. Louis, Missouri.

Abstract

The Agency for Healthcare Research and Quality (AHRQ) report "Diagnostic Errors in the Emergency Department" generated significant mass media interest with negative implications for the safety of contemporary emergency care. The assumptions and methodology underlying this report are problematic, while multiple ongoing efforts to improve the quality and quantity of diagnostic research are missed, neglected, or ignored. The AHRQ report identifies reasonable target diseases for targeting diagnostic quality improvement efforts, as well as viable methods by which to measure any initiatives impact on diagnostic error. We note additional opportunities to improve the status quo by funding emergency department-based diagnostic research and healthcare system-level patient safety research and highlighting innovative approaches to diagnostic science within emergency medicine.

Introduction

In December 2022, the Agency for Healthcare Research and Quality (AHRQ) released a comparative effectiveness review entitled "Diagnostic Errors in the Emergency Department: A Systematic Review" that received unprecedented levels of mass media coverage and swift condemnation from emergency medicine (EM) professional organizations.[1,2] To briefly summarize, the 744-page AHRQ report extrapolated from a total of three prospective studies external to the United States (U.S.) an overall diagnostic error rate of 5.7% (95% CI 4.4-7.1) and a misdiagnosis-related harm rate of 2.0% (95% CI 1.0-3.6) per U.S. emergency department (ED) visit.[3] The report actually identified 279 studies, including 41 listing the distribution of diseases associated with diagnostic error or misdiagnosis-related harms, 160 reporting diagnostic error rates, and 185 describing the root causes of diagnostic error, yet they extrapolated from three studies based on their assumptions and exclusion criteria. While we applaud those seeking to define and quantify EM diagnostic error rates, we are disappointed in this incomplete selection of studies, the authors' illogical extrapolation of outcomes, and underdeveloped contemplation of consequences or productive next steps.

The first study, a case control study from the Canary Islands off the coast of Spain published in 2006, identified ED returns as the adverse consequence of "diagnostic errors."[4] The study reviewed unscheduled returns to the ED within 72 hours. Of 32,523 eligible patients, there were 250 unscheduled returns (0.77%). Among these, 54% were again discharged from the ED, while very few were admitted to the intensive care unit or died (2% and 1%, respectively of the 250 ED returns which would represent 0.015% and 0.009% of the total eligible population, or 15 and 9 per 100,000 patient encounters). Additionally, the issue identified in 26% of these returns related to problems with post-ED follow-up care, which is typically beyond the control of EM physicians in the U.S., limiting the generalizability of this finding.

The second study, a prospective observational study from Switzerland of 755 consecutive patients compared the ED diagnosis with admitted patients with their hospital discharge diagnosis.[5] Diagnostic discrepancies between ED and hospital diagnoses occurred in 12.3% and were associated with an increased hospital length of stay (10 vs. 7 days) and mortality (8.6% vs. 3.8%). Not surprisingly, diagnostic discrepancies were associated with atypical patient presentations. While ED physicians certainly aim to make a correct diagnosis, patients often appropriately receive a preliminary diagnosis pending further work-up in inpatient or outpatient settings because further diagnostics are required to confirm a diagnosis. A patient admitted with the diagnosis of abdominal pain, who has no time-critical findings and ultimately receives a more specific diagnosis is not a victim of diagnostic error. The symptoms of some disease processes like appendicitis or cholecystitis often evolve over hours or days, so reducing diagnostic errors to 0% in ED settings is pathophysiologically unrealistic. Importantly, the authors did not evaluate any associated morbidity or mortality attributable to delays in diagnosis.

The third study, a prospective study of 518 patient visits in 2005 at one of two university-affiliated EDs in Canada, found that 2% (10/503, 95% CI 1%-3.6%) included diagnostic adverse events.[6] This study focused on high-acuity patients. To extrapolate from these studies that an ED with 25,000 annual visits will have 50 deaths due to error is inappropriate. Instead of essential and humanistic discussions around system issues that impact patient care on a daily basis, the oversimplistic, inaccurate, and sensationalistic headlines definitively declaring that 7 million people are misdiagnosed in EDs annually serves to catalyze further mistrust in the patient-physician relationship.[7] A different spin on the overall findings of this study actually support the commendable job achieved by EM, despite the healthcare system in which we practice.

The practice of medicine in diagnosis-heavy specialties such as EM is imperfect yet both humbling and rewarding.[8] Reducing diagnostic error is at one extreme an imperative and at the other an aspirational goal for improvement.[9] Research in diagnostic error is notoriously challenging. This is due in part to lack of standard definitions and the retrospective nature of its determination, often based on limited documentation and suffering from a fundamental inability to know the thought process and considerations of a provider and absence of information on framing and context as relates to medical decision-making.

Problematic Components of Report

1. Definition of Diagnostic Error or Diagnostic Delay

Obtaining consensus on cases representing "misdiagnosis" is challenging. Inclusion of a study that specifically targets cases with vague presentations, and changes in diagnosis of admitted patients are not the rightful target of inquiries into diagnostic error. Diagnosis is not just an outcome but is a process. A working diagnosis is not a final diagnosis regardless of venue or provider. Patient signs and symptoms evolve and deductive reasoning is assisted by serial examinations, laboratory and imaging studies that progress over time. This report used the National Academy of Medicine definition for diagnostic error as "the failure to (a) establish an accurate and timely explanation of the patient's health problem or (b) communicate that explanation to the patient."[3]

As society's medical safety net for all unscheduled acute care, whether pediatric, obstetric, geriatric,

surgical, dental, trauma, psychiatric emergencies, or more, the ED clinical encounter too often occurs with constraints of space, time, and resources. Hospital crowding and boarding of admitted patients in the ED combined with production pressures and hospital's priorities to minimize their patients "leaving without being seen" metrics heightens the diagnostic focus on excluding life-threatening conditions over other priorities.[10] Depending on the interpretation of "accurate and timely," the National Academy of Medicine's definition of diagnostic error might be unrealistic if not unsafe for the ED setting with the current state of the healthcare system. While conceptually feasible, satisfying such an expectation would require expansion of current EDs, construction of additional EDs, 24/7/365 availability of advanced diagnostic and consultative resources, and anticipation of increased length-of-stays in pursuit of uniform and definitive diagnoses.

In addition, exploring the second component of the National Academy of Medicine definition around communication, efforts to improve the transfer of medical information (between physician and patient or between healthcare teams) in ED settings continue, but strategies endorsed by AHRQ like "teach back" do not effectively improve patient comprehension of diagnosis and test results in ED settings.[11] Furthermore, evidence to support alternative communication strategies with patients and families is often sparse.[12] The AHRQ report does not address the relevance of the National Academy of Medicine definition for EM, nor does it sufficiently contemplate the unintended consequences of carelessly adapting ED processes to reduce diagnostic error to zero or the communication obstacles that exist.

2. Diagnostic Priorities of the ED

EM's role is the rapid evaluation, stabilization, and disposition of undifferentiated patients. While a working diagnosis is inherent to this mission, a final diagnosis is not. Diagnostic approaches are an inherent part of EM training with hypothetico-deductive, Bayesian and 'rule out worst case scenario' approaches all taught and used to achieve the above goal.[13,14] These cognitive approaches strive to efficiently identify time-dependent emergencies in which minutes or hours matter, but to ensure reasonable access to emergency care in an era of daily ED crowding the diagnostic approach simply does not include precision for all potential diagnoses.

The AHRQ report could be interpreted by physicians and malpractice attorneys as justification for an exhaustive approach to EM diagnostic testing, so as to reduce miss rates closer to 0%.[15] The drive

Figure 1 Test-Treatment Threshold Example

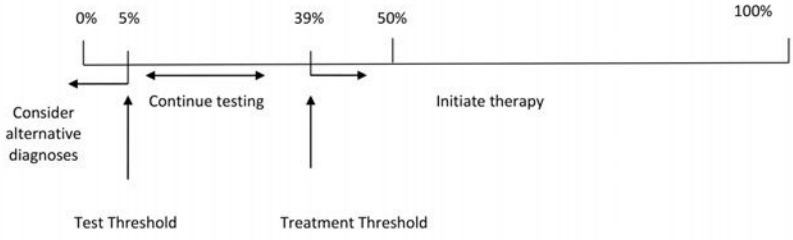
$T_{testing\ threshold} = [(P_{pos/nd}) \times (R_{rx})] \div [(P_{pos/nd} \times R_{rx}) + (P_{pos/d} \times B_{rx})] = 0.052$

$T_{treatment\ threshold} = [(P_{neg/nd}) \times (R_{rx}) - R_t] \div [(P_{neg/nd} \times R_{rx}) + (P_{neg/d} \times B_{rx})] = 0.387$

Where estimates below based upon a published diagnostic accuracy meta-analysis from *Academic Emergency Medicine*.

$P_{pos/nd}$ = probability of a positive result in patients without disease = 1-specificity = 1-0.9 = 0.10*
$P_{neg/nd}$ = probability of a negative result in patients without disease = specificity = 0.90
R_{rx} = risk of treatment in patients without disease = 0.155
R_t = risk of diagnostic test = 0.00037
$P_{pos/d}$ = probability of a positive result in patients with disease = sensitivity = 0.56
$P_{neg/d}$ = probability of a negative result in patients with disease = 1 – sensitivity = 1-0.54= 0.44
B_{rx} = benefit of treatment in patients with disease = 0.50†

Septic Arthritis Post Test Probability



* Using synovial white blood cell count >50000/μL
† Assumes Number Needed to Treat (NNT)= 2 for joint debridement plus antibiotics to reduce short-term mortality. This is an estimate since no randomized controlled trials were identified. One prospective trial provided an estimated 11% mortality of treated septic arthritis at a median of 39 days. If the mortality of untreated septic arthritis was 22% than the NNT would be 2.

Figure 1 reprinted with permission

for specificity in the ED is not feasible financially or from a patient flow perspective and it is not rational. More scientific approaches could be employed. For example, one approach to identifying subsets of patients most likely to benefit from less available or more invasive diagnostic testing is the test-treatment threshold.[16] The Academic Emergency Medicine Evidence Based Diagnostics series provides multiple quantitative examples of test-treatment thresholds for potentially life- or limb-threatening conditions like subarachnoid hemorrhage,[17] septic arthritis (Figure 1),[18] mesenteric ischemia,[19] and scaphoid fractures.[20] The harms of ED over-testing and associated over-diagnosis and over-treatment are quantifiable, yet this report does not acknowledge efforts aligned with Preventing Overdiagnosis or the Lown Institute to ensure that diagnostic testing occurs for patients most likely to benefit from that testing.[21,22]

3. Inadequate Quantity and Relevance of Included Studies

All were non-U.S. settings. One specifically included cases with vague complaints. Two studies occur in countries where EM is not a specialty with dedicated training and certification, whereas in the U.S. EM board certification has existed for over 40 years, raising valid questions about differences in care.[23] Canada has a very different system for follow up compared to that in the U.S.

The report downplays estimates of per-visit ED misdiagnosis-related harm rates from multiple retrospective studies that identify diagnostic errors based on some triggering event, such as a return visit or hospital admission,[24-27] arguing that these were single-institution studies, that insurance claims-based follow-up to ensure capture of medical events was not pursued, and because "this group of studies systematically underestimates harms, and likely does so by a wide margin."[3] Interestingly, these are observed to identify diagnostic errors resulting in harm and to underestimate those that result in minimal or minor harm. The one U.S.-based study among these had low overall risk of bias, and reported the lowest misdiagnosis-related adverse event rate (0.012% or 12 per 100,000) and misdiagnosis-related death rate (0.00073% or 0.73 per 100,000) of any of these studies.[24] Alarmingly, additional U.S.-based ED research exploring diagnostic error was neither included nor excluded in this AHRQ report, missing an opportunity for additional insight.[28]

4. Questionable Conclusions About the Root Cause of Diagnostic Errors

Malpractice claim reviews are the basis for this contention. However, any physician who has had a malpractice claim or served on a hospital credentialing committee reviewing those with a claim history knows that claims data is hardly concrete scientific evidence nor conclusive proof of error.[29] Concurrently, preventability assessments are notoriously subjective and retrospectively determined, fraught with hindsight and outcome biases.[30,31] Closed claim evaluations might arguably represent "tip of the iceberg" cases but are arrived at with a different agenda.

The science of cognitive decision-making is perplexing to study and effective interventions to reduce cognitive errors (or biases) remain elusive.[13,32] Nonetheless, patient safety experts in EM have acknowledged the importance of recognizing decision-making errors associated with premature closure, confirmation bias, search satisficing, and availability bias.[14] Yet, the 744-page report neglected to even acknowledge the progress of EM in understanding and avoiding cognitive errors.

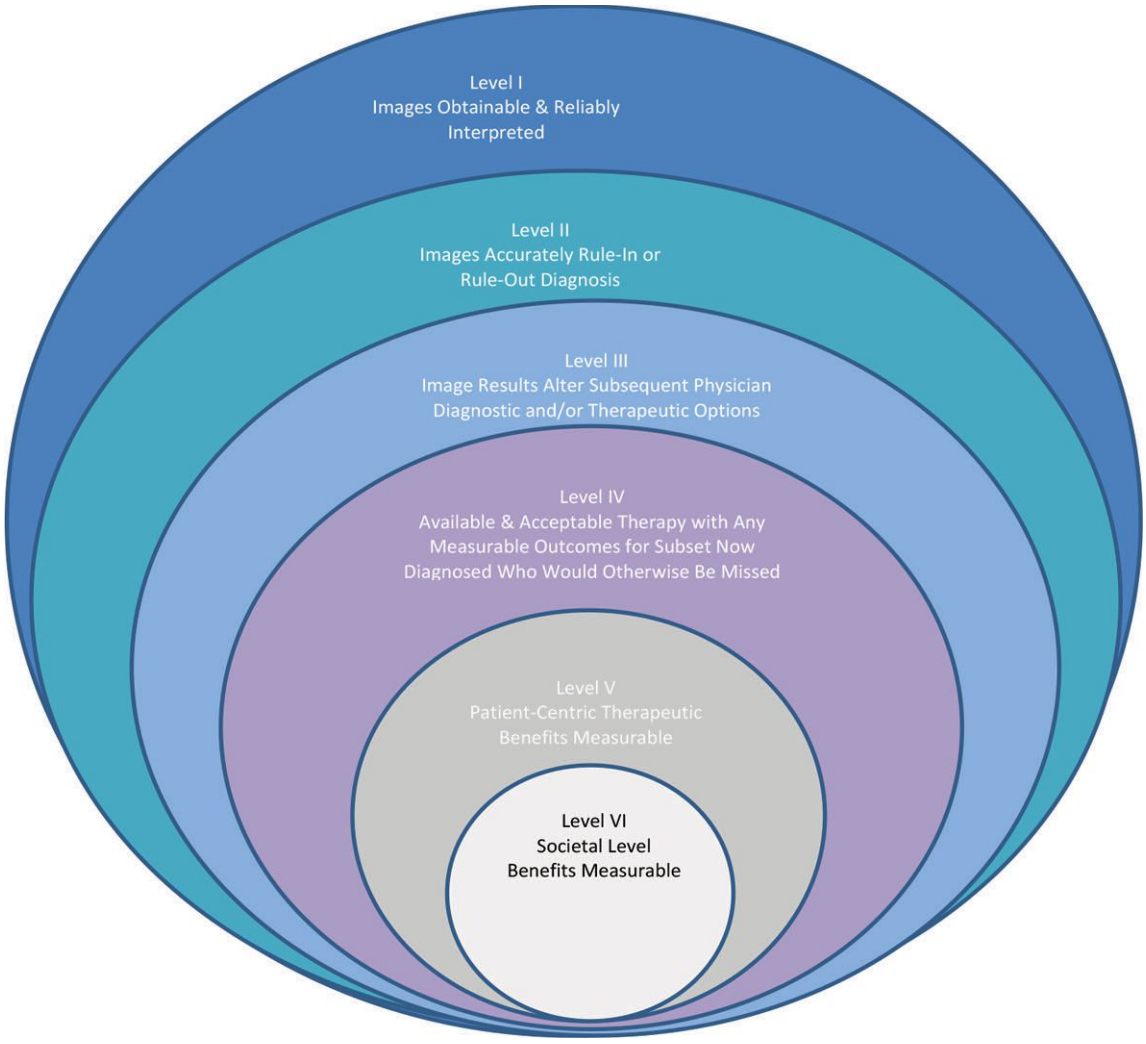
5. Face Validity and Transparency of External Review

The lead author of the report is a talented researcher but is a Neurologist, not an EM physician. As physicians working in EDs for decades, we would not presume to understand or opine on the complexities of diagnostic errors in the realm of inpatient or outpatient Neurology. Admittedly, the authorship team included two ED physicians. However, based on published reports, some of these reviewers believe their voices of caution related to the validity of these findings were neglected, and the extent to which EM opinions were incorporated into the report is uncertain.[33]

Additional Criticism

The AHRQ report also overlooks the reality that direct evidence for many diagnostic "tests"

Figure 2. Diagnostic Hierarchy of Evidence
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(which includes history, physical exam, labs, and imaging) that might be felt to be standard of care is often sparse,[34] biased,[35] and limited to studies quantifying accuracy without attaining higher levels of diagnostic proof such as patient-centered or society-centered outcomes consequential to those "tests."[36] Diagnostic approaches can sometimes be achieved with alternative (more available and/or less expensive) strategies and these strategies evaluated using randomized trial designs just like interventions, but as noted by the AHRQ authors too often those comparative effectiveness diagnostic trials are nonexistent or assess less relevant outcomes.[37] Figure 2 depicts the diagnostic hierarchy of evidence that identifies subsets of patients more likely to benefit from testing when randomized controlled trials are appropriately designed.[36,38] EM-derived clinical practice guidelines for chest pain and abdominal pain recently rendered weak or no recommendations for diagnostic approaches based upon the absence of compelling research.[39,40] Similarly, 91% of American College of Emergency Physician's Clinical Policy recommendations are not Level A (the highest category) and 50% are Level C.[41] The AHRQ report consistently neglects to highlight the paucity of diagnostic research upon which efforts to reduce diagnostic error could be built.

Despite these criticisms, and despite the media spin on this report, its Executive Summary begins with the statement that "overall diagnostic accuracy in the ED is high."[3] The AHRQ report also provides tangible next steps worth considering to further

improve the effectiveness of ED diagnostic decision-making, including Symptom-Disease Pair Analysis of Diagnostic Error for critical conditions associated with higher short-term risk if undiagnosed and untreated such as stroke or meningitis.[42] In addition, they propose the concept of "secret shoppers" or fake patients that could be deployed as real-world quality assessment tests across individual EDs.[43] They also review other opportunities to identify diagnostic errors including incident reports, automatic triggers for patients with unplanned ED revisits or escalations of care,[44,45] and Leveraging Patient's Experience to improve Diagnosis.[46] They also highlight important pitfalls in measuring diagnostic error, including differentiating discrepant diagnoses from errant processes, controlling for presenting disease severity, and over-estimating the preventability of harms.

Conclusion

As a specialty, EM continuously strives to optimize the balance between patient safety and pragmatic patient care in an increasingly challenging clinical milieu. For example, the Society for Academic Emergency Medicine Guidelines for Reasonable and Appropriate Care in the Emergency Department (https://www.saem.org/publications/grace), which are explicitly mentioned in the AHRQ report, apply rigorous GRADE methods and include patient perspectives to derive clinical recommendations for today's ED while also highlighting prominent diagnostic knowledge gaps for funders and researchers to consider.[47,48] Other Society for Academic Emergency Medicine efforts unacknowledged by the AHRQ report include AHRQ (and other agency) funded Consensus Conferences deriving hundreds of pages of research priorities for shared decision-making and advanced imaging in ED settings.[49,50] A diagnostic accuracy textbook synthesizing ED research for history, physical exam, clinical decision aids, labs, and imaging also exists.[51]

Undoubtedly, evidence-based pathways to improve the process, safety, outcomes, and costs of ED diagnostics exist. EM physicians seek to improve the care they deliver. However, funders must support EM-relevant, feasible, and impactful diagnostic science research opportunities that address the enormous knowledge gaps that currently exist.[52]

This report is significantly flawed and regrettably neglected opportunities to engage ED diagnostics experts to design, interpret, and synthesize existing research on diagnostic errors in EM. On behalf of ED physicians committed to our specialty and the patients for which we care, we invite AHRQ and other research funders to join and support us in taking the next steps to advance EM's capacity to diagnosis in the most accurate, efficient, cost-effective, and pragmatic manner possible.

References

1. ACEP, EM Organizations Issue Letter Regarding AHRQ Report on Diagnostic Errors in the ED. American College of Emergency Physicians, 2022. (Accessed February 16, 2023, at https://www.acep.org/news/acep-newsroom-articles/acep-em-organizations-issue-letter-regarding-ahrq-report-on-diagnostic-errors-in-the-ed/.)
2. Kaplan G, Stanton R. When a Report on Errors is all in Error: Review of the AHRQ Report on EM Diagnostic Errors. In: Stanton R, ed. ACEP Frontline: American College of Emergency Physicians; 2022.
3. Newman-Toker DE, Peterson SM, Badihian S, et al. Diagnostic Errors in the Emergency Department: A Systematic Review. Rockville MD: Agency for Healthcare Research and Quality; 2022:744.
4. Nuñez S, Hexdall A, Aguirre-Jaime A. Unscheduled returns to the emergency department: an outcome of medical errors? . Qual Saf Health Care 2006;15:102-8.
5. Hautz WE, Kämmer JE, Hautz SC, et al. Diagnostic error increases mortality and length of hospital stay in patients presenting through the emergency room. Scan J Trauma Resusc Emerg Med 2019;27:54.
6. Calder LA, Forster A, Nelson M, et al. Adverse events among patients registered in high-acuity areas of the emergency department: a prospective cohort study CJEM 2010;12:421-30.
7. Are 7M people misdiagnosed in EDs each year? A new study raises controversy. Advisory Board, 2022. (Accessed January 26, 2023, at https://www.advisory.com/daily-briefing/2022/12/19/ed-misdiagnoses.)
8. Wears RL. What makes diagnosis hard? Adv Health Sci Educ Theory Pract 2009;14:19-25.
9. Edlow JA, Pronovost PJ. Misdiagnosis in the Emergency Department: Time for a System Solution JAMA 2023;329:631-2.
10. Moskop JC, Sklar DP, Geiderman JM, Schears RM, Bookman KJ. Emergency department crowding, part 1--concept, causes, and moral consequences. Ann Emerg Med 2009;53:605-11.
11. Griffey RT, Shin N, Jones S, et al. The impact of teach-back on comprehension of discharge instructions and satisfaction among emergency patients with limited health literacy: A randomized, controlled study. J Commun Healthc 2015;8:10-21.
12. Carpenter CR, Leggett J, Bellolio F, et al. Emergency Department Communication in Persons Living With Dementia and Care Partners: A Scoping Review J Am Med Dir Assoc 2022;23:1313.e15-.e46.
13. Sandhu H, Carpenter C, Freeman K, Nabors SG, Olson A. Clinical decisionmaking: opening the black box of cognitive reasoning Ann Emerg Med 2006;48:713-9.
14. Kane B, Carpenter CR. Cognition and Decision Making. In: Fondahn E, De Fer TM, Lane M, Vannucci A, eds. The Washington Manual of Patient Safety and Quality Improvement. Philadelphia PA: Lippincott Williams & Wilkins; 2016.
15. Wears RL. The hunting of the snark, 2011 Ann Emerg Med 2011;58:465-7.
16. Pauker SG, Kassirer JP. The threshold approach to clinical decision

making N Engl J Med 1980;302:1109-17.
17. Carpenter CR, Hussain AM, Ward MJ, et al. Spontaneous Subarachnoid Hemorrhage: A Systematic Review and Meta-analysis Describing the Diagnostic Accuracy of History, Physical Examination, Imaging, and Lumbar Puncture With an Exploration of Test Thresholds. Acad Emerg Med 2016;23:963-1003.
18. Carpenter CR, Schuur JD, Everett WW, Pines JM. Evidence-based diagnostics: adult septic arthritis Acad Emerg Med 2011;18:781-96.
19. Cudnik MT, Darbha S, Jones J, Macedo J, Stockton SW, Hiestand BC. The diagnosis of acute mesenteric ischemia: A systematic review and meta-analysis. Acad Emerg Med 2013;20:1087-100.
20. Carpenter CR, Pines JM, Schuur JD, Muir M, Calfee RP, Raja AS. Adult scaphoid fracture. Acad Emerg Med 2014;21:101-21.
21. Carpenter CR, Raja AS, Brown MD. Overtesting and the Downstream Consequences of Overtreatment: Implications of "Preventing Overdiagnosis" for Emergency Medicine. Acad Emerg Med 2015;22:1484-92.
22. Dorsett M, Cooper RJ, Taira BR, Wilkes E, Hoffman JR. Bringing value, balance and humanity to the emergency department: The Right Care Top 10 for emergency medicine. Emerg Med J 2020;37:240-5.
23. Zink BJ. Anyone, Anything, Anytime: A History of Emergency Medicine. Philadelphia PA: Mosby - Elsevier; 2006.
24. Aaronson E, Borczuk P, Benzer T, Mort E, Temin E. 72h returns: A trigger tool for diagnostic error. Am J Emerg Med 2018;36:359-61.
25. Calder LA, Pozgay A, Riff S, et al. Adverse events in patients with return emergency department visits. BMJ Qual Saf 2015;24:142-8.
26. Heitmann MG, Sarwary M, Larsen JJ, Tingleff J, Hansen-Schwartz J. Readmittance rates within seven days are preferable in quality measuring of emergency departments Dan Med J 2016;63:A5267.
27. Vanbrabant P, Knockaert D. Short-term return visits of 'general internal medicine' patients to the emergency department: extent and risk factors. Acta Clin Belg 2009;64:423-8.
28. Sklar DP, Crandall CS, Loeliger E, Edmunds K, Paul I, Helitzer DL. Unanticipated death after discharge home from the emergency department. Ann Emerg Med 2007;49:735-45.
29. Kachalia A, Gandhi TK, Puopolo AL, et al. Missed and delayed diagnoses in the emergency department: a study of closed malpractice claims from 4 liability insurers Ann Emerg Med 2007;49:196-205.
30. Wears RL, Nemeth CP. Replacing hindsight with insight: toward better understanding of diagnostic failures Ann Emerg Med 2007;49:206-9.
31. Wears RL. The error of counting "errors". Ann Emerg Med 2008;52:502-3.
32. Sherbino J, Kulasegaram K, Howey E, Norman G. Ineffectiveness of cognitive forcing strategies to reduce biases in diagnostic reasoning: a controlled trial CJEM 2014;16:34-40.
33. AHRQ's Diagnostic Error Study. American College of Emergency Physicians, 2022. (Accessed January 27, 2023, at https://www.acepnow.com/article/ahrqs-diagnostic-error-study/.)
34. Carpenter CR, Oliveira J Silva L, Upadhye S, Broder JS, Bellolio F. A candle in the dark: The role of indirect evidence in emergency medicine clinical practice guidelines. Acad Emerg Med 2022;29:674-7.
35. Kohn MA, Carpenter CR, Newman TB. Understanding the direction of bias in studies of diagnostic test accuracy Acad Emerg Med 2013;20:1194-206.
36. Kanzaria HK, McCabe AM, Meisel ZM, et al. Advancing Patient-centered Outcomes in Emergency Diagnostic Imaging: A Research Agenda Acad Emerg Med 2015;22:1435-46.
37. El Dib R, Tikkinen KAO, Akl EA, et al. Systematic survey of randomized trials evaluating the impact of alternative diagnostic strategies on patient-important outcomes J Clin Epidemiol 2017;84:61-9.
38. Fryback DG, Thornbury JR. The efficacy of diagnostic imaging. Med Decis Making 1991;11:88-94.
39. Musey PI, Bellolio F, Upadhye S, et al. Guidelines for reasonable and appropriate care in the emergency department (GRACE): Recurrent, low-risk chest pain in the emergency department Acad Emerg Med 2021;28:718-44.
40. Broder JS, Oliveira J Silva L, Bellolio F, et al. Guidelines for Reasonable and Appropriate Care in the Emergency Department 2 (GRACE-2): Low-risk, recurrent abdominal pain in the emergency department. Acad Emerg Med 2022;29:526-60.
41. Venkatesh AK, Savage D, Sandefur B, Bernard KR, Rothenberg C, Schuur JD. Systematic review of emergency medicine clinical practice guidelines: Implications for research and policy. PLoS One 2017;12:e0178456.
42. Liberman AL, Newman-Toker DE. Symptom-Disease Pair Analysis of Diagnostic Error (SPADE): a conceptual framework and methodological approach for unearthing misdiagnosis-related harms using big data. BMJ Qual Saf 2018;27:557-66.
43. Weiner SJ, Schwartz A. Directly observed care: can unannounced standardized patients address a gap in performance measurement? . J Gen Intern Med 2014;29:1183-7.
44. Griffey RT, Schneider RM, Todorov AA. The Emergency Department Trigger Tool: A Novel Approach to Screening for Quality and Safety Events Ann Emerg Med 2020;76:230-40.
45. Griffey RT, Schneider RM, Sharp BR, Vrablik MC, Adler L. Practical Considerations in Use of Trigger Tool Methodology in the Emergency Department J Patient Saf 2021;17:e837-e42.
46. Gleason KT, Peterson SM, Dennison-Himmelfarb CR, et al. Feasibility of patient-reported diagnostic errors following emergency department discharge: a pilot study. Diagnosis 2020;8:187-92.
47. Carpenter CR, Bellolio MF, Upadhye S, Kline JA. Navigating uncertainty with GRACE: Society for Academic Emergency Medicine's guidelines for reasonable and appropriate care in the emergency department. Acad Emerg Med 2021;28:821-5.
48. Carpenter CR, Morrill DM, Sundberg E, Tartt K, Upadhye S. Nothing about me without me: GRACE-fully partnering with patients to derive clinical practice guidelines Acad Emerg Med 2022 (in press).
49. Special Issue: Proceedings of the 2016 AEM Consensus Conference: Shared Decision Making the Emergency Department. Wiley, 2016. (Accessed January 19, 2023, at https://onlinelibrary.wiley.com/toc/15532712/2016/23/12.)
50. Special Issue: Proceedings of the 2015 AEM Consensus Conference: Imaging in the Emergency Department. Wiley, 2015. (Accessed January 19, 2023, at https://onlinelibrary.wiley.com/toc/15532712/2015/22/12.)
51. Pines JM, Carpenter CR, Raja AS, Schuur JD. Evidence-Based Emergency Care: Diagnostic Testing and Clinical Decision Rules. 2nd ed. Oxford UK: Wiley-Blackwell; 2013.
52. Neumar RW, Blomkalns AL, Cairns CB, et al. Emergency medicine research: 2030 strategic goals Acad Emerg Med 2022;29:241-51.

