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Brief Report

Cloth Mask with Window as an Alternative to Opaque Mask for Students with Speech, Language, and Hearing Deficits for Infection Risk Mitigation

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ABSTRACT

Introduction. Visualization of oral movements and facial expressions is essential for learning, development, and communication, especially among students receiving speech and language services. This study aimed to assess the effectiveness of cloth masks with transparent windows as an alternative to opaque masks in mitigating the risk of droplet-transmitted infectious diseases.

Methods. Researchers measured the filtration efficiency of various medical and non-medical masks, both with and without transparent windows. A testing pipe, fitted with the selected masks, was used to deliver particulate matter (PM) at an airflow velocity mimicking human breathing. Particle size and airflow were measured using three real-time particle monitors positioned upstream and downstream of the masks. Filtration efficiency was then calculated for each of the eight masks.

Results. Mask efficiency varied based on build quality and material. Filtration efficiency for the four face masks with transparent windows ranged from 28.6% to 90%, with the single-layer mask performing the worst. All multi-layer masks with windows achieved filtration efficiencies greater than 70% for all particle sizes tested (1, 2.5, and 10 microns), exceeding that of the opaque cotton masks and approaching the filtration levels of surgical masks.

Conclusions. Given the high filtration efficiency of cloth masks with transparent windows, the authors conclude that these masks can reduce the transmission of SARS-CoV-2 and other droplet-transmitted infectious diseases while also improving communication for individuals with speech, language, and/or hearing impairments.

INTRODUCTION

The COVID-19 pandemic impacted education worldwide, with many schools closing and others having to adapt rapidly. Students with exceptionalities, such as those requiring speech and language instruction (SLI), often were left without access to specialized services. Given that nearly one-fifth of students with academic exceptionalities receive SLI, and 10% of Kindergarten through 12th grade (K-12) students are English Learners (ELs), the absence of SLI services during the pandemic was particularly concerning.[1,2] Due to the broad implications of school shutdowns, especially for marginalized and minority students, as well as those receiving special education services,[3-5] numerous organizations advocated for in-person learning with appropriate infection risk mitigation measures.[6-9]

Masking mandates became common in schools, with data showing reduced disease transmission among mask-wearers.[10] This aligned with existing literature indicating that masks decrease the risk of transmission for other droplet-transmitted infectious diseases such as influenza and tuberculosis.[11-13] As the education system moves forward post-pandemic, it is crucial to protect both students and educators from infectious diseases while ensuring equitable access to education for students requiring SLI.

SARS-CoV-2 is primarily spread through respiratory droplets, with larger particles typically traveling 1-2 meters from the source before settling. However, environmental factors (e.g., temperature, humidity, airflow) can cause larger droplets (100 µm diameter) to evaporate and shrink into smaller particles, known as droplet nuclei (<5 µm diameter), which allow for aerosol transmission. These droplet nuclei remain airborne longer (8 minutes to 41 hours) and can travel farther, potentially infecting others.[14,15]

During the pandemic, universal masking became a key strategy for preventing COVID-19.[16-18] Medical professionals primarily use N95 masks and Level 1 surgical masks. N95 masks are designed to filter out more than 95% of particles 0.3 microns or larger but can actually filter up to 99.8% of particles as small as 0.1 microns.[19] Surgical masks, though less efficient and more variable than N95s for smaller particles, still offer good protection.[19] Cloth masks, while variable in filtration, can perform comparably to surgical masks in some cases and were recommended for non-medical use during the pandemic due to their accessibility and reusability.[17,19,20]

Although masks are effective at reducing disease transmission, they can have unintended consequences for speech and language development and education. Since the visualization of oral movements and facial expressions is critical for EL and SLI students, traditional masks that cover much of the face can hinder communication for this population.[21,22] An alternative is face masks with transparent windows (FMTWs), which allow for better visualization of oral movements and expressions during communication. However, given their recent development, there is limited evidence on the filtration effectiveness of FMTWs.

This study aimed to evaluate whether FMTWs effectively filter respiratory droplets, making them a suitable alternative to standard masks for SLI students during infectious disease outbreaks.

METHODS

Target Particle Size. Previous research has shown that particles from a human sneeze range in size from 100 µm to 1000 µm,[23] large enough to carry respiratory pathogens such as measles (0.05-0.5 µm), influenza (0.1-1 µm), and *Mycobacterium tuberculosis* (1-3 µm). For this

study, particles with diameters of 1 µm, 2.5 µm, and 10 µm were chosen to test the effectiveness of various face masks.[24]

The experimental procedure consisted of three main steps: (1) particle generation, (2) measuring particle size with and without face masks, and (3) measuring airflow rate. Aerosols were generated by burning multiple incense sticks to create a well-mixed and stable condition in the generating chamber. Once the incense sticks were lit, a fan was used to direct airflow through the chamber's air inlet. The upstream particle concentration, with airflow, was measured and remained stable in the range of 600–800 µg/m^3, confirming steady conditions. The generated aerosols were then diluted with clean air and delivered to the testing pipe at an airflow speed of 1.5 m/s, simulating the breathing velocity of healthy adults.[25]

To calculate mask effectiveness, two real-time particle monitors (OPC-N3, Alphasense, UK) were used to measure aerosol particles both upstream (Figure 1, location A) and downstream (Figure 1, location B) of the face mask.

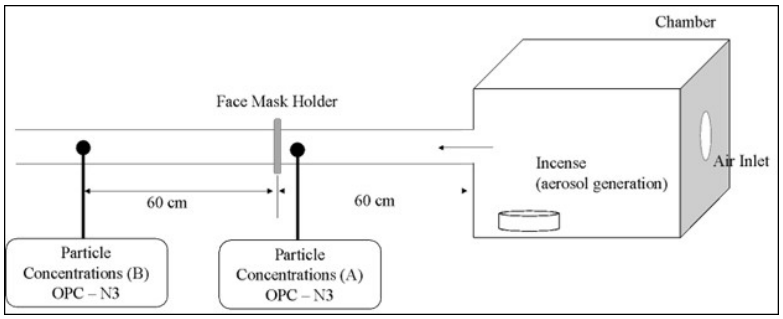

Figure 1. Experimental setup for the rapid screening test.

An Extech anemometer was used to measure airflow rates. Air velocity was measured both upstream and downstream to compare flow rate changes with and without masks. The filtration efficiency of each mask was calculated by comparing the particle concentrations at the upstream and downstream locations. The below equation was used:

$$Filter\ Efficiency\ (\%) = (1 - C_{downstream}/C_{upstream}) \times 100$$

$C_{downstream}$: Particle concentrations at the downstream of the face mask

$C_{upstream}$: Particle concentrations at the upstream of the face mask

Theory and Calculation. Filtration efficiency is expressed as the percentage of particles captured and retained by a filter medium.[26] In this study, the filtration efficiency of the masks was calculated to evaluate effectiveness in capturing aerosols generated during speaking and coughing.

RESULTS

As shown in Figure 2, eight selected masks were tested: N-95 mask (A), medical grade Level 1 surgical mask (B), and two different double layered cotton masks (C, D) were used as a reference (Table 1). Four different types of cloth FMTWs (E, F, G, and H) were used. All were installed on the mask holder and measured for at least 10 minutes.

Figure 2. Selected face masks.

Table 1 shows the mean and standard deviation (SD) of filter efficiency for the eight masks tested. Mask A (N-95) showed >99 % filter efficiency of all particles. Mask C had the lowest filter efficiency (14.7 – 41.7 %). The filter efficiencies of the four FMTWs (Masks E through H) varied from 28.6% to 90%. Overall, the lowest filter efficiency was shown when calculated based on PM 1 concentrations. Fabric and stitch type connecting the cloth to the window may have affected filter efficiency. Figure 2 shows a closer look of the four FMTWs. They all use the same stitch type, but face mask F has a double line with a large window. These two factors reduce the likelihood of particle leakage and increase filter efficiency. Mask E had the lowest filter efficiency and is the only tested mask with a single layer of fabric; it also has a single line stitch.

Table 1. Filter efficiency for masks with and without a clear window (per different size particles).

Face Mask	Material/Face Mask	Filter Efficiency (%) (SD)		
		PM 1*	PM 2.5*	PM 10*
A	N-95	99.4 (0.6)	99.6 (0.4)	99.7 (0.4)
B	Medical grade Level 1 surgical mask	83.6 (2.5)	86.6 (2.2)	87.9 (2.2)
C	Double layer cotton face mask #1	14.7 (5.2)	33.4 (6.1)	41.7 (7.3)
D	Double layer cotton face mask #2	53.0 (2.8)	73.1 (1.9)	79.5 (1.5)
E	Single-layered cloth mask with transparent window #1- polyester fabric	28.6 (5.7)	39.3 (7.3)	49.0 (7.2)
F	Multi-layered cloth mask with transparent window #2	87.2 (3.0)	89.6 (3.4)	90.0 (3.6)
G	Multi-layered cloth mask with transparent window #3	78.2 (5.3)	84.6 (3.9)	86.8 (3.2)
H	Multi-layered cloth mask with transparent window #4 - Home-made 2-layer 100% cotton fabric with 2-layer food grade storage bag window	75.1 (6.0)	81.0 (5.5)	82.8 (5.9)

*PM: Particulate matter

DISCUSSION

The goal of this study was to assess if FMTWs were comparable to other masks in filtering respiratory droplets. Three (F, G, H) of four FMTWs tested demonstrated comparable protection to double-layered cotton masks and the level 1 surgical mask. This suggests lab-based non-inferiority of FMTWs to multi-layered cloth masks for community-wide and school-based non-pharmaceutical COVID-19 mitigation strategies. Moreover, FMTWs may provide enhanced protection compared to double-layered cotton masks while also providing an increased advantage for communication. Interpreting results is more challenging for FMTWs due to their heterogeneous makeup. For example, mask F had a larger plastic window, limiting the cloth portion in the testing apparatus and complicating its results. Regardless, all multilayer FMTWs performed comparably to standard cloth masks and some approached filter efficiency of the surgical mask suggesting that these masks are effective in filtering respiratory droplets carrying infectious particles.

Results showed a large discrepancy in the filter efficiency of the two double-layered cotton masks (C, D) and the first FMTW (E) as compared to the subsequent three FMTWs (F, G, and H). This suggests that not all masks are created equally as materials and build quality may affect filtration efficiency. Across communities, masks have a variety of designs, materials, layers, and quality but despite differences evidence has shown the community health benefit of universal masking in the prevention of SARS-CoV-2 transmission.[10] In individual interactions, high quality, well-fitting masks that have a high filter efficiency are likely to be superior.

When working closely with students receiving SLI, it is important to use the mask that will provide the best protection from disease transmission and interfere the least with communication and learning. This research suggests that FMTWs will work well for these interactions by decreasing disease transmission and allowing visualization of oral movement and expression. FMTWs should also be considered for all types of instruction to young children as they are learning language and social development. When creating and manufacturing these masks, it is important to use multiple layers of cloth to surround the transparent window. There also may be benefit from a tighter or double stich pattern.

This study measured filter efficiency of a variety of masks. The measurements obtained for the medical masks are comparable to other reported filter efficiency studies. Still, there are limitations when applying these results to the prevention of SARS-CoV-2 and other droplet-transmitted infectious diseases. Mask efficacy is dependent on fit and compliance. This study did not assess how mask type may affect compliance or other potential difficulties with the transparent window such as fogging and saliva disrupting visualization through the window. In addition, comfort, oxygenation, and effect of chronic illness was not assessed in this study. Further studies should consider evaluating comfort, compliance, appropriate wear, and feasibility of prolonged wear of FMTWs.

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Keywords: COVID-19, SARS-CoV-2, masks, aerosolized droplets and particles, infectious disease droplet transmission.

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Brief Report

Factors Affecting Parental Intent to Vaccinate Against COVID-19 in Kansas

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ABSTRACT

Introduction. Vaccines have been highly effective in reducing severe illness and death from COVID-19, yet vaccine hesitancy remains a significant barrier to further lowering the incidence of morbidity and mortality. This study aimed to identify the factors influencing parental decisions about COVID-19 vaccination for their children in Kansas, including demographic variables, trust in medical professionals, vaccine safety, and the impact of misinformation.

Methods. Data were analyzed from Phase 3.7, Week 53 of the United States Census Bureau's Household Pulse Survey (N = 68,504), collected between January 4 and January 16, 2023. The analysis focused on data specific to the state of Kansas (N = 1,231), using standard descriptive statistics to assess the findings.

Results. The respondents were predominantly middle-aged, female, and Caucasian, with a high level of educational attainment and health insurance coverage. Among respondents, 45.7% (n = 563) had children under 18 living in their household. Of these, 73.5% (n = 414) expressed concerns that led them to refrain from vaccinating their children against COVID-19. The primary reasons for hesitancy included concerns about potential side effects, distrust in the vaccine's safety for children, and the belief that their children were not part of a high-risk group for having severe illness with COVID-19.

