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"Yet observation, I learned, does not require ownership or solutions. **It requires humility ... it force[s you] to witness without turning away. It demand[s] that [you] stay with discomfort long enough to learn from it."**

- Jane Fiorentino, *Wood, Graphite, and the Weight of Observation in Medicine*

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Adapted by S.J. Stewart from "The Veiled Nun" by Giuseppe Croff (Sculptor, Italy, c. 1863) courtesy of the National Gallery of Art Open Access and "Marsyas" by Balthasar Permoser (Sculptor, Germany, c. 1680-85) courtesy of The Met Open Access. The Cover Artwork is inspired by Issue 11's article: "Wood, Graphite, and the Weight of Observation in Medicine." *The Weight of Observation* explores how: "Observation ... does not require ownership or solutions. It requires humility. [It forces you] to witness without turning away. It demand[s] that [you] stay with discomfort long enough to learn from it." The Cover Artwork unfolds throughout the Issue as a choreography of looking and being seen. When the veiled observer turns away, the anguished man also shields his eyes, suggesting how withdrawal from another's suffering can deepen shame and isolation. As each figure gradually looks again, the sequence reframes observation as an act of humility: the willingness to remain present with discomfort long enough to learn from it.

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About HMSR

The Harvard Medical Student Review (HMSR) is student-founded, student-managed, and student-administered under the guidance of faculty and staff. Its mission is to provide a platform for students to contribute to important issues facing health and medicine through a variety of formats, including scholarly articles, editorials, and original artwork. Contributions are invited from the Harvard medical, dental, and public health schools, the rest of Harvard University, and other medical schools.

The works herein represent the views and opinions of the original authors and do not represent the views or opinions of the Harvard Medical Student Review or Harvard Medical School.

Dear readers,

We are pleased to present the newest issue of the Harvard Medical Student Review. The work collected here asks readers to pay closer attention: to the experiences that shape care, to the questions that emerge in clinical training, and to the evidence through which medicine examines and improves itself. Trainees often encounter medicine from a revealing vantage point. We are learning its formal structures while also seeing, sometimes for the first time, how those structures meet the complexity of patients' lives. That position creates space for questions, observations, and forms of scholarship that might otherwise be overlooked. HMSR exists to amplify those voices and give them a durable place within the medical literature.

This issue reflects the range of that work. It begins with art, continues through personal and clinical perspectives, and concludes with reviews of focused questions in medicine. The pieces differ in form and subject, but each reflects the value of sustained attention and the importance of giving trainees a forum in which to develop and share their ideas.

Since our last issue, we have continued to strengthen the systems that support this mission. We reorganized the HMSR website to make current and past issues easier to navigate, improved the consistency of article pages and author metadata, and standardized our workflow for publishing and archiving articles through Open Journal Systems. We also introduced DOI and metadata infrastructure so that HMSR publications are easier to cite, preserve, and discover.

These changes help ensure that trainee scholarship is not only published, but presented in a form that reflects its seriousness and allows it to remain accessible over time. As HMSR continues to grow, we hope to make it easier for student authors to share their work, contribute to ongoing conversations in medicine, and carry their scholarship forward in their academic and professional development.

We are grateful to the authors, artists, reviewers, and editors who made this issue possible. We hope the work that follows rewards close attention and demonstrates the value of the perspectives trainees bring to medicine.

Sincerely,

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Arts





"The Veiled Nun" by Giuseppe Croff (Sculptor, Italy, c. 1863) courtesy of the National Gallery of Art Open Access and **"Marsyas"** by Balthasar Permoser (Sculptor, Germany, c. 1680-85) courtesy of The Met Open Access.

Wood, Graphite, and the Weight of Observation in Medicine

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Keywords

global health; medical observation;
cultural humility; pediatric care;
reflective narrative

Abstract

This reflective narrative explores experiences in pediatric wards in Ghana, highlighting the power of observation, empathy, and cultural humility in global health. Using a pencil and journaling as a lens, the essay examines the challenges of witnessing human suffering, ethical dilemmas faced by caregivers, and the role of careful observation in understanding patient care and resilience. It reflects on how these experiences shaped the author's perspective on medical practice, emphasizing the importance of attentive observation, ethical reflection, and culturally informed empathy in global health and patient care.

Body

The other day, someone asked me: if you could keep only one thing in your household, what would it be? Without thinking, the first thing that came to mind was a pencil. I didn't pause, and I didn't weigh my options — just a pencil. I felt a little silly afterward. Everyone else was saying family, pets, treasured keepsakes, and here I was holding on to a piece of wood and graphite. Yet, as I flipped through my journal from Ghana, I realized that same pencil had carried me through everything I had witnessed. That pencil had been with me in every crowded ward and every quiet

observation, teaching me how to see, not just look. It taught me to notice, reflect on, and carry forward lessons hidden in things I might have previously overlooked. In Ghana, it became my bridge to understanding, my way of recording and processing everything my eyes and heart were taking in.

In medicine, observation is often treated as a preliminary step before action. In Ghana, I learned that in settings of scarcity, observation is the action. When technology is limited and resources are thin, care begins with sustained attention to bodies, behaviors, and context. The pencil slowed me down, helping me record what my eyes and instincts were learning long before I understood their implications.

The pediatric ward was unlike anything I had seen before. One bed sometimes held two or three children. Paint curled from the walls in sheets. The air felt thick and unmoving, disturbed only by the slow rotation of ceiling fans, as if even the machinery shared in the ward's exhaustion. There were no masks. Doctors were largely absent; surgeons arrived only every 2 weeks, traveling long distances to reach the hospital. Nurses, by contrast, were omnipresent. They moved between patients with quiet authority, relying on experience, touch, and observation to guide their care. Children were grouped into just a few

quadrants with no privacy. Their bodies were swollen, discolored, and frail. Malnutrition and illness were etched into every limb, cheek, and expression. Unlike hospitals in the United States, these children were not there for a cold or routine care; they were on the edge of survival.

What struck me most was how much clinical information was gathered without technology. Nurses assessed dehydration by pinching the skin and observing how readily it tightened back into its natural tension over the tissue beneath, as it does in healthy, well-hydrated bodies. They evaluated respiratory distress by counting breaths, watching chests rise irregularly, and listening for subtle changes in crying. A child's lethargy, the way their eyes barely met mine, and the subtle slump or rigidity of their posture conveyed more than any chart or number.

As I watched care unfold, I began to recognize patterns. A boy slouched in the corner, barely lifting his head. His breathing was shallow and uneven; his fingers trembled slightly, signaling dehydration and fatigue long before any vital signs were taken. Nearby, a girl clung tightly to her mother, rocking gently. Her face was pale but alert. The way she gripped her mother's shirt and tracked every movement in the room showed me where her fear began.

Being there, it became clear that medical care is more than protocols or technology; it is a careful choreography of attention, empathy, and resourcefulness. I watched nurses improvise constantly, diluting medications by hand and carefully rationing supplies as they moved from bed to bed. I saw one nurse hesitate before administering a treatment, scanning the room to assess which child appeared most unstable, knowing that time and supplies could not stretch

to everyone at once. When supplies ran low, a doctor explained how decisions were guided by clinical stability rather than order of arrival. These choices were not arbitrary; they were grounded in sustained observation. In that space, I began to understand that medicine is not only about diagnosis or treatment. It is about noticing, prioritizing, and responding thoughtfully to human needs.