Disclosure

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Citizen Science Informs How Missourians Interact With Ticks

by Deborah A. Hudman, MS & Matthew D. Combes, MS

Citizen science has great potential to provide public health managers with an affordable and effective way of investigating tickborne diseases.



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Abstract

Understanding which tick species Missourians interact with and where exposures occur can help prevent and diagnose tickborne diseases. A statewide survey of ticks and tickborne pathogens was conducted using citizen science. Missourians submitted 12,819 ticks from April-December 2021. In total, 71% of ticks were Amblyomma americanum, and 89% were collected from a person or a pet. These preliminary data provide tick distributions at the county level and identify patterns of direct tick exposure to humans.

Introduction

Missouri has approximately 17 species of hard ticks, including four medically important species that humans commonly encounter, *Amblyomma americanum* (Linnaeus, 1758), *Dermacentor variabilis* (Say, 1821), *Ixodes scapularis* (Say, 1821), and *Amblyomma maculatum* (Koch, 1844). These four species are generalist feeders, meaning they will attach and feed on a wide variety of animal species, including humans. In combination, these four species can transmit 12 distinct human pathogens, are implicated in three additional pathogens and one allergic reaction. Although Missouri has a diverse and abundant tick community, no comprehensive distribution map of these species exists.

There is a pressing need to increase tick surveillance in Missouri. Current surveillance measures for ticks in Missouri are limited to intermittent targeted sampling by university researchers.[1-29] These research projects are limited to small geographic areas within Missouri, but they have been combined to represent *A. americanum*, *D. variabilis*, and *I. scapularis* distributions at the county level.[30-32] The reports establishing these species distributions define an established tick population in a county by documenting the presence of six or more ticks or two different life stages collected during one year. In Missouri, 73 counties are classified as having established populations of *A. americanum*, 14 counties with *D. variabilis* populations, and 23 counties with *I. scapularis* populations; no cumulative reports at the county level exist for established populations of *A. maculatum*. Therefore, one of the objectives of this statewide survey was to provide a more complete,

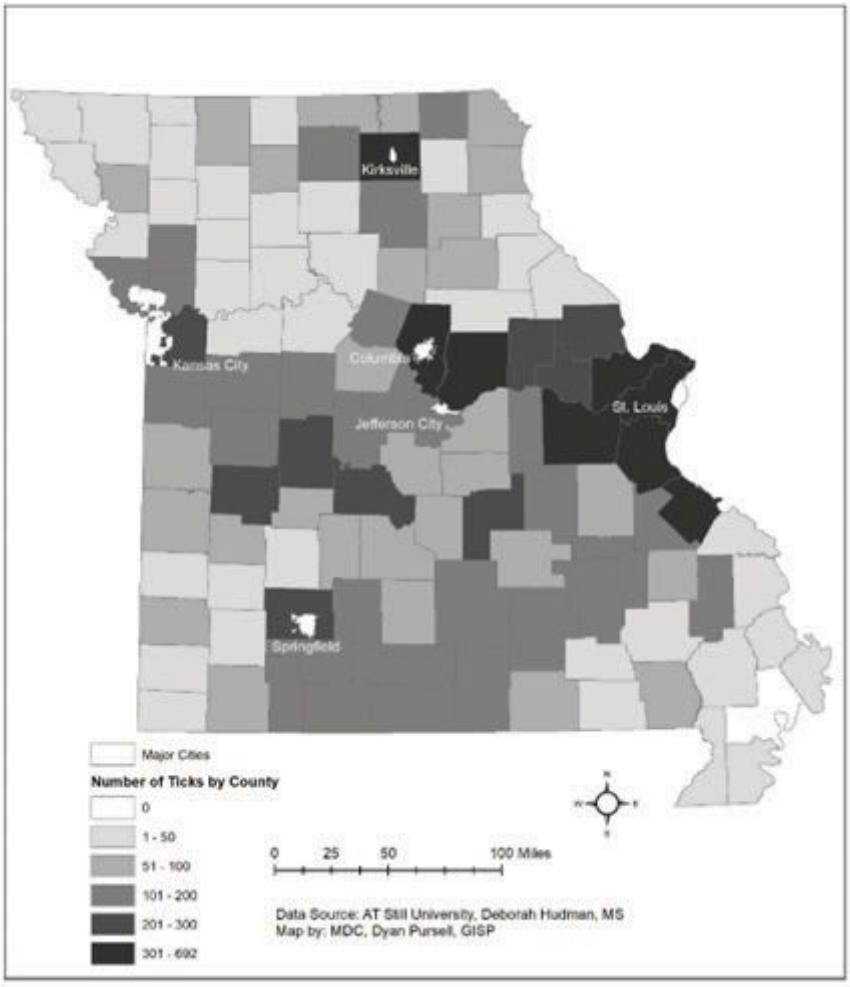


Figure 1. Map of Missouri indicating the range of ticks received by county from citizen scientists from April to December 2021.

accurate depiction of the distributions of these four tick species at the county level for the entire state of Missouri.

Data generated from citizen science is termed passive surveillance, where tick specimens are found and submitted by members of the public, but it can potentially result in bias toward specific geographic locations, tick species, and life stages. This type of collection also comes with uncertainty about where specimens were collected. Because of this inherent bias in passive surveillance, absence should not be inferred from our data.

Despite issues with passive surveillance, its use makes a statewide survey financially and logistically possible within a short time period. Additionally, passive surveillance can provide information on where and how people are being exposed to ticks during daily activities, which is rarely reported. Using data from the first nine months of collection, we report preliminary results on the distribution of four medically important tick species at the county level and how Missourians interact with those ticks.

Method

Tick Collection

Ticks were collected by citizen scientists between April and December 2021. Recruitment of participants was through an initial public relations campaign conducted by the Missouri Department of Conservation and a public website (http://www.atsu.edu/ticks). Additionally, news media outlets around the state promoted the research. The citizen scientists participated in the research by completing a submission form and mailing it with collected ticks to A.T. Still University. No personal identifying information was recorded (ie, name, age, or gender). Citizens who chose to participate volunteered their time and supplies (bags, cotton balls, envelopes, and stamps), so they incurred a monetary cost for participation.

Data Analysis

Ticks were identified morphologically at A.T. Still University using microscopes and published keys.[33-39] Ticks were identified by species, sex, and life stage and were recorded for presence at the county level. Additionally, if the submission form was completed, tick encounter data were compiled by type of encounter. Tick encounters were grouped into the following categories for where the tick was collected: on a person, pet, livestock, or wildlife (harvested or road kill); from a yard or garden; inside the home; or in a vehicle. Missouri has 114

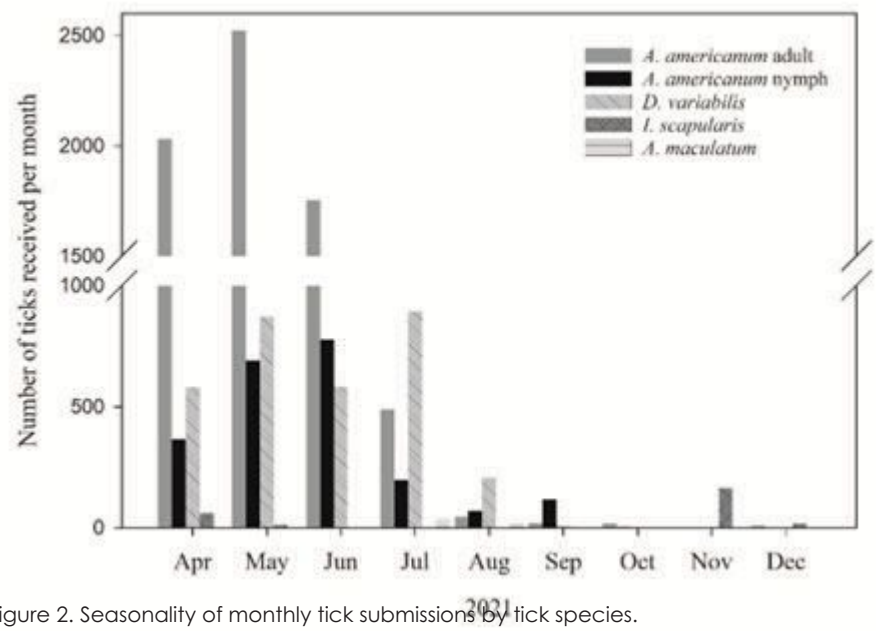


Figure 2. Seasonality of monthly tick submissions by tick species.

counties and one independent city, St. Louis. For ease of discussion, results are reported as 115 counties, treating St. Louis city as a county.

χ^2 analyses were performed to test whether male or female ticks were more frequently collected attached or unattached to a person, whether *A. americanum* nymphs or adults were more frequently collected attached or unattached to a person, and whether ticks were more frequently collected attached or unattached to a pet if the pet received a flea and tick treatment. All other data are descriptive.

Results

Tick Submissions

Between April and December 2021, citizen scientists submitted 12,819 samples. Ticks were submitted from all but New Madrid County (Figure 1). Including New Madrid, an average of 111 (median=73, range=0-692) submissions were received per county. The average number of ticks per submission was 3.1 (range=1-64). Eight tick species were identified from the 12,819 ticks that were submitted. *A. americanum* accounted for 71% (9127/12,819) of ticks overall. This proportion varied across counties; *A. americanum* accounted for 100% (40/40) of submissions in Carter county and 0% (0/18) in Carroll county. *D. variabilis* accounted for 25% (3145/12,819) of ticks overall, and county submissions ranged from 100% (18/18) in Carroll county to 0% (0/192) Reynolds county. Overall, 2% (280/12,819) of identified ticks were *I. scapularis*, and the remaining 2% consisted of a combination of *A. maculatum*, *Rhipecephalus sanguineus*, *Carios kelleyi*, *D. albipictus*, and *Haempaphysalis leporispalustris*.

A. americanum ticks were received from 111 of the 115 counties, averaging 60 (median=38, range=0-407) submissions per county. The threshold for establishing populations was reached in 105 of the 111 counties; one did not overlap with previously reported counties.[32] As a result, 106 (92%) of the 115 counties in Missouri now have an established population of *A. americanum*, increasing the county distribution status by 29%.

D. variabilis ticks were received from 108 of the 115 counties, averaging 27 (median=18, range=0-190) submissions per county. Passive surveillance accounted for 84 counties reaching established status; eight did not overlap with the 14 previously established counties.[31] As a result, 92 (80%) of the 115 counties in Missouri now have an established population of *D. variabilis*, increasing the county distribution status by 68%.

I. scapularis ticks were received from 57 of the 115 counties, averaging two (median=0, range=0-49) submissions per county. Passive surveillance accounted for 15 counties reaching established status, and four overlapped with the 23 previously established counties.[30] As a result, 34 (30%) of the 115 counties in Missouri now have an established population of *I. scapularis*, increasing the county distribution status by 7%.

Table 1. Number of Ticks Received by Encounter Type from April to December 2021

Species and Life Stage	Person	Pet	House	Livestock	Vehicle	Wildlife	Yard or Garden
A. americanum							
Adult female	2366	805	126	66	22	35	42
Adult male	2396	557	65	40	13	80	26
Nymph	1974	130	16	0	5	14	17
D. variabilis							
Adult female	896	574	139	2	4	0	21
Adult male	721	527	108	5	5	1	17
I. scapularis							
Adult female	35	66	0	1	0	63	0
Adult male	15	37	1	0	0	59	0
Nymph	2	0	0	0	0	0	0
A. maculatum							
Adult female	19	13	0	0	0	0	0
Adult male	26	9	0	0	0	0	0

A. maculatum submissions were received from 14 of the 115 counties, averaging 0.6 (median=0, range=0-37) submissions per county. Passive surveillance accounted for 2 counties, St. Clair and Ste. Genevieve, reaching an established status.

Seasonality of Exposure

Submissions for *A. americanum* adults peaked in May, *D. variabilis* and *A. maculatum* adults peaked in July, and *I. scapularis* adults peaked in November (Figure 2). *A. americanum* nymphs peaked in June but had a much diminished second peak again in September. Nymphs of *I. scapularis* were not submitted in sufficient numbers to assess seasonality.

Tick Encounters

Of ticks submitted, 67% were found on humans, 22% were found on pets, 2% were found on wildlife, 4% were found in the home, 4% did not specify where the tick came from, and the remaining 2% consisted of ticks collected from livestock, a yard, or garden, and vehicles. These general results varied among tick species.

Of submitted *A. americanum* ticks, 40% were adult females, 36% were adult males, and 24% were nymphs (Table 1). When submission forms specified encounter type, regardless of life stage, *A. americanum* were most commonly found on a person or a pet. When found on a person, 28% of females, 36% of males, and 52% of nymphs were attached (Table 2). When found on a pet, 66% of females, 65% of males, and 64% of nymphs were attached. Male *A. americanum* were attached to human hosts more often than expected, and females were unattached to human hosts more than expected (χ^2=30.00, df=1, *P*<.001). Nymphs were attached to human hosts more often than expected (χ^2=229.63, df=1, *P*<.001). *A. americanum* was more likely to be unattached when the pet was treated with flea and tick products and more likely to be attached when not treated (χ^2=15.71, df=1, *P*<.001).

Of submitted *D. variabilis* ticks, 54% were adult females, and 46% were adult males (Table 1). When submission forms specified encounter type, *D. variabilis* were most likely found on a person or a pet. When found on a person, 20% of females and males were attached (Table 2). When found on a pet, 54% of females and 50% of males were attached. No association was found between tick gender and attachment status (χ^2=.0000073, df=1, *P*=.998). *D. variabilis* was more likely to be unattached when the pet was treated with flea and tick products and more likely to be attached when not treated (χ^2=33.60, df=1, *P*<.001).

Of submitted *I. scapularis* ticks, 59% were adult females, 40% were adult males, and 1% were nymphs (Table 1). When submission forms specified encounter type, adults were most commonly found on a pet or on wildlife, while nymphs were found exclusively on a person. When found on a pet, 59% of females and 11% of males were attached (Table 2). Females were attached more often to human hosts than expected, and males were unattached

Table 2. Number of Ticks Received and Attached to a Person or Pet from April To December 2021

Species and Life Stage	Person	No. Attached (%)	Pet	No. Treated*	No. Attached (%)
A. americanum					
Adult female	2366	674 (28)	805	571	535 (66)
Adult male	2396	869 (36)	557	368	364 (65)
Nymph	1974	1026 (52)	130	84	83 (64)
D. variabilis					
Adult female	896	176 (20)	574	394	311 (54)
Adult male	721	144 (20)	527	359	261 (50)
I. scapularis					
Adult female	35	15 (43)	66	34	39 (59)
Adult male	15	2 (13)	37	28	4 (11)
Nymph	2	2 (100)	0		
A. maculatum					
Adult female	19	2 (11)	13	12	4 (31)
Adult male	26	1 (4)	9	8	4 (44)

*The number of reported pets that received some form of treatment for ticks.

to human hosts more than expected (χ^2=4.08, df=1, *P*=.04). *I. scapularis* was more likely to be unattached when the pet was treated with flea and tick products and more likely to be attached when not treated (χ^2=13.15, df=1, *P*=.001).

Of submitted *A. maculatum* ticks, 48% were adult females, and 52% were adult males (Table 1). When submission forms specified encounter type, adults were only found on a person or on a pet. When found on a person, 19% of females and 4% of males were attached (Table 2). When found on a pet, 31% of females and 44% of males were attached. There was no association between tick gender and attachment status (χ^2=0.79, df=1, *P*=.38).

Discussion

The current citizen science project was highly successful because over 12,000 ticks were collected from 99% of Missouri counties in 9 months. Knowledge of when and where the public encounters various tick species across seasons is critical for developing public health protection measures. For instance, the number of submissions of adult *A. americanum* peaked in May, but it peaked in June and September for nymphs. Most public campaigns to raise awareness of ticks and tickborne diseases occur in the spring or early summer since that is when most people enjoy the outdoors. However, with a resurgence of nymphs in September, fall awareness campaigns may be just as important. Typically, nymphs are undetected more often than adults, which may result in a higher risk of acquiring a tickborne disease. When *A. americanum* was discovered on a person, nymphs were more likely to be found attached (53%) than adults (33%). Also, *I. scapularis* submissions peaked in November, not during summer. These submissions coincided with white-tailed deer hunting season. Although *I. scapularis* was the only tick species more likely to be collected from a pet or wildlife than on a person, this information implies that hunters may be at higher risk for encountering *I. scapularis* in Missouri. As a result, hunters may be at higher risk for diseases that this tick species vectors, such as Lyme disease and anaplasmosis.

Knowing when people interact with ticks and where exposures occur is essential. It is well understood that outdoor activities increase the chances of encountering a tick, but other routes are also possible. In total, 455 ticks were encountered in the home unattached to humans or pets. Although *D. variabilis* only made up 25% of the ticks submitted, they were collected in the home more than any other tick species. We hypothesize that these ticks were introduced into the home on pets. Citizen scientists reported treating 69% of all pets with flea and tick products, and 40% of ticks collected on pets were *D. variabilis*. When submission forms specified tick attachment, 47% of *D. variabilis* were not attached to a pet. With approximately half of *D. variabilis* remaining unattached to pets, there is great potential for them to be introduced into the home. When collected from the home, both *A. americanum* and *D. variabilis*

were collected from a person's bed 11% of the time.

Citizen science informs how people interact with ticks but can also indicate which tick species and life stages are potentially unnoticed. The size of the tick seems to play a crucial role in the ability of people to detect them. Of these four species of tick, *D. variabilis* are typically the largest, and both sexes have white mottling on their dorsal scutum, which may aid in their detection. When *D. variabilis* were collected from a person, 20% were attached. In comparison, 37% of the smallest tick species (*I. scapularis*) were attached when found on a person. Notably, *I. scapularis* is darker in coloration with no white mottling, making them more challenging to detect. In addition, female *A. americanum* are typically larger than males and have a white dot on their dorsal scutum. Of *A. americanum* females, 29% were attached when collected from a person, while 37% of males were attached. Adult ticks are larger than nymphs, and as a result, nymphs often go undetected. Over half of all *A. americanum* nymphs and the *I. scapularis* nymphs were attached to a person.

The most frequent tick exposure for Missourians was from *A. americanum*. This species is present throughout the state; only 10 counties did not meet the criteria for an established population after nine months of sampling. *A. americanum* are the main vector of ehrlichiosis caused by *Ehrlichia chaffeensis* (human monocytic ehrlichiosis), *E. ewingii* (*E. ewingii* ehrlichiosis), and Panola Mountain *Ehrlichia* (Panola Mountain ehrlichiosis). In addition to ehrlichiosis, *A. americanum* can transmit the etiological agents that cause the Heartland virus, Southern tick-associated rash illness (STARI), and tularemia and have also been implicated with alpha-gal syndrome, a recently reported food allergy.[40] Since *A. americanum* is the most prevalent tick species encountered, it is essential to understand the distribution of these disease-causing agents in Missouri.

The data presented in the current preliminary report is from the first nine months of a 17-month study. In addition to receiving more ticks as the study progresses, we are testing a subset of the ticks submitted for the presence of *Borrelia*, *Ehrlichia*, *Francisella*, and *Rickettsia* bacteria. At the end of the study, we will generate a map of the distribution of these four tick species in Missouri that will include county-level data about the bacterial pathogens they carry. The fact that citizens submitted so many ticks in a such short time reflects Missourians' desire for knowledge of disease ecology and epidemiology. Citizen science has great potential to provide public health managers with an affordable and effective way of investigating tickborne diseases.

References

1. Allan BF. Influence of prescribed burns on the abundance of *Amblyomma americanum* (Acari: Ixodidae) in the Missouri Ozarks. *J Med Entomol*. 2009;46(5):1030-1036. doi:10.1603/033.046.0509

2.Allan BF, Dutra HP, Goessling LS, et al. Invasive honeysuckle eradication reduces tick-borne disease risk by altering host dynamics. *Proc Natl Acad Sci U S A*. 2010;107(43):18523-18527. doi:10.1073/pnas.1008362107

3.Bacon RM, Gilmore RD Jr, Quintana M, Piesman J, Johnson BJ. DNA evidence of *Borrelia lonestari* in *Amblyomma americanum* (Acari: Ixodidae) in southeast Missouri. *J Med Entomol*. 2003;40(4):590-592. doi:10.1603/0022-2585-40.4.590

4.Bacon RM, Pilgard MA, Johnson BJ, Piesman J, Biggerstaff BJ, Quintana M. Rapid detection methods and prevalence estimation for *Borrelia lonestari glpQ* in *Amblyomma americanum* (Acari: Ixodidae) pools of unequal size. *Vector Borne Zoonotic Dis*. 2005;5(2):146-156. doi:10.1089/vbz.2005.5.146

5. Berrada ZL, Goethert HK, Telford SR. Isolation of *Francisella tularensis tularensis*subpopulation A.I from Missouri lone star ticks. *Am J Trop Med Hyg*. 2008;79:781.

6. Berrada ZL, Goethert HK, Cunningham J, Telford SR 3rd. *Rickettsia rickettsii* (Rickettsiales: Rickettsiaceae) in *Amblyomma americanum* (Acari: Ixodidae) from Kansas. *J Med Entomol*. 2011;48(2):461-467. doi:10.1603/me10130

7. Brandsma AR, Little SE, Lockhart JM, Davidson WR, Stallknecht DE, Dawson JE. Novel *Ehrlichia* organism (Rickettsiales: Ehrlichieae) in white-tailed deer associated with lone star tick (Acari: Ixodidae) parasitism. *J Med Entomol*. 1999;36(2):190-194. doi:10.1093/jmedent/36.2.190

8. Brown HE, Yates KF, Dietrich G, et al. An acarologic survey and *Amblyomma americanum* distribution map with implications for tularemia risk in Missouri. *Am J Trop Med Hyg*. 2011;84(3):411-419. doi:10.4269/ajtmh.2011.10-05937.