Conclusions. These findings underscore persistent concerns about COVID-19 vaccine safety and efficacy among parents, even within a relatively well-educated and insured population. Addressing these concerns with targeted public health messaging and education could be essential in increasing vaccination rates among children in Kansas.

INTRODUCTION

Vaccines have proven highly effective in reducing severe illness and death.[1-3] For example, childhood vaccinations in the U.S. have dramatically reduced the incidence, morbidity, and mortality of targeted diseases, preventing nearly 21 million hospitalizations, 732,000 deaths, and 322 million cases of disease between 1994 and 2013.[4] Furthermore, a study by Zhou et al.[5] estimated that routine vaccination of a cohort born in 2009 would save $13.5 billion in direct healthcare costs and $68.8 billion in total societal costs. Despite the clear benefits, vaccine hesitancy remains a significant barrier,[6-8] with around 1 in 5 parents in the U.S. expressing vaccine hesitancy immediately before and after the onset of the COVID-19 pandemic.[9,10]

Although national polls show broad public support for long-standing routine vaccinations, such as those for measles, mumps, and rubella, this support is not mirrored for COVID-19 vaccines.[11] Fewer than half (45%) of U.S. adults believe the preventative health benefits of COVID-19 vaccines are high, and a majority perceive the risk of side effects as "medium" or "high."[11] Additionally, COVID-19 vaccination rates for people aged 6 months to 17 years are less than one-third of those for influenza, varying widely by jurisdiction.[12,13]

In Kansas, as in many other regions, parental intent to vaccinate their children against COVID-19 is shaped by a complex interplay of factors.[14] Previous studies suggest that vaccine hesitancy may stem from fears of government overreach, the influence of social media, concerns about safety and efficacy, and unfounded theories, all of which have contributed to distrust between patients and clinicians.[7,8,14]

Understanding these factors is necessary for developing targeted strategies to increase vaccination rates among children.[15] This study explored the various determinants affecting parental decisions regarding COVID-19 vaccination for their children in Kansas, including demographic variables, trust in medical professionals, and the influence of misinformation. By identifying the key drivers of vaccine hesitancy among parents, this research aims to inform public health interventions that can effectively address concerns and promote higher vaccination uptake in the pediatric population.

METHODS

This study utilized data from Phase 3.7, Week 53 of the U.S. Census Bureau's Household Pulse Survey (HPS; N = 68,504), collected between January 4 and January 16, 2023. Specifically, data from the state of Kansas were analyzed for this study (N = 1,231). The impetus for this research stemmed from a previous study that analyzed HPS data on a national level.[16]

The HPS was launched in April 2020 to provide insights into the impact of the COVID-19 pandemic on households across the U.S. Initially, data were collected in one-week intervals, but this shifted to two-week collection periods beginning with Phase 2 in August 2020. Subsequent data releases are referred to as "Weeks" to maintain consistency with earlier phases.[17] The Census Bureau used its Master Address File as the source for sampling Housing Units (HUs) in the survey, employing a systematic sampling approach to select 66 defined sample areas from the identified HUs, each of which was interviewed once.[17] Each HU was contacted by email and short message service, if available, using Qualtrics, an online data collection platform. In Week 53, 1,049,855 HUs were identified, and surveys were completed by 68,504 respondents.[18] A local Institutional Review Board (IRB) reviewed the data, confirming that they were publicly available and de-identified. Consequently, this analysis did not involve human subjects and did not require IRB oversight.

Statistical Analyses. Standard descriptive statistics were used to create a demographic profile, describe participant likelihood of

vaccinating their children against COVID-19, and to describe the reasons for COVID-19 vaccine hesitancy in parents in the State of Kansas.

RESULTS

Respondent Characteristics. Table 1 represents the demographic information of respondents. The average age of respondents was 52.9 years old (standard deviation [SD], 16.3); 61.0% were biological female; 59.2% identified as female; and 89.9% were heterosexual. Most respondents (57.7%) reported being married; 94.8% were not from Hispanic, Latino, or Spanish origin; 90.3% were Caucasian or White alone; 48.7 % completed a bachelor's or higher degree; 36.2% reported their household gross income as $75,000 or higher; and 43.2% had health insurance coverage through a current or former employer or union.

COVID-19 Vaccine Hesitancy. As shown in Table 2, just over 45.0% (n = 563) of respondents reported having children under 18 years old in their household. Among these respondents, a portion indicated they would definitely not vaccinate their children against COVID-19. Specifically, 41% (n = 43) of respondents with children under 5 years old, 41.2% (n = 49) with children aged 5-11 years, and 39.7% (n = 27) with children aged 12-17 years expressed this intention. Nearly 74% (n = 414) of the respondents with children in their household reported several reasons for not getting children the COVID-19 vaccine. The top three reported reasons were: concerns about side effects on the children (21.3%), not trusting the vaccines as safe for the children (15.0%), and children in the household not being members of a high-risk group (14.7%; Table 2).

DISCUSSION

This study aimed to determine the prevalence of COVID-19 vaccine hesitancy and assess contributing factors among parents of children in Kansas. The findings provide valuable state-level demographic data and insights into the mindsets and attitudes of those hesitant to vaccinate their children against COVID-19, allowing for more accurately targeted and effective future interventions to boost vaccination rates.

The data in Table 2 reveal that 45.7% (n = 563) of respondents reported having children under 18 years old at home. Among these families, there was a level of parental hesitancy regarding COVID-19 vaccination for children, with 73.5% (n = 414) of respondents expressing reluctance. This high level of hesitancy is consistent with trends observed in previous studies, where concerns about vaccine safety and side effects have been prominent factors.[16,19,20] Specifically, 21.3% (n = 88) of respondents in this study cited fears of potential side effects, a figure that aligns with existing literature emphasizing parental worries about adverse reactions, particularly given the rapid development and approval of COVID-19 vaccines.[16,21]

Additionally, 15.0% (n = 62) of respondents expressed concerns about vaccine safety, aligning with findings from other studies that highlight general mistrust as a major barrier to vaccine uptake.[22,23] While public concerns about COVID-19 vaccine safety are understandable, given reported risks such as anaphylaxis, myocarditis, and pericarditis,[24,25] evidence shows these adverse events are rare and mostly associated with certain types of COVID-19 vaccines.[26] Public education should emphasize the rarity of these incidents and encourage individuals with safety concerns to consider alternative COVID-19 vaccines from different manufacturers. Addressing parental concerns directly may help increase vaccination rates among children.[27]

Moreover, 14.7% (n = 61) of parents believed their children were not at high risk for severe COVID-19 outcomes. This perception is consistent with the broader public's understanding that children typically experience milder COVID-19 symptoms.[27] However, this belief overlooks the importance of vaccination in mitigating community transmission and protecting vulnerable populations, particularly those who are immunocompromised or unable to be vaccinated.[28,29]

The reluctance observed in this study emphasizes the need for targeted public health campaigns to address specific parental concerns, such as safety and side effects, while reinforcing the broader public health benefits of vaccination. Interventions to improve vaccine hesitancy should emphasize providing accurate, easily accessible information and being transparent in addressing parental concerns. A study by Shen et al.[30] recommends presenting vaccination as a default approach, being honest about side effects, providing credible resources supporting proven scientific facts, and focusing on the protection of the child. Furthermore, targeted discussions should include the proven safety and efficacy of the vaccines, as evidenced by prior studies and communications.[31-34]

Limitations. This study had several limitations that need to be addressed. First, the reliance on self-reported surveys may introduce recall bias. The cross-sectional design does not allow for the assessment of changing parental attitudes over time. Additionally, the data collection spanned only two weeks, from January 4 to January 16, 2023, which may not reflect current attitudes towards the COVID-19 vaccine. Parental understanding of the vaccine may have increased since then due to national and statewide educational initiatives. Future studies could address this by using longitudinal data.

Respondents found to be vaccine-hesitant were asked to select their reasons from predetermined options for concerns regarding the COVID-19 vaccine for their children. While this allowed for easy classification, a free-response survey might have provided more accurate reflections of their reasons. Although this approach would complicate data analysis, it could offer greater detail in follow-up studies.

Finally, some parents chose not to respond to the survey, and their views on vaccination might differ from those who reported vaccine hesitancy. Follow-up studies assessing changes in vaccination attitudes also could provide valuable insights into the effectiveness of initiatives in addressing parental concerns.

Table 1. Demographic information.

Characteristics	Measure (N = 1,231)
Age	
Mean (SD), y	52.9 (16.3)
Median	54
Minimum	18
Maximum	88
Marital status, no. (%)	
Never married	207 (16.8)
Married	710 (57.7)
Divorced	201 (16.3)
Separated	23 (1.9)
Widowed	82 (6.7)
Prefer to not answer	8 (0.6)
Biological sex, no. (%)	
Male	480 (39.0)
Female	751 (61.0)
Gender identity	
Male	465 (37.8)
Female	729 (59.2)
Transgender	8 (0.6)
None of these	14 (1.1)
Prefer to not answer	15 (1.2)
Sexual orientation	
Straight/heterosexual	1,107 (89.9)
Gay or lesbian	26 (2.1)
Bisexual	54 (4.4)
Something else	17 (1.4)
Prefer to not answer	15 (1.2)
I don't know	12 (1.0)
Ethnicity, no. (%)	
Hispanic, Latino, or Spanish origin	64 (5.2)
Not of Hispanic, Latino, or Spanish origin	1,167 (94.8)
Race, no. (%)	
Caucasian/White alone	1,111 (90.3)
African American/Black alone	38 (3.1)
Asian alone	21 (1.7)
Any other race alone, or race in combination	61 (5.0)
Highest degree/level of school completed, no. (%)	
Less than high school	6 (0.5)
Some high school	17 (1.4)
High school graduate or equivalent (for example GED)	166 (13.5)
Some college, but degree not received or is in progress associate degree (for example AA, AS)	305 (24.8)
Associate's degree (for example AA, AS)	138 (11.2)
Bachelor's degree (for example BA, BS, AB)	332 (27.0)
Graduate degree (for example master's, professional, doctorate)	267 (21.7)
Household gross income, no. (%)	
Less than $25,000	114 (9.3)
$25,000-$34,999	91 (7.4)
$35,000-$49,999	136 (11.0)
$50,000-$74,999	193 (15.7)
$75,000-$99,999	139(11.3)
$100,000-$149,999	176 (14.3)
$150,000-$199,999	62 (5.0)
$200,000 and above	69 (5.6)
Prefer to not answer	43 (3.5)
Missing	208 (16.9)
Health insurance coverage, no. (%)	*n* = 1,539*
Insurance through a current or former employer or union (self or through family member)	665 (43.2)
Purchased directly from ins company (self or through family member)	285 (18.5)
Medicare, for people 65 and older, or with certain disabilities	316 (20.5)
Medicaid, Medical Assistance, or any kind of government-assistance plan for low income/disability	104 (6.8)
TRICARE or other military health care	57 (3.7)
VA (including those who have ever used/enrolled for VA health care)	61 (4.0)
Indian Health Service	6 (0.4)
Other	45 (2.9)

* Raw numbers are more than the sample size because some participants reported multiple insurance coverage

Table 2. Respondents' information regarding COVID-19 and COVID-19 vaccines.

Characteristics	Measure (N = 1,231)
COVID-19 Vaccination status, no. (%)	
Received a vaccine	1,035 (84.1)
Not received a vaccine	181 (14.7)
Prefer to not answer	15 (1.2)
Tested positive or told by a physician or a health care provider that you have COVID?, no. (%) [at the time of the survey]	
Yes	611 (49.6)
No	583 (47.4)
Prefer to not answer	21 (1.7)
Missing	16 (1.3)
Children living in household	*n* = 563
Children under 5 in household	147 (26.1)
Children 5 through 11 years old in household	208 (36.9)
Children 12 through 17 in household	208 (36.9)
Likelihood of getting children vaccinated (under 5 years old), no. (%)	*n* = 103
Definitely get the children a vaccine	9 (8.7)
Probably get the children a vaccine	8 (7.8)
Be unsure about getting the children a vaccine	9 (8.7)
Probably NOT get the children a vaccine	20 (19.4)
Definitely NOT get the children a vaccine	43 (41.7)
I do not know the plans for vaccination of the children under 5 in my household	11 (10.7)
Prefer to not answer	3 (2.9)

Table 2. Respondents' information regarding COVID-19 and COVID-19 vaccines. *continued.*

Characteristics	Measure (N = 1,231)
Likelihood of getting children vaccinated (5 to 11 years old), no. (%)	*n* = 119
Definitely get the children a vaccine	8 (6.7)
Probably get the children a vaccine	5(4.2)
Be unsure about getting the children a vaccine	7 (5.9)
Probably NOT get the children a vaccine	29 (24.4)
Definitely NOT get the children a vaccine	49 (41.2)
I do not know the plans for vaccination of the children 5 to 11 in my household	16 (13.4)
Prefer to not answer	5 (4.2)
Likelihood of getting children vaccinated (12 to 17 years old), no. (%)	*n* = 68
Definitely get the children a vaccine	0 (0.0)
Probably get the children a vaccine	1 (1.5)
Be unsure about getting the children a vaccine	9 (13.2)
Probably NOT get the children a vaccine	19 (27.9)
Definitely NOT get the children a vaccine	27 (39.7)
I do not know the plans for vaccination of the children 12 to 17 in my household	10 (14.7)
Prefer to not answer	2 (2.9)
Reasons for not getting children vaccinated, no. (%)	*n* = 414
Concern about side effect of the COVID-19 vaccine for children	88 (21.3)
Plan to wait to see if it is safe/ may get later	38 (9.2)
Not sure if COVID-19 vaccine will work for children	9 (2.2)
Don't believe children need COVID-19 vaccine	56 (13.5)
Children in household not members of a high-risk group	61 (14.7)
Children's doctor has not recommended COVID-19 Vaccine	38 (9.2)
Parents/guardians in household do not vaccinate their children	7 (1.7)
Don't trust COVID-19 vaccines	62 (15.0)
Don't trust the government	38 (9.2)
Other reason	17 (4.1)

CONCLUSIONS

In conclusion, the high rate of COVID-19 vaccine hesitancy among parents and guardians in Kansas may be driven by concerns about side effects, safety, and the perceived risk of the disease. This study highlights key areas that initiatives can focus on to improve vaccine uptake and health outcomes. These initiatives could include public health campaigns centered on education, transparent communication, family-centered approaches using motivational interviewing, and making vaccines more accessible to increase vaccination rates among children. Addressing these concerns is important for controlling the spread of COVID-19 and achieving broader immunity in communities.