Among the many difficult scenes I encountered, one story lingered more than the others. The ward director told me about a mother who, faced with extreme hunger, had fed her child something that made my stomach twist: feces. My initial reaction was discomfort and confusion. I felt unsure how to record something so morally jarring, but over time I saw that survival often demands choices that feel incomprehensible from the outside. Yet as I spent more time on the ward, listening to staff, observing families, and beginning to understand the depth of food scarcity, the story shifted. Empathy requires resisting instinctive judgment and attending instead to the circumstances shaping behavior.

This lesson deepened when I began to notice that some mothers lied to doctors about what their children had eaten. At first, I interpreted this as simple deception. But reflecting on the story of the mother who had fed her child feces, and watching the ward over time, I began to see a more complex reality. These choices were shaped by fear: fear of blame, fear of judgment, spiritual beliefs, and the harsh costs of food and medical care. In that context, the act that initially shocked me became an act of survival. Some mothers guarded information the way they guarded their children, carefully managing what could endanger them. Over time, I began to notice how much could be revealed through behavior, pauses, and

even silence. Sitting with that realization reshaped my understanding of empathy, encouraging me to look beyond visible actions and consider the quieter forces influencing them.

For these care providers, truth in medicine often emerged through what bodies did rather than what patients could articulate. It surfaces in hesitation, in the places where eyes linger, in what remains unsaid. In one quadrant of the ward, a boy with legs swollen as tight as skin could stretch whimpered as a nurse balanced him on her lap. She checked his temperature with the back of her hand, followed the shallow rise of his chest, and pressed gently into his abdomen. After each touch, she paused. She watched his face closely, reading discomfort in the tightening of his jaw and the brief catch of his breath, asking nothing of a body too weak to answer.

Across the room, a mother held her infant upright against her chest, whispering prayers I could not understand. Her eyes moved constantly, darting toward the nurses and back to her child, searching for a signal, a promise, permission to hope. I wrote quickly, trying to capture not only what I saw but what it felt like to stand there: the heavy stretch of waiting, the vulnerability patients and their families carried as they were watched, and the quiet endurance that persisted even in that space.

Across Ghana, hospitals and clinics functioned almost interchangeably, bound together by the same shortages. Supplies moved unpredictably, access to laboratory testing was limited, and waiting for confirmation could mean waiting too long. Protocols differed from what I had been taught, not because they were careless, but because they had to be more responsive. Children were treated for malaria even when tests were unavailable or inconclusive, because in that

context, suspicion itself carried weight. I watched clinicians read bodies closely: a child whose skin burned with fever, another whose palms were pale and cool, and a toddler too weak to sit upright. I realized that danger could be recognized not through numbers alone, but through stillness. Through a child who no longer reached for their mother, or whose cry had softened into a faint sound. The clinicians counted breaths by watching ribs rise unevenly, noted how a child clung or did not cling to a mother's shirt, and listened to the pitch of a cry. Decisions were made quickly and deliberately, and treatment often began before certainty arrived. Experience replaced laboratory confirmation, and careful attention became essential. What could be seen, felt, and heard became the most reliable diagnostic tool. Observation did not supplement care; it made care possible.

Being there felt wrong at times. Walking through the ward with a notebook in hand felt intrusive, even voyeuristic. I questioned my presence constantly. What did it mean to observe suffering I could not alleviate, and was writing an act of preservation or extraction? I felt helpless, even guilty, at times, and worried that documenting someone else's pain might be exploitative. Yet observation, I learned, does not require ownership or solutions. It requires humility. The pencil did not fix anything, but it forced me to witness without turning away. It demanded that I stay with discomfort long enough to learn from it.

Amid the heaviness, small acts of humanity stood out sharply. A nurse made a silly face, and a child too weak to lift his head let out a quiet laugh. In another corner, a mother quietly offered words of encouragement to a fellow mother, her voice soft but steady. Nurses moved from bed to bed, whispering guidance or a quick joke, easing the

ward's tension in subtle ways. Beyond these gestures, I was struck by the trust the mothers extended to us — strangers and outsiders, Americans whose histories are so intertwined with exploitation. They let us see the realities of their sick children up close, granting us a window into their vulnerability. These moments mattered. I came to see that care is not only in treatments or protocols, but in the gestures that acknowledge each child and family as fully human. It is also in the courage it takes to let someone witness that humanity, and in the quiet courage of a provider who observes without rushing to heroic action.

Months later, I continue to reflect on what Ghana taught me. Scarcity revealed that care does not depend solely on abundance; it showed me how much can be done with attention, presence, and improvisation. Observation revealed that empathy is not passive; it is honed through careful watching, listening, and waiting. It must react and resonate with what it is given. I saw that medical knowledge alone was not enough; understanding the cultural context shaped how care was delivered and how it was received by patients and families. Putting into words the shock, discomfort, and fleeting moments of grace I witnessed transformed experience into responsibility. Writing became a reminder that

what we observe carries weight long after we leave. That bearing witness is not neutral, and it shapes the way we move through the world.

The pencil stays with me because of what it allows me to do. For me, observing carefully is part of acting ethically; it shapes when I intervene, when I listen, and how I consider care when resources are limited. Through it, I carry forward the voices, struggles, and resilience of people whose lives I was allowed to glimpse. The act of writing forces me to pause and truly observe, and in creating a record of what I witnessed, it allows those lessons to endure. It does not offer answers or absolution. It ensures, however, that my experiences are held carefully, thoughtfully, and with intention, shaping the way I think, feel, and act long after I leave.

Seeing, I learned, is never neutral. Every observation is layered: each detail carries physical, emotional, and contextual significance. Attending to patients, their environment, and moments of discomfort is itself a form of care. That is why a pencil is more than a simple object. It is a tool for witnessing, remembering, and honoring the weight carried by those who pay attention.

Perspectives





"Retreat from the Storm" by Jean-François Millet (French ca. 1846. Image courtesy of The Met Open Access.

Medical Respite: Practicing Stewardship for the Unhoused

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medical respite;
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health care stewardship

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Introduction to Medical Respite

Medical respite (MR) programs originated in Boston and Washington, D.C., in 1985 to provide shelter and resources to unhoused patients who were too sick to recover on the streets but not sick enough to remain hospitalized.^{1,2} Without respite, patients are discharged to the streets or to shelters, where environmental exposure, infection risk, and poor follow-up impair recovery — often leading to deterioration, readmission, or death. Recognizing this burden on patients and hospitals, many states followed Boston’s lead in implementing MR programs. However, access and utilization remain limited nationwide. This article examines the benefits, limitations, and prevalence of MR programs across the United States and argues that improving clinician awareness is a critical first step toward expanding access.

The Clinical Benefits of Medical Respite

For decades, studies have consistently demonstrated the clinical benefits of MR for unhoused patients. Homeless individuals have an

average of six emergency department visits annually, as compared with 1.6 visits among housed counterparts.³ Thirty-day revisit rates are 5.7 times as high in the emergency department and 1.9 times as high for inpatient admissions, reflecting poor post-hospital recovery.⁴ Although the cause of frequent readmissions is often multifactorial, unhoused patients are more likely to receive discharge plans that leave them vulnerable immediately after hospitalization. A Connecticut study of 98 unhoused patients found that 11% spent their first postdischarge night on the street, 66% went to shelters, 26% were discharged after dark, and 59% lacked a safe discharge plan.⁵ MR directly addresses these gaps.