9.Bondy PJ Jr, Cohn LA, Tyler JW, Marsh AE. Polymerase chain reaction detection of *Cytauxzoon felis* from field-collected ticks and sequence analysis of the small subunit and internal transcribed spacer 1 region of the ribosomal RNA gene. *J Parasitol*. 2005;91(2):458-461. doi:10.1645/GE-374R

10. Clay K, Klyachko O, Grindle N, Civitello D, Oleske D, Fuqua C. Microbial communities and interactions in the lone star tick, *Amblyomma americanum*. *Mol Ecol*. 2008;17(19):4371-4381. doi:10.1111/j.1365-294x.2008.03914.x

11. DeShields A, Borman-Shoap E, Peters JE, Gaudreault-Keener

M, Arens MQ, Storch GA. Detection of pathogenic *Ehrlichia* in ticks collected at acquisition sites of human ehrlichiosis in Missouri. *Mo Med*. 2004;101(2):132-136.
12. de la Fuente J, Manzano-Roman R, Naranjo V, et al. Identification of protective antigens by RNA interference for control of the lone star tick, *Amblyomma americanum*. *Vaccine*. 2010;28(7):1786-1795. doi:10.1016/j.vaccine.2009.12.007
13. Fritzsche A, Allan BF. The ecology of fear: host foraging behavior varies with the spatio-temporal abundance of a dominant ectoparasite. *Ecohealth*. 2012;9(1):70-74. doi:10.1007/s10393-012-0744-z
14. Hudman DA, Sargentini NJ. Detection of *Borrelia*, *Ehrlichia*, and *Rickettsia* spp. in ticks in northeast Missouri. *Ticks Tick Borne Dis*. 2016;7(5):915-921. doi:10.1016/j.ttbdis.2016.04.010
15.Kensinger BJ, Allan BF. Efficacy of dry ice-baited traps for sampling *Amblyomma americanum* (Acari: Ixodidae) varies with life stage but not habitat. *J Med Entomol*. 2011;48(3):708-711. doi:10.1603/me10275
16. Kollars TM Jr, Durden LA, Masters EJ, Oliver JH Jr. Some factors affecting infestation of white-tailed deer by blacklegged ticks and winter ticks (Acari:Ixodidae) in southeastern Missouri. *J Med Entomol*. 1997;34(3):372-375. doi:10.1093/jmedent/34.3.372
17. Kollars TM Jr, Oliver JH Jr, Durden LA, Kollars PG. Host association and seasonal activity of *Amblyomma americanum* (Acari: Ixodidae) in Missouri. *J Parasitol*. 2000;86(5):1156-1159. doi:10.1645/0022-3395(2000)086[1156:HAASAO]2.0.CO;2
18. Lockhart JM, Davidson WR, Stallknecht DE, Dawson JE. Site-specific geographic association between *Amblyomma americanum* (Acari: Ixodidae) infestations and *Ehrlichia chaffeensis*-reactive (Rickettsiales: Ehrlichieae) antibodies in white-tailed deer. *J Med Entomol*. 1996;33(1):153-158. doi:10.1093/jmedent/33.1.153
19. Loftis AD, Mixson TR, Stromdahl EY, et al. Geographic distribution and genetic diversity of the *Ehrlichia* sp. from Panola Mountain in *Amblyomma americanum*. *BMC Infect Dis*. 2008;8:54. doi:10.1186/1471-2334-8-54
20. Masters E, Granter S, Duray P, Cordes P. Physician-diagnosed erythema migrans and erythema migrans-like rashes following Lone Star tick bites. *Arch Dermatol*. 1998;134(8):955-960. doi:10.1001/archderm.134.8.955
21. Oliver JH Jr, Kollars TM Jr, Chandler FW Jr, et al. First isolation and cultivation of *Borrelia burgdorferi* sensu lato from Missouri. *J Clin Microbiol*. 1998;36(1):1-5. doi:10.1128/JCM.36.1.1-5.1998
22. Roland WE, Everett ED, Cyr TL, Hasan SZ, Dommaraju CB, McDonald GA. *Ehrlichia chaffeensis* in Missouri ticks. *Am J Trop Med Hyg*. 1998;59(4):641-643.doi:10.4269/ajtmh.1998.59.641
23. Santanello C, Barwari R, Troyo A. Spotted fever group Rickettsiae in ticks from Missouri. *Ticks Tick Borne Dis*. 2018;9(6):1395-1399. doi:10.1016/j.ttbdis.2018.06.008
24. Savage HM, Godsey MS, Lambert A, et al. First detection of Heartland virus (Bunyaviridae: Phlebovirus) from field collected arthropods. *Am J Trop Med Hyg*. 2013;89(3):445-452. doi:10.4269/ajtmh.13-02094.
25. Seddighzadeh A, Pinger RR, Zercher A, et al. Strains of *Ehrlichia chaffeensis* in southern Indiana, Kentucky, Mississippi, and North Carolina. *J Med Entomol*. 2009;46(6):1468-1473. doi:10.1603/033.046.0633
26. Smith DD, Frenkel JK, Smith EI. Intradermal infestation of a red fox (*Vulpes vulpes*) by the lone star tick (*Amblyomma americanum*). *J Wildl Dis*. 1986;22(1):122-124. doi:10.7589/0090-3558-22.1.122
26. Steiert JG, Gilfoy F. Infection rates of *Amblyomma americanum* and *Dermacentor variabilis* by *Ehrlichia chaffeensis* and *Ehrlichia ewingii* in southwest Missouri. *Vector Borne Zoonotic Dis*. 2002;2(2):53-60. doi:10.1089/153036602321131841
27. Weller SJ, Baldridge GD, Munderloh UG, Noda H, Simser J, Kurtti TJ. Phylogenetic placement of *Rickettsiae* from the ticks *Amblyomma americanum* and *Ixodes scapularis*. *J Clin Microbiol*. 1998;36(5):1305-1317. doi:10.1128/JCM.36.5.1305-1317.1998
28. Wormser GP, Masters E, Liveris D, et al. Microbiologic evaluation of patients from Missouri with erythema migrans. *Clin Infect Dis*. 2005;40(3):423-428. doi:10.1086/427289
29. Yu X, Piesman JF, Olson JG, Walker DH. Short report: geographic distribution of different genetic types of *Ehrlichia chaffeensis*. *Am J Trop Med Hyg*. 1997;56(6):679- 680. doi:10.4269/ajtmh.1997.56.679
30. Eisen RJ, Eisen L, Beard CB. County-scale distribution of *Ixodes scapularis* and *Ixodes pacificus* (Acari: Ixodidae) in the continental United States. *J Med Entomol*. 2016;53(2):349-386. doi:10.1093/jme/tjv237
31. Lehane A, Parise C, Evans C, Beati L, Nicholson WL, Eisen RJ. Reported county-level distribution of the American Dog Tick (Acari: Ixodidae) in the contiguous United States. *J Med Entomol*. 2020;57(1):131-155. doi:10.1093/jme/tjz119
32. Springer YP, Eisen L, Beati L, James AM, Eisen RJ. Spatial distribution of counties in the continental United States with records of occurrence of *Amblyomma americanum* (Ixodida: Ixodidae). *J Med Entomol*. 2014;51(2):342-351. doi:10.1603/me13115
33. Brinton EP, Beck DE, DMA. Identification of the adults, nymphs and larvae of tick of the genus *Dermacentor* Koch (Ixodidae) in the western United States. *Brigham Young University Science Bulletin, Biological Series*. 1965;5(4):1.
34. Durden LA. Keirans JE. *Nymphs of the genus Ixodes (Acari: Ixodidae) in the United States: Taxonomy, Identification Key, Distribution, Hosts, and Medical/Veterinary Importance*. Lanham: Entomological Society of America; 1996.
35. Keirans JE, Litwak TR. Pictorial key to the adults of hard ticks, family Ixodidae (Ixodida: Ixodoidea), east of the Mississippi River. *J Med Entomol*. 1989;26(5):435-448. doi:10.1093/jmedent/26.5.435
36. Keirans JE, Durden LA. Illustrated key to nymphs of the tick genus *Amblyomma* (Acari: Ixodidae) found in the United States. *J Med Entomol*. 1998;35(4):489-495. doi:10.1093/jmedent/35.4.489
37. Egizi AM, Robbins R.G., Beati L, et al. A pictorial key to differentiate the recently detected exotic *Haemaphysalislongicornis* Neumann, 1901 (Acari, Ixodidae) from native congeners in North America. *Zookeys*. 2019;(818):117-128. doi:10.3897/zookeys.818.30448
38. Clifford CM Anastos G, Elbl A. The larval Ixodid ticks of the Eastern United States. Miscellaneous Publications of the Entomological Society of America. 1961;2:213-237
39. Lindquist E, Galloway T, Artsob H, et al. *A Handbook to the Ticks of Canada (Ixodida: Ixodidae, Argasidae)*. Biological Survey of Canada: 2016.
40. Kennedy AC, Marshall E. Lone star ticks (*Amblyomma americanum*): an emerging threat in Delaware. *Dela J Public Health*. 2021;7(1):66-71. doi:10.32481/djph.2021.01.013

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Disclosure

None reported. **MM**

Development of Hands-On Skills in Diagnostics of Lung Diseases Using Ultrasonography in Undergraduate Medical Education

by Caleb Milius, BA, Logan Jepson, BS, Drew Maclaskey, BA, Vanessa Pazdernik, MS & Tatyana Kondrashova, MD, PhD

A COVID ultrasound lung simulator provides a unique opportunity for medical students to familiarize with ultrasound-specific findings of COVID while reducing scanning time and mitigating the potential spread and exposure of students to COVID.



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Abstract

This study evaluated advanced pulmonary ultrasonography training for COVID-19 lung examination. Students completed identical pretests and post-tests and a survey. Changes were found for individual questions and overall scores (all P≤.02), specifically image identification, previous material, and COVID-19 questions. Students were receptive to the training for education and future practice (P<.001), and they felt capable using ultrasound for diagnosis and management of COVID-19 patients. Pulmonary ultrasonography training should be considered for the medical school curriculum.

Introduction

The ability to diagnose pulmonary pathology quickly and accurately is an essential competency for physicians to optimize critical patient care. As such, point-of-care lung ultrasonography has clinical applications in the diagnosis and monitoring of the progression of disease when managing critically ill patients.[1] With the emergence of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome-coronavirus 2, physicians are working to optimize the screening, diagnosis, and management of COVID-19 patients.[2] Despite using dedicated stethoscopes for individual patients in accordance with World Health Organization guidelines, auscultation presents a high risk of nosocomial transmission of this disease.[3] Since lung pathology can develop before the manifestation of clinical symptoms or reliable polymerase chain reaction detection, physicians are using multiple imaging modalities to screen patients with suspected COVID-19.[4] Currently, chest radiography (CXR), computed tomography (CT), and ultrasonography are used clinically to diagnose and manage patients with suspected COVID-19.[5-7]

When compared with CXR and CT, lung ultrasonography is a more promising imaging modality for screening and diagnosis of COVID-19.[4] Patients with signs and symptoms of COVID-19 present with distinctive clinical characteristics that progress similarly on CT and lung ultrasonography.[8] A retrospective cohort study indicated that lung ultrasonography was more sensitive than CXR (88.9% vs 51.9%) for the diagnosis of COVID-19.[9] However, considering the high contagiousness of COVID-19 and the risk of

transporting hemodynamically unstable and hypoxemic patients, use of CT is limited in patients with suspected or established COVID-19. When evaluating COVID-19–related pathology, lung ultrasonography offers diagnostic results similar to those of CT while also providing benefits of decreased radiation exposure, cost, and fomite transmission.[4] Thus, lung ultrasonography can be used as the main imaging modality for management of COVID-19, and chest CT can be reserved for cases where ultrasonography does not provide a complete answer to the clinical question.[4] A basic understanding of ultrasonography's ability to diagnose and risk stratify patients may improve the workflow of emergency departments, monitor the progression of COVID-19, and identify lung pathology missed by traditional radiological imaging.[10]

We believe advanced pulmonary ultrasonography training, specifically for the identification and management of patients with COVID-19, is a valuable skill for future and practicing physicians to obtain. The Blue Phantom COVID-19 Ultrasound Lung Simulator (CAE Healthcare, Inc.) may provide a unique opportunity for medical students to familiarize themselves with ultrasound-specific findings of COVID-19 while reducing scanning time and mitigating the potential spread and exposure of students to COVID-19. Numerous studies have explored imaging modalities for diagnosing COVID-19 lung pathology, but to our best knowledge, there is no data on using a COVID-19 Ultrasound Lung Simulator to teach medical students or the effect of such training when following social distancing guidelines.

The purpose of the current study was to evaluate the potential importance of advanced pulmonary ultrasonography training for medical students for COVID-19 lung examination. We hypothesized that medical students would show improvements in learning ultrasound image identification skills and performing lung ultrasound to diagnose COVID-19 after the training.

Methods

Second-year osteopathic medical students (N=31) from A.T. Still University's Kirksville College of Osteopathic Medicine (ATSU-KCOM) participated in the current study. The A.T. Still University-Kirksville Institutional Review Board granted exempt status for all educational procedures used in the study.

Student participants received ultrasonography training through three semesters of clinical ultrasonography coursework as part of their undergraduate medical education. The clinical ultrasound course at ATSU-KCOM is taught during the first two years of medical school. During semester 1, students learn how to use the ultrasound machine and perform upper and lower limb musculoskeletal ultrasound and neck vascular and ocular ultrasound examinations. Semester 2 includes abdominal, echocardiography, upper and lower extremity vascular, and pelvic ultrasound examinations. Second-year ultrasound courses are more clinically oriented, so semester 3 focuses on lung, endocrine, obstetrics, gynecology, and breast ultrasound examinations.

An optional advanced ultrasonography pulmonary training session that focused on normal and COVID-19–associated lung ultrasonography findings was offered to second-year students. Since the start of the COVID-19 pandemic, ATSU-KCOM has implemented protocols to minimize the potential exposure of students while on campus. Before participating in the training session, students completed a standardized COVID-19 daily questionnaire, and their temperatures were taken before entry on campus. Students were not allowed to participate in the study if they had any symptoms of COVID-19 or any recent, possible exposure to COVID-19. Students were required to wear KN-95 masks for the entirety of the training session and maintain social distancing according to the Centers for Disease Control and Prevention recommendations.

Training was preceded by a PowerPoint presentation that explained the objectives and clinical relevance of the ultrasound exercise followed by a live demonstration using the Blue Phantom COVID-19 Ultrasound Lung Simulator (Figure 1). The simulator contained lung, chest wall, ribs (1-5), and the diaphragm. Pathological landmarks in the lung simulator were pulmonary edema, thickened pleural lining, diffused bilateral B-lines, subpleural consolidation, and skip lesions. The COVID-19 disease findings became more progressive inferiorly. The first intercostal space represented ultrasound findings of a healthy individual with thin, regular pleural lining and A-lines. The second and third intercostal space findings had thick, irregular pleural lining and B-lines. The fourth intercostal space showed COVID-19 consolidation and lesions. Participants performed lung ultrasound examination using a Mindray M7 with the linear transducer L4-12s with a frequency bandwidth of 8.0/10.0/12.0 MHz (Shenzhen Mindray Bio-Medical Electronics Co., Ltd.). Additional instruction on identifying lung pathology with ultrasonography was provided during the training time.

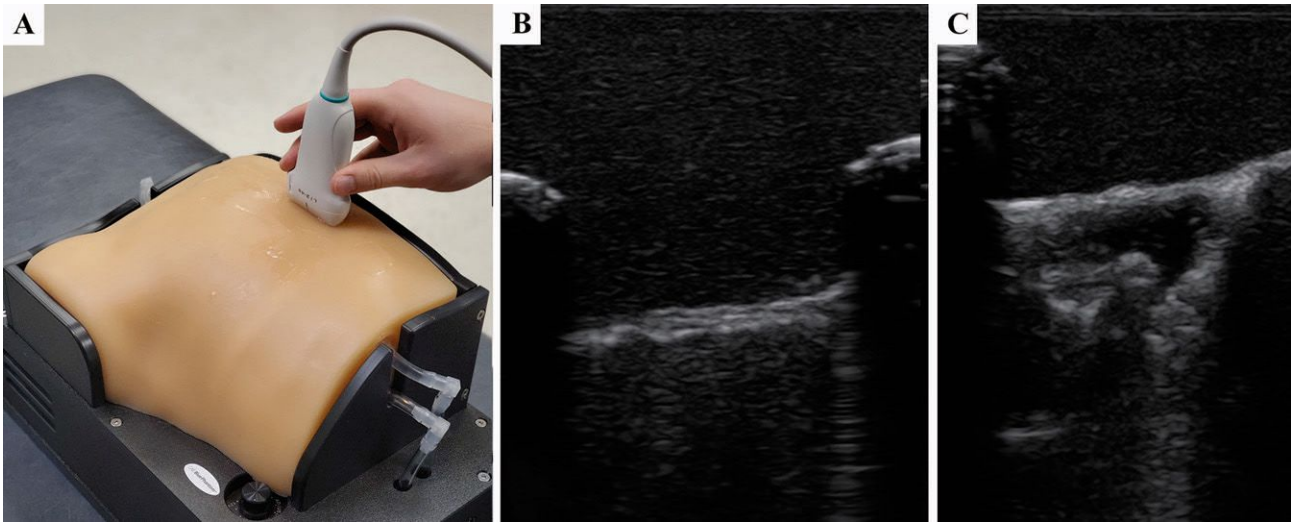


Figure 1. Ultrasound Training Simulator Used for the Advanced Pulmonary Training of the Current Study
A, COVID-19 Ultrasound Lung Simulator (CAE Healthcare, Inc.).
B, Ultrasound image showing a thickened and irregular pleural lining using the COVID-19 Ultrasound Lung Simulator.
C, Ultrasound image showing a subpleural consolidation using the COVID-19 Ultrasound Lung Simulator.

Before the advanced pulmonary ultrasonography training, medical students completed a 10-question pretest consisting of three types of questions: ultrasonography image identification skills, previous lung ultrasound knowledge, and new COVID-19 ultrasound knowledge (Appendix). Questions 3, 4, 9, and 10 assessed ultrasonography image identification skills; questions 1-5 assessed previous lung ultrasound knowledge; and questions 6-10 assessed new COVID-19 ultrasound knowledge. After completing the pulmonary training, students took an identical 10-question post-test along with a voluntary, anonymous paper survey created specifically for the current study. The 11-item survey included seven Likert-scale questions and four open-ended questions. The survey was designed to assess participant perception of ultrasound technology and its use for COVID-19 diagnosis and their perception of the pulmonary ultrasonography training. Likert-scale questions were the following:

1) I feel capable of operating an ultrasound machine to guide my diagnosis of lung pathology;

2) I feel capable of performing a lung ultrasound exam in a clinical setting;

3) I find it challenging to interpret a 2-dimensional (2D) ultrasound lung image;

4) I found the use of the Blue Phantom COVID-19 Simulator useful in the interpretation of 2D ultrasound lung images;

5) It was easy to identify structures on the Blue Phantom COVID-19 Simulator;

6) The knowledge of lung ultrasonography taught with the Blue Phantom COVID-19 Simulator was beneficial for the development of my clinical skills; and

7) I believe that ultrasound technology is useful for the diagnosis and management of COVID-19 patients.

A standard Likert scale (strongly disagree, disagree, neither agree nor disagree, agree, and strongly agree) was used to evaluate agreement or disagreement. The last four4 survey items were open-ended questions:

8) What is one thing you took away from the use of the Blue Phantom COVID-19 Simulator as a tool to better understand the pathologic findings associated with COVID-19?

9) What is one thing you would like to see as part of the COVID-19 training session which we did not include?

10) Please leave comments about the use of lung ultrasound technology in medical education; and

11) Please leave comments about your expected future use of lung ultrasound technology during your clinical rotations.

All data analyses were completed using SAS software version 9.4 (SAS Institute, Inc.). Frequency and percentage were reported for survey responses. The Wilcoxon signed rank test was used to test for differences from neither agree nor disagree in the median survey responses or for changes in test scores. A $P<.05$ was considered statistically significant.

Qualitative analyses of the open-ended questions were performed by searching for common words

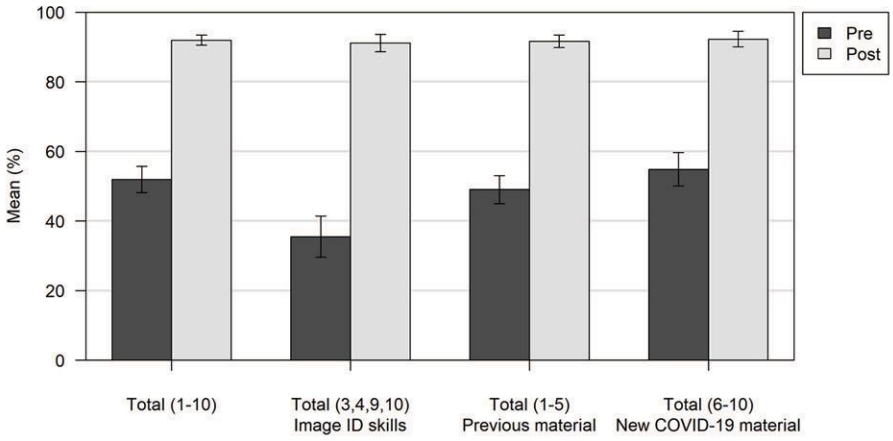


Figure 2. Performance of Medical Students on the Pretest (Pre) and Post-test (Post) by Total Score and by the Three Question Types. Error bars represent the standard error of the mean. Parenthetical notation indicates test question number.
Abbreviation: ID, identification.

and themes in the participant's open-ended survey responses. Examples of keywords included the following: pathology, disease progression, real patient, future practice, and beneficial. After completing a count of keyword usage, each entry was checked for responses that did not mention the keyword but included a theme related to it. For example, students who requested the opportunity to scan a COVID-19 patient were included in the category of those who used the keyword real patient.

Results

When comparing pretest with post-test results, improvements were found in medical student performance on post-test questions for 8 of the 10 questions, in total, and for each of the three question types ($P \leq .001$) (Figure 2).

Medical student responses to the survey Likert-scale questions are presented in the Table and Figure 3. For all Likert items except one, agreement was more likely than disagreement (all $P < .001$). When combining agree and strongly agree responses, 97% of students felt capable of operating an ultrasound machine to guide diagnosis of lung pathology, 94% felt capable of performing a lung ultrasound exam in a clinical setting, and 97% found structures on the COVID-19 Ultrasound Lung Simulator easy to identify. All students (100%) indicated that the knowledge of lung ultrasonography taught with the Blue Phantom COVID-19 Simulator was beneficial for the development of their clinical skills and that the ultrasound technology was useful for the diagnosis and management of COVID-19 patients. However, 32% found a 2D ultrasound lung image challenging to interpret ($P = .28$).

For the open-ended questions, the majority of medical students indicated the lung ultrasound training for COVID-19 was useful for more thorough understanding of COVID-19 pathological findings and identification of the progression of COVID-19 pneumonia when using ultrasound imaging. Qualitative analysis of the open-ended questions indicated 9 (29.0%) of the 31 students requested the opportunity to scan human models or patients with COVID-19, and 19 (61.2%) indicated benefit from the demonstration for learning lung pathology or the disease progression of COVID-19. Twenty-two (71%) students expressed interest in using lung ultrasound technology during future clinical experiences, and 10 (32.3%) felt the implementation of lung ultrasound technology was a beneficial component of the medical school curriculum.

Discussion

The current study evaluated the importance of advanced pulmonary ultrasonography training for medical students for COVID-19 lung examination. A survey was used to evaluate their perceptions of performing lung ultrasound for COVID-19 diagnosis and the pulmonary ultrasonography training, which was delivered using appropriate social distancing guidelines. At the time of the study, in-person learning was limited at ATSU-KCOM to prevent possible exposure to COVID-19, and using ultrasound simulators allowed development of practical skills without increasing the contact of students with each other. The use of the COVID-19 Ultrasound Lung Simulator made hands-on training for advanced pulmonary ultrasonography possible during the pandemic. Our results suggested that the majority of second-year medical students felt capable of operating an ultrasound machine to guide diagnosis of lung pathology and performing a lung ultrasound examination in a clinical setting.

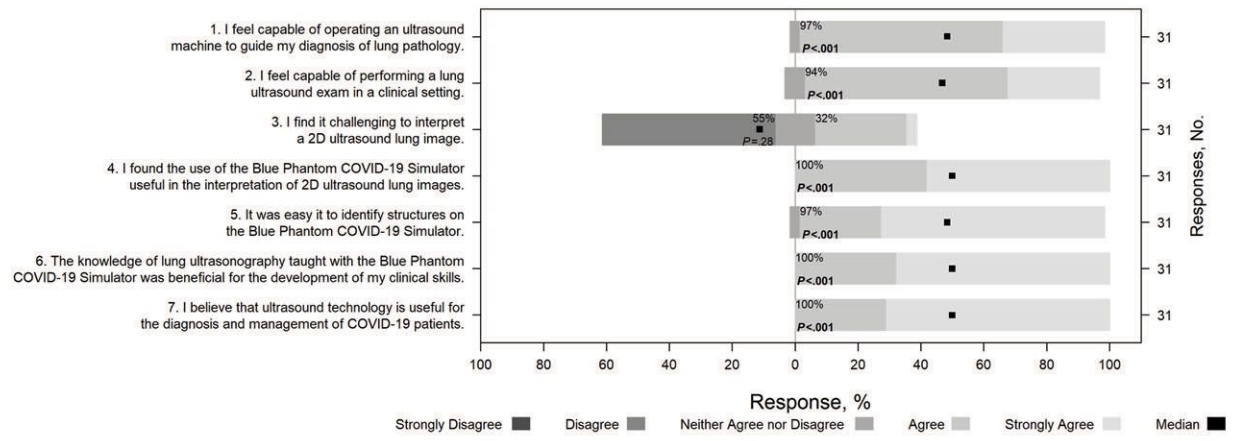


Figure 3. Medical Student Responses for All Likert-Scale Survey Questions. Wilcoxon signed rank test for median difference from neither agree nor disagree.
Abbreviation: 2D, 2-dimensional.

Further, 97% found structures on the Blue Phantom COVID-19 Ultrasound Lung Simulator easy to identify.

The format of this training exercise allowed students to interpret ultrasound images and identify normal and pathological structures on a simulator. All students were able to obtain images of normal lung ultrasound findings associated with a healthy individual, specifically, thin, regular pleural lining and A-lines. Students compared normal and abnormal ultrasound findings and visualized the progression of the COVID-19 disease inferiorly: they scanned and positively identified thick and irregular pleural lining, diffused B-lines, and COVID-19 subpleural consolidation and lesions. This finding suggested that students were indeed competent in ultrasound imaging and interpretation. Although 32% of students found it challenging to interpret a 2D ultrasound lung image, all students were able to find and interpret the assigned normal and abnormal lung structures using the COVID-19 Ultrasound Lung Simulator.

In a previous study, students trained to use ultrasound and simulators were better prepared to interpret images than classroom-based learners,[11] which highlights the importance of simulation-based learning in medical training. The ability to accurately identify and interpret ultrasound images is an important aspect of medical training, and it can have an impact on physician competence and patient safety. In a review investigating the role of medical simulation, physicians trained with simulation-based techniques outperformed and were more competent than traditionally trained physicians for a specific procedure.[12] Using simulation-based education also increased patient safety.[12] Given these benefits and the greater prevalence of simulation in education and training in the modern medical school curricula,[13] it is important to begin simulation training at the undergraduate medical student level. In the current study, medical students had completed three semesters of ultrasound coursework before the advanced pulmonary ultrasound training, which likely explains their high level of comfort with the ultrasound equipment and imaging. For the open-ended question about how the training could be improved, several suggestions were provided by students, such as using a "differential with other pathologies" or "possibly scanning post-COVID patients," providing "comparison with CT and CXR imaging," and including "future assessment of people who previously had COVID."

Qualitative analysis of our open-ended survey items found that 90.2% of students were overwhelmingly positive about the incorporation of lung ultrasound technology into the curriculum. One student suggested incorporating the COVID-19 lecture and demonstration into the core ultrasound curriculum. We found that 100% of students agreed the knowledge of lung ultrasonography taught with the Blue Phantom COVID-19 Simulator was beneficial for the development of their clinical skills. This finding was

supported by the open-ended survey responses, where students suggested they felt more prepared for rotations, residency, and practice of medicine during the pandemic. Further, the majority of students indicated that such training using the lung simulator gave them a more thorough understanding of the pathological signs and progression of COVID-19. One student indicated that "the pathologies associated with COVID-19 are very different from bacterial pneumonia. If you can identify the specific pathologies, you can be more effective at diagnosing early COVID-19." Therefore, ultrasound technology may have the additional benefit of enhancing the clinical reasoning of medical students. This assumption is supported by previous studies that found the use of ultrasound technology in medical education increased the clinical knowledge of students.[14-16]

Our qualitative analysis also found that students were overwhelmingly positive about the pulmonary ultrasonography training, and 71% indicated their intention to use lung ultrasound technology in future practice, which suggests students were receptive to incorporating pulmonary ultrasonography training into medical education and practice. Students indicated that "scanning a simulator is more beneficial than pictures" and "provides a better clinical, hands-on approach to book learning."

One limitation of the current study was the small sample size and the use of second-year medical students only. However, we specifically included only second-year medical students because they had already been exposed to lung ultrasound scanning techniques as part of the ATSU-KCOM ultrasound curriculum. Another reason for using second-year students was to reduce scanning time and mitigate the potential spread or exposure of students to COVID-19 during the pandemic.

Conclusion

In the current study, medical students showed marked improvement in their understanding of the aspects of lung ultrasonography after participating in an optional advanced pulmonary ultrasonography training session. The training helped students better understand COVID-19 lung pathological findings and improved their ultrasonography skills. It also boosted their confidence in performing ultrasound procedures in the pandemic setting. Students also indicated the pulmonary ultrasonography training was beneficial for future practice and, therefore, should be considered for inclusion in the core medical school curriculum. The undergraduate medical students were receptive, motivated, and capable of learning how to perform and interpret lung ultrasound imaging related to COVID-19 pathology. Taken together, results of the current study support further integration of ultrasound technology into early undergraduate medical education.