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Brief Report

Cost Burden of Cancer Screening in Kansas by Region and Rural/Urban Designation

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ABSTRACT

Introduction. In 2022, the U.S. healthcare expenditure totaled $4.5 trillion, representing 17.3% of its gross domestic product. Despite this, 26 million Americans remain uninsured, often relying on out-of-pocket payments for essential services like cancer screenings. Kansas, with its high uninsured rate, faces unique challenges, emphasizing the need to analyze the cost burden of these critical yet repeatable interventions.

Methods. Authors of this cross-sectional study analyzed hospital pricing transparency data for breast, lung, and colon cancer screening costs across 124 Kansas hospitals. Data on self-pay costs were collected and compared between urban and rural regions, as well as geographic price variations. Statistical analyses included measures of central tendency, Kruskal-Wallis tests, and Mann-Whitney U tests to evaluate differences.

Results. Pricing disparities were evident across Kansas. Urban hospitals charged higher prices for chest computed tomography (CT) scans, while rural hospitals had elevated costs for colonoscopies and mammograms. Notable price variation included Northeast Kansas colonoscopy prices, which ranged from $595 to $11,684. Rural residents faced a greater financial burden, spending 7% of their income on screenings compared to 6% for urban residents. Median screening prices statewide were $2,247 for colonoscopies, $1,109 for chest CT scans, and $228 for mammograms.

Conclusions. These disparities call for targeted policy interventions, such as Medicaid expansion, standardized pricing regulations, and increased support for low-cost clinics. Enhanced hospital pricing transparency is critical for empowering patients and reducing financial burdens. This study highlights the urgent need for equitable access to cancer screenings in Kansas.

INTRODUCTION

In 2022, the U.S. was estimated to have spent nearly 4.5 trillion dollars on healthcare, equating to roughly 17.3% of U.S. gross domestic product.[1] Despite the huge costs spent on healthcare, the U.S. remains one of the few countries in the developed world without a nationalized health service that provides a public option to all citizens. The vast majority of individuals living in the U.S. do carry insurance (92.1%), most of whom utilize private, employer-based health plans (54.2%), with the other biggest suppliers being government backed Medicaid (18.8%) and Medicare (18.7%) services.[2] However, there are still 26 million Americans who are uninsured and must pay their hospital bills out of pocket (7.9%).[2] The cost incurred from paying medical services out of pocket can be extensive.

A commonly seen cost associated with healthcare in the U.S., which is conducted multiple times over one's lifetime, is cancer screenings. A colonoscopy is one such procedure that must be conducted every 10 years, starting at the age of 45, for colorectal cancer screening.[3] Other methods exist for colon cancer screening, including tests like Cologuard; however, colonoscopy has remained the most used screening mechanism.[4] Breast cancer is another such malignancy that is screened for, and bilateral breast mammography is typically utilized for screening starting at the age of 40 and continuing each year until age 75.[5] Finally, another commonly performed screening procedure is low dose chest computed tomography (CT) scan for lung cancer. This is recommended in adults aged 50 to 80 years who have at least a 20 pack per year smoking history and currently smoke or have quit within the past 15 years and must be performed every year in those who qualify.[6]

The costs incurred from screening tests can be extensive for uninsured individuals, especially considering the costs must be paid in multiple instances over a lifetime. Differing hospitals and health systems charge varied prices for certain services. This can make it very difficult for an individual without health insurance to navigate what costs they might incur as a cash-pay patient. Kansas ranks in the top half of states with the most uninsured individuals, leaving a significant portion of the population vulnerable to the complex financial burden of cancer screening.[7] We sought to analyze cash costs for cancer screening services between rural and urban hospitals in Kansas and the differing costs incurred by geographic region at hospitals in designated regions of the state.

METHODS

For this cross-sectional cost analysis study, we utilized hospital pricing transparency data to collect charges associated with specific current procedural terminology (CPT) codes for cancer screening tests across all Kansas hospitals. The screenings analyzed included colon cancer (colonoscopy, CPT code 45378), lung cancer (chest CT scan without contrast, CPT code 71250), and breast cancer (bilateral screening mammography, CPT code 77067).

Data Collection. All 124 Kansas hospitals that were part of the Kansas Hospital Association were screened for the self-pay/cash costs of the above procedures, utilizing either hospital provided price estimator tools or hospital standard charge forms.[8] Some hospital websites had nonworking price estimator tools, corrupted standard charge forms, or no identifiable information related to hospital price transparency. As such, hospital charges were included only if pricing was available for at least one of the screening procedures above. Only the self-pay/cash cost of the CPT code charge was included in the data; no other costs related to other providers involved in performing the intervention, such as anesthesia provider charges, were included in our pricing data. Rural vs urban hospitals were defined based on their location within or outside of an urban designated census place of >50,000 people, as outlined by the USDA.[9]

Analysis. Descriptive statistics were used to extrapolate differences between rural and urban hospital cancer screening pricing points and

regional pricing data. Due to the skewed distribution of the data, medians were used for central tendency and Kruskal-Wallis tests and Mann-Whitney U tests were employed to examine statistical differences. Geographic pricing data also were summarized with hospitals grouped into regions based on Kansas Hospital Association district delineations.[10] State per capita income between rural and urban individuals also was gathered to calculate the percentage of income spent on care if all cancer screenings were conducted within a single calendar year.[11]

RESULTS

Sample Data. A total of 111 hospitals had cost data available for the three screenings under review. Table 1 summarizes the median cost of each screening and the breakdown of hospital frequency in rural areas, urban areas, and regionally. Screening procedures were not universally available statewide, resulting in the different sample sizes noted. The geographic region with the most hospitals included in the study was the northeast region with 27 total hospitals. The region with the fewest reporting hospitals was in the southeast region with 11 total hospitals.

Table 1. Median cost of screening and hospital frequency in Kansas.

	Colonoscopy		CT Without Contrast		Bilateral Mammogram	
Median cost statewide	$2,247.28		$1,109.19		$228.00	
Total # hospitals with service statewide	96		106		96	
# Hospitals rural	80	83%	91	86%	81	84%
# Hospitals urban	16	17%	15	14%	15	16%
# Hospitals northwest	15	16%	17	16%	16	17%
# Hospitals north central	10	10%	12	11%	10	10%
# Hospitals northeast	26	27%	27	25%	27	28%
# Hospitals southeast	10	10%	11	10%	9	9%
# Hospitals south central	23	24%	23	22%	21	22%
# Hospitals southwest	12	13%	16	15%	13	14%

Note: CT, Computed Tomography

Rural vs. Urban Pricing. Table 2 shows the breakdown of rural and urban median pricing and the range for all three screening interventions. Cash price screening services were noted to be more expensive in urban areas for chest CT scan, but more expensive rurally for colonoscopy and bilateral mammogram. Mann-Whitney U tests revealed no significant differences between the costs of each screening procedure in rural vs. urban hospitals with a standard $p < 0.05$ threshold.

Table 2. Rural vs. urban screening pricing.

	Colonoscopy	CT Without Contrast	Bilateral Mammogram
Rural hospitals	N=80	N=91	N=81
Median cost	$2,268.50	$1,031.30	$240.35
Minimum cost	$75.60	$120.80	$64.00
Maximum cost	$18,979.38	$3642.50	$596.00
Urban hospitals	N=16	N=15	N=15
Median cost	$1,745.50	$1,647.00	$179.00
Minimum cost	$902.20	$108.53	$63.00
Maximum cost	$14,686.00	$9,051.00	$806.00

*Values denoted in U.S. dollars.
Note: CT, Computed Tomography

Geographic Pricing. Regional hospital pricing data are denoted in Table 3 with the mean charges for each screening noted in U.S. dollars. The most expensive region for cash-pay colonoscopy was northcentral with a median price of $2,935.86. The least expensive region was the northeast at $1,866.33. Screening chest CT was noted to be least expensive in the northwest (median [Md] = $775.00) and most expensive in the southeast region (Md = $1,347.12). Screening mammography was noted to be more expensive in the northcentral region (Md = $270.61) and least expensive in the northeast (Md = $172.15). A Kruskal-Wallis test revealed statistically significant differences between regions for CT without contrast (χ^2 (5, n = 106) = 13.25, p = 0.021) and bilateral mammogram (χ^2 (5, n = 96) = 12.21, p = 0.032). Follow-up Mann-Whitney U tests of four comparisons for each, adjusting p utilizing a Bonferroni correction (p = 0.0125; 0.05/4), revealed the significant differences for CT without contrast were between the southcentral (Md = $1,329.00) and southwest (Md = $801.85) regions. Differences for bilateral mammogram were between the northwest (Md = $270.00) and northeast (Md = $172.15) regions, as well as the northeast and northcentral regions (Md = $270.61).

Rural vs. Urban Income Comparison. In 2021, the median household income in Kansas was $58,924.[11] Rural populations in Kansas have a median income of $51,545. Urban populations had a median yearly household income of $62,267.[11] The total median cash price for all noted services in a calendar year in rural areas was $3,540.15, which is equal to 7% of a rural individual's yearly income. The total median cash price in urban areas is $3,571.50, which is equal to 6% of an urban patient's yearly income.

Table 3. Regional hospital screening pricing.

		Colonoscopy	CT Without Contrast	Mammogram
Northwest hospitals	N	15	17	16
	Median	$2,571.43	$775.00	$270.00
	Range	$1,639.80-$5,930.37	$187.60-$2,010.00	$97.00-$472.83
North central hospitals	N	10	12	10
	Median	$2,935.86	$1225.00	$270.61
	Range	$1,549.00-$6,978.60	$702.60-$2,525.70	$150.00-$397.10
Northeast hospitals	N	26	27	27
	Median	$1,866.33	$1,104.38	$172.15
	Range	$595.00-$1,1684.00	$108.53-$4,429.00	$63.00-$806.00
Southeast hospitals	N	10	11	9
	Median	$2143.90	$1347.12	$197.00
	Range	$75.60-$4,314.88	$610.00-$2,328.85	$100.00-$581.73
South central hospitals	N	23	23	21
	Median	$2142.83	$1329.00	$246.00
	Range	$980.00-$18,979.38	$387.00-$9,051.00	$73.00-$596.00
Southwest hospitals	N	12	16	13
	Median	$2,101.76	$801.85	$202.30
	Range	$1,100.00-$3,966.36	$430.50-$3,642.50	$125.00-$358.10

Note: Values denoted in U.S. dollars. CT, Computed Tomography

DISCUSSION

Our study highlights that cash pricing for cancer screening services in Kansas varies significantly based on the rurality of the hospital and the geographic location where the service is received. Additionally, the percentage of annual income spent on these services differs between rural and urban populations. These disparities pose significant challenges, particularly for uninsured patients and those who must travel long distances to access care.

In 2024, the uninsured rate in Kansas reached 8.4%, representing 240,302 individuals.[12] Historically, uninsured rates have been higher in rural counties compared to urban ones.[13] Furthermore, uninsured patients tend to have lower annual incomes than their insured counterparts.[14] With rural residents also having lower median incomes than urban residents, these factors exacerbate the cost burden of cancer screening for uninsured individuals in rural areas.

Expanding Medicaid is one potential solution to reduce the financial burden of cancer screenings. Despite data demonstrating Medicaid's vital role in ensuring rural populations, Kansas has not adopted Medicaid expansion.[15] Rural hospitals, which already face higher rates of uncompensated care compared to urban hospitals, are disproportionately affected.[16] Most states with the highest levels of uncompensated care have similarly chosen not to expand Medicaid.[17]

Beyond Medicaid expansion, additional measures to address care costs for uninsured patients could include legislation to establish standardized pricing for self-pay patients and increased funding for free or low-cost clinics offering cancer screenings. Public education on the stark pricing variations between hospitals and the factors influencing these differences also are essential.