Studies consistently show that MR improves outcomes across various metrics. MR reduces 90-day readmissions by up to 50%, lowers emergency department visits by 1.2 visits per patient, and decreases hospitalizations by 29%.^{6,7} When readmission occurs, MR paired with permanent supportive management reduces the length of stay by 2.7 days.⁷ MR also increases scheduled outpatient visits by 192.6%, representing a major step toward

sustained care.⁸ Beyond clinical metrics, MR addresses social determinants of health: a California study found that 59% of participants secured stable housing or reunited with relatives after discharge.⁹ Benefits extend across conditions, including postsurgical recovery, traumatic brain injury, HIV care, and outpatient antibiotic therapy.^{10–14} Notably, one study found no significant outcome differences between patients with and those without substance use disorders, countering assumptions that substance use disorders limit treatment success because of greater complexity of care.¹⁵

The Financial Impact of Medical Respite

Research similarly shows that MR is financially advantageous for hospitals. On average, unhoused patients stay 4.1 days longer, costing \$4094 more than housed patients.¹⁶ In Florida and Connecticut, inpatient care costs for unhoused patients exceeded reimbursement by 48% and 26%, respectively.¹⁷ Discharge delays driven by housing instability significantly increase costs. In Minnesota, unhoused patients accounted for 42.9% of nonmedical discharge delays during a study period.¹⁸

Accordingly, MR delivers substantial financial relief by reducing emergency department visits, admissions, and length of stay.^{13,19–21} One analysis found that hospitals saved \$1.81 for every \$1 invested in MR, largely by avoiding inpatient costs.¹⁷ In 2016, intravenous antibiotics were identified as a major driver of prolonged hospitalization among unhoused patients. For those discharged to MR for outpatient parenteral antimicrobial therapy (OPAT), completion rates reached 87%, saving institutions an average of \$25,000 per case.¹⁴ These findings position MR as a cost-effective, patient-centered solution for the unhoused.

Limitations and Constraints

Despite its benefits, MR faces significant limitations nationwide. To understand these obstacles, it is helpful to examine utilization in New York City (NYC), home to the largest unhoused population in the nation.²² In 2022, NYC Health + Hospitals (H+H) served more than 64,000 unhoused patients, including 1100 who had used MR since its inception.²³ At that time, H+H maintained 51 MR beds, increasing to 75 by April 2025. According to the National Institute for Medical Respite Care (NIMRC), three additional New York programs provide a combined 150 beds.²⁴ This shortage of beds reflects similar, although less severe, capacity limitations in other states (Table 1) and underscores significant gaps in funding across the country.

California's outperformance of New York reflects expanded MR funding under the 2022 CalAIM Medicaid initiative.²⁵ Still, California and New York face persistent shortages, underscoring the issue's complexity. MR programs rely on Medicaid, federal and state subsidies, hospital budgets, and private funding. Yet the financial beneficiaries are often not the funders — an issue termed the “wrong pocket problem.”²⁶ There is reduced incentive for hospitals and other players to invest when those paying are not the ones reaping direct financial benefits. Other strategies, such as hospital contract incentives and private insurance partnerships, also remain largely underused.

Funding is not the only barrier. As a relatively new public health initiative, MR lacks standardized program and admission requirements. NYC's Department of Health (DoH), for example, recently advanced standardization. In August 2024, the DoH required programs to provide essential services: 24/7 room and board, including three meals and two snacks daily; care coordination, including transportation, telehealth, and benefit assistance; family support; wellness checks; counseling; and

mental health therapy. Staff must be trained in first aid and basic life support (BLS).²⁷ Eligibility criteria were also clarified: patients must be 18 years of age or older with a qualifying medical condition. Patients must be self-directed, able to perform activities of daily living (ADLs), and able to respond appropriately in emergencies, or they must have an established care team. Those posing safety risks are excluded. Therefore, careful assessment of a patient's functional status may allow teams to coordinate physical and occupational therapy during admission, potentially reducing unnecessary exclusion of some of the most vulnerable patients who might otherwise benefit from medical respite. In addition, because qualifying conditions are not explicitly defined, clinicians retain significant discretion in determining eligibility.

In hospitals, clinicians and social workers initiate referrals by identifying candidates and drafting service plans that outline clinical, social, behavioral, interpersonal, and coordination needs, along with a discharge plan. This information must be submitted 72 hours before discharge.²⁸ MR staff verify the information, meaning that coordination can require at least 4 days and substantial bedside advocacy. Once admitted, in states such as New York that fund MR through Medicaid waivers, patients must be enrolled in Medicaid for reimbursement and may stay up to 90 days per 12-month period.²⁹

Even with standardized guidelines, creating MR programs and referring patients remains complex. This is again emblematic of many other states. A Duke-based review of affiliated hospitals in the Southeast found that only 8% of unhoused patients qualified for MR. Emergency department discharges without respite were declined for insufficient medical need (63%), ongoing acute care needs (16.3%), or leaving against medical advice (6.2%).³⁰ Among inpatients, ineligibility stemmed from lack of medical necessity (42.5%), housed status (13.6%), or psychiatric instability (5.5%).³⁰ Other states

impose further barriers; Los Angeles requires active Medi-Cal or Medicare insurance.³¹ The impact of this procedural complexity is difficult to quantify, although at least two studies have cited low MR bed occupancy as evidence. An Ohio pilot study reported 77% occupancy from 2022 through 2023 despite high demand, and Washington State reported 59 to 60% utilization from 2023 through 2024.^{32,33} These rates indicate that funding and bed supply are not the sole obstacles to MR utilization.

MR coordination demands time, collaboration, and sustained advocacy. Integrating automated tools into electronic health records, simplifying referral paperwork, and shortening approval time could reduce administrative burden, but such solutions remain uncommon. Therefore, empowering all care team members to initiate MR discussions throughout patient admission may increase referrals. Medical students may be uniquely positioned to support this process, because they often have more time to conduct thorough social and discharge-planning assessments to identify patients who may benefit from MR early in the admission course.

Conclusion

MR is a powerful tool for physicians, social workers, students, and hospital leaders alike to improve care for unhoused patients and the systems that serve them. For patients, MR provides safe discharge planning that supports long-term clinical outcomes, housing stability, and quality of life, aligning with ethical principles of stewardship and nonmaleficence. For hospitals, MR generates cost savings and reduces systemwide strain. However, MR remains a limited resource nationwide, resulting in lengthy referrals and restricted admissions that leave vulnerable patients without access.

First and foremost, funding for MR must increase — a complex problem requiring multidisciplinary collaboration among hospitals, insurers, and relevant government agencies. Second, the referral process needs to be streamlined, an improvement that will take coordination among MR programs, clinicians, and hospitals. For these two steps to come to fruition, however, the extent of the demand for MR must be demonstrated. This third step begins with increased provider awareness of MR and advocacy on behalf of our unhoused patients. By

better demonstrating the need for MR, clinicians can strengthen the case for expanded funding and simplified referral pathways. Cities such as New York have already begun scaling programs as a result, adding 25 beds in recognition of MR's positive effect on outcomes and costs.³⁴ Ultimately, greater clinician engagement can align the interests of unhoused patients, hospital systems, and third-party payers, all of whom benefit from expanded access to MR.

Table 1. Medical respite programs in the six states with the most homelessness, as ranked by the 2024 census count of people experiencing homelessness.*

Rank	State	2024 Census ¹	No. of Programs (est.) ²	No. of Beds (est.) ³
1	California	187,084	80+	At least hundreds — 518+ at Illumination Foundation alone
2	New York	158,019	4	~150+ (NYC H+H, Comunilife, ICL)
3	Washington	31,554	16	~70+ (Seattle & King County programs)
4	Florida	31,362	7	~50+ (Sulzbacher, Pinellas Hope, others)
5	Massachusetts	29,360	6	~140+ (Barbara McInnis & Kirkpatrick Houses)
6	Texas	27,987	5	~80+ (Austin, Houston programs)

¹ 2024 U.S. Department of Housing and Urban Development Point-in-Time Count; ² program totals compiled from National Institute for Medical Respite Care (NIMRC) listings; ³ bed estimates compiled from publicly available program data and NIMRC. Values are estimates. *Table produced in R (4.5.1).