References

1. Lichtenstein DA. BLUE-protocol and FALLS-protocol: two applications of lung ultrasound in the critically ill. Chest. 2015;147(6):1659-1670.
2. Duggan NM, Shokoohi H, Liteplo AS, Huang C, Goldsmith AJ. Best practice recommendations for point-of-care lung ultrasound in patients with suspected COVID-19. J Emerg Med. 2020;59(4):515-520.
3. Marinella MA. COVID-19 pandemic and the stethoscope: do not forget to sanitize. Heart Lung. 2020;49(4):350.
4. Peng QY, Wang XT, Zhang LN, Chinese Critical Care Ultrasound Study Group (CCUSG). Findings of lung ultrasonography of novel corona virus pneumonia during the 2019–2020 epidemic. Intensive Care Med. 2020;46(5):849-850.
5. Wong HYF, Lam HYS, Fong AHT, et al. Frequency and distribution of chest radiographic findings in patients positive for COVID-19. Radiology. 2020;296(2):E72-E78.
6. Zhao S, Lin Q, Ran J, et al. Preliminary estimation of the basic reproduction number of novel coronavirus (2019-nCoV) in China, from 2019 to 2020: a data-driven analysis in the early phase of the outbreak. Int J Infect Dis. 2020;92:214-217.
7. Bar S, Lecourtois A, Diouf M, et al. The association of lung ultrasound images with COVID-19 infection in an emergency room cohort. Anaesthesia. 2020;75(12):1620-1625.
8. Smith MJ, Hayward SA, Innes SM, Miller ASC. Point-of-care lung ultrasound in patients with COVID-19: a narrative review. Anaesthesia. 2020;75(8):1096-1104.
9. Pare JR, Camelo I, Mayo KC, et al. Point-of-care lung ultrasound is more sensitive than chest radiograph for evaluation of COVID-19. West J Emerg Med. 2020;21(4):771-778.
10. Abrams ER, Rose G, Fields JM, Esener D. Point-of-care ultrasound in the evaluation of COVID-19. J Emerg Med. 2020;59(3):403-408.
11. Chung GKWK, Gyllenhammer RG, Baker EL. The effects of practicing with a virtual ultrasound trainer on FAST window identification, acquisition, and diagnosis. CRESST Report 787. Los Angeles: National Center for Research on Evaluation, Standards, and Student Testing (CRESST); 2011.
12. Kunkler K. The role of medical simulation: an overview. Int J Med Robot. 2006;2(3):203-210.
13. Kondrashova T, Coleman C. Enhancing learning experience using ultrasound simulation in undergraduate medical education: student perception. Med Sci Educ. 2017;27(3):489-496.
14. Akaike M, Fukutomi M, Nagamune M, et al. Simulation-based medical education in clinical skills laboratory. J Med Invest. 2012;59(1-2):28-35.
15. Issenberg SB, Scalese RJ. Simulation in health care education. Perspect Biol Med. 2008;51(1):31-46.
16. Solomon SD, Saldana F. Point-of-care ultrasound in medical education: stop listening and look. N Engl J Med. 2014;370(12):1083-1085.

Disclosure

None reported. **MM**

Histological Structure of the Medial and Lateral Patellofemoral Ligaments and Implications for Reconstructive Surgery and Anterior Knee Pain

by Austin Veteto, MS, Michael McIntyre, DC, Michelle Hintz, DO, Michael Cramberg, MPH & Peter Kondrashov, PhD

An analysis of medial patellofemoral ligament reconstruction outcomes, over 26% of individuals had complications including pain, recurrent subluxation/dislocation, hypermobility/apprehension, instability, patellar fracture, and the need for corrective surgery.



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Abstract

Biomechanically, the patellofemoral joint is one of the most complex human articulations and a common source of pain for active adults and adolescents, particularly females.[1-4] Patellofemoral disorders account for 20%-40% of all knee problems seen in family practice, sports medicine, and orthopedic clinics.[1, 3-5]

Introduction

The knee retinaculum has been identified as a trigger point for anterior knee pain,[2] and it has been suggested that the medial patellofemoral ligament (MPFL), the second and thickest layer of the medial retinaculum, is responsible for patellofemoral pain in adolescents.[6-8] Anterior knee pain centered in the MPFL has been associated with tightness, impingement, and overuse of the lateral retinaculum, which affects the lateral patellofemoral ligament (LPFL).[6] It has been estimated that patellofemoral pain syndrome, a subset of anterior knee pain specifically implicating the patellofemoral joint, accounts for 25%-40% of knee problems seen in sports-injury clinics.[4]

With an incidence rate in adolescents of 29 per 100,000, patellar dislocation may result from failure of soft connective tissue restraints (eg, MPFL and LPFL as the primary medial and lateral stabilizers of the patella) to maintain proper tracking of the patella along the patellar groove.[7, 9-11] Lateral dislocation from medial instability is more common than medial dislocation and has been extensively studied.[11, 12] Recurrent dislocation ranges from 15% to 69% after conservative (nonoperative) treatment, whereas less than 4% of individuals experience subsequent dislocation after surgical repair.[9, 13] The stability of the patellofemoral joint is largely governed by the alignment of the lower limbs; patellar orientation, position, and tracking; q-angle; retinacular tightness; and surrounding muscular strength and tightness.[14] Thus, many variations can contribute to instability. Further, there are over 100 distinct surgical protocols to address MPFL injuries alone, which should concern patients, researchers, and clinicians alike.[15]

Graft tissues used in reconstructive procedures for the MPFL and LPFL often use the gracilis tendon, hamstring tendon, quadriceps tendon, or semitendinosus tendon.[15, 16] Typical ligaments and tendons, like those used in these procedures, are composed primarily of dense connective tissue and rarely contain other elements.

In a meta-analysis of MPFL reconstruction outcomes, over 26% of individuals had complications with their procedures.[13] These complications included pain, recurrent subluxation/dislocation, hypermobility/apprehension, instability, patellar fracture, and the need for corrective surgery.[13] These frequent complications are not well understood even though the gross anatomy of the MPFL and its biomechanical participation in the patellofemoral joint are well studied.[7, 17, 18] The same is true for the LPFL.[10, 12, 19] Despite the well-characterized gross anatomy of the MPFL and LPFL, their microscopic structure is unknown and has been only superficially described, which impedes understanding of the role of these structures in patellofemoral pain syndrome and knee stability. The histology of the MPFL has been likened to other ligaments that have uniformly oriented collagen fibers and elongated fibroblasts.[17] The LPFL has been studied much less extensively than the MPFL and, to our knowledge, its histology has not been previously described. Therefore, the purpose of the current study was to describe the histological composition of the MPFL and LPFL and to compare them histologically to other knee ligaments to better define their role in knee stability and pain generation.

Methods

The local institutional review board approved all procedures used in the current study. Knees from 10 human cadavers (six male, four female; age range: 46-87 years) were evaluated. Samples of the MPFL, LPFL, medical collateral ligament (MCL), anterior cruciate ligament (ACL), and quadriceps tendon (QT) were collected from a single knee (chosen randomly) from each cadaver. Age, sex, side (right or left knee), significant medical history, and cause of death were recorded for each cadaver. After excision, tissues were fixed in 10% neutral buffered formalin for one day. After fixation, tissue samples were placed in 50% alcohol for 60 minutes and then stored in 70% alcohol until embedded in paraffin, sectioned into 8-µm or 12-µm sections, and stained with hematoxylin and eosin, Masson's trichrome, or orcein.

Slides were scanned at 20× magnification, and four nonoverlapping 10 × 10 grids (grid cells 200 µm × 200 µm) were digitally superimposed on the image.[20] One of the four grids was then chosen randomly to be counted. For each of the 121 intersections on the grid, the type of tissue was identified as dense connective tissue, loose connective tissue, vasculature, nerve tissue, or adipose tissue. If nothing appeared at an intersection, the closest tissue type to that intersection was counted in its place. The same approach was used for histological artifacts.

Statistical Analysis

Random-intercept logistic regression models were used to test for differences in the proportions of tissue types (eg, dense connective tissue) between knee ligaments and the QT, where the outcome variable was the proportion of the tissue type. Random paraffin blocks and cadaver effects allowed for possible correlations of the proportion of tissue type among repeated measures across the paraffin block and across different blocks on the same cadaver. For the vasculature tissue type outcome, the odds ratio was calculated for MPFL, LFPL, and MCL to ACL and QT. Data were reported as mean percentage, standard error, and 95% confidence interval (CI). All analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC). $P \leq .05$ was considered statistically significant.

Results

Tissue analysis showed significant differences in the histological composition of the studied ligaments and tendon (Table 1). The MPFL was made up of 66.9% dense connective tissue, 22.8% loose connective tissue, 2.2% vasculature, 0.3% nerves, and 2.0% adipose tissue (Figure 1). The proportions of dense connective tissue and loose connective tissue were different in the MPFL when compared with the other ligaments and QT (all $P<.001$). The number of blood vessels in the MPFL was very similar to the LPFL ($P=.94$), but different from the other ligaments and QT (all $P<.001$). The MPFL contained more nerves than the LPFL ($P=.04$); the other ligaments

Table 1. Mean Percentage of Tissue Proportions for All Studied Knee Ligaments and the Quadriceps Tendon

Tissue Type	Mean Percentage (SE)				
	MPFL	LPFL	MCL	ACL	QT
Dense connective	66.9 (3.8)	80.6 (2.7)	95.2 (0.8)	99.0 (0.2)	99.1 (0.2)
Loose connective	22.8 (2.7)	17.2 (2.2)	3.7 (0.6)	0.9 (0.2)	0.8 (0.1)
Vasculature	2.2 (0.4)	2.2 (0.4)	1.1 (0.2)	0.1 (0.03)	0.1 (0.03)
Nerves	0.3 (0.07)	0.2 (0.05)	-	-	-
Adipose	2.0 (1.4)	0.03 (0.02)	0.02 (0.02)	-	-

Abbreviations: ACL, anterior cruciate ligament; LPFL, lateral patellofemoral ligament; MCL, medial collateral ligament; MPFL, medial patellofemoral ligament; QT, quadriceps tendon.

and QT had none. The MPFL contained more adipose tissue than the LPFL and MCL (P<.001). The ACL and QT had no adipose tissue.

The LPFL was made up of 80.6% dense connective tissue, 17.2% loose connective tissue, 2.2% vasculature, 0.2% nerves, and 0.03% adipose tissue (Table 1 and Figure 1). The proportions of dense connective tissue and loose connective tissue were different in the LPFL when compared with the other ligaments and QT (all P<.001). The number of blood vessels in the LPFL was very similar to the MPFL (P=.94), but different from the other ligaments and QT (all P<.001). The LPFL contained fewer nerves than the MPFL (P=.04). The LPFL contained roughly the same amount of adipose tissue as the MCL (P=.70), which was less than the MPFL (P<.001).

The MCL was made up of 95.2% dense connective tissue, 3.7% loose connective tissue, 1.1% vasculature, and 0.02% adipose tissue (Table 1 and Figure 1). The proportions of dense connective tissue and loose connective tissue were different in the MCL when compared with the other ligaments and QT (all P<.001). The number of blood vessels was different in the MCL when compared with the other ligaments and QT (all P<.001). The amount of adipose tissue in the MCL was the same as in the LPFL (P=.70), but less than in the MPFL (P<.001)

The ACL was made up of 99.0% dense connective tissue, 0.9% loose connective tissue, and 0.1% vasculature; it had no nerves or adipose tissue (Table 1 and Figure 1). The proportion of dense connective tissue was different in the ACL when compared with the MPFL, LPFL, and MCL (all P<.001), but similar to the QT (P=.55). Likewise, the proportion of loose connective tissue was different in the ACL when compared with the MPFL, LPFL, and MCL (all P<.001), but similar to the QT (P=.53). The number of blood vessels in the ACL was very similar to the QT (P=.79), but different from the other ligaments (all P<.001).

The QT was made up of 99.1% dense connective tissue, 0.8% loose connective tissue, and 0.1% vasculature; it had no nerves or adipose tissue (Table and Figure). The proportion of dense connective tissue was different in the QT when compared with the MPFL, LPFL, and MCL (all P<.001), but similar to the ACL (P=.55). Likewise, the proportion of loose connective tissue was different in the QT when compared with the MPFL, LPFL, and MCL (all P<.001), but similar to the ACL (P=.53). The number of blood vessels in the QT was very similar to the ACL (P=.79), but different from the other ligaments (all P<.001).

The MPFL and LPFL had a diverse histological composition that included blood vessels of different sizes, nerves, and adipose tissue (Figure). The MPFL, LPFL, and MCL had vasculature that was more prominent than in the ACL and QT. The odds of vasculature was 14.9 (95% CI, 10.8 to 20.6) times greater in the MPFL, LFPL, and MCL than in the ACL and QT.

Discussion

Traditionally, ligaments of the knee were treated as one group and were thought to be composed

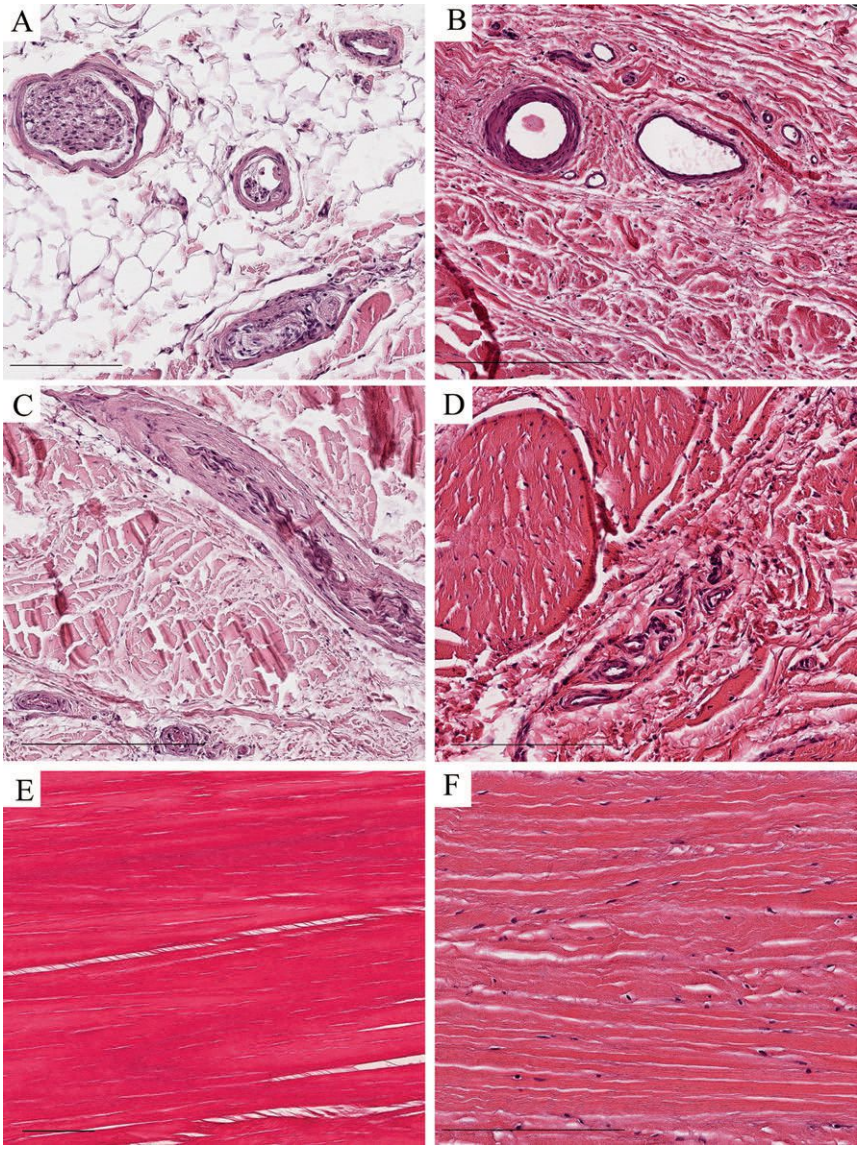


Figure 1. Histology of knee tendons and ligaments (stained with hematoxylin and eosin). A. Medial patellofemoral ligament, scale bar equals 0.3 mm; B. Medial patellofemoral ligament, scale bar equals 0.1 mm; C. Lateral patellofemoral ligament, scale bar equals 0.2 mm; D. Medial collateral ligament, scale bar equals 0.1 mm; E. Anterior cruciate ligament, scale bar equals 0.3 mm; F. Quadriceps tendon, scale bar equals 0.3 mm.

almost entirely of dense connective tissue. The MPFL was thought to have the same composition as well.[17] However, our data indicated that the MPFL and LPFL differ from this typical model. These two ligaments were similar to each other and more similar to the retinaculum because they contained loose connective tissue and had extensive vascular supply and innervation, which are typically limited in ligaments like the ACL. Dense regular connective tissue was still the dominant tissue type found in all studied ligaments and tendon. The ACL and QT were histologically nearly identical with over 99% dense connective tissue and only trace amounts of loose connective tissue and vasculature. The MPFL, LPFL, and MCL had more histological diversity and contained a significant amount of loose connective tissue. Vasculature was present in each of the structures studied, and most blood vessels were found in the MPFL and LPFL. The MCL had about half the number of blood vessels as the MPFL and LPFL and approximately an order of magnitude more than the ACL and QT. Adipose tissue was found to varying degrees in the MPFL, LPFL, and MCL. The MPFL had more adipose tissue than the LPFL and MCL, but the relative amount varied from cadaver to cadaver. Although nerves have been identified in the ACL in a previous study,[21] they were only identified in the MPFL and LPFL in the current study. The greater relative abundance of nerve tissue in these ligaments indicates their importance for proprioception and pain generation. Because the observed nerves had small diameters, they likely represent sensory terminal branches rather than motor branches passing through the tissue. Based on the absence of targets for motor innervation in these ligaments, we concluded that these nerve fibers were afferent.

The current study had sampling bias as a limitation. All knee specimens were obtained from cadavers from a gross anatomy laboratory, and all cadavers were donated through the body donation program. Further, the average age at death was 73 years, which may have affected results since aging

has a significant impact on ligament structure.[22] Future studies should include different age groups to evaluate the effects of aging on MPFL and LPFL histology. Another limitation is that we were unable to confirm that the nerve fibers found in the MPFL and LPFL represented afferent fibers. Future studies should focus on the ultrastructural or immunohistochemical analysis of these fibers to determine their type.

Conclusion

In the current study, the presence of vasculature in the MPFL, LPFL, and MCL indicated the ability of these ligaments to self-heal, thus suggesting that conservative treatment is still a viable option for the management of tears in these structures. Both the MPFL and LPFL contained a significant number of nerves, which suggested the possible involvement of these ligaments in pain generation. Most surgical repair methods disrupt these ligaments, so although these treatments may increase knee stability, they may also lead to patellofemoral pain syndrome. The diverse histological composition of the MPFL and LPFL and the presence of loose connective tissue, vasculature, and nerves in these ligaments suggest they may represent thickenings of the knee capsule.

References

1. Zaffagnini S, Giordano G, Bruni D, Muccioli GMM, Marcacci M. Pathophysiology of Lateral Patellar Dislocation. In: Zaffagnini S, Dejour D, Arendt EA, eds. Patellofemoral Pain, Instability, and Arthritis: Clinical Presentation, Imaging, and Treatment. Berlin, Heidelberg: Springer Berlin Heidelberg; 2010:17-27.
2. Biedert RM, Sanchis-Alfonso V. Sources of anterior knee pain. Clin Sports Med. 2002;21(3):335-347.
3. Rothermich MA, Glaviano NR, Li J, Hart JM. Patellofemoral pain: epidemiology, pathophysiology, and treatment options. Clin Sports Med. 2015;34(2):313-327.
4. Gaitonde DY, Ericksen A, Robbins RC. Patellofemoral Pain Syndrome. Am Fam Physician. 2019;99(2):88-94.
5. Sanchis-Alfonso V. Pathophysiology of Anterior Knee Pain. In: Zaffagnini S, Dejour D, Arendt EA, eds. Patellofemoral Pain, Instability, and Arthritis: Clinical Presentation, Imaging, and Treatment. Berlin, Heidelberg: Springer Berlin Heidelberg; 2010:1-16.
6. Luhmann SJ, Schoenecker PL, Dobbs MB, Gordon JE. Adolescent patellofemoral pain: implicating the medial patellofemoral ligament as the main pain generator. J Child Orthop. 2008;2(4):269-277.
7. Baldwin JL. The anatomy of the medial patellofemoral ligament. Am J Sports Med. 2009;37(12):2355-2361.
8. Blackman AJ, Smith JC, Luhmann SJ. Arthroscopic Lateral Retinacular Release in Adolescents With Medial Patellofemoral Ligament-centered Knee Pain. J Pediatr Orthop. 2016;36(3):268-273.
9. Colvin AC, West RV. Patellar instability. J Bone Joint Surg Am. 2008;90(12):2751-2762.
10. Capkin S, Zeybek G, Ergur I, Kosay C, Kiray A. An anatomic study of the lateral patellofemoral ligament. Acta Orthop Traumatol Turc. 2017;51(1):73-76.
11. Huber C, Zhang Q, Taylor WR, Amis AA, Smith C, Hosseini Nasab SH. Properties and function of the medial patellofemoral ligament: a systematic review. Am J Sports Med. 2020;48(3):754-766.
12. Shah KN, DeFroda SF, Ware JK, Koruprolu SC, Owens BD. Lateral patellofemoral ligament: an anatomic study. Orthop J Sports Med. 2017;5(12):2325967117741439.
13. Shah JN, Howard JS, Flanigan DC, Brophy RH, Carey JL, Lattermann C. A systematic review of complications and failures associated with medial patellofemoral ligament reconstruction for recurrent patellar dislocation. Am J Sports Med. 2012;40(8):1916-1923.
14. Witvrouw E, Werner S, Mikkelsen C, Van Tiggelen D, Vanden Berghe L, Cerulli G. Clinical classification of patellofemoral pain syndrome: guidelines for non-operative treatment. Knee Surg Sports Traumatol Arthrosc. 2005;13(2):122-130.
15. Mistry JB, Bonner KF, Gwam CU, Thomas M, Etcheson JI, Delanois RE. Management of Injuries to the Medial Patellofemoral Ligament: A Review. J Knee Surg. 2018;31(5):439-447.
16. Saper MG, Shneider DA. Medial patellar subluxation: diagnosis and treatment. Am J Orthop (Belle Mead NJ). 2015;44(11):499-504.
17. Hinckel BB, Gobbi RG, Demange MK, et al. Medial Patellofemoral Ligament, Medial Patellotibial Ligament, and Medial Patellomeniscal Ligament: Anatomic, Histologic, Radiographic, and Biomechanical Study. Arthroscopy. 2017;33(10):1862-1873.
18. Tanaka MJ, Chahla J, Farr J, 2nd, et al. Recognition of evolving medial patellofemoral anatomy provides insight for reconstruction. Knee Surg Sports Traumatol Arthrosc. 2019;27(8):2537-2550.
19. DeFroda SF, Shah KN, Lemme N, Koruprolu S, Ware KJ, Owens BD. Biomechanical Properties of the Lateral Patellofemoral Ligament: A Cadaveric Analysis. Orthopedics. 2018;41(6):e797-e801.
20. Sundberg MD. An Introduction to Stereological Analysis: Morphometric Techniques for Beginning Biologists. In: Goldman CA, Andrews SE, Hauta PL, Ketchum R, eds. Tested studies for laboratory teaching. Vol 6: Proceedings of the 6th Workshop/ Conference of the Association for Biology Laboratory Education (ABLE); 1992:51-72.
21. Schutte MJ, Dabezies EJ, Zimny ML, Happel LT. Neural anatomy of the human anterior cruciate ligament. J Bone Joint Surg Am. 1987;69(2):243-247.
22. Hasegawa A, Otsuki S, Pauli C, et al. Anterior cruciate ligament changes in the human knee joint in aging and osteoarthritis. Arthritis and rheumatism. 2012;64(3):696-704.

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Disclosure

None reported. **MM**

Morphometric Analysis of Pyramidalis Muscle in Midwestern Americans: A Cadaveric Approach

by Samantha Hutzley, BS, Erin Ruden, MS, Kasey Vanden Bosch, MS, Brynn Schubert, BS & Shanu Markand, PhD

The findings of this study highlight the clinical importance of variations in the presence and morphometric characteristics of the pyramidalis muscle.



Samantha Hutzley, BS, **Erin Ruden, MS**, Kasey Vanden Bosch, MS, are medical students, Brynn Schubert, BS, is a biomedical sciences student, and Shanu Markand, PhD, (above), is in the Department of Anatomy; all are at A.T. Still University, Kirksville College of Osteopathic Medicine, Kirksville, Missouri.

Abstract

The pyramidalis muscle (PM) is an abdominal muscle with unclear function. The current study determined the presence of the PM in Midwestern American cadavers. Of 33 cadavers, 22 had bilateral PM (12 [54.5%] female, 10 [45.5%] male). Overall, variation was observed in PM measurements with a mean length of 1.7 inches, and a mean width of 0.3 inches. Results highlight variations in the presence and morphometric characteristics of the PM, suggesting underlying clinical implications.

Introduction

The pyramidalis muscle (PM) is a triangular muscle that is positioned anterior to the distal rectus abdominis muscle and is within the rectus sheath.[1] Its inferior attachments include tendinous fibers to the superior pubis and ligamentous fibers to the anterior pubic symphysis. Superiorly, it diminishes in size and ends as a pointed apex that attaches medially at the linea alba between the pubis and umbilicus.[1] The PM receives its vascular supply from branches of the inferior epigastric artery.[1] Innervation is highly variable, ranging from the ventral rami of T12-L2 spinal nerves, with fibers traveling in anterior cutaneous branches of the subcostal nerve or the ilioinguinal nerve or in the genital branch of the genitofemoral nerve.[2] The PM is thought to have a role in tensing the linea alba[1]; however, its exact physiological role is unclear, and no dysfunction is observed in its absence.[3]

The prevalence and morphometric variations of the PM are not well documented in the literature. Its reported prevalence ranges from as low as 30%[4] to 100%,[5] but there is limited data on variability between sexes and ethnic groups. Moreover, the majority of previous studies focused on Asian and European populations.[6] Although the physiological role of the PM is unclear, it has many clinical applications. For example, the PM may be an ideal candidate for using a small muscle-free flap[3] to create a myofascial sling to improve urethral sphincter incompetence,[7] and its cells

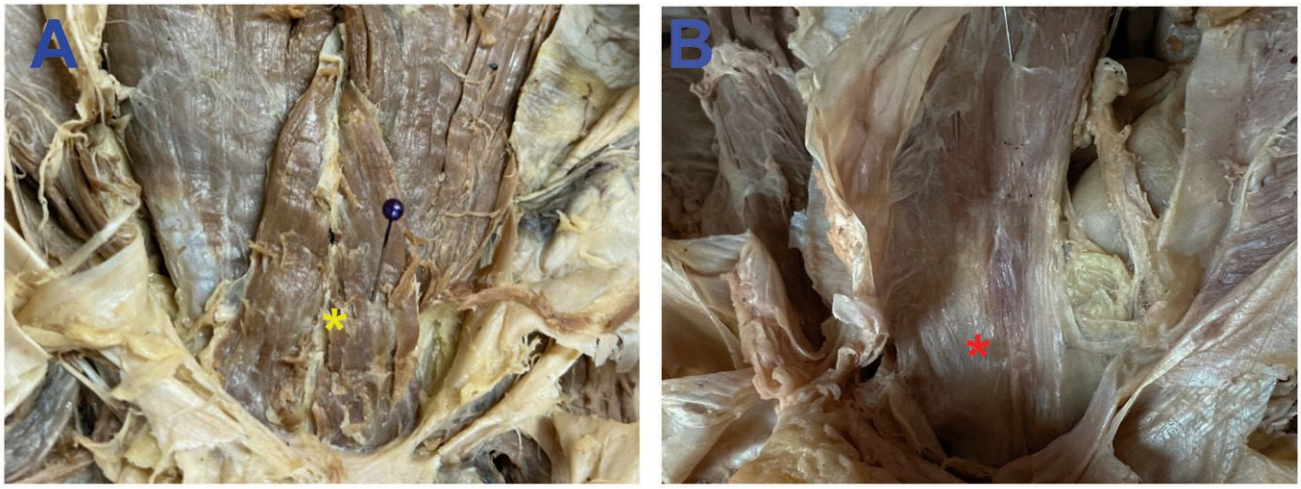


Figure 1. Presence or Absence of the Pyramidalis Muscle in Midwestern American Cadavers
A, Pyramidalis muscle bilaterally present, indicated by a blue pinhead and yellow asterisk.
B, Pyramidalis muscle absent, indicated by a red asterisk. The anterior abdominal region is shown.



Figure 2. Unilateral Presence of the Pyramidalis Muscle on the Right Side in a Single Cadaver Indicated by a purple pinhead.

may be cryopreserved and used as a source of stem cells to improve post-prostatectomy stress urinary incontinence.[8] The PM is frequently encountered by surgeons and often used as a midline landmark for incisions in the lower abdominal wall.[9] This muscle may also affect athletic groin pain through the pyramidalis–anterior pubic ligament–adductor longus complex.[5] Therefore, the purpose of the current study was to determine the presence of the PM in Midwestern American cadavers. Specifically, we wanted to assess the prevalence and morphological variability of the PM and investigate differences in outcomes between female and male cadavers.