Our data revealed significant price discrepancies for identical services. For instance, the cash price for a colonoscopy in Northeast Kansas ranged from $595 to $11,684. Such variation is likely due to multiple factors, including negotiated reimbursement rates with insurers, hospital operating costs, and cross-subsidization, where profitable services offset the costs of less profitable ones. These findings underscore the importance of pricing transparency from hospitals, enabling patients to make informed decisions about where to receive care.

Limitations. This analysis is not without limitations, as not all hospitals had usable or accessible pricing transparency data. Furthermore, many patients may elect to have their screening tests done at outpatient surgery centers or in other clinic sites across the state, and the pricing in these locations may be different than from the testing received in community or tertiary care hospitals.

CONCLUSIONS

The cost of cancer screenings in Kansas poses a significant financial challenge for many individuals, particularly the uninsured. Expanding Medicaid could be a key intervention to reduce these costs, ensuring that uninsured residents gain access to necessary care regardless of their ability to pay. By extending coverage to all uninsured Kansans, Medicaid expansion could make cancer screenings more accessible and affordable.

Other viable strategies to address the high costs of cash-pay care include setting standardized price points for self-pay services, increasing funding and support for free and low-cost clinics, and educating the public about the significant price variations between hospitals. These efforts could empower patients to make informed decisions while alleviating financial barriers.

Additionally, factors such as negotiated reimbursement rates with insurers, hospital operating costs, and cross-subsidization likely contribute to the wide range of screening costs across the state. Addressing these underlying causes may further improve affordability. Given the substantial return on investment for preventive care, exploring these interventions is both practical and essential for promoting equitable healthcare access in Kansas.

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Keywords: rural health, medically uninsured, health care costs, cancer screening

KANSAS JOURNAL of MEDICINE

Case Report

Tophaceous Gout in the Axial Skeleton: An Unusual Case with Key Imaging Characteristics

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INTRODUCTION

Gout is a common form of inflammatory arthritis, characterized by the deposition of monosodium urate crystals in joints and soft tissues.[1] The prevalence of gout in the U.S. is estimated to be approximately 3.9%, according to a National Health and Nutrition Examination Survey.[2] While most cases present as intermittent flares of monoarthritis, chronic tophaceous gout is a more severe form of the disease.[3] It is distinguished by the formation of tophi, which are large aggregations of monosodium urate crystals surrounded by inflammatory cells and tissues.[3]

The gold standard for diagnosing gout is joint aspiration or lesional biopsy, with visualization of the needle-shaped monosodium urate crystals under polarized light microscopy.[3] However, the clinical presentation and imaging findings of tophaceous gout can be nonspecific, often mimicking other conditions such as rheumatoid arthritis, infection, or malignancies.[4-6] Although magnetic resonance imaging (MRI) findings in gout lesions may resemble those of other inflammatory, infectious, or neoplastic conditions, computed tomography (CT) and dual-energy CT can provide crucial information for a more accurate diagnosis.[7]

In this case report, we present a detailed account of a patient with chronic tophaceous gout involving the thoracic spine, emphasizing the clinical presentation, and imaging findings. This unusual presentation highlights the importance of considering gout in the differential diagnosis of paraspinal masses and the critical role of different imaging modalities in reaching the correct diagnosis.

CASE REPORT

A 39-year-old male with a history of chronic variable immunodeficiency, disseminated histoplasmosis, and poorly controlled tophaceous gout presented with altered mental status, chest pain, and shortness of breath. Physical examination revealed focal swelling of the right elbow, multiple metacarpophalangeal and interphalangeal joints in both hands, and the right metatarsophalangeal joint, all corresponding to known gouty tophi. Additionally, there was generalized swelling and tenderness, along with pitting edema in both lower extremities.

An electrocardiogram was unremarkable. Initial laboratory work-up showed leukopenia, iron deficiency, and elevated C-reactive protein. The uric acid level was elevated at 6.1 mg/dL (target < 3 mg/dL), despite the patient taking 300 mg of allopurinol daily. A lumbar puncture revealed significantly elevated white blood cell and total protein levels, with findings positive for John Cunningham virus, also known as human polyomavirus 2. MRI of the brain showed confluent T2 hyperintense signal in the bilateral supratentorial white matter (Figure 1), consistent with progressive multifocal leukoencephalopathy.

A CT scan of the chest revealed multifocal paraspinal soft tissue masses along the thoracic spine, involving adjacent vertebrae and ribs, with sharply demarcated osseous erosions (Figure 2). Subsequent MRI of the thoracic spine showed multiple T1 and T2 hypointense enhancing paraspinal masses with associated osseous involvement and erosion (Figures 3 and 4). Some masses extended along the posterior intercostal spaces and transverse foramina into the adjacent epidural space, causing thecal sac narrowing and spinal cord compression.

While the sharply demarcated osseous erosions on CT suggested tophaceous gout or lymphoma, other possibilities included metastatic disease, plasmacytoma, and infection. A dual-energy CT scan revealed extensive uric acid deposition in the paraspinal and intercostal regions of the thoracic spine (Figure 5). A CT-guided needle biopsy at T8-T9 confirmed the diagnosis of gout.

The patient's gout treatment plan included increasing the dose of allopurinol and initiating recombinant uricase (such as pegloticase) to achieve better disease control. However, due to the complexity of his medical conditions and subsequent clinical deterioration, the patient chose palliative care and passed away one month after his initial presentation.

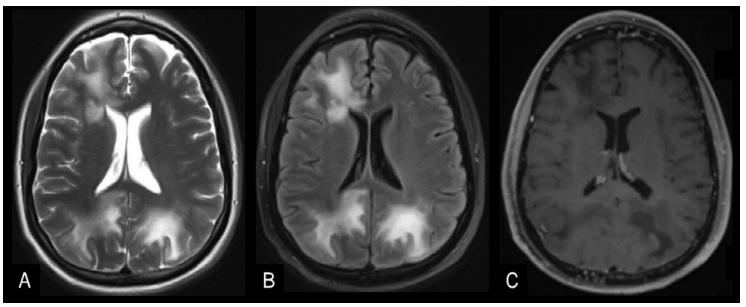

Figure 1. Axial T2 (A) and FLAIR (B) MRI images of the brain showing geographic and confluent T2 and FLAIR hyperintense signal involving the bilateral supratentorial white matter. Axial postcontrast T1 (C) demonstrates no associated enhancement.

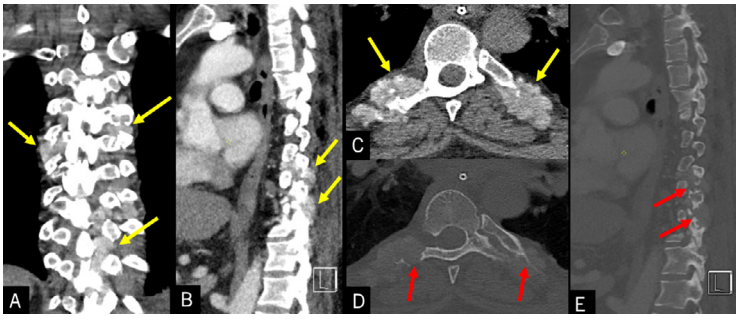

Figure 2. (A-C) Coronal, sagittal, and axial CT reformats demonstrate multiple paraspinal soft tissue masses with internal amorphous calcification (yellow arrows). (D-E) Axial and sagittal CT reformats with bone kernels demonstrate sharply demarcated osseous erosions (red arrows).

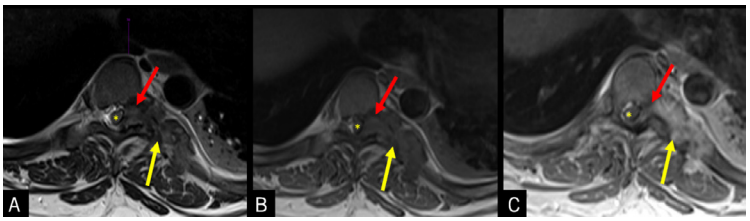

Figure 3. Axial MRI images of the thoracic spine demonstrate multiple paraspinal T2 hypointense (A) and T1 hypointense (B) masses with post contrast enhancement (C) (yellow arrows). The mass is noted to involve the posterior thoracic spinal elements, paraspinal soft tissues, and intercostal space. Some of these masses are noted to extend through the neural foramina into the epidural space (red arrows) with associated compression of the spinal cord (asterisk).

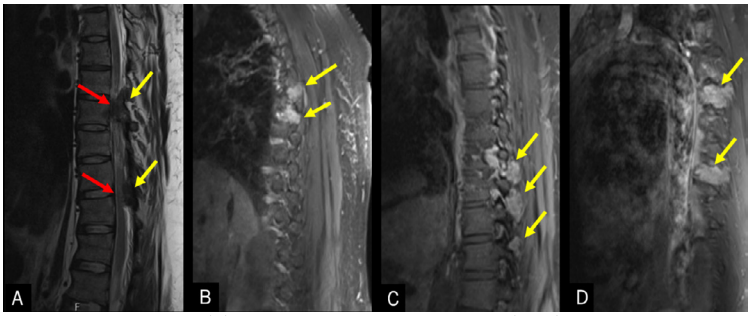

Figure 4. Sagittal T2 (A) and postcontrast sagittal T1 (B-D) MRI images of the thoracic spine again show the multifocal T2 hypointense, enhancing masses involving the adjacent vertebral bodies and posterior elements (yellow arrows). Some of these masses extend into the epidural space causing thecal sac narrowing and spinal cord compression at T7-8 and T10-11 levels (red arrows).

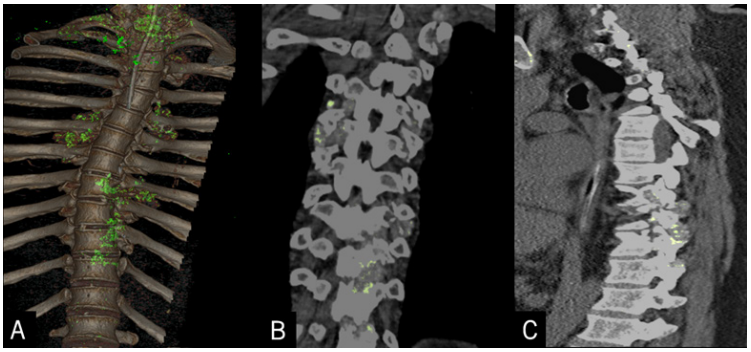

Figure 5. 3D reconstruction (A), and coronal (B) and sagittal (C) reformats of dual-energy CT with color mapping of the thoracic spine demonstrating green color-coded pixels in the paraspinal masses, indicating monosodium urate crystal deposition, confirming the diagnosis of gout.

DISCUSSION

Gout typically manifests in the peripheral joints, however as many as 29% of patients with gout have CT findings in the axial skeleton.[8] The prevalence of spinal gout is estimated to be up to 35% based on small studies, though the true value is still unknown due to some patients being asymptomatic.[9,10] When symptomatic, spinal tophaceous gout typically presents with back or neck pain resulting from compression of the spinal cord or nerve roots.[11] The lack of specific symptoms may lead to delayed diagnosis. In our patient, with a complex history and a myriad of non-specific imaging findings, suspicion of possible infection or disseminated metastasis could have masked the etiology of the spinal masses. Keeping a broad differential diagnosis and recognizing the imaging characteristics of gout are critical in differentiating these masses from other potential pathologies.

Conventional radiographs are the first line imaging tool in evaluation of rheumatic diseases. Classic radiograph findings of gout include well-demarcated marginal and juxta-articular erosions.[12] Chronic tophaceous gout typically have well defined punched out erosions.[13] CT typically demonstrates tophi as lesions with well-demarcated corticated osseous erosions and overhanging margins at the intra-articular and extra articular sites.[14] This finding was key in the presented case, as it raised suspicion for gout over other differential diagnoses, prompting further investigation. MRI in gout is considered sensitive but not specific with imaging features overlapping with other pathologies, so confirmatory support often is needed in the form of biopsy or other imaging modalities.[14] The typical appearance of tophaceous gout on MRI is lobulated lesions with intermediate or low T1 signal intensity, heterogenous signal intensity on T2 weighted sequences, and homogenous postcontrast enhancement.[14,15] Tophaceous lesions can cause mass effect resulting in spinal canal and neuroforaminal stenosis, and ligamentum flavum hypertrophy.[15] Gout tophi also can cause erosion of the facet joints leading to joint effusion.[15]

Dual-energy CT is an advanced imaging technique that can differentiate different substances based on the level of X-ray absorption. This is useful in detecting monosodium urate crystal deposition by using photon energy levels that correlate with monosodium urate crystals. A meta-analysis of 11 studies done by Ogdie et al.,[16] showed that dual-energy CT has a sensitivity of up to 0.90 and a specificity of up to 0.93 in gout diagnosis, compared to the standard of joint aspiration and crystal identification by polarized light microscopy.[17] Using dual-energy CT in conjunction with other imaging studies will allow for confirmation of suspected diagnosis. Spinal gout is initially treated with conservative management including anti-inflammatories and urate lowering therapy.[9] In patients with neurological symptoms, surgical treatment is recommended.[9]

CONCLUSIONS

This case underscores the importance of recognizing classic imaging features in the diagnosis of tophaceous gout, particularly in atypical or complex presentations. Both CT and MRI can help visualize masses and refine the differential diagnosis, while advanced imaging techniques like dual-energy CT add further value by confirming the diagnosis. It also emphasizes the need for considering a broad differential and employing a comprehensive diagnostic approach when evaluating patients with spinal masses.