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"The Death of Adonis" by Anthonie Waterloo (Dutch, 17th century). Image courtesy of The Met Open Access.

When Medicine Meets Mortality: Rethinking Medical Futility through a Cultural Lens

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Keywords

medical futility; end-of-life care; cultural humility; medical ethics; palliative care

Abstract

Medical futility — treatment that is unlikely to produce meaningful benefit — generates some of health care's most difficult ethical conflicts. Physicians assess benefit through evidence-based metrics, whereas families interpret these situations through frameworks shaped by culture, faith, and personal values. This disconnect fuels tension, especially around end-of-life care, in which aggressive intervention may cause suffering even as families view withdrawal as abandonment. I examine how cultural attitudes influence these decisions and argue that certain models of "cultural competency training" — particularly those emphasizing generalized beliefs associated with specific demographic groups — may inadvertently worsen conflicts by encouraging stereotyping rather than fostering genuine listening. Effective navigation requires early communication, institutional flexibility, and acknowledgment of medicine's inability to answer questions about life's meaning.

A Moment That Changed Everything

Last year, I watched a family and medical team talk past each other for days. An elderly man with end-stage heart failure had occupied an ICU bed for

weeks. His kidneys were failing, he needed maximum ventilator support, and cardiology had run out of options. The attending told us students that continuing care was "medically futile." The patient would die in the hospital regardless, and treatments were causing unnecessary suffering.

When the team suggested comfort measures, the daughter refused. She understood that her father was dying. She simply could not accept that stopping treatment was right. "We don't give up on our family," she said. For her, withdrawing support meant abandonment, perhaps even causing death rather than allowing disease to take its natural course.

Frustration built on both sides. Residents spoke of "wasted resources," a framing that reflects a clinical ethics of stewardship: finite ICU beds, ventilators, and nursing hours that could benefit other patients with more reversible conditions. From this view, prolonging care without the prospect of meaningful recovery may itself constitute harm. The attending and residents were not acting from indifference or efficiency alone. They were likely motivated by commitments to nonmaleficence — the duty to avoid causing harm — and to professional integrity, which includes honest prognostication. There may also have been a sense of obligation to the broader

patient population competing for scarce critical care resources.

Meanwhile, the daughter felt judged, as though her devotion to her father was an obstacle rather than an expression of love and duty. Neither side was wrong. They were just operating from incompatible frameworks about what was happening in that room.

That experience crystallized something: medical futility is not really medical. It is where medicine crashes into philosophy, culture, and deeply personal beliefs about life's value.

Why “Futility” Defies Definition

Medical futility sounds straightforward until you try to pin it down. Physiologic futility seems clearer: if someone has widespread cancer, failing organs, and is coding, CPR will not restore sustainable cardiac function. The intervention simply cannot achieve its basic goal.

Qualitative futility is where everything breaks down. Here, physicians say the outcome is not worth achieving. But that is a value judgment, not a medical fact. Someone on a ventilator in a persistent vegetative state has a beating heart. The machine works perfectly. Whether that constitutes life worth maintaining depends entirely on values, not science.

Doctors assess outcomes through specific lenses: survival duration, functional capacity, and cognitive ability. These may feel objective but reflect particular assumptions about what makes life worthwhile. A family viewing biological existence as inherently valuable is not irrational. They are weighing different factors and asking different questions.

When doctors declare treatment futile through a framework that prioritizes experiential quality of life and individual autonomy, and families demand

continuation from a framework that emphasizes communal obligation, biological sanctity, or the moral responsibility of not withdrawing life, they are not disagreeing about facts. They start from incompatible beliefs about what benefit actually means. The conflict between nonmaleficence — avoiding harm — and a family's sense of moral responsibility to sustain life is not resolvable through better data. It is a genuine values conflict.

Death Is Not Universal

Your cultural assumptions about death stay invisible until you encounter someone who does not share them.

Western biomedical ethics treats death as fundamentally individual, emphasizing patient autonomy and frank prognosis discussions. We see dignity as involving acceptance once treatment stops helping. Pushing for intervention past that point reads as denial.

Yet many cultural and religious traditions approach death very differently. In numerous communities across East Asia, South Asia, the Middle East, and Latin America, death is understood as a communal event. When someone dies, it affects family honor, community cohesion, and spiritual well-being. Medical decisions ripple outward, affecting everyone. Some families view maximum treatment as fulfilling sacred obligations, not as prolonging suffering, but as honoring life. Withdrawal registers as betrayal.

Religious beliefs compound this complexity. Islamic teaching holds that only Allah determines life's end. For some Muslim families, withdrawing support feels like usurping divine authority. Hindu concepts of karma shape how families understand suffering's spiritual purpose and what constitutes a “good death.” Catholic doctrine about life's sanctity can complicate comfort with “allowing natural death”

versus actively stopping treatment. These are not monolithic positions, because interpretation varies widely within each tradition, but they illustrate how profoundly religious frameworks shape what intervention means.

What strikes me is this: medical teams rarely recognize their own perspective as equally cultural. The bioethical principles taught in medical school — autonomy, beneficence, nonmaleficence, and justice — are not universal truths. They emerged from Western liberal thought and particular historical moments in medical ethics. When physicians frame their viewpoint as simply “medical” while describing families’ convictions as “cultural beliefs requiring sensitivity,” they miss something crucial. Both sides bring cultural frameworks. One just happens to dominate institutional culture.

The Cultural Competency Paradox

Medical education has long emphasized “cultural competency,” broadly understood as training focused on acquiring knowledge about generalized beliefs and practices associated with particular cultural or demographic groups. The goal is that if doctors understand diverse perspectives on death and illness, they will navigate conflicts more skillfully. We learn that certain Asian cultures prioritize collective decisions, Jehovah’s Witnesses refuse blood products, and Orthodox Jewish communities hold specific beliefs about brain death.

This approach creates the very problems it aims to solve. My critique here is directed primarily at simplified or older models of cultural competency, and at the informal or hidden curriculum that persists in many clinical environments, rather than at the best current curricula, some of which already emphasize cultural humility, reflexivity, and open-ended inquiry. The problem arises when training,

whether formal or informal, treats culture as predictive.

Real humans resist categorization. Two Muslim patients might hold opposite end-of-life views, both rooted in Islamic interpretation. Someone from a collectivist culture might have thoroughly individualized beliefs. Well-intentioned demographic preconceptions become sophisticated stereotyping.

Framing futility conflicts as cultural misunderstandings also obscures what is actually happening. Sometimes, culture is not the issue at all. Families from identical backgrounds make opposite decisions because of different personalities, health care experiences, trust levels, or ways of processing grief. When we attribute every conflict to culture, we miss other dynamics that matter more.

Here is what troubles me most: teaching “about” cultures through generalizations creates illusions of understanding. You complete a module on Hispanic families preferring family-centered decisions, and suddenly, you think you understand the specific family sitting across from you. That assumption interferes with genuine listening. You stop hearing them. You are just fitting what they say into predetermined categories.