Methods

The current study was conducted as part of a gross anatomy dissection course and used donor bodies of Midwestern Americans from the Gift of Body Program at A.T. Still University's Kirksville College of Osteopathic Medicine. All procedures in the current study were considered exempt by the A.T. Still University-Kirksville Institutional Review Board.

For dissection of the PM, a midline incision was made from the xiphoid process to the pubic symphysis. Skin, fat, and other subcutaneous tissues were removed to visualize the rectus sheath. The rectus sheath was then transected horizontally

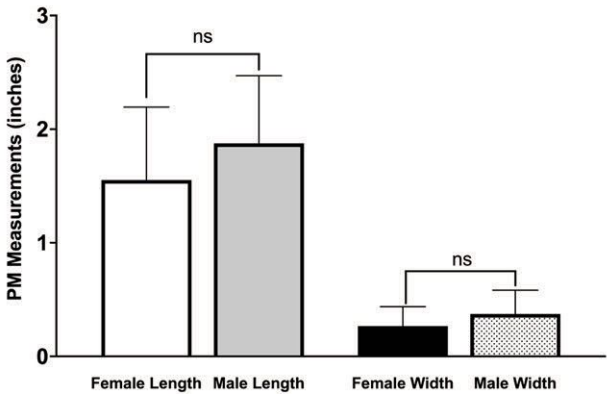


Figure 3. Variations in the Length and Width of the Pyramidalis Muscle in Midwestern American Cadavers. Length and width were measured with a caliper in inches. Data are reported as mean and standard deviation. An unpaired t test found no significant (ns) differences in the length or width of the pyramidalis muscle (PM) between females and males (both P>.21).

just lateral to the umbilicus bilaterally and vertically at the medial margin, leaving the linea alba intact. This vertical incision was extended inferiorly to the pubic symphysis. The rectus abdominis muscle was separated from the rectus sheath using blunt dissection, exposing the PM on its anterior inferior surface. The presence or absence of the PM on both sides was noted (Figure 1), and calipers were used to measure the maximum length and width in inches. The maximum length was measured from the insertion of the PM on the pubic crest to the muscle apex, and width was measured at the widest part of the muscle.

Statistical Analysis

The presence or absence of the PM was summarized using frequency and percentage for the overall sample and for female and male cadavers. Data for length and width were analyzed using mean and standard deviation (SD). An unpaired *t* test with Welch's correction was used to determine whether there were differences in PM length and width between females and males. Data were analyzed using GraphPad Prism software version 6 (GraphPad Software Inc., La Jolla, CA). A $P \leq .05$ was considered significant.

Results

Thirty-three cadavers (15 [45.5%] female, 18 [54.5%] male) of Midwestern Americans were included in the current study. Age at death ranged from 29 to 96 years. Bilaterally, the presence of the PM was observed in 22 (66.7%) cadavers. Of those, 12 (54.5%) were female and 10 (45.5%) were male. The PM was observed more frequently in females (12/15, 80.0%) than in males (10/18, 55.6%). There was 1 (4.5%) occurrence of a unilateral PM on the right side in a male (Figure 2).

The length and width of the PM varied among cadavers. Overall, the mean (SD) length was 1.7 (0.6) inches, and the mean (SD) width was 0.3 (0.1) inches. In females, the mean (SD) length was 1.6 (0.6) inches, and the mean (SD) width was 0.3 (0.2) inches (Figure 3). In males, the mean (SD) length was 1.9 (0.4) inches, and the mean (SD) width was 0.4 (0.08) inches. When comparing these outcomes between females and males, no differences were found for length (P=.24) or width (P=.21).

Discussion

In the current study, we wanted to determine the presence of the PM in Midwestern American cadavers. We identified the PM in 66.7% of our 33 cadavers. In previous studies,[4-6] the presence of the PM was highly variable (30%-100%). In a 2020 systematic review and meta-analysis,[6] the reported presence of the PM was 82.3%, which is higher than our 66.7%. That study[6] also found significant heterogeneity among racial and ethnic groups, and the highest frequency of the PM (100%) was reported in a small study (N=7) of North Americans. In the current study, the presence of the PM occurred more often in females (80.0%) than in males (55.6%). This finding differed from previous studies investigating Indian[10] and Kenyan[11] cadavers but supported studies of Greek[12] and Brazilian[13] cadavers.

Few studies have evaluated morphometric characteristics of the PM in Americans. Instead, most studies have investigated these characteristics in the Asian, European, and

South American populations.[6] Although our measured PM morphometric characteristics were variable, we found no statistically significant differences between females and males, which was congruent with other studies.[12-14] Our observed variations in the size of the PM were also consistent with other studies.[6]

A better understanding of the anatomy of the PM is important for clinical implications. For example, the PM is used as a muscle flap for foot and ankle injuries,[3] as a myofascial bladder sling for improvement of urethral sphincter competence,[7] and as a source of muscle stem cells.[8] Therefore, since variations in the morphometric characteristics seem to be common, these variations must be considered for clinical applications.

A limitation of the current study was the smaller sample size. Further, the PM measurements in cadavers may not represent physiologically because of embalming effects on the muscle tissue. However, the current study highlights the importance of anatomical variation in the PM and adds value to our current understanding of the anatomy of this muscle. Future studies should focus on combining cadaveric studies with different imaging modalities.

Conclusion

In the current study, the PM was found in two-thirds of our Midwestern American cadavers, and more females than males had the PM. Of those cadavers with the PM, the length and width of the muscles varied but were not statistically significant between the sexes. These findings highlight the clinical importance of variations in the presence and morphometric characteristics of the PM. Given that the physiological role of the PM is unclear, our results may elucidate the function of this muscle and explain why no physiological dysfunction is observed when it is absent.

References

1. Standring S, ed. Gray's Anatomy: The Anatomical Basis of Clinical Practice. 41st ed. Elsevier Limited; 2016.
2. Tokita K. Anatomical significance of the nerve to the pyramidalis muscle: a morphological study. Anat Sci Int. 2006;81(4):210-224. doi:10.1111/j.1447-073x.2006.00148.x
3. Van Landuyt K, Hamdi M, Blondeel PH, Monstrey S. The pyramidalis muscle free flap. Br J Plast Surg. 2003;56(6):585-592. doi:10.1016/s0007-1226(03)00211-x
4. Dickson MJ. The pyramidalis muscle. J Obstet Gynaecol. 1999;19(3):300. doi:10.1080/01443619965138
5. Schilders E, Bharam S, Golan E, et al. The pyramidalis–anterior pubic ligament–adductor longus complex (PLAC) and its role with adductor injuries: a new anatomical concept. Knee Surg Sports Traumatol Arthrosc. 2017;25(12):3969-3977. doi:10.1007/s00167-017-4688-2
6. Cirocchi R, Cheruiyot I, Henry BM, et al. Anatomical variations of the pyramidalis muscle: a systematic review and meta-analysis. Surg Radiol Anat. 2020;43(4):595-605. doi:10.1007/s00276-020-02622-4
7. Mingin GC, Youngren K, Stock JA, Hanna MK. The rectus myofascial wrap in the management of urethral sphincter incompetence. BJU Int. 2002;90(6):550-553. doi:10.1046/j.1464-410x.2002.02973.x.
8. Sumino Y, Hirata Y, Hanada M, Akita Y, Sato F, Mimata H. Long-term cryopreservation of pyramidalis muscle specimens as a source of striated muscle stem cells for treatment of post-prostatectomy stress urinary incontinence. Prostate. 2011;71(11):1225-1230. doi:10.1002/pros.21338
9. Skandalakis JE, Skandalakis PN, Skandalakis LJ. Surgical Anatomy and Technique: A Pocket Manual. 2nd ed. Springer; 2000.
10. Das SS, Saluja S, Vasudeva N. Biometrics of pyramidalis muscle and its clinical importance. J Clin Diagn Res. 2017;11(2):AC05-AC07. doi:10.7860/jcdr/2017/24179.9276
11. Kipkorir V, Olabu B, Ongeti K, et al. Prevalence and pubo-umbilical index of pyramidalis muscle in a select Kenyan population. Surg Radiol Anat. 2021;43(9):1461-1466. doi:10.1007/s00276-021-02733-6
12. Natsis K, Piagkou M, Repousi E, et al. Morphometric variability of pyramidalis muscle and its clinical significance. Surg Radiol Anat. 2015;38(3):285-292. doi:10.1007/s00276-015-1550-4
13. Hojaij FC, Kogima RO, Moyses RA, Akamatsu FE, Jacomo AL. Morphometry and frequency of the pyramidalis muscle in adult humans: a pyramidalis muscle's anatomical analysis. Clinics (Sao Paulo). 2020;75:e1623. doi:10.6061/clinics/2020/e1623
14. Kaur H, Singla RK, Brar RS, Singla M. Study of the morphometry of the pyramidalis muscle and its incidence in the Indian population. Int J Anat Res. 2016;4(2):2207-2211. doi:10.16965/ijar.2016.179

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Disclosure

None reported. **MM**

Medical Students' Diagnostic Accuracy and Treatment Plans

by Neal R. Chamberlain, PhD, Patricia S. Sexton, DHEd, Matthew R. Hardee, DO & Robert W. Baer, PhD

Diagnostic accuracy and treatment plans can depend on physician mentors, medical school curricula, patient diagnoses, and level of difficulty in differential development.



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Abstract

Physician-mentored patient rounds (PMPR) were used to assess diagnostic accuracy and treatment plans of preclinical medical students. During 4 PMPR sessions, students gathered patient history, observed a physical exam, analyzed diagnostic tests, and developed treatment plans for a patient with chronic obstructive pulmonary disease. Of 470 students, 99.4% correctly diagnosed the patient. Nearly 78% prescribed long-acting beta-agonists or long-acting muscarinic antagonists. Most included appropriate pharmacologic treatments. Only 47% included smoking cessation in their treatment.

Introduction

Adult learners want to know why they are learning something.[1-3] They also need to be motivated to learn and are more motivated when it occurs in the right context. For example, medical students want to know how their learning applies to the things they will do as physicians.[4] Students correctly answering a multiple-choice question about the diagnosis and treatment of chronic obstructive pulmonary disease (COPD) does not guarantee that they will be able to diagnose and treat a patient presenting with COPD. Although clinical vignettes provide history and physical exam findings, they cannot determine whether a student can obtain that information from a patient. A goal of physician-mentored patient rounds (PMPR) is to provide students with a relevant means to practice history taking, use physical exam findings, order diagnostic tests, and develop differential diagnoses and treatment plans in a clinical context. Students need practice thinking clinically, and PMPRs provide a way to practice these skills.

While students apply their knowledge and skills, educators use PMPR data to observe preclinical students' clinical reasoning and provide feedback. Information about these clinical abilities can also be given to preceptors so that they are aware of clinical test ordering abilities, diagnostic reasoning capabilities, and treatment biases of students.

In a previous study, we reported which resources medical students used after a PMPR.[5] Although most used appropriate resources, students rarely used textbooks when searching for information.[5] In another study, we observed that almost all preclinical students can

narrow their differential diagnoses list to the most likely diagnosis.[6] The current study was conducted to determine whether preclinical students order appropriate tests, determine the correct diagnosis for a COPD patient, and develop an appropriate treatment plan according to published guidelines.[7] We believe such data from PMPRs will also provide preceptors with important knowledge about the abilities of preclinical medical students.

Methods

The current study used a nonexperimental design and a convenience sample of second-year medical students from 3 classes at a single osteopathic medical school.[6] The PMPR occurred during the fall semesters of 2016, 2017, and 2018 (classes of 2019-2021). The class of 2019 had not participated in a PMPR, but both classes of 2020 and 2021 had participated 2 previous PMPRs. The protocol for the study was reviewed by the local institutional review board and was exempted from further review. The same patient and physician participated in the PMPR. The patient gave informed consent to participate and to have their medical information used during the PMPR.

Physician-Mentored Patient Rounds

The PMPR occurred over 4 weeks (one 30-minute session per week) and has been previously described.[6,8] During the study, all classes followed a patient with chief complaints of chronic cough, shortness of breath, sputum production, and a 30 pack-year history of smoking. The patient had a FEV_1/FVC ratio (forced expiratory volume in 1 second to forced vital capacity) of 0.41 post-bronchodilator, a predicted FEV_1 of 0.79, no history of exacerbations requiring hospitalization, and a COPD assessment test score of less than 10 according to the Global Initiative for Chronic Obstructive Lung Disease classification (GOLD 2A).[7]

Each PMPR occurred in a room that accommodated 172 students. The patient was present in the room and participated during sessions 1 and 2. During session 1, the students obtained the patient's history by asking the patient questions. During session 2, the students observed a physician-modeled physical exam of the patient. The physician asked the students for the types of physical exams they wanted the physician to perform. After obtaining patient permission, the physician performed the requested exam and told the class what they found. After the history and physical exam sessions, students were asked to order diagnostic tests (laboratory tests, procedures, and imaging). Diagnostic test results were provided in session 3. At the end of session 3, students were asked to provide a most likely diagnosis and develop a treatment plan. During session 4, the most likely diagnosis was determined, appropriate treatment plans were identified, and management of the patient's care was discussed. Before the PMPR, students had been previously exposed to the 2018 GOLD guidelines in their internal medicine course.[7] Specifically, they were taught the 2018 GOLD guidelines for treatment of a COPD patient with a GOLD 2A classification. The 3 types of recommended treatments include the following:

1. Short-term treatment with short-acting beta-agonists (SABA) or short-acting muscarinic antagonists (SAMA),
2. Long-term treatment with long-acting beta-agonists (LABA) or long-acting muscarinic antagonists (LAMA),
3. Nonpharmacologic treatments, such as smoking cessation, pulmonary rehabilitation, self-management (lifestyle changes), avoidance of irritants/allergens, and vaccinations.

Students were required to sign in to the PMPR by scanning a QR code on their electronic devices. Each session had a unique QR code, and faculty were present to prevent students from signing in for other students.

Physician-Mentored Patient Round Assignments

To obtain credit for the PMPR, students were required to attend each PMPR session and submit assignments. Students received Google Form assignments by email 2 hours after each session. Students had 3 days to submit each assignment. Students estimated the time they spent on assignments and submitted the time spent using the Google Form.

Table 1. Diagnostic Tests Ordered by Students After Physician-Mentored Patient Round Session 2

Diagnostic Test	No. Students Ordering Test (%)
Laboratory test	
Complete blood count	417 (89)
Metabolic panel	292 (62)
Arterial blood gas	172 (37)
D-dimer	115 (24)
Brain natriuretic peptide	114 (24)
Purified protein derivative (Mantoux test)	50 (11)
Alpha-1-antitrypsin	39 (8)
Sputum culture	31 (7)
Troponin	30 (6)
Cardiac enzymes	30 (6)
Hemoglobin A1C	19 (4)
C-reactive protein	14 (3)
Lipid panel	14 (3)
Urinalysis	8 (2)
None	8 (2)
Procedure	
Pulmonary function testing	428 (91)
Electrocardiogram	270 (58)
Echocardiogram	65 (14)
Cardiac stress testing	53 (11)
None	17 (4)
Allergy testing	15 (3)
Imaging	
Chest radiograph	393 (84)
Chest computed tomography	170 (36)
Echocardiogram	102 (22)
Ultrasound of chest	47 (10)
None	5 (1)

During session 2, students were asked to develop a differential of 5 diagnoses and to order diagnostic tests based on their differential. Student responses were aggregated into a database, analyzed, and summarized for the physician to give feedback during the subsequent session. Summarized feedback was converted into histogram graphs. Figure construction and conversion to PowerPoint (Microsoft) was performed using R statistical software.[9]

During session 3, the physician provided feedback data from the diagnostic tests and asked the students to narrow the differential to the most likely diagnosis and develop a treatment plan. Students were asked the following questions to facilitate development of their treatment plans:

1. What short-term medications would you order for this?
2. What long-term medications would you order for this patient?
3. What nonpharmacologic treatments would you order for this patient?

Statistical Analysis

Student data were de-identified before analysis, and a unique identifier was given to each student to match student responses across sessions. The current study included the analysis of the assignments from sessions 2 and 3, where students ordered diagnostic tests, determined the most likely diagnosis, and provided a treatment plan. Descriptive statistics (mean [SD]) were used to quantify class attendance and to determine the mean time spent on assignments. All other data were summarized using frequency and percentage.

Results

Data from 470 students were included in the study. The total number of students in the classes of 2019, 2020, and 2021 was 516 (172 students/class). Attendance and assignment completion for sessions 2 and 3 were not mandatory but gave students an opportunity to obtain points for their internal medicine course (0.45% of total points in course).[6,7]

Table 2. Short-Term Pharmacologic Treatments Suggested by Students After Physician-Mentored Patient Round Session 3

Pharmacologic Treatment	No. Students (%)
Albuterol[a]	380 (79)
Ipratropium[a]	40 (8)
SABA[b]	22 (5)
None	19 (4)
Levalbuterol[a]	6 (1)
ICS[b]	6 (1)

Treatments in bold are included in the GOLD guidelines for a patient with COPD GOLD 2A.[7]
[a]Albuterol and levalbuteral are short-acting beta-agonists; ipratropium is a short-acting muscarinic antagonist.
[b]Students used the abbreviation rather than giving the drug name.
Abbreviations: ICS, inhaled corticosteroids; SABA, short-acting beta-agonist.

Table 3. Long-Term Pharmacologic Treatments Suggested by Students After Physician-Mentored Patient Round Session 3

Pharmacologic Treatment	No. Students (%)
Tiotropium[a]	190 (40)
Salmeterol[a]	152 (32)
Indacaterol[a]	35 (7)
Fomoteral[a]	30 (6)
Fluticasone[b]	18 (4)
Budesonide[b]	10 (2)
LABA or LAMA[c]	10 (2)
ICS[c]	8 (2)
Albuterol[d]	6 (1)
None	6 (1)
Roflumilast	4 (0.9)
ICS + LABA or LAMA[c]	4 (0.9)

Treatments in bold are included in the GOLD guidelines for a patient with COPD GOLD 2A.[7]
[a]Salmeterol, indacaterol, and fomoteral are long-acting beta-agonists; tiotropium is a long-acting muscarinic antagonist.
[b]Fluticasone and budesonide are inhaled corticosteroids.
[c]Students used the abbreviation rather than giving the drug name.
[d]Albuterol is a short-acting beta-agonist.
Abbreviations: ICS, inhaled corticosteroids; LABA, long-acting beta-agonists; LAMA, long-acting muscarinic antagonists.

Overall, 91.1% of students attended and completed assignments for sessions 2 and 3. The mean student assignment completion time was 33.6 (16.8) minutes. The maximum time was 150 minutes, and the minimum time was 5 minutes.

Students' Diagnostic Test Orders

For the session 2 assignment, all students included a diagnosis associated with the patient's cardiovascular or pulmonary system.

All but 8 students ordered at least 1 laboratory test (Table 1). The most commonly ordered laboratory tests were a complete blood count (89%, 417/470) and metabolic panel (292/470, 62%) followed by arterial blood gas (37%, 172/470), D-dimer (24%, 115/470), and brain natriuretic peptide (24%, 114/470). Students ordered a mean of 2.9 tests with a median of 3 tests (range=0-9).

All but 17 students ordered at least 1 diagnostic procedure (Table 1). The most commonly ordered procedures were pulmonary function testing/spirometry (91%, 428/470) and electrocardiogram (58%, 270/470). Students ordered a mean of 1.8 tests with a median of 2 tests (range=0-5).

All but 5 students ordered at least 1 imaging test (Table 1). The most commonly ordered imaging tests were a chest radiograph (84%, 393/470) and chest computed tomography (36%, 170/470) followed by an echocardiogram (22%, 102/470). Students ordered an average of 1.8 tests with a median of 2 tests (range=0-5).

Students' Diagnostic Accuracy

For the session 3 assignment, nearly all students (99.4%, 467/470) chose COPD, emphysema, or chronic bronchitis as their most likely diagnosis. Three students chose histoplasmosis, pneumoconiosis, or sarcoidosis.

Table 4. Nonpharmacologic Treatments Suggested by Students After Physician-Mentored Patient Round Session 3

Nonpharmacologic Treatment	No. Students (%)
Smoking cessation	222 (47)
Pulmonary rehabilitation	132 (28)
Supplemental oxygen	90 (19)
None	72 (15)
Self-management (lifestyle changes)	71 (15)
Avoidance of irritants/allergens	54 (11)
Vaccine (influenza)	38 (8)
Vaccine (pneumococcal)	35 (7)
BiPAP or CPAP	18 (4)
Education	14 (3)
Lung resection or lung transplant	13 (3)
Vaccines (not specified)	6 (1)
Miscellaneous others	6 (1)
Osteopathic manipulative treatment (high-velocity, low-amplitude treatment for thoracic somatic dysfunctions)	2 (0.4)
Occupational or physical therapy	2 (0.4)
Osteopathic manipulative treatment (rib raising)	1 (0.2)

Treatments in bold are included in the GOLD guidelines for a patient with COPD GOLD 2A.[7]
Abbreviations: BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure.

Students' Treatment Plans

Based on the patient's history, physical exam, and diagnostic test results, the patient was diagnosed and classified as a patient with COPD GOLD 2A (MRH).[7] Overall, 26% (122/470) of students mentioned the GOLD guidelines when defending their most likely diagnosis and treatment plan.

Nearly all students (94.7%, 445/470) ordered appropriate short-term pharmacologic treatments for the patient (Table 2). Some suggested no short-term treatment (4%, 19/470). A small number of students included inhaled corticosteroids (ICS) in their short-term treatment plans (1%, 6/470).

Most students (87.8%, 412/470) ordered long-term pharmacologic treatments for this patient as recommended in the 2018 GOLD treatment guidelines[7] (Table 3). Some suggested monotherapy with ICS (1.7%, 8/470). A few students suggested no treatment (1.3%, 6/470). Other students suggested treatments used in more severe cases of COPD: ICS (7.6%, 40/470) and roflumilast 0.9% (4/470). The nonpharmacological treatment of supplemental oxygen (19%, 90/470) was also suggested (Table 4).

Although 5 different nonpharmacologic treatments are recommended by the 2018 GOLD guidelines,[7] 15% (70/470) of students did not include a nonpharmacologic treatment in their plan (Table 4). Most students (80%, 376/470) included 1-3 nonpharmacologic treatments in their plan. Smoking cessation (47%, 222/470) and pulmonary rehabilitation (28%, 132/470) were the most common treatments suggested. Of other nonpharmacologic treatments, 15% (71/470) suggested self-management, 17% (80/470) suggested vaccination, 11% (54/470) suggested avoidance of irritants/allergens, and 2.8% (13/470) suggested lung resection/transplant in their plans.

Five students included 5 nonpharmacologic treatments in their plans, and only 1 student included all 5 of the nonpharmacologic treatments recommended by the 2018 GOLD guidelines.[7] Four students suggested supplemental oxygen instead of one of the recommended treatments.

A few students (0.6%, 3/470) included osteopathic manipulative therapy (OMT) in their plans (Table 4). Suggested OMT treatments included rib raising (1 student) and high-velocity, low-amplitude treatments for thoracic somatic dysfunctions (2 students). Six students suggested an osteopathic manipulative medicine consult.

Discusion

The PMPR sessions of the current study were developed to give preclinical medical students a

better context for their learning.[4] It also gave students an opportunity to practice applying information they were learning in class. For example, students asked the patient questions during the history taking. They proposed exams during the physical exam, and they ordered diagnostic tests and analyzed the data. From that information, they were able to complete the assignments of developing a differential diagnosis, choosing a most likely diagnosis, and creating a treatment plan. The PMPR sessions also allowed us to observe the ability of students to apply learned knowledge. Further, we were able to observe which parts of the history, physical exam, and diagnostic testing were important to students, resulting in a baseline measure of our students' diagnostic test ordering abilities, diagnostic accuracy, and ability to develop treatment plans. Importantly, the PMPR provided a glimpse into what our students may apply when they encounter a patient in the real world.

Most students did not order an excessive number of diagnostic tests. They averaged 3 laboratory tests, 2 procedures, and 1 imaging test. Since students did not know the patient's symptoms were due to a lung pathology, tests to rule out cardiovascular pathologies were warranted. A marked number of students ordered cardiac enzyme levels (174 students), electrocardiograms (270 students), and echocardiograms (167 students). Because we incorporate ultrasound in our first-year and second-year curricula, that may explain why 47 students ordered a chest ultrasound.

When a patient is experiencing dyspnea, chronic cough, or sputum production and has a history of exposure to risk factors, COPD should be included in a student's differential diagnosis.[7] In our PMPR, the patient had dyspnea, chronic cough, sputum production, and a history of smoking cigarettes. Further, to definitively diagnose COPD, spirometry is required. Over 90% of students ordered spirometry or pulmonary function testing, but over 95% ordered chest radiographs and computed tomography. Even though chest radiographs and computed tomography cannot be used to make a COPD diagnosis, nearly all students ordered at least 1 of these tests. Perhaps they chose these 2 tests because they reveal the extent of existing lung damage. At this stage in their education, some students may still be unable to distinguish between tests required for diagnosis and tests that clarify the patient's current disease state. Although preceptors may be frustrated when students order diagnostic tests that do not facilitate diagnosis, they should consider that the students are not aware of the differences between these types of tests.

Even though most students did not order the essential test for diagnosis of COPD (spirometry), nearly all of them were able to identify the most likely diagnosis. The physician provided the results of the patient's pulmonary function tests in session 3, which may explain this result. However, 3 students chose a diagnosis other than COPD. Their differential diagnoses for sessions 1 and 2 included COPD, emphysema, and chronic bronchitis. When these students were asked during session 3 to give their most likely diagnosis, they suggested something else. One student switched because the patient was exposed to asbestos. Even though pulmonary function testing indicated the patient had obstructive airway disease, the student settled on a diagnosis of pneumoconiosis. The 2 remaining students settled on the diagnoses of histoplasmosis and sarcoidosis because of something they saw in the chest radiograph. Although word associations are commonly used in medical education (eg, asbestos and pneumoconiosis), they may result in the wrong diagnosis when given more weight than patient data. Therefore, as students enter clerkships, preceptors should be aware that some may disregard patient data because they rely too heavily on word associations.

The PMPR of the current study allowed us to see whether students applied their course content during a clinical encounter. During the PMPR, the physician mentor asked students to interpret diagnostic test results, and nearly all of them were able to apply what they had learned in class about pulmonary function testing to identify the obstructive nature of the patient's

condition. Further, they successfully applied their internal medicine knowledge and used the GOLD guidelines to classify their patient and justify treatment. Even though they were not asked to classify the patient according to GOLD guidelines, 26% (122/470) mentioned the GOLD guidelines in their assignment.

The PMPR also indicated the types of treatments that students considered appropriate. Most students prescribed appropriate pharmacologic agents, and they usually suggested the medications taught in their pharmacology and internal medicine courses. When asked which resources they used to develop their treatment plans, most indicated they used lecture notes from these 2 courses (data not shown). When students suggested treating the patient with short-term medications, over 90% selected a SABA or SAMA for the patient. Even though the pharmacology lecturer stated COPD patients experience little benefit from ICS monotherapy,[10] a few students prescribed it. When students did not suggest a SABA or SAMA, it was generally because they thought long-acting agents would be more beneficial. For long-term treatments, almost 90% of students selected a LABA or LAMA. About 10% of students did not suggest any long-term treatment, instead prescribing monotherapy with ICS, a SABA, or roflumilast.