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Keywords: gout, axial spondyloarthritis, gouty arthritis

KANSAS JOURNAL of MEDICINE

Case Report

Working Backwards: Splenic Infarcts from Left Ventricular Thrombus

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INTRODUCTION

Splenic infarction is a rare but significant complication often linked to embolic events, with an incidence of 8.9 per 100,000 person-years.[1,2] It is frequently overlooked as a cause of abdominal pain, though improved imaging modalities now aid in its recognition, even as up to 30% of splenic infarcts remain asymptomatic.[3] A primary source of emboli is thrombus formation within the left ventricle (LV) in patients with heart failure, particularly heart failure with reduced ejection fraction (HFrEF). HFrEF, defined by a left ventricular ejection fraction (LVEF) ≤ 40%, predisposes patients to intracardiac thrombi formation due to blood stasis.[4] Here, we present a rare case of splenic infarction secondary to a LV thrombus in a patient with HFrEF.

CASE REPORT

A 59-year-old male with a history of HFrEF presented to the emergency department with sudden, sharp left upper quadrant abdominal pain. Diagnosed with heart failure 12 years prior, his condition had been managed with medications, though his LVEF remained at 30-35%. Four days before presentation, he had a fall, resulting in a bruise and pain unresponsive to pain medications.

On arrival, the patient's vital signs were stable except for elevated blood pressure. Physical examination revealed tenderness in the left upper quadrant without signs of an acute abdomen. Cardiovascular examination showed signs consistent with chronic heart failure, including a displaced apical impulse and a third heart sound (S3).

Laboratory results were unremarkable. An electrocardiogram showed normal sinus rhythm, and a chest X-ray indicated cardiomegaly without pulmonary congestion. Given his history, an echocardiogram was performed, revealing severe LV dysfunction and a large, mobile thrombus measuring 2.2 cm within the LV (Figure 1), with a new LVEF of 20-25%. An abdominal computerized tomography (CT) scan (Figure 2) confirmed splenic infarction, identifying two regions of infarction in the spleen and occlusion of the superior mesenteric artery (SMA) with distal reconstitution, likely due to embolization from the LV thrombus. The chronic nature of the SMA occlusion was suggested by reconstituted flow beyond the occlusion.

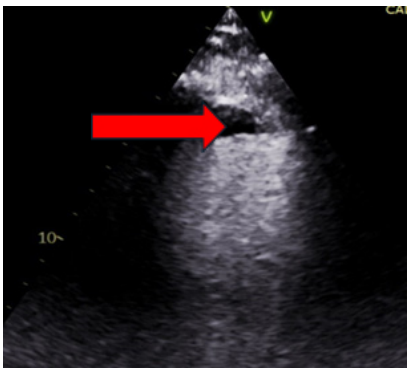

Figure 1. Left ventricular (LV) apical thrombus.

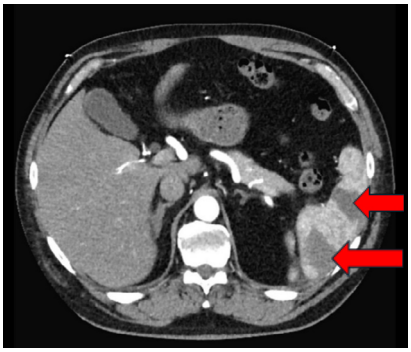

Figure 2. Splenic infracts on abdominal computerized tomography scan.

The patient was diagnosed with splenic infarction secondary to embolization from a LV thrombus, a complication of HFrEF. He was initiated on anticoagulation therapy with intravenous heparin, later transitioning to apixaban. His heart failure management also was optimized, including adjustments to his beta-blocker dose and the addition of spironolactone.

Additional workup for hypercoagulability and splenic infarction included: lactate dehydrogenase (LDH) <140 U/L (indicating no excessive cell turnover), erythrocyte sedimentation rate (ESR) 31 mm/hr (slightly elevated), anticardiolipin antibodies (IgG, IgM, IgA) <2 (arguing against anti-phospholipid syndrome), protein C activity 160%, protein S activity 97% (indicating absence of hereditary hypercoagulable states), ANA negative (arguing against autoimmune disease), QuantiFERON negative (indicating no tuberculosis), and *Histoplasma* antigen negative (indicating no histoplasmosis).

The patient's symptoms gradually improved, and follow-up imaging showed partial resolution of the LV thrombus. He was discharged on long-term anticoagulation therapy to reduce future thromboembolic risk, with ongoing monitoring of heart function and the thrombus.

This case underscores the risk of embolic complications in patients with HFrEF, especially with LV thrombi. Splenic infarction, though rare, should be considered in HFrEF patients with acute abdominal pain. Early imaging diagnosis and prompt anticoagulation initiation are crucial to prevent complications and improve patient outcomes.

DISCUSSION

Splenic infarction, a rare cause of abdominal pain, is more likely to occur in patients with splenomegaly, often due to hematologic malignancies. In fact, between 50-72% of patients with chronic myelogenous leukemia or myelofibrosis may experience splenic infarction.[5] Cardioembolic phenomena, such as those from atrial fibrillation, valvular disorders, and atrial septal defects (ASDs), also increase the risk of

infarcts. In immunocompromised patients, septic emboli should be considered, and up to 40% of patients may be asymptomatic.[6] Less common causes include autoimmune diseases, connective tissue diseases, surgical complications, post-transplant conditions (pancreas and liver), or infections like Brucella.[7] Clinically, splenic infarction usually presents as left upper quadrant pain, often accompanied by fever, nausea, or vomiting.[8]

A thorough investigation is essential to determine the cause of splenic infarction. Initial workup should evaluate splenic size and potential hematologic causes, including malignancies. While no specific laboratory tests confirm splenic infarction, up to 50% of patients may show leukocytosis with a white blood cell count >12,000/mm.[3,9] Although a study has linked elevated D-dimer levels to splenic infarcts,[6] this association has not been consistently validated. CT scans are the preferred imaging modality in acute cases, typically revealing a characteristic pyramidal wedge shape.[10] For more established infarcts, ultrasound can reveal a "bright band sign" (highly hyperechoic linear bands within lesions of varying ages).[11] However, ultrasound is limited in diagnostic value due to challenges in visualizing splenic parenchyma and high inter-operator variability, with only 18% sensitivity, though color Doppler may enhance this by detecting areas without blood flow.[12,13]

Cardioembolic causes, including atrial fibrillation and valvular vegetations, should be evaluated via electrocardiogram and echocardiogram. In the absence of arrhythmias like atrial fibrillation, LV thrombus formation due to reduced ejection fraction (EF) occurs at an annual rate of 0.9 to 5.5%.[13] While reduced EF can result in LV thrombus,[14,15] it has not been clearly linked to splenic infarction, and management protocols are not well-defined. Current guidelines do not recommend prophylactic anticoagulation for heart failure with reduced EF, as indicated in the COMMANDER HF trial.[16]

This case highlights the importance of a comprehensive workup in patients with splenic infarction and underscores the need for further evidence to clarify any potential association between HFrEF and splenic infarction.

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Keywords: Splenic, infarction, thrombus, heart failure

KANSAS JOURNAL of MEDICINE

Case Report

Uncommon Presentation of Metastatic Melanoma to the Breast

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INTRODUCTION

Melanoma is the sixth most common malignancy in women and the fifth most common in men, making it the most lethal form of skin cancer.[1,2] Approximately 20% of patients with melanoma develop metastatic disease, with common sites of metastasis including the lungs, liver, bone, and brain.[1,3,4] Metastasis to the breast is rare, accounting for less than 3% of all breast masses. However, melanoma is one of the most frequent extramammary malignancies found in the breast.[5] Lesions originating from melanomas on the trunk or upper extremities are more likely to metastasize to breast tissue compared to those originating on the lower extremities.[5]

Breast metastases often present with nonspecific imaging features, resembling both benign and malignant breast masses. Consequently, breast radiologists must maintain a high degree of clinical suspicion for metastasis when assessing suspicious breast findings in patients with a history of non-breast malignancies. This is especially critical, as breast metastases are associated with a relatively worse prognosis.[1]

The following case highlights the unique clinical presentation and diagnostic challenges faced in evaluating a premenopausal woman diagnosed with metastatic melanoma. Her presentation included symptoms and imaging findings that initially raised concern for primary inflammatory breast carcinoma (IBC), underscoring the importance of thorough clinical evaluation in such complex cases.

CASE REPORT

A 47-year-old woman with a history of recurrent melanoma on the ventral side of the right upper abdomen and biopsy-proven right axillary nodal metastasis presented for dedicated breast imaging 19 months after her initial melanoma diagnosis. Her prior treatments included wide local excision, axillary nodal dissection, and systemic therapy with nivolumab and relatlimab. This presentation followed findings on a recent positron emission tomography (PET) scan, which demonstrated heterogenous increased fluorodeoxyglucose (FDG) uptake in the lateral portion of the right breast with a maximum standardized uptake value of 9.2 (Figure 1). These findings were suspicious for metastatic melanoma; however, a differential diagnosis included primary breast malignancy, warranting further imaging and tissue diagnosis.

Between the PET scan and dedicated breast imaging, the patient developed diffuse right breast hardening, skin thickening, and a peau d'orange appearance – clinical symptoms highly suspicious for IBC. Diagnostic mammography revealed global asymmetry of the right breast with asymmetric enlargement, diffuse skin and trabecular thickening, and areas of architectural distortion (Figure 2). Breast ultrasound showed diffuse abnormal non-mass tissue, accompanied by an irregular mass with indistinct margins centered at 12 o'clock, 9 cm from the nipple (Figure 3). No morphologically abnormal lymph nodes were identified in the right axilla, consistent with her prior axillary nodal dissection. While imaging findings strongly suggested IBC, metastatic melanoma remained a differential diagnosis given her medical history.

An ultrasound-guided biopsy confirmed metastatic melanoma. Subsequent breast magnetic resonance imaging (MRI) revealed numerous partially necrotic enhancing masses throughout the right breast parenchyma and skin, accompanied by asymmetric skin thickening, enhancement, and subcutaneous edema (Figure 4). The left breast showed no abnormal findings.

Following her diagnosis of metastatic melanoma to the breast, the patient underwent clinical management involving medical and radiation oncology. Treatments included chemoradiation therapy and participation in a tumor-infiltrating lymphocyte therapy trial. Unfortunately, the patient passed away 28 months after her initial melanoma diagnosis and eight months following the detection of breast metastasis.

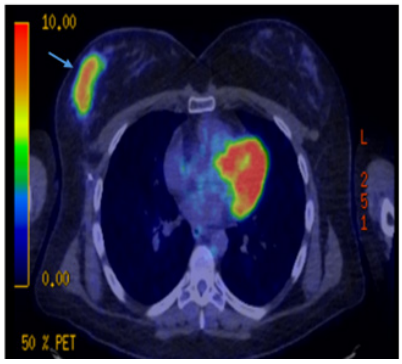

Figure 1. FDG-PET demonstrating heterogenous mass-like uptake in the lateral right breast (arrow).

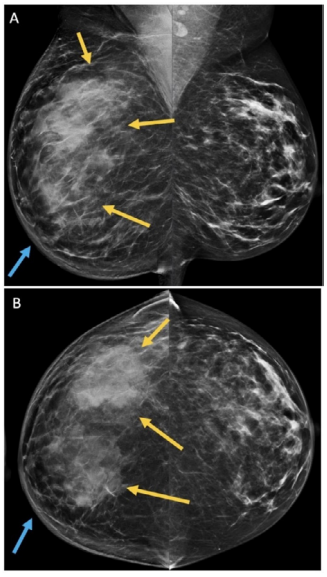

Figure 2. Bilateral diagnostic mammography mediolateral oblique (a) and craniocaudal (b) synthetic 2-D images demonstrate global right breast asymmetry (yellow arrows) with diffuse skin thickening (blue arrows) and trabecular thickening.