Cultural awareness matters deeply. But the goal should not be accumulating facts. It should be cultivating a fundamentally different stance: approaching every patient expecting surprise, staying curious about individual perspectives, and remaining alert to how your own assumptions shape what seems obviously natural or correct.

What Actually Helps

Start conversations earlier. Many conflicts escalate because critical discussions happen only during crises. When someone is actively dying, families

cannot process information clearly. Beginning conversations about values and goals before serious illness emerges gives everyone time to absorb difficult realities gradually. This requires acknowledging uncertainty explicitly rather than presenting prognoses as more definitive than they actually are.

Recognize value conflicts for what they are. Sometimes families understand the medical situation perfectly but disagree about what should happen. That is not failed communication. It is a genuine ethical disagreement. Recognition changes everything. Value conflicts may never fully resolve, but you can navigate them with mutual respect intact.

Involve palliative care sooner. Palliative specialists excel at eliciting what matters to people rather than persuading them toward predetermined decisions. But they typically enter only after curative treatments have clearly failed, which frames palliative care as surrender. Early involvement alongside other treatments might prevent conflicts from escalating in the first place.

Create flexible institutional policies that explicitly account for the structural realities of health care. Hospitals operate with finite resources: ICU beds, ventilators, and specialist time. A family's right to have their values respected must coexist with the institution's obligations to other patients and to clinical staff. Effective policies emphasize how conflicts get resolved rather than predetermining outcomes. In practice, this might include mandating timely ethics consultation, outlining time-limited trials of aggressive intervention with preagreed reassessment points, facilitating transfers to providers willing to continue care, and creating clear processes for unilateral clinical decisions when consensus is genuinely impossible. The goal is to structure disagreement without

simply empowering physicians to override families, or families to demand indefinite continuation of care, without institutional accountability.

Reconceptualize competency itself. Emphasize cultural humility over cultural knowledge. Recognize the limits of your understanding. Commit to continuous learning. Constantly examine your own assumptions. Frame awareness as an ongoing practice you inhabit, not information you acquire once and move on from.

Living at the Boundary

Medical futility fascinates me precisely because it resists resolution. No algorithm produces the right answers. Better science will not settle these disputes. Clearer ethical reasoning will not either. Questions about life's meaning are not medical questions, and different answers are not more or less correct. They are fundamentally incommensurable.

These situations will arise constantly in my future practice. Patients will die. Families will demand treatments that, by clinical judgment, cause harm. My assessment will clash with deeply held religious convictions. I will feel institutional pressure around resource allocation and the needs of other patients. I will not resolve these tensions neatly, maybe ever. What I am trying to develop now is the capacity to stay present in impossible moments without demanding resolution: to listen without assuming someone's background tells me what they think, to admit uncertainty instead of hiding behind medical authority, and to recognize my values about dignity and quality of life as exactly that — my values, not universal truths everyone should obviously share.

Perhaps what matters most is not cultural fluency but ethical maturity. Can I acknowledge deep disagreement without dismissing it? Can I respect positions I personally find troubling? Can I maintain

genuine relationships with people whose choices disturb me? Can I accept that some tensions exist to be managed thoughtfully rather than solved definitively? Medicine operates where technical expertise meets existential questions, right at the boundaries of human experience. Learning to inhabit that uncomfortable space without demanding false certainty might be the most crucial skill I can develop, not because it makes difficult situations easier — they will remain agonizing no matter what — but because that kind of presence, the willingness to show up fully for people when there simply are not good options available, might be what patients and their families actually need most from their physicians.

The daughter in that ICU did not need her medical team to agree with her decision. She needed them to respect it, to treat her as someone making a profoundly difficult choice from a legitimate moral framework, not as an obstacle to delivering good medical care. Respect, in this context, means something specific: it does not require the team to endorse her choice, to abandon their clinical judgment, or to continue treatment indefinitely. It means treating her reasoning as worthy of genuine engagement, not as irrational resistance to be overcome, and explaining honestly what the institution can and cannot do, and why. The space between agreement and respect is exactly where medical futility's real work happens.





"Après la saisie (After the Seizure)" by Jean-Louis Forain (Artist, French, 1852 – 1931).
1908. Image courtesy of the National Gallery of Art.

Prolonged Seizure with Respiratory Arrest in a Resource-Limited Setting during a Global Health Service Trip

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Ethics statement: Informed consent was not obtained because the patient could not be contacted after the clinical encounter. The case report contains no identifiable patient information, and all details have been fully deidentified in accordance with conventional ethical reporting standards.

Keywords

seizure emergency; ictal central apnea; epilepsy; global health; resource-limited setting

Abstract

Seizure emergencies in low-resource settings present unique challenges because of limited access to diagnostics, antiseizure medications, and emergency services. Global health literature emphasizes the importance of rapid, coordinated interventions when standard treatments are unavailable. During an annual service-learning trip in the Dominican Republic, an adolescent patient with a history of transient loss of consciousness presented to a temporary outreach clinic. While awaiting referral planning, the patient became emotionally distressed and developed a generalized tonic-clonic seizure, followed by recurrent seizures and apnea. A care team including medical students, residents, nurses, pharmacists, and attending physicians provided continuous monitoring and supportive management with airway protection, bag-valve-mask ventilation, intravenous access, and dextrose-containing fluids. No antiepileptic

diagnostic equipment or medications were available. The patient experienced prolonged seizure activity with recurrent respiratory arrest, suspected to represent ictal central apnea (ICA). Oxygen saturation fell to the low 70s but stabilized above 92% with sustained ventilation. We hypothesize that recurrent episodes of respiratory arrest represented ICA, contributing substantially to the severity of presentation. Emergency care continued for approximately 30 to 60 minutes until transfer by emergency medical services. The patient was later hospitalized and discharged without neurologic deficits. This case highlights the clinical and logistical challenges of managing seizure emergencies in resource-limited environments and underscores the lifesaving potential of rapid, coordinated interdisciplinary action. Even without access to pharmacologic therapy or advanced diagnostics, effective teamwork and decisive supportive care proved critical.

Introduction

Seizures remain a significant global health concern, affecting millions worldwide and contributing substantially to morbidity, mortality, and reduced quality of life. The point prevalence of active epilepsy is estimated at 6.4 per 1000 people, with a lifetime prevalence of approximately 7.6 per 1000 and an annual incidence of 61 per 100,000 person-years.^{1,2} The burden is disproportionately higher in low- and middle-income countries, particularly in rural and remote regions, where limited access to health care infrastructure, diagnostic tools, and pharmacologic therapies substantially impedes effective management.^{3,4}

In these settings, preventable or acquired neurologic insults, including central nervous system infections, perinatal brain injuries, traumatic brain injuries, and metabolic disturbances, contribute to a higher prevalence of epilepsy.^{5,6} Despite this elevated disease burden, up to 75% of individuals with epilepsy in low- and middle-income countries remain untreated. This situation represents a substantial disparity driven by systemic challenges such as antiseizure drug shortages, lack of trained providers, scarce diagnostic resources, and sociocultural stigma.^{7,8} Together, these barriers accentuate an urgent need for adaptable, evidence-based seizure management strategies that can be feasibly integrated into rural health systems.^{9,10}

Seizure emergencies in resource-limited contexts underscore the importance of interdisciplinary preparedness and adaptive clinical reasoning. In such environments, where electroencephalography (EEG), neuroimaging, and abortive therapies may be unavailable, management often relies on rapid recognition of semiology, airway protection, and supportive care, particularly when confronting rare but life-threatening seizures complicated by ictal central apnea (ICA).¹¹

Emerging clinical research has emphasized the significance of ICA as a semiologic marker with both diagnostic and prognostic implications. ICA, defined as a transient cessation of breathing during seizures, occurs most frequently in focal epilepsies of temporal lobe origin and is strongly associated with mesial temporal structures, particularly the amygdala and hippocampus.^{12,13} Mesial temporal lobe epilepsy, one of the most prevalent and treatment-resistant focal epilepsies in children, is often associated with mesial temporal sclerosis, a common cause linked to early brain injury or febrile seizures.¹⁴ Furthermore, experimental and clinical studies demonstrate that amygdala involvement in seizure propagation can directly disrupt respiratory regulation, resulting in apnea even in the absence of overt motor features.^{15,16} Clinically, ICA may present as abrupt behavioral arrest, fear, or unresponsiveness, which may represent subtle signs that are easily overlooked, particularly in children.