It was also informative to see which nonpharmacologic treatments students suggested in their treatment plans. Less than half suggested smoking cessation even though the patient currently smoked 1 pack of cigarettes/day, and just over a quarter suggested pulmonary rehabilitation. Studies have shown smoking cessation, pulmonary rehabilitation, self-management, avoidance of irritants/allergens, and vaccinations (pneumococcal and influenza) slow the progression of COPD.[11-15] Even though students were aware of these 5 nonpharmacologic treatments recommended by 2018 GOLD guidelines,[7] only 1 of 470 students included all 5 in their plan. Further, 15% did not suggest any nonpharmacologic treatments. Most students included 1-3 nonpharmacologic treatments in their plans. Fortunately, the 2 treatments with the most evidence for slowing progression of COPD, smoking cessation and pulmonary rehabilitation, were the most commonly suggested treatments. Surprisingly, just over 15% of students included vaccinations in their plans. Since these 3 classes of students started medical school, prevention of illness has been increasingly emphasized in our curriculum, yet when given the opportunity to apply this knowledge many students did not.

In addition to omitting important nonpharmacologic treatments, some students included treatments that are better for later stages in the disease process. Almost 20% of students suggested supplemental oxygen in their treatments even though they did not know whether the pharmacologic and nonpharmacologic treatments would improve the patient's condition. There are several possible explanations for this finding. Currently, our institution does not have a course that focuses solely on nonpharmacologic treatments. As such, nonpharmacologic treatments are mentioned in conjunction with pharmacologic treatments during the internal medicine course. Further, this result suggests more time is spent on pharmacologic treatments in the pharmacology and internal medicine courses. Therefore, our students may place higher importance on pharmacologic treatments than on nonpharmacologic treatments. In addition, students may lack experience with modifying treatment plans when patients do not respond to treatment or progress in their disease process in spite of treatment. Even in clerkships, the ability to modify treatment plans can be difficult for preceptors to model.[18] Unfortunately, lack of experience with managing the care of chronic conditions is common, and it is often a difficult clinical experience for students to encounter. In session 4 of the PMPR, the physician mentor discussed long-term management of a COPD patient and the importance of

nonpharmacologic treatments, like smoking cessation.

Although studies reporting the use of OMT in the treatment of COPD patients are mixed,[16,17] a small number of students suggested OMT in their treatment plans. This finding may reflect the uncertainty of using OMT for COPD.

Conclusion

The current study had several limitations. The study was conducted at a single medical school, so results may not apply to other institutions. Further, only 1 physician mentor led all PMPR sessions, and only 1 patient diagnosis was used. Diagnostic accuracy and treatment plans may depend on physician mentors, medical school curricula, patient diagnoses, and level of difficulty in differential development.[19] Therefore, results may not be generalizable and should be interpreted with caution.

References

1. Knowles MS. The Adult Learner. Vol 44. Routledge; 2014. doi:10.4324/9781315816951
2. Wlodkowski RJ, Ginsberg MB. Enhancing Adult Motivation to Learn: A Comprehensive Guide for Teaching All Adults. 4th ed. San Francisco: Jossey-Bass; 2017.
3. Palis A, Quiros P. Adult learning principles and presentation pearls. Middle East Afr J Ophthalmol. 2014;21(2):114-122. doi:10.4103/0974-9233.129748
4. Berkhout JJ, Helmich E, Teunissen PW, van der Vleuten CPM, Jaarsma ADC. Context matters when striving to promote active and lifelong learning in medical education. Med Educ. 2018;52(1):34-44. doi:10.1111/medu.13463
5. Chamberlain NR, Sexton PS, Hardee MR, Baer RW. Resources utilized by preclinical medical students during patient morning rounds. Med Sci Educ. 2016;26(3):283-286. doi:10.1007/s40670-016-0279-y
6. Chamberlain NR, Sexton PS, Hardee MR, Baer RW. Physician-mentored patient rounds to observe and assess entrustable professional activities 1 and 2 in preclinical medical students. J Am Osteopath Assoc. 2018;118(3):199-206. doi:10.7556/jaoa.2018.039
7. Augusti AG, Vogelmeier C. Global Initiative for Chronic Obstructive Lung Disease: Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease 2018 Report. Published 2018. Accessed October 25, 2022. https://goldcopd.org/archived-reports/
8. Chamberlain NR, Sexton PS, Hardee MR, Baer RW. Use of large-group patient rounds to characterize pre-clerkship medical students' ability to perform three entrustable professional activities. Med Sci Educ. 2016;26(3):481-489. doi:10.1007/s40670-016-0265-4
9. R CoreTeam. R: a language and environment for statistical computing. Accessed October 25, 2022. https://www.r-project.org/.
10. Tashkin DP, Strange C. Inhaled corticosteroids for chronic obstructive pulmonary disease: what is their role in therapy? Int J Chron Obstruct Pulmon Dis. 2018;13(6):2587-2601. doi:10.2147/COPD.S172240
11. van Eerd EA, van der Meer RM, van Schayck OC, Kotz D. Smoking cessation for people with chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2016;(8):CD010744. doi:10.1002/14651858.CD010744.pub2
12. Casaburi R, Kukafka D, Cooper CB, Witek TJ, Kesten S. Improvement in exercise tolerance with the combination of tiotropium and pulmonary rehabilitation in patients with COPD. Chest. 2005;127(3):809-817. doi:10.1378/chest.127.3.809
13. Obaseki DO, Erhabor GE, Gnatiuc L, Adewole OO, Buist SA, Burney PG. Chronic airflow obstruction in a Black African population: results of BOLD study, Ile-Ife, Nigeria. COPD. 2016;13(1):42-49. doi:10.3109/15412555.2015.1041102
14. Walters JA, Smith S, Poole P, Granger RH, Wood-Baker R. Injectable vaccines for preventing pneumococcal infection in patients with chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2010;(11):CD001390. doi:10.1002/14651858.CD001390.pub3
15. Lopez AD, Shibuya K, Rao C, et al. Chronic obstructive pulmonary disease: current burden and future projections. Eur Respir J. 2006;27(2):397-412. doi:10.1183/09031936.06.00025805
16. Simonelli C, Vitacca M, Vignoni M, Ambrosino N, Paneroni M. Effectiveness of manual therapy in COPD: a systematic review of randomised controlled trials. Pulmonology. 2019;25(4):236-247. doi:10.1016/j.pulmoe.2018.12.008
17. Cicchitti L, Martelli M, Cerritelli F. Chronic inflammatory disease and osteopathy: a systematic review. PLoS One. 2015;10(3):e0121327. doi:10.1371/journal.pone.0121327
18. Wagner EH, Austin BT, Davis C, Hindmarsh M, Schaefer J, Bonomi A. Improving chronic illness care: translating evidence into action. Health Aff. 2001;20(6):64-78. doi:10.1377/hlthaff.20.6.64
19. Elstein AS. Evidence base of clinical diagnosis: clinical problem solving and diagnostic decision making: selective review of the cognitive literature. BMJ. 2002;324(7339):729-732. doi:10.1136/bmj.324.7339.729

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Conflict of Interest: The authors declare that they have no conflict of interest.

Ethical Approval: All procedures performed involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (A.T. Still University-Kirksville Institutional Review Board) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent: Informed consent was obtained from all individual participants included in the study. **MM**

Molecular Tumor Board Case Series: Targeted Treatments For Cancer And Their Toxicities: Amivantamab-Induced Linear IgA Bullous Dermatosis

by Lindsey Douglass, PharmD, Beth Gustafson, PharmD & Janakiraman Subramanian, MD

This case highlights the importance of close monitoring for toxicity in patients on targeted treatments.



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Abstract

In the era of targeted treatments based on next generation sequencing (NGS) analysis, clinicians must be diligent in aligning patients with treatments giving them the best chance of survival while weighing the risk of toxicity caused by agents targeting specific gene mutations. In this case, we describe a patient with Epidermal Growth Factor Receptor (EGFR) exon 20 insertion mutation positive recurrent lung adenocarcinoma who received amivantamab and experienced severe dermatologic toxicity.

Introduction

Epidermal growth factor receptor (EGFR) mutation affects approximately 32% of patients with non small cell lung cancer, most commonly in exons 18-21.[1] Mutations in this gene are more common in never- or light former smokers with adenocarcinoma histology.[1] Gefitinib was the first anti-EGFR tyrosine kinase inhibitor approved by the Food and Drug Administration (FDA) for advanced NSCLC in 2003, marking the beginning of EGFR-targeted treatments in NSCLC.[2] To date, five anti-EGFR therapies have been approved for use in NSCLC.[3]

Amivantamab-vmjw is a fully human bispecific antibody epidermal growth factor (EGF) and mesenchymal epithelial transition (MET)-directed antibody indicated for locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations who have progressed on or after platinum-based chemotherapy.[4] It was approved by the FDA under accelerated approval May 2021 based on the findings of the CHRYSALIS trial.[5] Patients were included in this clinical trial if they had metastatic or unresectable NSCLC and a qualifying EGFR or MET mutation or amplification, including EGFR exon 20 insertion mutation after progression with platinum-based chemotherapy. A total of 81 patients were assessed for efficacy, all of which had an EGFR exon 20 insertion mutation, and an overall response rate of 40% was observed with a median duration of response of 11.1 months. Rash was the most common adverse effect, with 86% of patients experiencing at least Grade 1 toxicity and 4% exhibiting Grade 3 or 4 rash. Of

the 15 patients that required dose reductions, 11 were due to rash. Two of five treatment-related discontinuations were due to rash.[5]

Case Presentation

The patient is a 64-year old Caucasian male with a past medical history of hyperlipidemia, hypertension, and hypothyroidism. He is a 10-pack year former cigarette smoker who quit in 1994. He was diagnosed with stage IB left lower lobe adenocarcinoma of the lung in June 2011 who was treated with lobectomy followed by adjuvant cisplatin and pemetrexed for four cycles. In 2014, disease of the right lower lobe was discovered, treated with a wedge resection, and determined to be stage IA. In 2017, he underwent radiation of the left upper lobe for increased avidity on PET scan. The patient was closely monitored until December 2020 when he had biopsy confirmed recurrent adenocarcinoma in the left lower lobe of the lung. His computed tomography (CT) chest and abdomen found continued slight enlargement of several pulmonary nodules and left mediastinal pleural nodularity.

Next generation sequencing (NGS) was performed on the biopsy specimen which revealed an EGFR exon 20 inframe insertion (EGFR p.D770_N771insGF), NKX2-1 copy number gain, PD-L1 negative. The patient was discussed at the molecular tumor board January 2021. At the time, there were no EGFR exon 20-targeted therapies FDA approved, so recommendations included clinical trials open for amivantamab and mobocertinib as well as off-label osimertinib. No clinical trials were available locally, so the decision was made to initiate off-label osimertinib. Osimertinib was well tolerated, but unfortunately by December 2021, CT scans showed disease progression in the chest with increasing left upper lobe nodularity and a slight increase in left pleural thickening with increased small pleural effusion. Osimertinib was stopped and decision was made to transition to amivantamab-vmjw.

He initiated amivantamab December 2021. His first infusion was interrupted by a grade 2 infusion reaction which resolved quickly with supportive care and was able to resume and complete his infusion without further incident. Premedications were escalated and no further infusion reactions occurred. The patient developed a grade 1 non-itching rash on his chest and back eight days after his initial amivantamab infusion that he treated with clindamycin topical gel that had been previously prescribed (Figures 1-4). A H1 antihistamine was also prescribed. When he presented to the clinic for cycle 1 day 22, the rash had spread to his face and had associated pruritus and redness. It remained grade 1, possibly grade 2. He was counseled on sun protection and amivantamab and clindamycin gel were continued.

His next provider visit occurred with cycle 2 day 15. His rash remained stable. The addition of minocycline and amivantamab dose reduction were discussed but ultimately the patient opted to continue treatment with no changes. A seven-day course of minocycline was prescribed six days later after the patient contacted the clinic requesting a medication to expedite rash healing which did not help in relieving symptoms so a course of azithromycin was prescribed.

When the patient presented to clinic for cycle 3 day one, his rash was noted to have worsened to a grade 3 erythematous maculopapular rash with scaling and crusting involving his face, scalp, and ears as well as a more mild rash on his upper back and chest. Amivantamab was held and the patient was initiated on cephalexin and a methylprednisolone dose-pack. A dermatology referral was also placed.

Dermatology assessed the patient eight days later and favored a drug-related eruption. A punch biopsy of the rash on the forehead which showed neutrophilic and chronic inflammation, most suggestive of linear IgA bullous dermatosis. Varicella zoster, herpes simplex virus, T. pallidum, acid fast bacteria, and fungal organism staining were all negative. Hydroxyzine was prescribed for itching.

Five days later due to treatment refractory rash, dapsone 50 mg and prednisone 0.5 mg/kg daily were initiated by the treating oncologist. One week later, improvement noted in his rashes and dapsone and prednisone were continued. The following week prednisone taper was initiated, and he remained on dapsone. His restaging scans showed stable disease in his chest and abdomen. His oncologist noted marked improvement in his rash at his most



Figure 1. Rash after two cycles of amivantamab



Figure 2. Rash four weeks after the last dose of amivantamab



Figure 3. Rash five weeks after the last dose of amivantamab, one week after dapsone and prednisone initiation



Figure 4. Rash four weeks after dapsone and prednisone initiation

recent office visit, approximately one-month post-initiation of dapsone and steroids; and prednisone will be tapered over the next month. Dapsone will continue for the next several weeks and be reassessed for discontinuation. His quality of life has been impacted due to the photosensitive nature of the rash and is primarily confined to his home. He maintains an ECOG performance status of 1 and has no other complaints. Due to the severity of rash, he will not be rechallenged with amivantamab.

Discussion

This is to our knowledge the first known reported case of linear IgA bullous dermatosis (LABP) in a patient exposed to amivantamab. In contrast to acneiform rash which is typically precipitated by EGFR inhibitors and characterized by superficial perifolliculitis and keratinocytic dysmataturation, LABP is a rare idiopathic or drug-induced autoimmune blistering disease characterized by the linear deposition of IgA at the dermoepidermal junction.[6] In most patients with LABP, the inciting factor is not known, although multiple case reports have documented drug exposure as a precipitating factor.[7]

The management of LABP includes dapsone, an immunomodulatory sulfone with a history of successful treatment in dermatologic disorders characterized by neutrophilic infiltrates.[8-9] Our patient, while refractory to standard therapies for EGFR inhibitor induced acneiform rash, responded well to dapsone treatment, with lessening of rash within one week of concomitant oral prednisone and dapsone.

Bispecific antibodies, such as amivantamab, are among the most promising therapeutic advances in cancer treatment. Bispecific antibodies are engineered antibodies with two distinct target antigens or epitopes.[10] In trials, amivantamab, the only currently approved bispecific antibody for solid tumors had an infusion reaction rate of 65% and rash of 86%, albeit ≥ Grade 3 in 3% and 4% respectively.[5] Notably, there was one reported case of toxic epidermal necrosis (TEN). Study authors hypothesized that a lack of selectivity against the wild-type EGFR and the bispecific nature of the drug may affect the safety profile of the drug.[5]

Cutaneous reactions, particularly skin rash, are the most common adverse effect of EGFR inhibitors, affecting nearly all patients receiving these agents. EGF receptors are expressed on epithelial tissue, skin, hair follicles, and along

the gastrointestinal tract. EGFR signaling results in cellular proliferation, migration, and differentiation and mutations often result in constitutively activated form, driving cancer growth. Rash often presents within the first few weeks of treatment initiation, peaks by four to six weeks, and most often present on the head and upper trunk.[11-12] Rashes are often tender, itchy erythematous papules which transform into pustules then that then crust. There is a lack of controlled trials, so treatment is primarily based on expert consensus. Common supportive care strategies include: use of mild soaps, thick, fragrance-free moisturizers and urea-based products, and avoiding irritants, sun exposure, and washing with hot water. Tetracycline antibiotics may be considered. For patients that develop rash, treatment with low-potency topical corticosteroids or clindamycin is indicated. Anti-histamines can be considered for pruritus. If patients require escalated therapy, tetracycline antibiotics are preferred if not already prescribed, ordering higher potency topical corticosteroids, and low dose isotretinoin. Short courses of corticosteroids may also be indicated if the rash does not improve.[11, 13] Patients should be monitored for and treated if they develop bacterial superinfection. If the rash is refractory, oral antibiotics with systemic corticosteroids should be implemented.[13] The amivantamab labeling suggests considering a dose reduction if a patient has persistent Grade 2 dermatologic toxicity after two weeks of supportive care.[4] For Grade 3 toxicity, amivantamab should be held, oral steroids initiated, and a dermatology evaluation should be considered.[4]

Conclusion

This case highlights the importance of close monitoring for toxicity in patients on targeted treatments. Agents granted accelerated review by the FDA may have reduced patient safety data due to limited total patient exposures compared to agents approved through the traditional process. These therapies require heightened awareness to quickly identify adverse events and initiate and escalate appropriate management. Open lines of communication with the patient are essential to ensure timely treatment to prevention of further decline.

Next generation sequencing and targeted therapies have revolutionized cancer treatment paradigms. However, targeted therapies have additional complications that must be considered when assessing the benefit of initiating these treatments. Our patient was able to receive two cycles of treatment before experiencing toxicity requiring permanent drug discontinuation. Two months after amivantamab initiation, he had stable scans and remained on close observation but experienced mediastinal and hilar adenopathy progression on his five month scans and was initiated on a new line of therapy.

References

1. Kumari N, Singh S, Haloi D, et al. Epidermal growth factor receptor mutation frequency in squamous cell carcinoma and its diagnostic performance in cytological samples: a molecular and immunohistochemical study. World J Oncol. 2019;10(3):142-150. doi:10.14740/wjon1204
2. Gefitinib. Prescribing information. AstraZeneca pharmaceuticals LP. Accessed April 4, 2022. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=827d60e8-7e07-41b7-c28b-49ef1c4a5a41
3. Chen R, Manochakian R, James L, et al. Emerging therapeutic agents for advanced non-small cell lung cancer. J Hematol Oncol. 2020;13:58. doi:10.1186/s13045-020-00881-7
4. Amivantamab. Prescribing information. Janssen biotech, Inc. Accessed April 5, 2022. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=1466c070-9f97-4fa4-a955-6a6b59981fb8
5. Park K, Haura EB, Leighl NB, et al. Amivantamab in EGFR exon 20 insertion-mutated non-small-cell lung cancer progressing on platinum chemotherapy: initial results from the CHRYSALIS phase I study. J Clin Oncol. 2021;39(30):3391-3402. doi:10.1200/JCO.21.00662
6. Guide SV, Marinkovich MP. Linear IgA bullous dermatosis. Clin Dermatol. 2001;19(6):719-27. doi: 10.1016/s0738-081x(00)00185-1
7. Chanal J, Ingen-Housz-Oro S, Ortonne N, et al. Linear IgA bullous dermatosis: comparison between the drug-induced and spontaneous forms. Br J Dermatol. 2013;169(5):1041-1048. doi:10.1111/bjd.12488
8. Fortuna G, Marinkovich MP. Linear immunoglobulin A bullous dermatosis. Clin Dermatol. 2012;30(1):38-50. doi:10.1016/j.clindermatol.2011.03.008
9. Piette EW, Werth VP. Dapsone in the management of autoimmune bullous diseases. Dermatol Clin. 2011;29(4):561-564. doi:10.1016/j.det.2011.06.018
10. Ma J, Mo Y, Tang M, et al. Bispecific antibodies: from research to clinical application. Front Immunol. 2021;12:626616. doi:10.3389/fimmu.2021.626616
11. Fabbrocini G, Panariello L, Caro G, Cacciapuoti S. Acneiform rash induced by EGFR inhibitors: review of the literature and new insights. Skin Appendage Disord. 2015;1(1):31-37. doi:10.1159/000371821
12. Holcmann M, Sibilia M. Mechanisms underlying skin disorders induced by EGFR inhibitors. Mol Cell Oncol. 2015;2(4):e1004969. Published 2015 Jun 1. doi:10.1080/23723556.2015.1004969
13. Lacouture, ME, Anadkat, MJ, Bensadoun, RJ. et al. Clinical practice guidelines for the prevention and treatment of EGFR inhibitor-associated dermatologic toxicities. Support Care Cancer. 2011;19:1079–95. doi:10.1007/s00520-011-1197-6

Disclosure

None reported. **MM**

Training Strategies to Optimize Cardiovascular Durability and Life Expectancy

by James H. O'Keefe, MD, Evan L. O'Keefe, MD, Ryan Eckert, MD & Carl J. Lavie, MD

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Physical fitness is the single best predictor of life expectancy and healthspan. Try to achieve and maintain a high level of physical fitness throughout life.



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Abstract

The optimal dose of physical activity and best types of exercise for improving cardiovascular (CV) durability and optimizing longevity are unknown. The purpose of this article is to review the recent literature on the effects of duration and intensity of exercise, physical fitness, and specific types of training/sports on long-term CV health and life expectancy.

A systematic review of recent studies (2011 to 2022) was conducted using PubMed. Studies were included if they addressed the topic of fitness and/or exercise dose/type and CV health and/or life expectancy. Epidemiological studies show that cardiorespiratory fitness (is inversely related to risk of all-cause mortality, with no increased mortality risk in the most fit cohort. Being unfit is among most potent risk factors for all-cause mortality. Moderate PA (MPA) and vigorous PA (VPA) were associated with reduced CV and all-cause mortality in a recent definitive study. Paradoxically, high doses of MPA reduced both CV and all-cause mortality better than did high doses of VPA. A large meta-analysis showed that strength training was independently associated with lower rates of all-cause mortality and CV disease, though the best outcomes were associated with a cumulative dose of about 60 minutes/week. Physical interactive play is strongly associated with improved life expectancy. Physical fitness is a key determinant of CV health and life expectancy. Moderate to vigorous exercise, strength training and interactive sports are associated with improved life expectancy. Very large volumes of strenuous exercise and/or weightlifting may not be the ideal for optimizing longevity.

Introduction

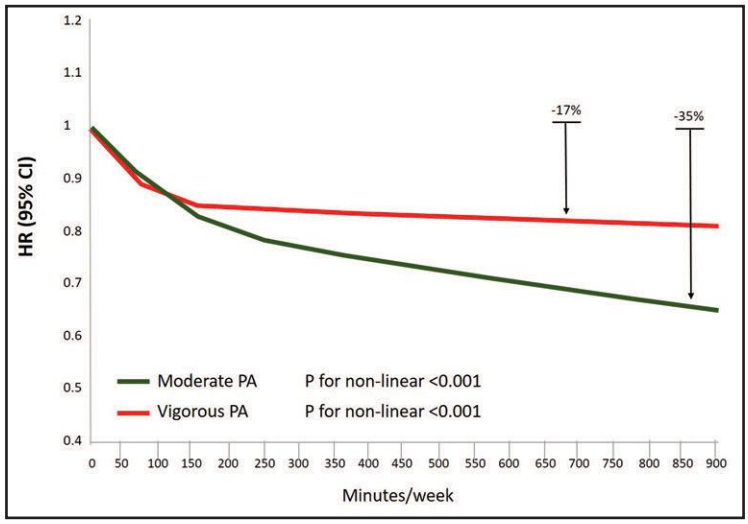
Physical activity is one of the key factors for achieving and maintaining cardiovascular (CV) health and improving both life expectancy and healthspan—the period of one's life spent in good health free from disabilities of aging.[1] However, the ideal duration and intensity of PA, and types of exercise for optimizing lifelong CV health, longevity, and healthspan are unknown. To address this question, we conducted a systematic review of studies from 2011 to 2022 using the PubMed database. Search terms included: exercise, physical activity, CV fitness, sports, outdoor activity,

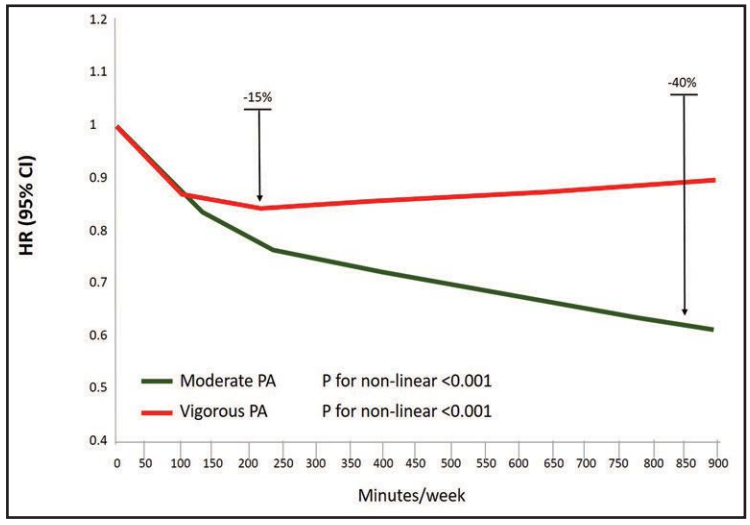
gardening, dogs, life expectancy, longevity, healthspan, CV events, and CV mortality. The most current meta-analyses and large, long-term prospective studies were selected preferentially.

Dose and Intensity of Exercise and Mortality Reduction

A landmark, long-term, prospective, cohort study evaluated the links between leisure-time physical activity duration and intensity with all-cause mortality and cause-specific mortality.[2] They concluded: "Higher levels of long-term leisure-time vigorous and moderate physical activity achieve the maximum benefit of mortality reduction."[2] Although this is arguably the best long-term prospective epidemiological study addressing the topic of exercise dose and mortality reduction, their conclusions were somewhat misleading due to over-generalization.

The relationships between dose of exercise and risk of death during follow up were distinctly different for vigorous physical activity (VPA) than for moderate physical activity (MPA). First and foremost, very high levels of MPA reduced risk of cardiovascular disease (CVD) mortality and all-cause mortality substantially better than very high levels of VPA (Figure 1A and 1 B). Secondly, the reductions in CVD mortality and all-cause mortality were maximized at ~150 minutes/week of VPA; doses >150 minutes/week of VPA were associated with a plateau in all-cause mortality, and a modest but progressive loss of CVD mortality reduction (slight reverse-J curve) at higher doses. In contrast, MPA reduced CVD mortality and all-cause mortality in dose-dependent, inverse relationships—the higher the dose of MPA the lower the number of deaths during the study.





Figures 1a, 1b. Hazard ratios (HR) for all-cause mortality (1a) and CV disease (CVD) mortality (1b) as a function of dose of VPA and MPA.[2] Used with permission.

This Harvard School of Public Health study that included 116,221 individuals assessed 15 times during 30 years of follow up suggests that if one's goal is optimizing long-term CV health and overall longevity, more is better for moderate-intensity exercise. However, the same cannot be said for vigorous exercise, where optimal benefits are achieved at approximately 150 minutes/week. MPA typically includes activities like walking, hiking, gardening, housework, dancing, shopping, golf, pickle ball, doubles tennis, volleyball, and leisurely bike riding. In contrast, VPA typically involves strenuous bicycling, running, or swimming, or high-intensity interval training (HIIT), singles tennis, basketball, or other activities that cause heart-pounding, sweat-producing, breathlessness.

This fits well with the hypothesis of extreme exercise cardiotoxicity/cardiac overuse injury, which is particularly relevant for middle-aged and older individuals.[3-5] A large amount of vigorous exercise, though required for attaining peak physical

performance, may not be necessary for maximizing life expectancy and cardiac durability. Very strenuous exercise acutely increases the risk of CVD events (myocardial infarction, sudden cardiac arrest) particularly for individuals who are in mid-life and beyond.[5, 6] Admittedly, these catastrophic CVD events are very rare, but more common issues such as orthopedic injuries and over-training issues may force individuals to curtail or abandon excessively strenuous exercise regimens.

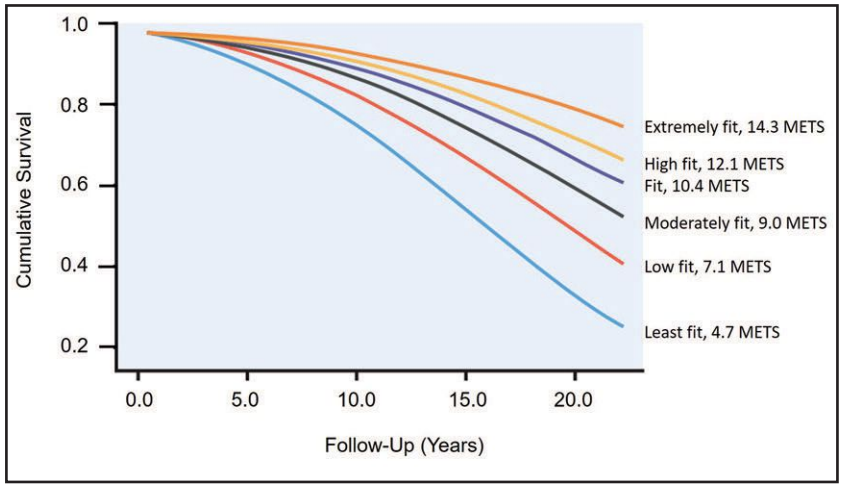


Figure 2. Survival Curves According to Cardiorespiratory Fitness Categories as measured by time achieved on a Bruce protocol treadmill exercise test.[13] Used with permission.