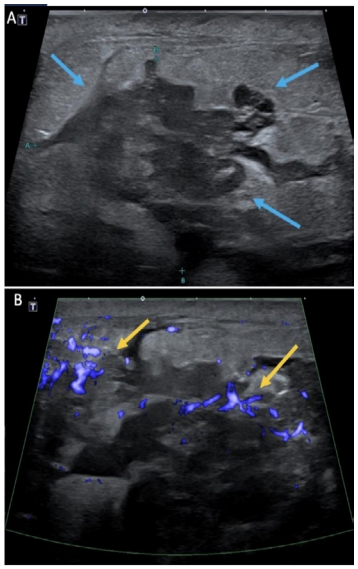

Figure 3. Sonographic grayscale (a) and power doppler (b) images demonstrate diffuse abnormal non-mass tissue with an associated irregular mass with indistinct margins (blue arrows) demonstrating increased blood flow (yellow arrows), corresponding to the mammographic asymmetry. This tissue was targeted for percutaneous ultrasound-guided biopsy.

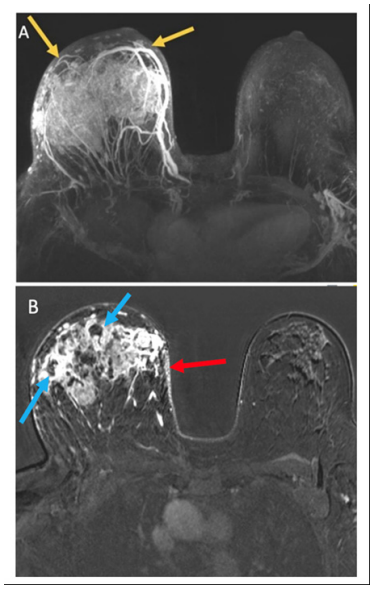

Figure 4. Breast MRI maximum intensity projection (MIP) (a) and axial subtracted contrast-enhanced image (b) demonstrate asymmetric right breast enlargement and enhancement (yellow arrows) with multiple contiguous, irregular, enhancing and partially necrotic masses (blue arrows) throughout the right breast in addition to skin enhancement and thickening (red arrow). The left breast demonstrates no suspicious findings.

DISCUSSION

Breast metastases from extramammary malignancies can occur through hematogenous or lymphatic routes.[6] Hematogenous spread is more common and typically presents as solitary or multiple round or oval circumscribed masses, lacking spiculated margins, calcifications, or architectural distortion. These metastases can mimic benign lesions such as cysts or fibroadenomas and are less likely to involve axillary lymph nodes. Conversely, lymphatic spread, though less frequent, leads to tumor obstruction of lymphatic channels.[7] This results in skin and trabecular thickening, subcutaneous edema, lymphedema, and lymphadenopathy, which closely resemble advanced or inflammatory primary breast malignancy.

In this case, the imaging findings included diffuse skin and trabecular thickening, architectural distortion, and subcutaneous edema. The absence of lymphadenopathy was attributed to the patient's prior axillary dissection. IBC, a rare but aggressive form of breast cancer, constitutes 2-4% of breast cancer cases and 7% of breast cancer-related mortality in the U.S.[8] It frequently presents with nonspecific features such as breast edema and erythema, hallmarks of the disease, and also may exhibit imaging findings typical of primary breast malignancy, including mass formation, calcifications, or architectural distortion, all accompanied by skin thickening. When no underlying mass is present, the findings may resemble mastitis, further complicating diagnosis.[8,9]

CONCLUSIONS

This case underscores the diagnostic complexity of metastatic cancer to the breast due to overlapping clinical and imaging characteristics with primary breast malignancy. A known history of metastatic melanoma raised suspicion for secondary malignancy; however, the imaging features were indistinguishable from primary IBC. Accurate diagnosis is essential, as both metastatic melanoma and IBC are rare and aggressive malignancies requiring distinct treatment approaches. Radiologists and clinicians must maintain a broad differential diagnosis and prioritize timely biopsy to guide management.

The increasing prevalence of melanoma, coupled with its aggressive metastatic behavior, calls for heightened vigilance when these patients present with new breast findings. This case demonstrates the indispensable role of advanced imaging and biopsy in establishing an accurate diagnosis and guiding treatment decisions. Although the prognosis for metastatic melanoma remains poor, continued advancements in early detection and characterization of metastatic patterns may improve patient outcomes. Future research should focus on refining diagnostic strategies to better identify and address metastases, ultimately enhancing care for patients with aggressive malignancies.

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Keywords: melanoma, inflammatory breast neoplasms, mammography

KANSAS JOURNAL of MEDICINE

Case Report

A Case of Olanzapine Resistance from Heavy Smoking and Clinical Considerations

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INTRODUCTION

Cytochrome P450 (CYP) enzymes play a critical role in the metabolism of numerous drugs. Substances that inhibit or induce CYP enzymes can lead to suboptimal medication responses or toxicity.[1] Olanzapine, a second-generation antipsychotic, is widely used to manage various psychiatric disorders.[2] Its mechanism of action involves antagonism of post-synaptic dopamine D2 receptors in the mesolimbic pathway and 5-hydroxytryptamine (serotonin) 2A receptors in the frontal cortex.[3]

First approved in 1996 for treating schizophrenia, olanzapine remains a cornerstone therapy for schizophrenia, bipolar disorder, and treatment-resistant bipolar depression when combined with fluoxetine.[4,5] It also is commonly used off-label for conditions such as acute agitation, delirium, anorexia nervosa, and chemotherapy-induced vomiting.[5] Olanzapine's broad therapeutic utility stems from its dose-dependent receptor occupancy, enabling diverse clinical applications. Its rapid onset of action, particularly via intramuscular administration, which achieves peak plasma concentrations within 15-45 minutes, makes it especially effective for managing acute agitation in non-adherent or uncooperative patients.[5]

Smoking has a significant impact on olanzapine's efficacy due to the induction of hepatic Cytochrome P450 1A2 (CYP1A2) enzymes by polycyclic aromatic hydrocarbons found in cigarette smoke.[2,6] Olanzapine is primarily metabolized by CYP1A2, and its accelerated clearance in smokers often results in subtherapeutic serum concentrations, necessitating higher doses to achieve therapeutic effects.[2] Importantly, nicotine replacement therapies, such as gum or patches, and vaping do not induce CYP1A2 because they lack combustion-related hydrocarbons.[7,8] This distinction is crucial in assessing olanzapine's efficacy among smoking patients.

The prevalence of smoking in the U.S. general population was 11.5% in 2021, according to the Centers for Disease Control and Prevention.[9] However, smoking rates among individuals with mental illnesses are three to four times higher.[10,11] Given the high prevalence of smoking in this demographic, clinicians must account for patients' smoking status when evaluating olanzapine's therapeutic response.

Despite its lower risk of extrapyramidal side effects compared to first-generation antipsychotics,[12] olanzapine carries notable risks. It has a black-box warning for increased mortality in elderly patients with dementia-related psychosis.[5] Additionally, olanzapine may exacerbate metabolic issues, including hyperglycemia, dyslipidemia, and weight gain, particularly in obese patients.[13,14]

We present a case illustrating olanzapine resistance due to CYP1A2 induction by smoking, emphasizing the need for careful consideration of smoking status in treatment planning.

CASE REPORT

A 71-year-old male with a history of major neurocognitive disorder, possibly frontotemporal dementia with behavioral disturbances, alcohol use disorder, tobacco use disorder, and chronic obstructive pulmonary disease, was admitted due to worsening agitation and insomnia over the past three weeks. His home medications included aspirin 81 mg orally once daily, citalopram 20 mg orally once daily, clopidogrel 75 mg orally once daily, and zolpidem 10 mg orally at bedtime.

The patient had exhibited escalating behavioral issues, including frequent removal from local restaurants and bars for outbursts, repeated angry phone calls berating family members, and severe damage to his home. A computed tomography scan of the head without contrast on admission revealed involutional changes and atrophy with a frontal lobe predominance, as well as a prior small high-frontal infarct with encephalomalacia.

On admission, his home medications of aspirin, citalopram, and clopidogrel were continued. However, zolpidem 10 mg was discontinued to avoid potential cognitive and psychomotor side effects. A nicotine patch (21 mg/day) was initiated due to his two-pack-per-day smoking habit. The patient also was started on olanzapine at 5 mg nightly, which was titrated to 15 mg over a week to address agitation and insomnia. Despite this, his symptoms persisted, and he frequently required PRN (as-needed) medications for agitation.

The treatment team suspected a CYP1A2 interaction related to the patient's smoking, which can accelerate olanzapine metabolism, reducing its efficacy. Given the likelihood that the patient would resume smoking post-discharge, the team concluded that olanzapine might not be an optimal choice. A cross-taper from olanzapine to risperidone was initiated.

During the transition, the patient showed significant improvement. On risperidone 2 mg daily, he was noticeably calmer and no longer required PRN medications. His sleep duration also increased from an average of three hours per night to six and a half hours. The patient was eventually discharged to an assisted living facility, where he continues to do well.

DISCUSSION

Smoking has been shown to induce the activity of CYP1A2,[6] an enzyme primarily responsible for metabolizing olanzapine.[2] The processes of CYP enzyme induction and inhibition are complex and vary in their onset and resolution. Induction typically takes days to weeks, as it involves the synthesis of additional enzymes, and it may take even longer for enzyme activity to return to baseline levels after discontinuing the inducer.[15] In contrast, inhibition occurs more rapidly.

It has been demonstrated that smokers clear olanzapine more quickly, often requiring higher doses to achieve therapeutic effects.[16] In the case of our patient, even after escalating the olanzapine dose to 15 mg, symptoms failed to improve significantly. However, switching to risperidone, which is predominantly metabolized by cytochrome

P450 family 2 subfamily D member 6 (CYP2D6),[17] led to a rapid and complete resolution of symptoms.

Although it is well-established that smoking accelerates olanzapine clearance,[16] there are currently no formal guidelines for adjusting olanzapine doses based on smoking status. Research suggests that nonsmokers may require a 30-50% dose reduction compared to smokers to achieve similar plasma concentrations.[18] This poses a significant challenge for clinicians, especially since more than 60% of patients with schizophrenia are smokers.[11] Furthermore, when patients stop smoking, often during hospitalization, where smoking is prohibited, olanzapine levels can increase by 30-40% due to the loss of CYP1A2 induction, potentially leading to toxicity.[16]

Determining the appropriate olanzapine dose requires consideration of various factors, including sex, age, and the number of cigarettes smoked daily.[19] Previous reports have indicated that CYP1A2 induction reaches a ceiling effect at approximately 10 cigarettes per day, with no further induction observed beyond that threshold.[20,21] Given the elevated prevalence of smoking among patients with mental health illnesses, clinicians also must consider the duration and magnitude of a patient's smoking history when tailoring olanzapine therapy.

Awareness of CYP enzyme interactions is crucial for optimizing clinical outcomes. Selecting an alternative antipsychotic upon admission may expedite symptom resolution, reduce hospital stays, and alleviate caregiver burden. Post-discharge, the efficacy of olanzapine may diminish if patients resume smoking, further underscoring the importance of considering alternative therapies in smokers.

Additionally, increasing olanzapine doses to counteract reduced efficacy in smokers may heighten the risk of dose-related side effects, as some are metabolite-driven. A thoughtful approach to assessing smoking status and potential CYP interactions is essential for selecting the most appropriate antipsychotic regimen, ensuring therapeutic efficacy while minimizing adverse effects.[22,23]

CONCLUSIONS

Despite olanzapine's efficacy in treating various psychiatric conditions, clinicians should consider alternative antipsychotics for smokers due to its interaction with CYP1A2. This enzyme is critical to olanzapine metabolism, potentially reducing its effectiveness and requiring higher doses in smokers. Choosing antipsychotics less affected by smoking-induced enzyme activity may provide more consistent treatment outcomes and reduce the need for frequent dose adjustments. Thus, careful assessment of smoking status and its impact on drug metabolism is vital in selecting the most effective antipsychotic therapy to ensure optimal patient outcomes.

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Keywords: Cytochrome P-450 CYP1A2, cigarette smoking, olanzapine, enzyme induction, drug resistance

KANSAS JOURNAL of MEDICINE

Case Report

Concurrent Small Cell and Non-Small Cell Lung Cancers: The Diagnostic and Management Challenges of Synchronous Primary Lung Tumors

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INTRODUCTION

Lung cancer patients may present with two distinct primary tumors simultaneously, a condition termed synchronous primary lung cancers (SPLC), or they may develop a second primary lung cancer during or after treatment of the initial tumor, referred to as metachronous primary lung cancer.[1] Advancements in lung cancer screening, surveillance, and management have led to an increase in the incidence of these conditions, posing significant challenges in accurate diagnosis, classification, and management.[1] These challenges arise from the complexities of obtaining tissue samples from multiple intrapulmonary lesions, distinguishing the molecular and histological profiles of different tumors, and addressing the lack of consensus on management strategies, which often depend on the degree of similarity between tumors.[1,2]

Although SPLC is increasingly recognized, it remains uncommon, with a reported prevalence of 0.5% to 5%.[3] SPLC typically is defined as the presence of two or more anatomically distinct cancerous regions within the lungs that are not connected via common lymphatic channels.[3] This scenario raises critical questions about which lesions should be prioritized for biopsy in patients with multiple suspicious lung lesions. Current guidelines highlight the importance of multidisciplinary team (MDT) involvement, including radiologists, oncologists, pathologists, thoracic surgeons, and pulmonologists, to accurately define SPLCs and determine the most appropriate lesions to biopsy within the broader clinical context.[4]

In this report, we describe the case of a woman diagnosed with SPLCs exhibiting two distinct histological types of cancer.