Importantly, ICA often precedes scalp EEG seizure onset by several seconds, conferring diagnostic value in the early recognition of focal seizures.^{17,18} In a large prospective cohort study, ICA was observed in 47% of patients with focal epilepsy, with temporal lobe epilepsy demonstrating a significantly higher association with ICA than extratemporal epilepsies.^{15–17,19,20} Similarly, a multicenter study of 126 patients showed that ICA occurred exclusively in focal epilepsy, involving 36.5% of seizures, frequently preceding EEG onset and, in some cases, representing the sole clinical manifestation of seizure activity; temporal lobe epilepsy again showed a strong association with ICA.¹⁵ Further supporting its localization value, a prospective intracranial EEG study demonstrated that the presence of ICA predicted mesial temporal seizure onset with approximately fourfold greater odds and high specificity, implicating mesial temporal structures such as the amygdala and hippocampus in seizure propagation.²¹ Recognition of ICA may

therefore aid in anatomo-electroclinical correlation and inform electrode placement, a critical step in presurgical evaluation to guide treatment. In addition, small case series have documented ICA as the initial or primary seizure manifestation in patients with temporal lobe epilepsy, underscoring its potential to occur subclinically and to serve as a subtle but localizing semiologic feature.^{13,22}

Although the sensitivity of ICA remains limited, its relative specificity for mesial temporal seizure onset supports its role as a noninvasive semiologic biomarker. Collectively, these findings highlight the growing clinical relevance of ICA in seizure localization and diagnostic evaluation while underscoring the need for further studies to determine its effect on clinical outcomes and management strategies.

During an annual service-learning trip in the Dominican Republic, medical trainees and clinicians encountered a pediatric patient with prolonged seizures complicated by recurrent respiratory arrest. This paper presents the case, which illustrates the challenges and opportunities for improving seizure care in underserved global health settings and highlights the diagnostic utility of ICA in the absence of advanced resources. By situating the case within the broader literature on seizure semiology and global health, we aim to emphasize scalable strategies for seizure recognition and management in resource-limited environments.

Case Report

An adolescent patient presented to a temporary outreach clinic during an annual service-learning trip in a rural setting in the Dominican Republic for evaluation of recurrent episodes of transient loss of consciousness. History was obtained from the patient and caregiver with interpreter assistance.

The patient reported recurrent episodes over several months characterized by brief loss of consciousness with rapid return to baseline. Episodes were sometimes associated with reduced oral intake and heat exposure. The patient described emotional distress preceding some episodes. No prodromal palpitations, chest pain, dyspnea, vertigo, or visual disturbances were reported. There was no known personal or family history of seizures, neurologic disease, or congenital heart disease.

On the basis of the clinical history, the initial working impression was syncope related to hypovolemia or hypoglycemia, and referral for neurologic evaluation was recommended. Near the conclusion of the visit, the patient became visibly distressed and experienced abrupt loss of consciousness.

The patient was placed supine with leg elevation. Airway, breathing, and circulation were initially intact, though the patient was unresponsive. After approximately 30 seconds, focal tremors of the right hand progressed to a generalized tonic-clonic seizure. The patient was turned laterally and protected from injury. No abortive antiseizure medications were available.

Following brief postictal recovery, the patient experienced recurrent tonic-clonic seizures accompanied by intermittent apnea. Initial ventilation was performed with mouth-to-mask techniques because of equipment malfunction until bag-valve-mask ventilation was established. Oxygen saturation transiently dropped to the low 70s and improved to the mid-90s with effective ventilation. Capillary glucose was normal.

Over the ensuing 30 to 60 minutes, the patient experienced recurrent seizures with intermittent respiratory arrest, with some apneic episodes lasting several minutes and requiring continuous bag-valve-mask ventilation. Intravenous access was obtained, and dextrose-containing fluids were initiated. Oxygen saturation was maintained above

92%, and other vital signs remained stable. Upon arrival of emergency medical services, the patient was postictal but breathing spontaneously and was transferred to a local hospital.

According to subsequent communication with local contacts, the patient was hospitalized and treated for seizures, underwent further neurologic evaluation, and was discharged home within several days without residual neurologic deficits. Details of his inpatient diagnostic workup remain unknown.

Discussion

The differential diagnosis for this adolescent patient presenting with recurrent transient loss of consciousness evolving into focal-to-generalized seizures includes temporal lobe epilepsy, psychogenic nonepileptic seizures (PNES), syncope, and metabolic or systemic causes. An official diagnosis could not be confirmed because of the absence of EEG, neuroimaging, and laboratory studies, which are essential for identifying structural abnormalities, localizing seizure onset, and excluding metabolic or infectious causes. Nonetheless, clinical semiology strongly favored temporal lobe epilepsy. The presence of ICA, a psychic aura with fear and sadness, focal motor onset, and lack of an immediate return to baseline between seizures suggested an origin in the mesial temporal structures. Importantly, the patient's earlier brief episodes may have been attributable to vasovagal syncope or PNES, whereas the event we witnessed was more consistent with an epileptic seizure. Overall, this case highlights how clinical judgment and semiologic analysis remain essential when diagnostic resources are scarce, allowing clinicians to delineate a proper treatment course for a neurologic condition.

As a limitation, although evidence increasingly supports ICA as a semiologic feature associated with temporal lobe seizures, there are currently no

published cohort studies or controlled trials that directly compare clinical outcomes on the basis of whether ICA was explicitly incorporated into diagnostic algorithms or treatment decision making. The existing literature primarily characterizes the incidence, localization value, and semiologic features of ICA in focal epilepsies, most often within specialized monitoring environments such as video EEG or intracranial EEG studies. Consequently, the effect of ICA recognition on treatment outcomes, particularly in resource-constrained settings, remains insufficiently studied. Nevertheless, this case underscores the clinical importance of recognizing seizure-associated apnea, because unrecognized peri-ictal respiratory compromise may carry substantial risk and be fatal, warranting prompt clinical attention.

Equally significant is how this case illustrates effective seizure management by a structured and interdisciplinary medical team operating in a low-resource environment. Each team member, whether student, nurse, pharmacist, resident, or attending physician, assumed a clear role, which minimized delays and prevented confusion. The team effectively applied basic life support principles in parallel, ensuring airway protection, monitoring cardiorespiratory status, and maintaining patient safety throughout the event. The absence of role confusion or conflict enabled the team to operate efficiently despite limited resources. This experience reinforces the importance of having necessary equipment and confident providers trained in Advanced Life Support for Cardiac Arrest and Pediatric Advanced Life Support frameworks during any emergency or code situation. In addition, clearly assigning responsibilities and promoting mutual respect among providers from diverse backgrounds is crucial for achieving optimal outcomes.