For an individual whose goal is to decrease the risk of CVD and boost life expectancy, a routine of MPA appears to be adequate. Although chronically performing very high doses of VPA may attenuate some of the benefits bestowed by less extreme efforts, this is relevant for only about 2.5% of the United States (U.S.) adult population.[7] This is not to say that VPA is harmful; it substantially reduces all-cause mortality and CVD mortality compared to a sedentary lifestyle. Yet, the magnitude of the mortality and CVD risk reductions with high doses of VPA do not appear to be as substantial as for high doses of MPA.[3, 4] In the Lee study, chronically doing very high doses of moderate exercise reduced risks of all-cause mortality and CVD mortality at least two-fold better compared to chronically performing very high doses of vigorous exercise.[2]

At the other extreme, a sedentary lifestyle—which affects about half of the U.S. adult population—is associated with worse health outcomes and diminished life expectancy.[7, 8] After sitting more than 60 minutes, the levels of blood glucose, triglycerides and inflammatory markers begin to rise.[9] Even light or moderate activity mitigates these adverse effects of sedentary behavior without unduly increasing orthopedic injuries or cardiac risks.

Throughout the last three million years of hominin evolution, our ancestors' existence necessitated a very physically active lifestyle. Adults would usually accumulate 14,000 to 16,000 steps/day, mostly in the form of walking three to eight miles, often while carrying objects such as wood, food, water, and children.[10, 11] Hunter-gatherer humans' daily subsistence required large amounts MPA with smaller doses of interspersed VPA—this is the activity pattern for which we remain genetically adapted.[7, 12] This evolutionary template would seem to be a logical guide to structuring an ideal activity pattern for promoting optimum health and longevity.

The Survival of the Fittest

A recent Veterans Affairs (VA) study in the Journal of the American College of Cardiology that followed 750,302 U.S. veterans up to 20 years reported that cardiorespiratory fitness (CRF) as measured by performance in treadmill testing was strongly related to survival in a graded continuous manner.[13] The best survival rates among both men and women were noted in those who attained peak exercise level of 14 metabolic equivalents (METs). No increased risk of premature mortality was noted in the most fit cohort (Figure 2).[13, 14] Importantly, being in the least fit cohort carried a greater mortality risk and any other traditional risk factor including age, diabetes, smoking, chronic kidney disease, hypertension, atrial fibrillation, obesity, prior CVD, and cancer.

A very recently updated meta-analysis of 37 studies with nearly 2.3 million participants with nearly 110,000 deaths supported the prognostic importance of CRF, as everyone MET increase was associated with an 11% reduction in mortality.[15] Compared with the lowest tertile of CRF, those in the highest tertile of CRF had a 45% lower mortality, highlighting the fact that fitness is one of the strongest predictors of survival.[14-16]

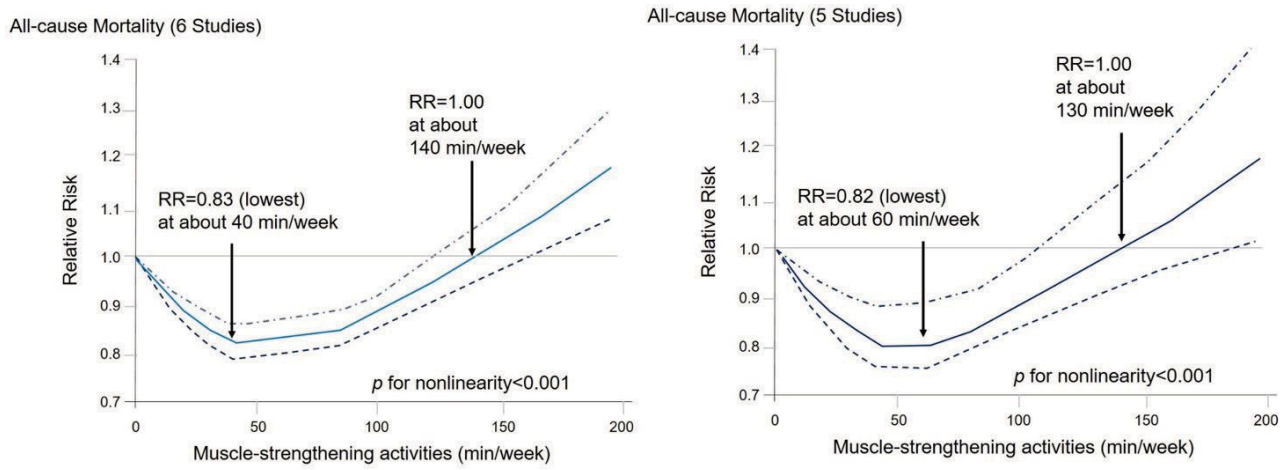


Figure 3. J-shaped dose–response curves for weekly dose of muscle-strengthening activities and all-cause mortality.[19] Used with permission.

The hypothesis that life expectancy is best among individuals demonstrating the highest levels of fitness seems to be at odds with the recent Lee study[2] showing that large amounts of moderate exercise are better than large amounts of vigorous exercise for reducing mortality and CVD risks. Presumably, vigorous exercise produces higher levels of fitness than moderate exercise. Still, there are many factors that determine one's fitness, including general health, genetics, nutrition, and body composition, not just the amount and types of exercise performed. In the VA study, CVD risk factors like obesity, smoking, diabetes, hypertension, chronic kidney disease and overall disease burden were progressively more unfavorable going from the most fit to the least fit categories.[13] This is a bidirectional causal relationship, with arrows going both ways: a normal-weight, non-smoking person with favorable genes, who is eating well and following a generally healthy lifestyle will have an easier time maintaining high fitness even if they are not performing large volumes of vigorous exercise. On the other hand, an excellent exercise regimen will improve multiple CVD risk factors such as body composition, blood pressure, blood glucose, chronic inflammation, and bone health—and these benefits are conferred by both MPA and VPA.

High Intensity Interval Training (HIIT)

One alternative for maintaining high CRF without doing large volumes of VPA is HIIT, which is an efficient exercise regimen characterized by short, repeated bouts of intense exercise.[17] HIIT protocols lead to better improvements in maximum oxygen uptake than protracted sessions of continuous moderate or strenuous exercise, with better adherence and lower risk.[17] Once or twice weekly HIIT sessions might be better for achieving high levels of fitness without having to do exhaustive and prolonged bouts of strenuous exercise.[17, 18] This would maintain very high fitness levels but avoid the longevity benefit plateau that appears to be present with very high doses of VPA.

Clearly, aerobic fitness as measured by treadmill performance is a powerful predictor of life expectancy, but other dimensions of physical fitness including strength, balance, flexibility, and body composition have also been shown to be important for optimal functioning and wellbeing. These non-aerobic fitness parameters also exert significant independent effects on life expectancy and healthspan.

J-Shaped Risk Reduction from Strength Training

A recent comprehensive meta-analysis reported that about 30 to 60 minutes/week of strength training (also referred to as resistance training) produced significant risk reductions of 17% for all-cause mortality, 18% for CVD events, and 9% for all cancer.[19] Joint analysis between strength training and aerobic activities revealed that a greater benefit was obtained for all-cause mortality, CVD mortality and total cancer mortality when these two types of exercise were combined. This important finding about the synergism of

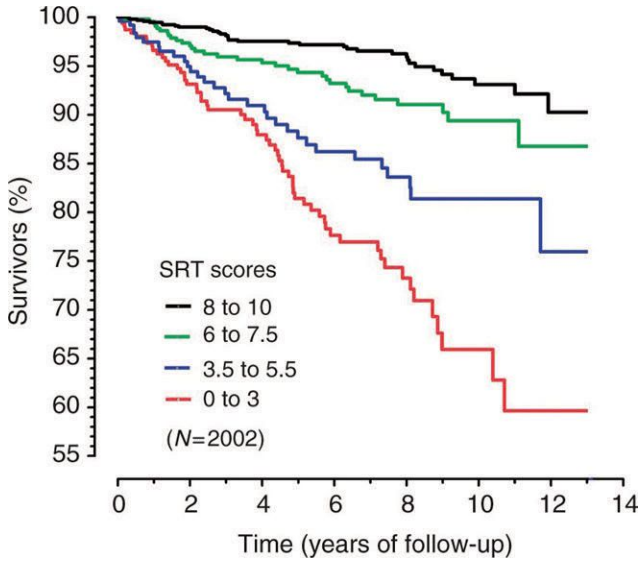


Figure 4. Kaplan-Maier survival curves based on SRT scores.[31] Used with permission.

aerobic conditioning and resistance training has been confirmed by previous meta-analyses, and strongly suggests that adding muscle-strengthening activities to routine of cardio activities may provide additional benefits for preventing disease and improving life expectancy.[19, 20]

However, in this recent comprehensive meta-analysis by Momma et al., the survival curves were J-shaped—benefits were completely lost at strength training durations of ~130 to 140 minutes/week, with possible harm at progressively higher doses (Figure 3).[19] Another meta-analysis showed that doing resistance-training sessions one or two times/week was associated with reduced risk of all-cause mortality, although increasing the frequency to three or more sessions/week was not.[20] In contrast, aerobic exercise tends to follow a reverse-J curve whereby some of the conferred benefits for CV health and life expectancy may be lost at the highest levels of strenuous exercise, but even very high doses of VPA do not increase risk of premature mortality or CVD compared to a sedentary lifestyle.[4, 21]

Adults who are inactive lose 3% to 8% of total muscle mass/decade, which is accompanied by increased fat accumulation and decreased resting metabolic rate.[22] Strength training can reverse these abnormalities by increasing muscle mass and resting metabolic rate, with a reduction in visceral fat.[22] Resistance training also improves physical performance, cognitive function/mood, blood pressure, insulin sensitivity, glucose metabolism, and lipid levels.[22, 23] Additionally, strength training augments bone mineral density and functional independence, and supports CV health.[22, 23] The World Health Organization (WHO) recommends that muscle-strengthening activities be performed at least twice a week.[24]

Grip strength has been proposed to be useful biomarker of aging.[23] Strong observational evidence suggests that grip strength is an accurate way to assess current and future strength, physical functionality, bone mineral density, risk for fractures, and vulnerability to hospitalization.[25, 26] Grip strength is also highly predictive for multiple health outcomes including all-cause and disease-specific mortality, and surprisingly, even cognitive function.[25, 26] Weightlifting, gardening, and competitive sports are all practical strategies for maintaining or improving robust grip strength.

Other Fitness Dimensions: Balance, Flexibility, Body Composition

Balance is an aspect of fitness that has been shown to decline steeply starting about 50 years of age. The ability to balance one's body can be assessed by simply standing on one leg. In a prospective study of 1,702 individuals followed for seven years, the ability to successfully complete the 10-second one-legged standing test was independently associated with all-cause mortality.[27] In a multivariable adjusted model incorporating age, sex, body mass index and other comorbidities, the hazard ratio for all-cause mortality was higher 84% higher (P<0.001) for the cohort who could not stand on one leg for 10 seconds without losing their balance and having to put the other foot on the floor.[27] Furthermore, the ability to stand on one leg for 10 seconds provided incremental prognostic information beyond age, sex and other relevant fitness and clinical variables.[28] Balance is highly trainable. Yoga and tai chi are forms of MPA done in social settings that improve balance and flexibility.[29]

Arising from the floor is a basic task required for autonomous functioning. The sitting-rising test (SRT) is a simple and quick assessment based on the ability to sit on the floor and then rise.[30] A score ranging from zero to five is achieved for each the sitting and the rising phase, with one point being subtracted from

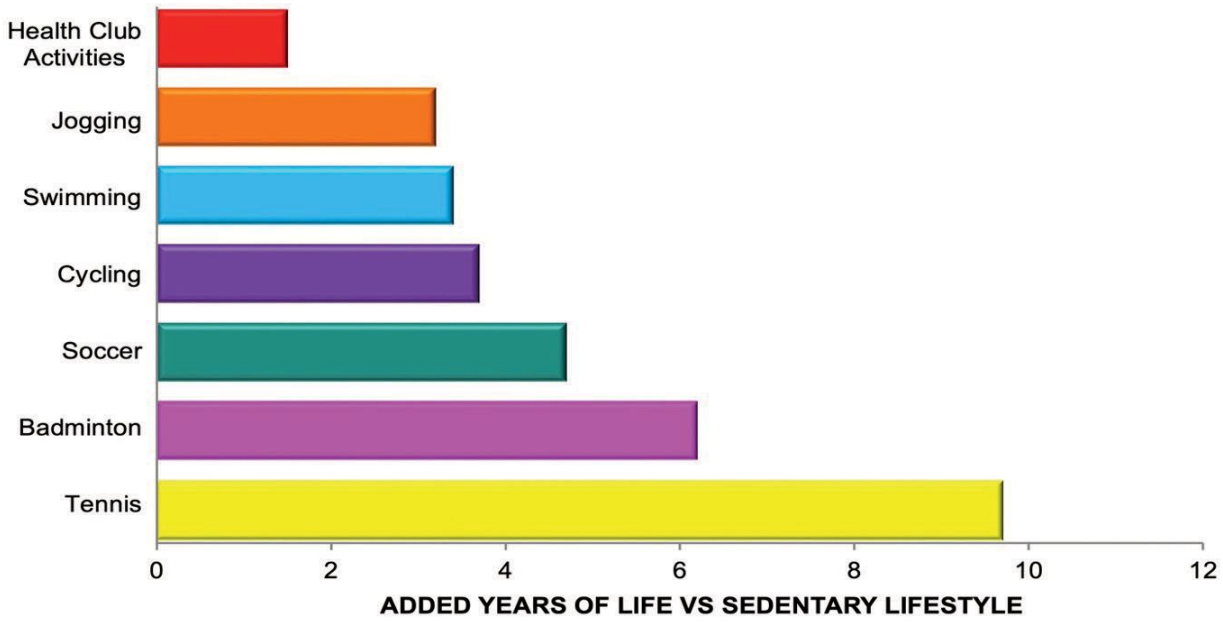


Figure 5. Life expectancy gains according to sports/exercises performed by individuals in the Copenhagen City Heart Study.[3] Original author no permission needed.

five for each support used (hand, forearm, and knee); the two scores are added together for a maximum score of 10. The SRT simultaneously evaluates the fundamental non-aerobic components of physical fitness—flexibility, balance, muscle strength, and body composition—which turn out to be important for optimal functioning and survival.

A prospective study of 2,002 subjects with ages ranging from 51–80 years showed that low SRT scores were associated with a higher all-cause mortality risk during follow up.[31] A low score on the SRT was associated with >six-fold higher all-cause mortality; the vast majority of deaths in this study occurred in participants with low SRT scores (Figure 4).[31] In contrast, only two subjects with a perfect SRT score of 10 (ability to sit and stand without placing a hand or knee on the floor) died during a follow-up time of 6.3 years. The predictive power of this simple test that requires no aerobic effort is similar to that seen with cardiorespiratory fitness as measured on treadmill testing.

The Power of Play

The best types of exercise for improving life expectancy and mental health appear to be social sports such as tennis, golf, badminton, pickleball, soccer, basketball, volleyball, softball, touch football, baseball, and group exercise. The activities that involve interactive physical play not only improve fitness, but also promote interpersonal bonding and reduce stress.

In the Copenhagen City Heart Study, adults who reported frequently participating in tennis or other racquet sports or team sports such as soccer lived significantly longer than individuals who were sedentary.[3] After statistical adjustment for multiple potential confounders, the people who play social sports also had longer life expectancies than those who regularly did other types of exercise, some of which are strenuous but are typically done by oneself, such as running, swimming, and cycling (Figure 5).[3] This finding that interactive social sports have a halo effect on health, well-being, and longevity has been corroborated in other large prospective registry studies.[32, 33] In the U.S., about three of four people play some form of sports when they are in school and in young adulthood, but unfortunately after age 25 years, only one in four still plays a sport regularly.[34]

Social support independent of exercise exerts potent positive effects on health, wellbeing and life expectancy.[35] Engaging in team sports or group exercise not only confers the physical health benefits of exercise, but also fosters interpersonal connection and tends to

brighten mood and reduce anxiety.[32] Thus, playing a sport that requires a partner or a team or doing group exercise may result in distinctive psychological and physiological effects that amplify the benefits of the exercise.[3] Moreover, because interactive physical play is usually perceived as fun, participants tend to do it more often than a joyless workout.

Nature Therapy

Growing evidence suggests a positive association between time spent in natural environments and good mental and physical health.[36] A recent study assessed the dose-response relationship of "nature therapy" by focusing on the amount of time spent by 19,806 adults during a typical week outdoors in green spaces like parks, woodlands and countryside or by blue spaces such as lakes and beaches.[37] Those who spent ≥120 minutes/week in nature were 59% more likely to report good health and 23% more likely to report wellbeing compared with those who reported spending no time in nature. The authors concluded that spending at least two hours/week of outdoor recreation time may be a threshold for achieving the nature dividend for health and wellbeing.

Notably, nature exposure can improve health and mood even if the person is not exercising while in the natural setting.[37] Shinrin-yoku (forest-bathing), is a popular therapy in Japan that has been shown to have psychological and CV benefits (reduced blood pressure and pulse, lower levels of cortisol and inflammatory markers) when individuals are being active or passive while in natural settings such as woodlands, mountains, lakes, streams, etc., rather than urban settings.[38]

Even so, exercise performed in nature appears to be more psychologically beneficial than physical activity in other locations.[39] Gardening is popular worldwide and is practical form of leisure-time activity that involves immersion in nature, relaxation, multi-faceted movements, exposure to potentially beneficial microbes and sunlight. Gardening is consistently linked to physical and mental health benefits as well as longevity.[40]

Exercise with a dog is virtually always done outside. Individuals who adopt a dog into their home compared to non-dog owners are approximately 14 times more likely ($P < 0.001$) than to be recreational walkers and four times more likely to meet current exercise guidelines of 150 minutes/week ($P < 0.001$).[41] Furthermore, a prospective register-based nationwide study from Sweden that included 3,432,153 individuals with 12 years of follow-up found that dog ownership for people who were otherwise living alone was associated with significant all-cause mortality reduction of 33%, HR 0.67 (95% CI, 0.65–0.69), and CVD mortality reduction of 36%, HR 0.64 (0.59–0.70).[42] People living in multiple-person households also benefited from dog ownership with less impressive but still highly significant reductions in risks of all-cause mortality and CVD mortality (11% and 15% reductions, respectively).

Summary

- Physical fitness is the single best predictor of life expectancy and healthspan. Try to achieve and maintain a high level of physical fitness throughout life.
- More is better for moderate-intensity exercise with respect to CV health and life expectancy. Vigorous exercise is also beneficial for optimizing life expectancy and healthspan, but maximal benefits are achieved at 150 minutes/week.
- HIIT is a time-efficient strategy for attaining and maintaining high-level CRF. Regular participation in team sports or other forms of physical interactive play is associated with good mental health and longevity.
- Shoot for at least two hours/week spent outdoors in natural settings (green spaces or blue spaces). Gardening and adopting a dog are practical strategies for accomplishing this goal.
- Aim for two sessions/week of strength training for a cumulative time of about 40 to 60 mins/week, ideally not exceeding 150 mins/wk.
- Incorporate flexibility and balance training sessions like yoga or tai chi.
- Allow ample time for rest, relaxation, recovery, and sleep after strenuous exertion.

References

1. Thompson PD, Eijsvogels TMH, Kim JH. Can the Heart Get an Overuse Sports Injury? NEJM Evid. 2022;2(1):Online. doi: 10.1056/EVIDra2200175.
2. Lee DH, Rezende LFM, Joh HK, et al. Long-Term Leisure-Time Physical Activity Intensity and All-Cause and Cause-Specific Mortality: A Prospective Cohort of US Adults. Circulation. 2022;146(7):523-524.
3. Schnohr P, O'Keefe JH, Holtermann A, et al. Various Leisure-Time Physical Activities Associated With Widely Divergent Life Expectancies: The Copenhagen City Heart Study. Mayo Clin Proc. 2018;93(12):1775-1785.
4. Schnohr P, O'Keefe JH, Lavie CJ, et al. U-Shaped Association Between

Duration of Sports Activities and Mortality: Copenhagen City Heart Study. Mayo Clin Proc. 2021;96(12):3012-3020.
5. Schnohr P, O'Keefe JH, Marott JL, Lange P, Jensen GB. Dose of jogging and long-term mortality: the Copenhagen City Heart Study. J Am Coll Cardiol. 2015;65(5):411-419.
6. Franklin BA, Thompson PD, Al-Zaiti SS, et al. Exercise-Related Acute Cardiovascular Events and Potential Deleterious Adaptations Following Long-Term Exercise Training: Placing the Risks Into Perspective-An Update: A Scientific Statement From the American Heart Association. Circulation. 2020;141(13):e705-e736.
7. O'Keefe EL, Lavie CJ. A Hunter-Gatherer Exercise Prescription to Optimize Health and Well-Being in the Modern World. J Sci in Sport and Exercise. 2021;3:147-157.
8. Dunstan DW, Dogra S, Carter SE, Owen N. Sit less and move more for cardiovascular health: emerging insights and opportunities. Nat Rev Cardiol. 2021;18(9):637-648.
9. Dogra S, Wolf M, Jeffrey MP, et al. Disrupting prolonged sitting reduces IL-8 and lower leg swell in active young adults. BMC Sports Sci Med Rehabil. 2019;11(23.
10. O'Keefe JH, Vogel R, Lavie CJ, Cordain L. Achieving hunter-gatherer fitness in the 21(st) century: back to the future. Am J Med. 2010;123(12):1082-1086.
11. Irimia A, Chaudhari NN, Robles DJ, et al. The Indigenous South American Tsimane Exhibit Relatively Modest Decrease in Brain Volume With Age Despite High Systemic Inflammation. J Gerontol A Biol Sci Med Sci. 2021;76(12):2147-2155.
12. O'Keefe JH, O'Keefe EL, Lavie CJ. The Goldilocks Zone for Exercise: Not Too Little, Not Too Much. Mo Med. 2018;115(2):98-105.
13. Kokkinos P, Faselis C, Samuel IBH, et al. Cardiorespiratory Fitness and Mortality Risk Across the Spectra of Age, Race, and Sex. J Am Coll Cardiol. 2022;80(6):598-609.
14. Lavie CJ, Arena R, Kaminsky LA. Making the Case to Measure and Improve Cardiorespiratory Fitness in Routine Clinical Practice. Mayo Clin Proc. 2022;97(6):1038-1040.
15. Laukkanen JA, Isiozor NM, Kunutsor SK. Objectively Assessed Cardiorespiratory Fitness and All-Cause Mortality Risk: An Updated Meta-analysis of 37 Cohort Studies Involving 2,258,029 Participants. Mayo Clin Proc. 2022;97(6):1054-1073.
16. Lavie CJ, Sanchis-Gomar F, Ozemek C. Fit Is It for Longevity Across Populations. J Am Coll Cardiol. 2022;80(6):610-612.
17. Ito S. High-intensity interval training for health benefits and care of cardiac diseases - The key to an efficient exercise protocol. World J Cardiol. 2019; 11(7):171-188.
18. Mendelson M, Chacaroun S, Baillieul S, et al. Effects of high intensity interval training on sustained reduction in cardiometabolic risk associated with overweight/obesity. A randomized trial. J Exerc Sci Fit. 2022;20(2):172-181.
19. Momma H, Kawakami R, Honda T, Sawada SS. Muscle-strengthening activities are associated with lower risk and mortality in major non-communicable diseases: a systematic review and meta-analysis of cohort studies. Br J Sports Med. 2022;56(13):755-763.
20. Saeidifard F, Medina-Inojosa JR, West CP, et al. The association of resistance training with mortality: A systematic review and meta-analysis. Eur J Prev Cardiol. 2019;26(15):1647-1665.
21. O'Keefe EL, Torres-Acosta N, O'Keefe JH, Lavie CJ. Training for Longevity: The Reverse J-Curve for Exercise. Mo Med. 2020;117(4):355-361.
22. Westcott WL. Resistance training is medicine: effects of strength training on health. Curr Sports Med Rep. 2012;11(4):209-216.
23. Lu Y, Li G, Ferrari P, et al. Associations of handgrip strength with morbidity and all-cause mortality of cardiometabolic multimorbidity. BMC Med. 2022;20(1):191.
24. Bull FC, Al-Ansari SS, Biddle S, et al. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. Br J Sports Med. 2020; 54(24): 1451-1462.
25. Bohannon RW. Grip Strength: An Indispensable Biomarker For Older Adults. Clin Interv Aging. 2019;14:1681-1691.
26. Wu Y, Wang W, Liu T, Zhang D. Association of Grip Strength With Risk of All-Cause Mortality, Cardiovascular Diseases, and Cancer in Community-Dwelling Populations: A Meta-analysis of Prospective Cohort Studies. J Am Med Dir Assoc. 2017;18(6):551 e517-551 e535.
27. Araujo CG, de Souza ESCG, Laukkanen JA, et al. Successful 10-second one-legged stance performance predicts survival in middle-aged and older individuals. Br J Sports Med. 2022;56(17):975-980.
28. Marcori AJ, Monteiro PHM, Oliveira JA, Doumas M, Teixeira LA. Single Leg Balance Training: A Systematic Review. Percept Mot Skills. 2022;129(2):232-252.
29. Welford P, Osth J, Hoy S, Diwan V, Hallgren M. Effects of yoga and aerobic exercise on wellbeing in physically inactive older adults: Randomized controlled trial (FitForAge). Complement Ther Med. 2022;66:102815.
30. Araujo CGS, Castro CLB, Franca JFC, Araujo DS. Sitting-rising test: Sex- and age-reference scores derived from 6141 adults. Eur J Prev Cardiol. 2020; 27(8):888-890.
31. Brito LB, Ricardo DR, Araujo DS, Ramos PS, Myers J, Araujo CG. Ability to sit and rise from the floor as a predictor of all-cause mortality. Eur J Prev Cardiol. 2014;21(7):892-898.
32. Chekroud SR, Gueorguieva R, Zheutlin AB, et al. Association between physical exercise and mental health in 1.2 million individuals in the USA between 2011 and 2015: a cross-sectional study. Lancet Psychiatry. 2018;5(9):739-746.
33. Oja P, Kelly P, Pedisic Z, et al. Associations of specific types of sports and exercise with all-cause and cardiovascular-disease mortality: a cohort study of 80 306 British adults. Br J Sports Med. 2017;51(10):812-817.
34. Blendon RJ, Benson JM, Sayde JM, et al. Poll: Three in four adults played sports when they were younger, but only one in four still play. In: Harvard, ed. Boston, MA: Harvard T.H. Chan School of Public Health; 2015: https://www.hsph.harvard.edu/news/press-releases/poll-many-adults-played-sports-when-young-but-few-still-play/.
35. Holt-Lunstad J, Smith TB, Layton JB. Social relationships and mortality risk: a meta-analytic review. PLoS Med. 2010;7(7):e1000316.
36. White MP, Elliott LR, Taylor T, et al. Recreational physical activity in natural environments and implications for health: A population based cross-sectional study in England. Prev Med. 2016;91:383-388.
37. White MP, Alcock I, Grellier J, et al. Spending at least 120 minutes a week in nature is associated with good health and wellbeing. Sci Rep. 2019;9(1):7730.
38. Park BJ, Tsunetsugu Y, Kasetani T, Kagawa T, Miyazaki Y. The physiological effects of Shinrin-yoku (taking in the forest atmosphere or forest bathing): evidence from field experiments in 24 forests across Japan. Environ Health Prev Med. 2010;15(1):18-26.
39. Thompson Coon J, Boddy K, Stein K, Whear R, Barton J, Depledge MH. Does participating in physical activity in outdoor natural environments have a greater effect on physical and mental wellbeing than physical activity indoors? A systematic review. Environ Sci Technol. 2011;45(5):1761-1772.
40. Soga M, Gaston KJ, Yamaura Y. Gardening is beneficial for health: A meta-analysis. Prev Med Rep. 2016;5:92-99.
41. Westgarth C, Christley RM, Jewell C, German AJ, Boddy LM, Christian HE. Dog owners are more likely to meet physical activity guidelines than people without a dog: An investigation of the association between dog ownership and physical activity levels in a UK community. Sci Rep. 2019;9(1):5704.
42. Mubanga M, Byberg L, Nowak C, et al. Dog ownership and the risk of cardiovascular disease and death - a nationwide cohort study. Sci Rep. 2017; 7(1):15821.