CASE REPORT

The patient was a 67-year-old woman with a medical history of hypertension, dyslipidemia, hypothyroidism, a 50 pack-year smoking history, and chronic obstructive pulmonary disease (COPD). Her family history is significant for cancer, as her father had been diagnosed with both prostate cancer and a brain tumor.

Initial Presentation and Imaging. In March 2022, a chest computed tomography (CT) scan performed to monitor stable, bilateral, sub-centimeter pulmonary nodules revealed:

- Right upper lobe: 5 x 4 mm nodule
- Right lower lobe: 5 mm nodule
- Left costophrenic angle: 5 mm nodule

The nodules remained stable over time. Additionally, a spiculated, irregular mass in the right lower lobe was identified, measuring 2.7 x 2.5 cm, without associated lymphadenopathy. Background emphysematous changes were noted. A CT-guided core needle biopsy of the right lower lobe mass yielded negative results for malignancy.

Loss to Follow-Up and Recurrence. The patient remained asymptomatic and was lost to follow-up until May 2024, when a chest CT was performed following an abnormal chest X-ray. This revealed:

- Enlargement of the right lower lobe mass to 4.9 x 4.5 cm
- A right perihilar lymph node measuring 3 x 2.2 cm, suggestive of nodal metastasis

The previously identified bilateral pulmonary nodules remained stable. A repeat CT-guided biopsy confirmed invasive, moderately differentiated squamous cell carcinoma. The patient was referred to oncology for further evaluation and consideration of chemoradiation.

Advanced Imaging and Biopsy. A positron emission tomography (PET) scan revealed:

- Intense hypermetabolic activity in the right lower lobe mass
- Hypermetabolic metastatic adenopathy in the right hilum and a suspicious right paratracheal lymph node

Endobronchial ultrasound-guided biopsy of the right hilar mass revealed small cell lung cancer (SCLC), distinct from the squamous cell carcinoma (SCC) diagnosed in the right lower lobe.

Diagnosis and Management. The patient's cancer was staged as:

- Non-small cell lung cancer (NSCLC; Squamous Cell Carcinoma): Stage IIA (T2b N0 M0): Tumor > 4 cm but ≤ 5 cm (T2b), with no nodal involvement (N0) and no distant metastasis (M0)
- SCLC: Limited stage, with nodal involvement attributed to the SCLC diagnosis

The patient underwent concurrent chemoradiation, consisting of four cycles of cisplatin and etoposide with radiotherapy starting from the second cycle. Plans were made to initiate adjuvant immunotherapy with durvalumab.

DISCUSSION

SPLCs remain rare.[3] As a result, clinicians often attribute multiple lesions in the same lung, particularly when one lesion is anatomically downstream from another to intrapulmonary spread rather than distinct primary tumors. However, accurate differentiation between multiple primary lung cancers and intrapulmonary spread is critical, as it significantly impacts both management strategies and prognosis. While most synchronous multiple primary lung cancers share similar histologic features, this case illustrates that lesions also can exhibit markedly different histologic characteristics.[1,5]

This case underscores the growing importance of precise histopathologic and molecular characterization for each lung lesion in suspected SPLC. With the rise of personalized cancer treatments, such as targeted therapies and immunotherapy agents tailored to specific molecular mutations, accurate identification of each primary lesion is essential for optimal treatment planning.

The presented case also highlights the diagnostic complexity of SPLC and emphasizes the need for thorough staging, including tissue

biopsy, to avoid misdiagnosis and ensure appropriate management. It also serves as a reminder that SPLCs easily can be overlooked without a high index of suspicion. A multidisciplinary team approach is crucial to navigating these challenging cases and optimizing patient outcomes.

SPLC poses unique management challenges that directly can affect prognosis.[6] Unlike NSCLC, which uses the Tumor, Node, Metastasis staging system, SCLC is primarily staged as limited or extensive disease.[7] Standard treatment for limited-stage SCLC includes four cycles of cisplatin and etoposide with concurrent thoracic radiotherapy.[7] The ADRIATIC trial demonstrated improved progression-free and overall survival with durvalumab as adjuvant therapy for up to two years in patients who show no disease progression after standard chemoradiotherapy, without requiring prior molecular biomarker testing.[8] This treatment strategy aligns with the regimen used for the patient described.

Surgical intervention rarely is indicated for SCLC and is reserved for limited-stage cases without lymph node involvement or other contraindications.[7] Conversely, early-stage NSCLC (Stages I/II) typically is managed with surgical resection or radiotherapy for non-surgical candidates, with adjuvant therapies tailored to specific mutations and clinical indications.[9] The described patient, a non-surgical candidate, is being treated with radiotherapy and platinum-based chemotherapy, an effective approach for NSCLC cases without driver mutations.[9]

There are no established guidelines specifically addressing SPLC, making multidisciplinary collaboration and sound clinical judgment indispensable.[6] Prognosis in SPLC is influenced by factors such as tumor size, histology, and stage. Cases with distinct histologies, like the one presented here, often carry a worse prognosis.[6] This highlights the importance of individualized treatment plans and continued research into SPLC management.

CONCLUSIONS

This case underscores the critical role of multidisciplinary collaboration in the diagnosis and management of SPLCs. A comprehensive approach that includes detailed imaging evaluations and targeted tissue biopsies is essential for distinguishing between multiple primary lung cancers and intrapulmonary metastasis. Accurate differentiation directly guides treatment strategies and significantly influences patient outcomes and prognosis.

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Keywords: synchronous neoplasms, multiple primary neoplasms, lung neoplasms

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Case Report

A Case Report of Futibatinib-Induced Calciphylaxis

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INTRODUCTION

Calciphylaxis is a rare disorder characterized by the calcification of the intima and media of arterioles and small arteries.[1] This pathological calcification typically affects cutaneous vessels in patients with end-stage renal disease (ESRD), leading to reduced perfusion, tissue ischemia, and subsequent necrosis. The resulting skin lesions often are intensely painful and highly susceptible to infection, which can progress to sepsis. This combination of severe pain and infection risk makes calciphylaxis a significant cause of morbidity and mortality in ESRD patients, with a one-year mortality rate of approximately 50% and frequent hospitalizations.[1]

Calciphylaxis occurs in approximately 0.04-4.00% of ESRD patients and is thought to be associated with disturbances in parathyroid hormone (PTH), calcium, phosphorus, and vitamin D levels, common metabolic abnormalities in ESRD.[1] Elevated phosphorus levels in secondary or tertiary hyperparathyroidism can bind with calcium, leading to vascular deposits and cutaneous necrosis. However, the pathophysiology is not fully understood, as many ESRD patients with PTH axis disturbances do not develop calciphylaxis. Moreover, calciphylaxis has been documented in individuals with normal PTH, calcium, phosphorus, and vitamin D levels.[1]

While calciphylaxis is most seen in ESRD patients, it also can occur in those without renal disease, a condition referred to as *non-uremic* calciphylaxis (NUC).[2] NUC has been associated with autoimmune and connective tissue disorders, obesity, diabetes mellitus, and solid organ malignancies, including cholangiocarcinoma. Certain medications, such as warfarin, glucocorticoids, and calcium-based phosphate binders, also are recognized as risk factors for NUC.[2]

Futibatinib, a novel fibroblast growth factor receptor-2 (FGFR2) inhibitor, is used in the treatment of FGFR2-rearranged cholangiocarcinoma.[3] The phase II FOENIX-CCA2 study demonstrated a 42% response rate and a median duration response of 9.7 months for patients treated with futibatinib.[3] However, a meta-analysis of three clinical trials involving futibatinib revealed that 82% of participants developed hyperphosphatemia, often within six days of initiating therapy.[4] The following case describes a patient with FGFR2-positive metastatic intrahepatic cholangiocarcinoma who developed NUC associated with futibatinib use.

CASE REPORT

A 64-year-old female was diagnosed with unresectable cholangiocarcinoma in January 2024 after an abdominal and pelvic computed tomography (CT) scan revealed a large, ill-defined mass in the right hepatic lobe. Biopsy confirmed the diagnosis. The patient began treatment with gemcitabine, cisplatin, and pembrolizumab in February 2024. Subsequent Guardant 360® genetic testing in March 2024, a high-sensitivity panel evaluating mutations in 739 genes, identified an FGFR2-ciliary rootlet coiled-coil, rootletin (CROCC) gene fusion. However, a chest CT in early April 2024 revealed disease progression with extensive metastases. Due to poor tolerance of the initial chemotherapy regimen, the patient was transitioned to futibatinib in late April 2024 to target her FGFR2 mutation. She tolerated the therapy well until June 2024, when she presented with worsening bilateral lower extremity edema and painful, necrotic wounds on her medial calves, prompting hospital admission (Figure 1).

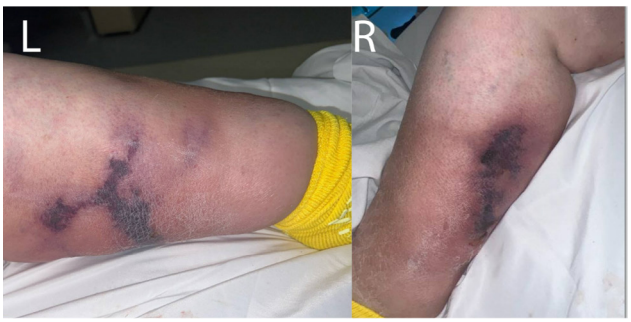

Figure 1. Images of patient's lower extremity wounds upon her initial admission in June 2024.

On admission, her phosphorus level was 6.4 mg/dL, calcium was 9.6 mg/dL, and creatinine was 0.76 mg/dL. The patient was started on sevelamer (1,600 mg three times daily) and underwent lesion biopsy. Futibatinib was discontinued due to suspected FGFR inhibitor-induced hyperphosphatemia and calciphylaxis. Additionally, her outpatient calcium acetate for hyperphosphatemia prophylaxis was discontinued. By the second day of admission, her phosphorus levels normalized, and sevelamer was discontinued. Biopsy results, returned four days post-admission, confirmed calciphylaxis. She was initiated on sodium thiosulfate (STS) at 25 grams three times weekly and received maintenance intravenous (IV) fluids. Over the next 10 days in the hospital, her phosphorus levels normalized; however, she developed symptomatic hypercalcemia, with levels peaking at 12 mg/dL and symptoms of nausea, vomiting, and constipation. These were managed with normal saline, calcitonin, and zoledronate.

After initial improvement and discharge, the patient was readmitted two weeks later for worsening pain in her bilateral lower extremity wounds, which were malodorous with occasional bleeding. She denied fever, purulent drainage, or other systemic symptoms. On admission, her calcium was 13.2 mg/dL, while phosphorus remained normal at 3.1 mg/dL. CT imaging showed marked bilateral subcutaneous stranding, edema, and superficial defects at the wound sites, while magnetic resonance imaging (MRI) revealed bilateral cellulitis without osteomyelitis. Treatment included resumed STS (25 grams three times weekly), calcitonin, and IV fluids, leading to normalized calcium levels.

Wound cultures identified a polymicrobial infection, and the patient was started on a seven-day IV course of ampicillin/sulbactam (3

grams every six hours). Despite treatment, STS was discontinued on the fourth day due to limited response. Surgical options were deemed inadvisable by plastic surgery. Endocrine evaluation revealed normal levels of thyroid-stimulating hormone, thyroxine, cortisol, osteocalcin, parathyroid hormone-related peptide, and procalcitonin, with low levels of vitamin D (29.5 ng/mL) and parathyroid hormone (5.6 pg/mL). She was discharged after one week on a three-day course of oral amoxicillin/clavulanate, with follow-up for wound care and oncology.

Five days post-discharge, she returned to her oncologist with worsening pain, nausea, and further deterioration of her wounds, which were more erythematous and malodorous (Figure 2). Her calcium was elevated at 12.7 mg/dL, necessitating readmission. Treatment included normal saline, calcitonin, and zoledronate. Repeat wound cultures showed heavy growth of *Escherichia coli*, prompting a resumed IV course of ampicillin/sulbactam. Her calcium levels normalized within two days, allowing her to transition to denosumab for long-term hypercalcemia management. After a six-day IV antibiotic course, she transitioned to oral amoxicillin/clavulanate for four days. Wound care focused on supportive measures, including normal saline rinses, *MediHoney*® application, and daily dressing changes. Following her third hospitalization, the patient elected hospice care and passed away shortly thereafter. A timeline of her three hospital admissions is summarized in Table 1.