Furthermore, access to contact information for local health care professionals and the emergency response system enabled rapid activation of

emergency medical services and transfer to a nearby hospital for definitive management. This underscores the importance of establishing referral pathways and emergency communication strategies before deployment, which should be standard practice for medical service trips. Mobile care teams have also demonstrated the ability to manage status epilepticus effectively in the field, with one report showing that a mobile medical team achieved seizure control as quickly as or faster than an emergency department team in rural Japan.²³

This case emphasizes a critical deficiency in seizure management: the restricted availability of abortive antiseizure medications in resource-limited settings. During medical service missions, the transport of controlled substances, including intravenous benzodiazepines, is frequently constrained by the regulatory frameworks of host countries. These restrictions can impede the ability to deliver timely pharmacologic interventions for seizures. Under ideal circumstances, prolonged seizures lasting beyond 2 minutes are treated as medical emergencies necessitating immediate drug therapy. Consequently, the inclusion of accessible nonintravenous formulations, such as intranasal midazolam or rectal diazepam, in emergency kits should be considered.

It is also imperative to acknowledge that the administration of abortive antiseizure medications, particularly benzodiazepines, requires preparedness for potential respiratory adverse effects. In this case, the patient was already exhibiting ICA, and benzodiazepine administration could have further suppressed respiratory drive or prolonged apnea. In such circumstances, the medical team must be equipped to provide immediate respiratory support, including supplemental oxygen and, if necessary, airway protection and endotracheal intubation. Although flumazenil can reverse benzodiazepine-induced sedation and respiratory depression, its use is generally contraindicated in patients with epilepsy

or status epilepticus, because it may precipitate seizures by antagonizing γ -aminobutyric acid-mediated inhibition.^{24,25} Therefore, flumazenil should not be considered a safe alternative to appropriate airway management in patients with seizure-related respiratory compromise. In our situation, we lacked the necessary airway equipment; therefore, even if benzodiazepines had been available, we could not have proceeded safely with that treatment. Although the availability of antiseizure medications could substantially mitigate seizure-related morbidity, medical teams must remain cognizant of the potential adverse effects associated with these medications. Thus, it is essential to ensure that appropriate equipment, training, and fail-safes are in place to facilitate effective responses in emergencies.

In addition to medical logistics, broader barriers such as cultural stigma and misconceptions surrounding seizures often further delay treatment seeking in low-resource communities. Accordingly, local partnerships and community education campaigns can help counteract these challenges by promoting awareness that epilepsy is a treatable, noncontagious neurologic condition rather than a supernatural or social curse.²⁶ Technology also offers innovative pathways to bridge disparities: wearable monitoring devices, mobile health applications, and handheld diagnostic tools, such as portable ultrasonography, can augment care in the absence of advanced hospital infrastructure. Although not substitutes for continuous EEG or imaging, these tools can assist in the timely recognition, stabilization, and referral of patients with epilepsy in rural areas and have been effectively used for procedures including peripheral intravenous placement, endotracheal tube insertion, and thoracentesis.²⁷

Conclusion

This case, encountered during an annual service trip to the Dominican Republic, illustrates the complexities of diagnosing and managing epilepsy in low-resource settings while demonstrating the effectiveness of rapid, team-based responses grounded in basic life support principles and strong local partnerships. For medical service trips, the lessons learned emphasize the necessity of predeployment basic life support and seizure-response training, the establishment of emergency referral systems, and consideration of carrying safe, effective nonintravenous anticonvulsants. Beyond logistics, addressing stigma and fostering community education remain essential to reducing the treatment gap for epilepsy globally. By integrating clinical vigilance, strategic preparedness, structured teamwork with clearly designated roles, and local collaboration, medical service trips can improve outcomes for vulnerable patients and serve as a model for global health practice in underserved communities.

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Reviews





"Study for 'Autopsy at the Hôtel-Dieu'" by Henri Gervex (Painter, French, 1852 - 1929). 1876. Image courtesy of the National Gallery of Art.

Correlation Between Diabetes Prevalence and ICU and Hospital Length of Stay Across Studies: A Systematic Review and Meta-Analysis

Keywords

diabetes mellitus;
cardiopulmonary bypass;
length of stay

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Abstract

Background: Diabetes mellitus elicits considerable concern regarding perioperative outcomes in cardiac surgery. This systematic review endeavors to elucidate the effect of diabetes on ICU and hospital length of stay (HLOS) after cardiopulmonary bypass (CPB) in cardiac surgery.

Methods: A comprehensive search of PubMed, Scopus, Embase, and the Cochrane Library was conducted, targeting clinical trials published between 2004 and 2024. The primary outcome assessed was the correlation between the proportion of diabetic patients and ICU length of stay. Secondary outcomes included the correlation between the proportion of diabetic patients and HLOS, as well as the relationships among the proportion of diabetic patients, ICU length of stay, mean age, sex distribution, and BMI. Weighted correlation analyses were used.

Results: Thirteen studies involving 1588 patients were included. The weighted correlation between the proportion of diabetic patients and ICU length of stay was -0.176 ($P=0.57$), indicating a weak and nonsignificant association. Nine studies involving 905 patients analyzed HLOS, revealing a weak but

statistically significant negative correlation (-0.255 , $P=0.0020$). The mean age of patients was 64.7 years, which did not significantly affect ICU length of stay (coefficient, 0.065 ; $P=0.51$). The sex distribution comprised 25.0% female and 75.0% male participants, with significant differences across studies (chi-square statistic, 38.764; $P<0.01$). BMI analysis showed a mean BMI of 27.2, which also did not significantly affect ICU length of stay (coefficient, -0.20549 ; $P=0.7657$).

Conclusions: Diabetes does not significantly affect ICU length of stay but is associated with shorter hospital stays. This unexpected finding warrants further investigation, particularly given the limited number of studies contributing data to the HLOS analysis. Significant differences in sex distribution across studies highlight the need to consider sex as a variable in future research. Although age and BMI were not significant factors in ICU length of stay, they remain important for postoperative outcomes. Future research should address these limitations to enhance the reliability of findings and improve postoperative care for diabetic patients.

Introduction

Cardiopulmonary bypass (CPB) is a critical technique in cardiac surgery, providing essential support to the heart and lungs during complex procedures.¹ Introduced into clinical practice in the 1950s,² CPB has revolutionized cardiac surgery by allowing operations that would otherwise be impossible. Despite its undeniable benefits, CPB is associated with a range of complications, including systemic inflammation, organ dysfunction, and coagulation disorders.³

Diabetic patients, who constitute a significant proportion of those undergoing cardiac surgery,⁴ are particularly susceptible to the complications associated with CPB. Diabetes mellitus is a chronic disease characterized by persistent hyperglycemia, leading to vascular damage, an increased risk of infection, and inflammation.⁵ In diabetic patients, the exacerbated inflammatory response during CPB can aggravate these conditions, resulting in higher risks of morbidity and mortality.⁶

One of the primary concerns for diabetic patients undergoing CPB is the length of stay in the intensive care unit (ICU). Prolonged ICU stays not only increase the risk of hospital-acquired complications, such as nosocomial infections, but also contribute to higher health care costs and socioeconomic burden.⁷ Identifying the factors that prolong ICU stays in diabetic patients is crucial for developing management strategies that can improve clinical outcomes and reduce associated costs.

The existing literature on the effect of diabetes on ICU length of stay after CPB is extensive but presents conflicting results. Some studies suggest that diabetic patients have a significantly longer ICU stay than nondiabetic patients,^{8,9} whereas others find no significant differences between the two groups.^{10,11} These discrepancies may be attributable

to differences in study designs, populations studied, and definitions of outcomes.