Disclosure

None reported.

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Awareness with Recall: Review and Guide to Electroencephalographic Depth-of-Anesthesia Monitoring

by Rachel L. Rios, BA & Ben Julian A. Palanca, MD, PhD

Awareness with Recall is rare but carries a serious risk of psychological sequelae. Steps towards recognition in the intra- and postoperative periods are critical for mitigating harm.



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Abstract

Awareness with recall is an uncommon but potentially devastating neurological complication following perioperative care. End-tidal anesthetic gas concentration alarms can supplement usual care to reduce risk. Processed electroencephalographic (EEG) measures provided by depth-of-anesthesia monitors may be helpful, particularly for high-risk patients. Interpretation of EEG waveforms may supplement these processed EEG metrics to minimize risk of awareness with recall.

Case Summary

A 63-year-old man undergoing cardiac surgery was monitored with intraoperative frontal electroencephalography (EEG) for surveillance against awareness under general anesthesia and to minimize excessive anesthetic administration (Figure 1). The commercial depth-of-anesthesia (DOA) monitor displayed multiple measures consistent with wakefulness and concerning for intraoperative awareness. In contrast, the raw EEG waveform provided reassuring patterns consistent with deep general anesthesia. The erroneous metrics persisted for at least 10 minutes without clinical signs of awareness (tachycardia, hypertension, or movement). Despite end-tidal anesthetic gas concentrations compatible with surgical anesthesia, additional propofol was administered. Transient hypotension requiring vasopressor infusions ensued as a result of excessive anesthetic administration. Multiple episodes of discordant EEG waveforms and measures occurred. Given these frequent events, a modified Brice interview was conducted on postoperative day 2, but elicited no evidence of awareness with recall (AWR). This case demonstrates the utility of EEG waveform interpretation when processed EEG measures arise that are concerning for AWR.

Introduction

Clinical Significance

Intraoperative awareness with recall (AWR), a potentially devastating complication of general anesthesia, is defined as unintentional consciousness during general anesthesia with subsequent recollection of intraoperative events. AWR is distinct from awareness without explicit recall of intraoperative experiences, a relatively common phenomenon of unclear clinical significance.[1] AWR has an incidence of approximately one to two patients out of 1,000.[2]

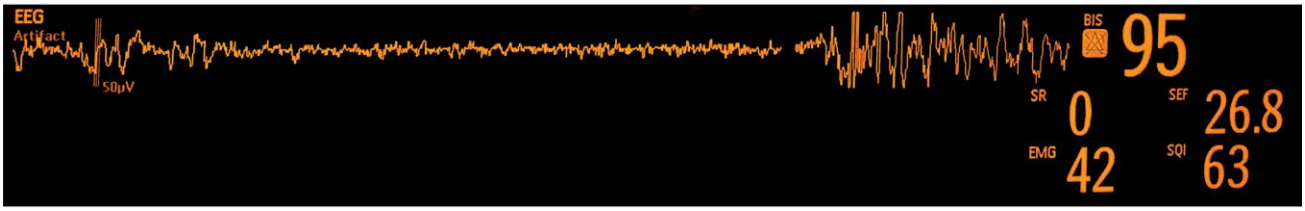


Figure 1. A Bispectral Index™ (BIS) monitor displays processed EEG values concerning for possible awareness during general anesthesia, inconsistent with the displayed EEG waveform.

Despite its rarity, it is one of the most common fears reported by presurgical patients.[3] Following surgery, recall of distressing intraoperative memories can carry considerable psychological consequences, including post-traumatic stress disorder (PTSD).[4,5] AWR increases the postoperative risk of developing PTSD symptoms by at least 25%.[4] Memories of paralysis are particularly associated with long-term sequelae.[6] Moreover, AWR can present medicolegal ramifications. AWR cases make up 2% of all malpractice claims against anesthesiologists, and the financial burden of these claims has only increased over time.[7] Damages can exceed $1 million.[7] The potentially severe repercussions of AWR underscore the importance of identifying cases, mitigating risk factors, and employing preventative measures.

Detection

AWR cases are challenging to detect. Intraoperatively, patients who subsequently develop AWR often lack the classical signs of light anesthetic depth (tachycardia, hypertension, and movement).[8] Postoperatively, routine post-anesthesia evaluations on the day of surgery may miss cases of AWR, as memories of intraoperative events can surface days or even weeks later.[9] In addition, the method used to conduct these postoperative assessments affects the likelihood of detecting AWR. Estimates of AWR incidence that rely on spontaneous patient reports are up to an order of magnitude lower[6,10] than estimates made using structured assessments such as the modified Brice interview (Table 1).[11,12] Further complicating the identification of AWR, patient descriptions of these diverse experiences may be vague. Some commonly reported elements of intraoperative memories include auditory perceptions, pain, paralysis, and varying levels of distress.[9,12-14] Patients typically recount short experiences, with most lasting less than five minutes.[6] The brevity and heterogeneity of intraoperative memories can make it difficult to distinguish true AWR from false reports, intraoperative dreaming, or distorted memories of perioperative events, such as postoperative sedation in the intensive care unit. Overall, as few as 25% of AWR reports are made directly to the responsible anesthesia provider,[6] hindering postoperative referral for psychiatric follow-up.

Table 1: Modified Brice Interview. This is a preferred method for assessing patients for awareness with recall.[11]

Modified Brice Interview
What was the last thing you remember before anesthesia?
What is the first thing you remember after waking up?
Do you remember anything between going under anesthesia and waking up?
Did you dream during your procedure?
What was the worst thing about your operation?

Risk Factors

Preoperative risk assessment for AWR necessitates consideration of patient characteristics, clinical context, and anesthetic approach. Large-scale audits and closed-claims analyses have identified female sex and young age as risk factors;[8,15] however, this association has been challenged by some prospective studies.[2] Patients with ASA physical status III or IV, an indicator of overall poor health, are likely at greater risk than ASA I-II patients.[2] Prior AWR appears to be a significant risk factor as well—one study demonstrated a five-fold increase in risk for patients with a prior history.[16] It has been proposed that genetic factors underlie this elevated risk, but a single responsible gene has not yet been identified.[17] The risk for AWR is greater during anesthetic induction and emergence.[15] Total intravenous anesthesia (TIVA),[8,12] neuromuscular blockade,[8,15] and omission of pre-medication[12] have also been associated with increased AWR risk. Additionally, emergency conditions, after-hours surgeries, and certain types of surgery (cardiac, thoracic, and obstetric) confer

greater risk.[15] Because many risk factors are not easily modifiable, preventative strategies are paramount.

Causes and Prevention

AWR occurs when the hypnotic and amnesic components of a general anesthetic fail to sustain disconnected consciousness and ablate memory.[18] Contributing factors include medication errors, equipment problems, miscommunication regarding remaining operative time, lack of vigilance, and anesthetic under-dosing to maintain hemodynamic stability.[6-8] Up to 75% of these cases are preventable,[6] emphasizing the need for additional measures beyond the standard of care to reduce the likelihood of AWR.

Interventions that promote amnesia and adequate anesthetic depth can be employed to reduce AWR risk. End-tidal anesthetic gas (ETAG) monitoring, pre-medication, and electroencephalographic (EEG) neuromonitoring are part of a multipronged approach for AWR prevention. Monitoring ETAG concentration and instituting low concentration alarms have been shown to reduce AWR incidence and are now standard practice.[19] There is limited evidence supporting pharmacologic interventions to prevent or terminate suspected AWR.[20] A recent meta-analysis reported a protective effect of benzodiazepines, consistent with the known amnestic properties of these medications.[21] Scopolamine has also been employed as a preventative measure given its ability to inhibit intraoperative dreaming and/or recall of intraoperative dreams by potentiating anesthetic depth or ablating memory formation.[22] Initiating a background infusion of propofol could theoretically reduce the risk of AWR while weaning cardiopulmonary bypass during cardiac surgery.[23] The development of depth-of-anesthesia (DOA) monitors has made intraoperative EEG more accessible and practical for detecting periods of light anesthesia that may risk intraoperative awareness.

EEG-based Depth-of-Anesthesia Monitors: Introduction

EEG-based DOA monitors utilize several forehead electrodes to record brain electrical activity from the scalp (Figure 2). The electrical potential across two scalp electrodes is amplified to yield the EEG waveform. Signal processing algorithms then integrate measures of EEG signal waveforms such as the frequency, amplitude, and power (amplitude squared). These processed EEG (pEEG) metrics are combined into single index values intended to correspond with a patient's level of arousal, which can be used to quickly gauge anesthetic depth.

The first commercially available EEG-based DOA monitor was the Bispectral Index™ (BIS) Monitor. The BIS uses a proprietary algorithm to generate an index between 0 and 100, with lower numbers intended to correlate with increased anesthetic depth. BIS values between 40 and 60 purportedly indicate depth suitable for general anesthesia with minimal risk of AWR. Several randomized controlled trials (RCTs) have demonstrated the utility of BIS monitoring for AWR prevention.[24-28] A 2019 meta-analysis showed that BIS guidance reduces the risk of AWR by 64% compared to clinical signs alone.[29] The BIS monitor and ETAG alarms appear to be similarly effective.[29] When anesthetic concentration cannot be easily measured, such as during TIVA, DOA monitors may be particularly useful.[27] Other DOA monitors utilizing pEEG, such as the GE-Datex-Ohmeda S/5 Entropy™ Module and the Narcotrend® monitor, have not been utilized in RCTs assessing AWR incidence as a primary outcome. Given the paucity of research on the role of other pEEG-based DOA monitors in AWR prevention, the remainder of this review will focus primarily on waveforms and BIS pEEG measures.

There are several limitations to BIS-guided anesthesia that likely extend to other frontal-EEG guided DOA monitors. Because they collect data from a limited number of EEG channels over frontal brain regions, the values they calculate cannot account for electrical activity across the entire brain. In addition, index values within the manufacturer-recommended ranges for general anesthesia do not necessarily preclude AWR. Secondary analysis of data from a large AWR trial could not identify a threshold BIS value that reliably prevents AWR.[30] Other factors limiting the utility of the BIS include interindividual differences in BIS values, output delays, and the device's vulnerability to artifacts. Changes in DOA monitor output can lag up to two minutes behind changes in states of consciousness, potentially delaying recognition of light anesthesia.[31] Artifacts related to external factors in the operating room, such as head movement, cardiopulmonary bypass,[32] and forced air warmers,[33] can yield inaccurate BIS values. Furthermore, medications that are commonly used in the operating room, such as ketamine and nitrous oxide, can contribute to erroneous BIS indices.[34] Muscle paralytics have been shown to reduce BIS values without affecting arousal in awake,

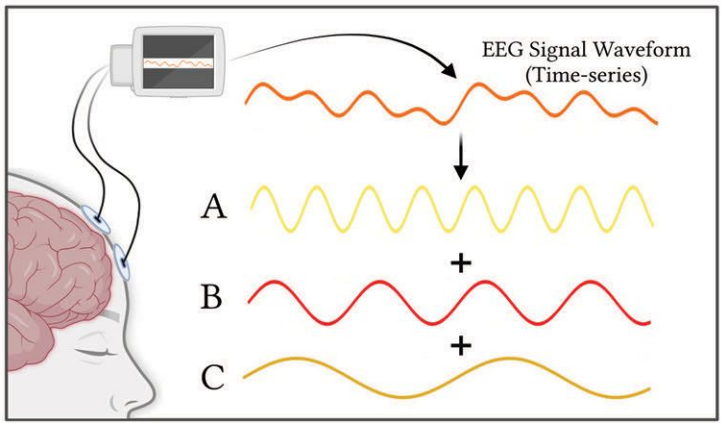


Figure 2. Depth-of-Anesthesia (DOA) monitors process cortical electroencephalographic (EEG) signals to generate waveforms and frequency components. EEG DOA monitors amplify the voltage measured across two scalp electrodes. The signal time-series (A) represents voltage over time. The signal can be decomposed into superimposed waves of varied frequencies, amplitudes, and phases (B, C, and D). Processed EEG (pEEG) metrics are calculated using algorithms that incorporate the signal time-series and/or component waves.

non-sedated volunteers.[35] Given these limitations, it is not surprising that discrepancies frequently arise between clinical status and DOA monitor outputs. In these cases, understanding the metrics provided by DOA monitors and recognizing common intraoperative waveform patterns can improve clinical decision-making regarding AWR.

EEG-based Depth-of-Anesthesia Monitors: Metrics and Waveform Patterns

DOA monitors commonly provide both pEEG measures and visualization of the signals. Signal waveforms are commonly represented visually on a plot of the voltage over time, or time-series (Figure 2). Because pEEG index calculations incorporate combinations of time-based or frequency-based measures, the signal waveform should correlate with the pEEG indices.

Review of the metrics provided by the BIS display are instructive (Figure 3A-F). In addition to the Bispectral index, the monitor can provide an EEG waveform, a signal quality index (SQI), electromyography (EMG), spectral edge frequency (SEF), and burst suppression ratio (SR). SQI values ranging from 50 to 100 suggest quality EEG signal acquisition. The SEF and SR deserve further elaboration as they can assist in the interpretation of the BIS index and signal waveform.

The dominant frequency of oscillations in the EEG signal should be consistent with the SEF. The SEF is the frequency at which 95% of the signal power resides at the reported frequency or lower. In an awake non-sedated individual, the distribution of frontal EEG power typically generates an SEF above 20 Hz (20 waves per second). For example, an SEF of 25, as seen during wakefulness, would indicate that most of the signal power is at frequencies of 25 Hz or lower. This would be consistent with the presence of alpha (8-13 Hz), beta (13-30 Hz), and gamma oscillations (> 30 Hz), which are associated with intact cognition. Figure 3A provides an example of the BIS monitor display for an awake patient who did not receive pre-medication. The EEG waveform demonstrates high frequency oscillations and a higher-amplitude spike consistent with a blink or eye movement (red arrow). The SEF is lower than would be expected for an awake patient, likely due to poor signal quality (SQI of 36).

The frequencies of EEG oscillations generally decline with decreasing levels of arousal. Frequency can be estimated during surgery by freezing the waveform display and counting the number of peaks (or troughs) in one second. Figure 3B shows the BIS monitor output for a sedated patient during induction of general anesthesia. As the induction agent takes effect, slower waves emerge, and SEF and EMG values decline. An SEF between 10 and 20 is common during general anesthesia and may be accompanied by emergence of oscillations in the theta band (4-8 Hz). These theta oscillations mirror those observed during non-rapid eye movement sleep. Figure 3C demonstrates theta waves, a BIS < 60, and an SEF close to 10. This constellation of observations, consistent with general anesthesia, suggests a low AWR risk. With increasing anesthetic depth, as shown in Figure 3D, EEG slow waves (blue arrow) may be observed. These low-frequency (< 4 Hz) oscillations resemble those seen during slow wave sleep.

Additional GABAergic anesthetic exposure can generate a burst suppression (BS) pattern in the EEG waveform, as shown in Figure 3E. Low amplitude (< 10 mcV) periods of cortical suppression are punctuated by bursts of mixed-frequency activity (green arrows) arising from thalamocortical circuitry. The clinical significance of BS is controversial, but the duration of intraoperative BS has been explored as a prognostic marker for postoperative delirium risk.[36] The extent of BS is quantified by the BIS monitor as the SR. The SR



Figure 3. EEG Waveforms and Corresponding Bispectral Index™ (BIS) pEEG Measures During Wakefulness and Different States of General Anesthesia. The monitor displays a signal waveform and multiple measures, including the BIS, suppression ratio (SR), spectral edge frequency (SEF), electromyographic activity (EMG), and signal quality index (SQI). (A) Awake, without pre-medication. The higher-amplitude spike (red arrow) is consistent with a blink or eye movement. (B) Sedated state during induction of general anesthesia. (C) General anesthesia. (D) General anesthesia with slow waves (blue arrow). (E) Burst suppression. Periods of suppression are punctuated by high-frequency oscillations (bursts, green arrows) in the waveform. (F) Isoelectricity. Spikes corresponding to ECG QRS complexes (orange arrow) create artifacts in the waveform.

represents the percentage of time spent in suppression over a 60-second window. The SR of 3% in Figure 3E is likely an underestimate; changes in pEEG metrics often lag behind changes in the EEG waveform. In Figure 3F, the elevated SR is consistent with the 10-second period of continuous suppression (isoelectricity) observed in the EEG waveform. The SEF is falsely elevated, likely due to the presence of electrocardiographic (ECG) artifacts. Spikes corresponding to ECG QRS complexes, marked by the orange arrow in Figure 3F, can assist in the visual identification of BS. These spikes are visible during periods of cortical suppression, such as at the end of the waveform in Figure 3D and between bursts of higher-frequency activity in Figure 3E. DOA monitors can interpret these spikes as high-frequency EEG activity, yielding falsely high BIS and SEF values.

EEG-based Depth-of-Anesthesia Monitors: A Pragmatic Approach

Appropriate skin preparation, filter usage, and voltage scale selection optimizes EEG signal acquisition. Dead skin and oils, which can impair conduction of electrical potentials, should be cleansed from the skin with an alcohol pad prior to electrode placement. Filters improve visualization and interpretation of the EEG waveform by reducing artifact effects. Enabling the filter setting can exclude low frequency artifacts (e.g., head motion and electronic signal drift) and high frequency artifacts (e.g., electrocautery and electrical interference). The voltage scale should be set to a value that maximizes the differentiation of waveform peaks and troughs. Using an appropriate voltage scale is particularly important in older patients, who often exhibit lower EEG amplitude. Low-amplitude waves are easier to distinguish using a smaller scale (e.g., 50 mV). In younger patients, a 50 mV or 100 mV scale is typically appropriate.

Acquiring EEG signals prior to induction of general anesthesia provides a baseline pattern that can contextualize intraoperative EEG waveforms and pEEG metrics (Figure 3A). During surgery, a BIS > 60 is concerning when the SEF is near 20 and the signal waveform shows higher EEG frequencies that resemble the pre-induction baseline pattern. Such instances should prompt rapid administration of additional anesthetic to prevent or terminate AWR. Due to the time delay in BIS calculation, reversion to a reassuring EEG waveform will precede normalization of BIS values. A BIS < 60 provides reassurance that AWR is unlikely when it is accompanied by metrics and waveforms consistent with deep anesthesia (Figure 3C). These include an SEF near 10, an SR > 0, and EEG waveforms that do not resemble the awake baseline pattern, such as slow waves or BS (Figure 3D-F).

It can be challenging to assess DOA and AWR risk when EEG waveforms and pEEG measures are discordant. Discordance can often be attributed to artifacts. For example, muscle activity (accompanied by rising EMG values) can account for an increasing BIS that is not explained by emergence of higher frequency EEG oscillations.[37] Given the vulnerability of pEEG measures to artifacts, interpretation of the waveform should take precedence over pEEG measures. The case discussed above (Figure 1) illustrates the utility of this

approach. BS can be readily identified in the EEG waveform, despite the elevated BIS and SEF values displayed by the monitor. The SR failed to register BS. The waveform pattern, indicative of deep anesthesia, provided reassurance that awareness was unlikely. Such contextual considerations may help optimize the interpretation of DOA monitor outputs to minimize both AWR risk and unintended iatrogenesis prompted by spurious pEEG metrics.

Conclusion

AWR is rare but carries a serious risk of psychological sequelae. Steps towards recognition in the intra- and postoperative periods are critical for mitigating harm. End-tidal anesthetic gas alarms provide a backstop for inadvertent underdosing of inhaled agents. EEG waveforms and pEEG metrics afforded by DOA monitors can be integrated to detect light anesthetic planes that risk AWR. Comparison to pre-induction EEG waveforms and pEEG metrics and assessment of concordance aid in interpretation and detection of false alarms.

References

1. Lennertz R, Pryor KO, Raz A, et al. Connected consciousness after tracheal intubation in young adults: an international multicentre cohort study. Br J Anaesth. 2022.
2. Sebel PS, Bowdle TA, Ghoneim MM, et al. The incidence of awareness during anesthesia: a multicenter United States study. Anesth Analg. 2004;99(3):833-839.
3. Ruhaiyem ME, Alshehri AA, Saade M, Shoabi TA, Zahoor H, Tawfeeq NA. Fear of going under general anesthesia: A cross-sectional study. Saudi J Anaesth. 2016;10(3):317-321.
4. Whitlock EL, Rodebaugh TL, Hassett AL, et al. Psychological sequelae of surgery in a prospective cohort of patients from three intraoperative awareness prevention trials. Anesth Analg. 2015;120(1):87-95.
5. Leslie K, Chan MT, Myles PS, Forbes A, McCulloch TJ. Posttraumatic stress disorder in aware patients from the B-aware trial. Anesth Analg. 2010;110(3):823-828.
6. Cook TM, Andrade J, Bogod DG, et al. 5th National Audit Project (NAP5) on accidental awareness during general anaesthesia: patient experiences, human factors, sedation, consent, and medicolegal issues. Br J Anaesth. 2014;113(4):560-574.
7. Kent CD. Awareness during general anesthesia: ASA closed claims database and anesthesia awareness registry. ASA Monitor. 2010;74(2):14-16.
8. Domino Karen B, Posner Karen L, Caplan Robert A, Cheney Frederick W. Awareness during Anesthesia : A Closed Claims Analysis. Anesthesiology. 1999;90(4):1053-1061.
9. Sandin RH, Enlund G, Samuelsson P, Lennmarken C. Awareness during anaesthesia: a prospective case study. Lancet. 2000;355(9205):707-711.
10. Pollard RJ, Coyle JP, Gilbert RL, Beck JE. Intraoperative awareness in a regional medical system: a review of 3 years' data. Anesthesiology. 2007;106(2):269-274.
11. Mashour GA, Kent C, Picton P, et al. Assessment of intraoperative awareness with explicit recall: a comparison of 2 methods. Anesth Analg. 2013;116(4):889-891.
12. Errando CL, Sigl JC, Robles M, et al. Awareness with recall during general anaesthesia: a prospective observational evaluation of 4001 patients. Br J Anaesth. 2008;101(2):178-185.
13. Kent CD, Posner KL, Mashour GA, et al. Patient perspectives on intraoperative awareness with explicit recall: report from a North American anaesthesia awareness registry. Br J Anaesth. 2015;115 Suppl 1:i114-i121.
14. Schwender D, Kunze-Kronawitter H, Dietrich P, Klasing S, Forst H, Madler C. Conscious awareness during general anaesthesia: patients' perceptions, emotions, cognition and reactions. Br J Anaesth. 1998;80(2):133-139.
15. Pandit JJ, Andrade J, Bogod DG, et al. 5th National Audit Project (NAP5) on accidental awareness during general anaesthesia: summary of main findings and risk factors. Br J Anaesth. 2014;113(4):549-559.
16. Aranake A, Gradwohl S, Ben-Abdallah A, et al. Increased risk of intraoperative awareness in patients with a history of awareness. Anesthesiology. 2013;119(6):1275-1283.
17. Sleigh JW, Leslie K, Davidson AJ, et al. Genetic Analysis of Patients Who Experienced Awareness with Recall while under General Anesthesia. Anesthesiology. 2019;131(5):974-982.
18. Sanders RD, Tononi G, Laureys S, Sleigh JW. Unresponsiveness ≠ unconsciousness. Anesthesiology. 2012;116(4):946-959.
19. Wang J, Zhang L, Huang Q, et al. Monitoring the end-tidal concentration of sevoflurane for preventing awareness during anesthesia (MEETS-PANDA): A prospective clinical trial. Int J Surg. 2017;41:44-49.
20. Mashour GA, Avidan MS. Pharmacologic approaches to the prevention of intraoperative awareness. Expert Rev Neurother. 2011;11(5):611-613.
21. Messina AG, Wang M, Ward MJ, et al. Anaesthetic interventions for prevention of awareness during surgery. Cochrane Database Syst Rev. 2016;10(10):Cd007272.
22. Toscano A, Pancaro C, Peduto VA. Scopolamine prevents dreams during general anesthesia. Anesthesiology. 2007;106(5):952-955.
23. Dowd NP, Cheng DC, Karski JM, Wong DT, Munro JA, Sandler AN. Intraoperative awareness in fast-track cardiac anesthesia. Anesthesiology. 1998;89(5):1068-1073; discussion 1069A.
24. Myles PS, Leslie K, McNeil J, Forbes A, Chan MT. Bispectral index monitoring to prevent awareness during anaesthesia: the B-Aware randomised controlled trial. Lancet. 2004;363(9423):1757-1763.
25. Avidan MS, Jacobsohn E, Glick D, et al. Prevention of intraoperative awareness in a high-risk surgical population. N Engl J Med. 2011;365(7):591-600.
26. Avidan MS, Zhang L, Burnside BA, et al. Anesthesia awareness and the bispectral index. N Engl J Med. 2008;358(11):1097-1108.
27. ZHANG C, XU L, MA Y-q, et al. Bispectral index monitoring prevent awareness during total intravenous anesthesia: a prospective, randomized,double-blinded, multi-center controlled trial. Chinese Medical Journal. 2011;124(22):3664-3669.
28. Mashour GA, Shanks A, Tremper KK, et al. Prevention of intraoperative awareness with explicit recall in an unselected surgical population: a randomized comparative effectiveness trial. Anesthesiology. 2012;117(4):717-725.
29. Lewis SR, Pritchard MW, Fawcett LJ, Punjasawadwong Y. Bispectral index for improving intraoperative awareness and early postoperative recovery in adults. Cochrane Database Syst Rev. 2019;9(9):Cd003843.
30. Shanks AM, Avidan MS, Kheterpal S, et al. Alerting thresholds for the prevention of intraoperative awareness with explicit recall: a secondary analysis of the Michigan Awareness Control Study. Eur J Anaesthesiol. 2015;32(5):346-353.
31. Zanner R, Pilge S, Kochs EF, Kreuzer M, Schneider G. Time delay of electroencephalogram index calculation: analysis of cerebral state, bispectral, and Narcotrend indices using perioperatively recorded electroencephalographic signals. Br J Anaesth. 2009;103(3):394-399.
32. Tewari P, Skinner H. Cardiopulmonary Bypass Machine Can Interfere with Accuracy of BIS Monitor. Anesthesia & Analgesia. 2007;105(2):534.
33. Bose S, Lewis B, Farag E. Interference with BISTM values from a forced-air warming device. BJA: British Journal of Anaesthesia. 2012;108(1):168-168.
34. Hirota K. Special cases: ketamine, nitrous oxide and xenon. Best Pract Res Clin Anaesthesiol. 2006;20(1):69-79.
35. Schuller PJ, Newell S, Strickland PA, Barry JJ. Response of bispectral index to neuromuscular block in awake volunteers. Br J Anaesth. 2015;115 Suppl 1:i95-i103.
36. Fritz BA, Kalarickal PL, Maybrier HR, et al. Intraoperative Electroencephalogram Suppression Predicts Postoperative Delirium. Anesth Analg. 2016;122(1):234-242.
37. Bruhn J, Bouillon TW, Shafer SL. Electromyographic activity falsely elevates the bispectral index. Anesthesiology. 2000;92(5):1485-1487.

Disclosure

None reported.

MM



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