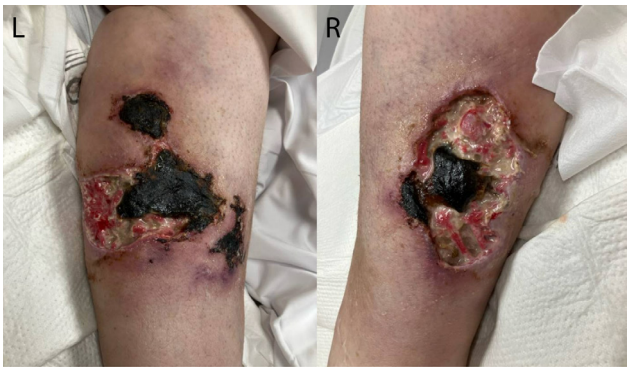

Figure 2. Images of patient's lower extremity wounds upon her third admission in August 2024.

DISCUSSION

To our knowledge, this is the first reported case of NUC in a patient taking futibatinib. However, similar cases have been documented with other FGFR inhibitors, such as erdafitinib and pemigatinib.[5,6] Additionally, data from the FOENIX-CCA2 trial have prompted the inclusion of a statement in futibatinib's safety profile acknowledging the association of soft tissue mineralization with its use. However, this profile does not explicitly warn providers about the potential for calciphylaxis.[7]

The exact mechanism of calciphylaxis remains unclear, but much of the current understanding stems from Hans Selye's 1962 theory of "sensitizers" and "challengers."[8] Sensitizers, including secondary hyperparathyroidism, hypercalcemia, and hyperphosphatemia, create a predisposed state, while challengers initiate the disease process.[8] Modern studies have built on this theory, highlighting that abnormalities in calcium-phosphate homeostasis play a central role.[9,10] In particular, low levels of calcium-phosphate binding proteins, such as matrix G1a protein, and imbalances between calcification promoters (e.g., bone morphogenetic proteins 2 and 4) and inhibitors (e.g., fetuin-A) appear to contribute to the ectopic deposition of hydroxyapatite crystals, a hallmark of calciphylaxis.[9]

Table 1. A detailed timeline of the patient's diagnosis with cholangiocarcinoma and subsequent development of *non-uremic* calciphylaxis.

Date	Event
January 2024	The patient was diagnosed with cholangiocarcinoma
April 2024	The patient began futibatinib after her disease progressed on her initial regimen and cytogenetics revealed an FGFR2 mutation
June 2024	The patient presented to her medical oncologist with bilateral lower extremity edema and painful, necrotic wounds on her medial thighs bilaterally, leading to hospital admission.
Hospital Admission 1 (June 2024)	Biopsy of the wounds demonstrated calciphylaxis. The patient undertook a two-week course of sodium thiosulfate (25 grams, three times per week) before being discharged.
Hospital Admission 2 (July 2024)	The patient was readmitted to the hospital for worsening wound pain. She undertook an additional four-day course of sodium thiosulfate before discontinuation due to lack of improvement.
Hospital Admission 2 (July 2024)	The patient developed sepsis, with wound cultures demonstrating polymicrobial infection and MRI demonstrating bilateral cellulitis. The patient was started on a seven-day course of IV ampicillin/sulbactam (3 grams every six hours) before being discharged on PO amoxicillin/clavulanate for a three-day course. Her infection improved with this therapy.
Hospital Admission 3 (August 2024)	Five days after discharge from her second admission, the patient was directly admitted from her medical oncologist's office due to worsening pain and malodorous discharge from her wounds. Evaluation revealed sepsis.
Hospital Admission 3 (August 2024)	Wound cultures demonstrated heavy growth of Escherichia coli. The patient undertook a six-day course of IV ampicillin/sulbactam (3 grams every six hours) before being transitioned to PO amoxicillin/clavulanate for an additional four days. Her infection improved with this therapy.
September 2024	Following discharge from her third hospitalization, the patient elected for hospice care. She passed away within her first week in hospice.

Note: FGFR2, fibroblast growth factor receptor-2; MRI, magnetic resonance imaging; IV, intravenous; PO: oral

In this case, cholangiocarcinoma, previously identified as a risk factor for calciphylaxis,[2] may have acted as a sensitizer, while futibatinib and the subsequent development of hyperphosphatemia and hypercalcemia likely served as challengers, catalyzing the onset of NUC. Interestingly, cholangiocarcinoma has been associated with elevated levels of fetuin-A, which might ostensibly reduce the risk of calciphylaxis.[10] Despite this, it is plausible that other, unidentified imbalances between calcification

promoters and inhibitors exist in patients with cholangiocarcinoma, which could underlie its link to calciphylaxis.

Finally, the patient's use of calcium acetate for hyperphosphatemia prophylaxis may also have contributed, as calcium-based supplements are recognized risk factors for NUC.[11] Further research is needed to better elucidate the interplay of these factors in the development of calciphylaxis in patients with cholangiocarcinoma and those receiving FGFR inhibitors.

Calciphylaxis is associated with significant morbidity and mortality, with one-year mortality rates exceeding 50%.[1] Although the combination of dialysis and STS has shown efficacy in non-randomized trials for patients with uremic calciphylaxis, demonstrating improvement in up to 70% of cases,[1] there is no established therapy for patients with NUC.[2] Moreover, a recent meta-analysis on STS use in uremic calciphylaxis found no significant benefit, raising questions about its therapeutic potential.[12] Given the lack of validated, effective treatments for NUC, health care providers administering futibatinib should remain vigilant about the potential for this adverse effect.

When patients taking futibatinib develop suspicious skin lesions, the medication should be immediately held, and the patient referred for biopsy to confirm the diagnosis. If calciphylaxis is diagnosed, futibatinib should be permanently discontinued. Given the role of elevated phosphate levels in calciphylaxis pathophysiology, hyperphosphatemia should be managed with phosphate binders like sevelamer or lanthanum. Calcium-based phosphate binders, such as calcium acetate, should be avoided, as calcium supplementation has been identified as a risk factor for calciphylaxis.[11] Patients using calcium-based binders for osteopenia or osteoporosis should discontinue these medications upon starting futibatinib.

Patients require close monitoring, particularly for systemic or local signs of wound infection, as sepsis secondary to wound infection is the leading cause of death in calciphylaxis.[1] Referrals to wound care teams and provision of adequate analgesia are essential.

Although no definitive treatment exists for NUC, STS commonly is used due to its efficacy in uremic calciphylaxis and reports of successful outcomes in NUC.[13] If STS proves ineffective, alternative approaches include combination therapy with iloprost and STS or surgical debridement with split-thickness skin grafting.[13,14] Both strategies have shown promise in case reports, but further research is needed to establish their role as first-line treatments.

Emerging therapies for NUC focus on targeting vascular calcification pathways. These include agents like fetuin-A or matrix G1a protein (MGP), with potential benefits from vitamin K supplementation in patients with vitamin K deficiency to activate MGP. SNF472, a selective inhibitor of vascular calcification that prevents hydroxyapatite deposition in vessel walls, has demonstrated improved wound healing and quality of life in calciphylaxis patients during phase 2 trials.[15] Currently in phase 3 trials, SNF472 represents a promising advancement in NUC management.

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Commentary

The Importance of Basic Research Knowledge in Undergraduate Medical Education

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With the United States Medical Licensing Examination® Step 1 going pass-fail, many medical students are seeking new ways to distinguish themselves and enhance their competitiveness during the residency application process. One effective approach is engaging in research or scholarly activities, which has led some medical schools to incorporate these activities into their curricula. For instance, many institutions, such as The University of Kansas School of Medicine, offer programs like Honors in Research or Certificate of Distinction in Research, which enable students to excel in research.[1-7] Those who complete these program requirements receive a diploma and recognition in their Medical Student's Performance Evaluation (Dean's) letter. However, despite these opportunities, many students lack foundational research skills, and some medical schools lack courses to address this gap. This underscores the importance of basic research knowledge, not only for meeting program requirements but also for fostering well-rounded physicians.

With this shift in emphasis, the need to integrate basic research knowledge into medical education has become more important than ever. Future health care professionals must not only develop strong clinical skills but also cultivate a foundational understanding of research principles. This dual focus ensures that medical students are equipped to contribute to evidence-based practice, keep pace with scientific advancements, and ultimately improve patient outcomes.[8-10]

Moreover, integrating research into medical education plays a key role in developing physicians who are both skilled clinicians and critical evaluators of medical literature. Research involvement enhances career prospects,[11,12] deepens the understanding of evidence-based medicine,[13] and builds essential analytical skills.[14] A strong foundation in research methods and validity measures enables physicians to critically appraise studies, apply findings to patient care, and contribute to medical advancements.[11,15,16] Strengthening research competencies among medical students thus is essential in shaping the future of healthcare.

Additionally, the medical field is one of continuous innovation and discovery, requiring health care professionals to maintain a commitment to lifelong learning.[11,17] Research knowledge encourages medical students to stay updated with the latest scientific developments,[14] a commitment that is fundamental for adapting to emerging diagnostic tools, treatment approaches, and preventive measures.[13] By fostering research literacy early in their careers, medical students are better prepared to navigate the evolving landscape of medicine.[12]

Alongside lifelong learning, a basic knowledge of research is essential for assessing study designs and evaluating the validity of their conclusions. This foundational understanding enables medical students to analyze a study's methodology and data,[15] identify strengths and weaknesses,[16,18] and examine the credibility of its results.[14,15] Recognizing the value of this knowledge is key to ensuring that clinical decisions are based on sound evidence,[15] a practice that helps uphold the integrity of scientific findings and ultimately benefits patient care.

In addition, basic research knowledge helps medical students to distinguish between clinical and statistical significance, an important skill for making informed patient care decisions. Statistical significance, often shown through a p-value, indicates the likelihood that findings are not due to chance.[17] However, this does not always mean the effect is meaningful in a clinical setting.[17,19] Clinical significance assesses the practical impact on patient outcomes, which is important for determining the true applicability of findings to patient care.[17]

With evidence-based practice at the heart of modern medicine,[13,16] medical students need a strong grounding in research methodology, critical appraisal, and statistical analysis. Learning to interpret and apply research findings empowers future physicians to make well-informed clinical decisions, customize treatments to individual patients, and advocate for the most effective interventions.[14,15,20]

Consider, for example, a study examining how anxiety and body weight predict systolic blood pressure. If the results show a positive slope of 0.23 for weight, indicating a 0.23 mmHg increase in blood pressure per pound gained, this suggests that weight management could play a crucial role in blood pressure control. Insights like these enable health care professionals, including medical students, to make informed decisions that positively impact patient care.

Ultimately, integrating research knowledge into medical education directly improves patient outcomes.[8-10] Physicians skilled in evaluating clinical evidence can deliver high-quality, personalized care informed by the latest insights,[14,15] enhancing treatment efficacy and building trust with patients who are increasingly engaged in their healthcare decisions.[21-28]

Medical research drives clinical innovation,[29,30] and medical students trained in research principles are more likely to engage in investigative work that contributes to new therapies, technologies, and protocols.[30] Encouraging research participation during medical training nurtures critical thinking and problem-solving abilities,[16,18,20,31,32] paving the way for breakthroughs that can transform patient care.[13-15]

Finally, the COVID-19 pandemic has underscored the importance of research in addressing global health challenges.[33] Medical students with a solid research foundation are better equipped to understand disease epidemiology, assess public health interventions, and support effective policies.[26] This readiness is needed in responding to future health crises, positioning medical professionals as essential contributors to public health.[34-36]

Recommendations

Given the value of research in medical education, medical schools should increase student involvement by offering early exposure to research opportunities, incorporating basic research methodology into the curriculum, and creating mentorship programs that connect medical students with experienced, compensated faculty. Schools also should establish flexible research pathways to accommodate diverse interests and career goals, ensuring that all medical students have the support and resources needed to pursue meaningful research. Recognizing and rewarding medical student research through awards, publications, and conference opportunities further can encourage participation and underscore the importance of research in medical education.

Access to free biostatistics and statistical resources is essential for medical students conducting research. These tools allow students to design rigorous studies, analyze data accurately, and draw valid conclusions, which are critical to producing high-quality research. By providing these resources, medical schools empower students to engage in evidence-based inquiry, develop critical thinking skills, and contribute meaningfully to medical knowledge. This support fosters a culture of research excellence and prepares future physicians to critically appraise scientific literature and apply findings to patient care.

Finally, requiring a basic understanding of research as a prerequisite for medical school admission could better prepare medical students to engage in scholarly activities and critically evaluate medical literature, aligning them with the demands of a research-driven medical field.

CONCLUSIONS

Incorporating basic research knowledge into undergraduate medical education is not just an academic pursuit; it is essential to preparing competent, innovative, and adaptable physicians. As the medical field continues to evolve, the ability to critically appraise research, stay current with scientific advancements, and contribute to clinical innovation will be indispensable. By prioritizing research literacy, medical schools equip future health care professionals to meet the challenges of tomorrow and deliver the highest standard of care to their patients.

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Disclosure: Samuel Ofei-Dodoo is the Editor-in-Chief of the *Kansas Journal of Medicine*.

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