This systematic review aims to consolidate the existing evidence and provide a comprehensive assessment of the effect of diabetes on ICU length of stay after CPB. By pooling and analyzing data from multiple studies, we seek to answer the question: Is the proportion of diabetic patients in studies of cardiac surgery with CPB associated with a significant difference in ICU and hospital length of stay?

Overall, this systematic review seeks to fill a critical knowledge gap regarding the effect of diabetes on ICU length of stay after CPB, providing a comprehensive overview that can guide clinical practice and future research. By addressing this issue, we aim to improve the management and outcomes of diabetic patients undergoing cardiac surgery, ultimately contributing to better patient care and health care resource utilization.

Importantly, this study adopts an ecological, study-level approach, examining whether variation in the proportion of diabetic patients across published trials is associated with differences in mean ICU and hospital length of stay. As such, the analysis does not compare outcomes between individual diabetic and nondiabetic patients.

Methods

Search Strategy and Databases

To ensure a comprehensive and systematic review, we used a meticulous search strategy across multiple reputable scientific databases. The databases used for this review included PubMed, Scopus, Embase, and the Cochrane Library, chosen for their extensive coverage of medical and clinical research. We used a combination of keywords and Medical Subject Headings (MeSH) related to

diabetes, cardiopulmonary bypass, cardiac surgery, and hospital length of stay. The primary search terms included "diabetes mellitus," "extracorporeal circulation," "cardiopulmonary bypass," "cardiac surgery," and "hospital length of stay." Boolean operators (AND, OR) were used to refine the search and ensure the inclusion of all pertinent studies. The search terms used were: ("Diabetes Mellitus" OR "Diabetes" OR "Diabetic patients" OR "Type 1 Diabetes" OR "Type 2 Diabetes" OR "T1D" OR "T2D") AND ("Extracorporeal Circulation" OR "Cardiopulmonary Bypass" OR "CPB" OR "Cardiac Bypass" OR "Heart-Lung Machine" OR "Heart-Lung Bypass" OR "Extracorporeal Life Support" OR "ECLS") AND ("Cardiac" OR "Heart" OR "Coronary") AND ("Surgery" OR "Operation" OR "Procedure").

The search strategy was applied to each database, specifically focusing on clinical trials from the past 20 years, without language restrictions. In addition, the reference lists of the identified articles were manually screened to uncover any studies that might have been missed in the initial search.

Inclusion and Exclusion Criteria

Studies were included if they met the following criteria: (1) clinical trials published between January 1, 2004, and December 31, 2024; (2) involvement of patients who underwent CPB during cardiac surgery; (3) inclusion of both a control group and an intervention group; and (4) reporting of ICU length of stay and the number of diabetic patients in the control group. Studies were excluded if they were case reports, review articles, editorials, or conference abstracts, or if they exhibited significant methodological flaws or a high risk of bias, as determined during the quality-assessment phase.

Data Extraction Process

This systematic review uses an ecological, study-level design. Rather than performing patient-level

comparisons between diabetic and nondiabetic individuals, we analyzed the proportion of diabetic patients reported in each study and examined its correlation with aggregate outcomes, including mean ICU and hospital length of stay. Data extraction was carried out independently by two reviewers to minimize bias and errors. A standardized data-extraction form was used to ensure consistency. For each included study, the following data were extracted: basic study information, including author names, publication year, country, and study design; participant characteristics, including number of participants, age, sex distribution, BMI, and diabetes status; surgical details, including type of cardiac surgery performed; and outcomes, including the primary outcome of ICU length of stay and the secondary outcome of hospital length of stay. Any discrepancies between the reviewers regarding data extraction were resolved through discussion, and a third reviewer was consulted if consensus could not be reached.

It is important to note that this study does not perform patient-level comparisons between diabetic and nondiabetic individuals. Instead, we used an ecological approach by analyzing the proportion of diabetic patients reported in each study and assessing its correlation with aggregate outcomes such as mean ICU length of stay and hospital length of stay.

In addition, information regarding the study setting — including the country of origin, number of participating centers, and time frame of data collection — was extracted to assess potential sources of institutional heterogeneity. Of the 13 included studies, 7 were conducted at a single center and 6 were multicenter trials, ranging from 2 to 25 institutions. Most multicenter studies reported standardized perioperative protocols; however, one explicitly stated that no uniform anesthetic or surgical practices were used across centers. Such

variability may represent a significant confounding factor, because differences in institutional practices, discharge criteria, and postoperative management can independently affect outcomes such as ICU and hospital length of stay, regardless of diabetes status.

Information on diabetes status was extracted from the baseline-characteristics tables reported in each study. Although most studies classified patients as diabetic or nondiabetic, few provided specific diagnostic criteria such as glycemic thresholds, medication use, or HbA1c levels. In some cases, diabetic patients were described as having type 2 diabetes; in others, no additional details were provided. This heterogeneity in diabetes definition was considered a limitation of the analysis.

Quality Assessment of Included Studies

The quality and risk of bias of the included studies were assessed with validated tools appropriate for the study designs. Randomized, controlled trials were evaluated with the Cochrane Risk of Bias 2 (ROB 2) tool, which assesses potential biases in randomization, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Each study was independently assessed by two reviewers. The studies were categorized as having a low, moderate, or high risk of bias on the basis of the assessment criteria.

Reporting and Registration

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure transparency and rigor in reporting. The review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) to promote transparency and prevent duplication of efforts.

Statistical Analysis

The primary statistical analysis focused on establishing the weighted correlation between the proportion of diabetic patients and length of stay in the ICU. The weighted correlation coefficient was calculated, considering the number of participants (N) in each study to ensure that studies with larger sample sizes had a proportionately greater influence on the results. Secondary analyses were conducted to assess HLOS and the relevance of mean age, sex distribution, and body-mass index (BMI) across the included studies.

Therefore, for the primary outcome, we analyzed the control groups from 13 clinical trials,¹²⁻²⁴ encompassing a total sample size of 1588 patients. Furthermore, a weighted correlation analysis was performed to examine the relationship between the proportion of diabetic patients and HLOS. For the HLOS analysis, studies with missing data on hospital length of stay were excluded, resulting in 9 studies,^{12,14-18,22-24} with a total sample size of 905 patients being included in this analysis.

To evaluate the age distribution, the weighted mean age was calculated, again using the number of participants as the weight. For this analysis, studies with missing age data were excluded, resulting in a total of 12 studies,^{12-15,17-24} with a combined sample size of 1564 participants. The sex-distribution differences across the studies were assessed with a weighted chi-square test, with 11 articles^{12-19,21,23,24} included, resulting in a total sample size of 1405 participants. For the BMI analysis, the weighted mean BMI was calculated. Studies without BMI data were excluded, resulting in 7 studies^{12-17,21} with a combined sample size of 1039 participants. To understand the potential effect of age and BMI on ICU length of stay, a weighted least-squares (WLS) regression analysis was performed, including the mean age and mean BMI as predictors, weighted by the number of participants in each study.

Results

The search strategy identified a total of 613 articles across the three databases. After duplicates were removed, 481 unique articles remained. These articles were screened on the basis of titles and abstracts, resulting in 64 articles deemed potentially relevant. Full-text reviews of these articles were conducted, leading to the exclusion of 51 articles that did not meet the inclusion criteria. Ultimately, 13 studies were included in the systematic review, providing data on ICU length of stay and the number of diabetic patients.

Study Characteristics

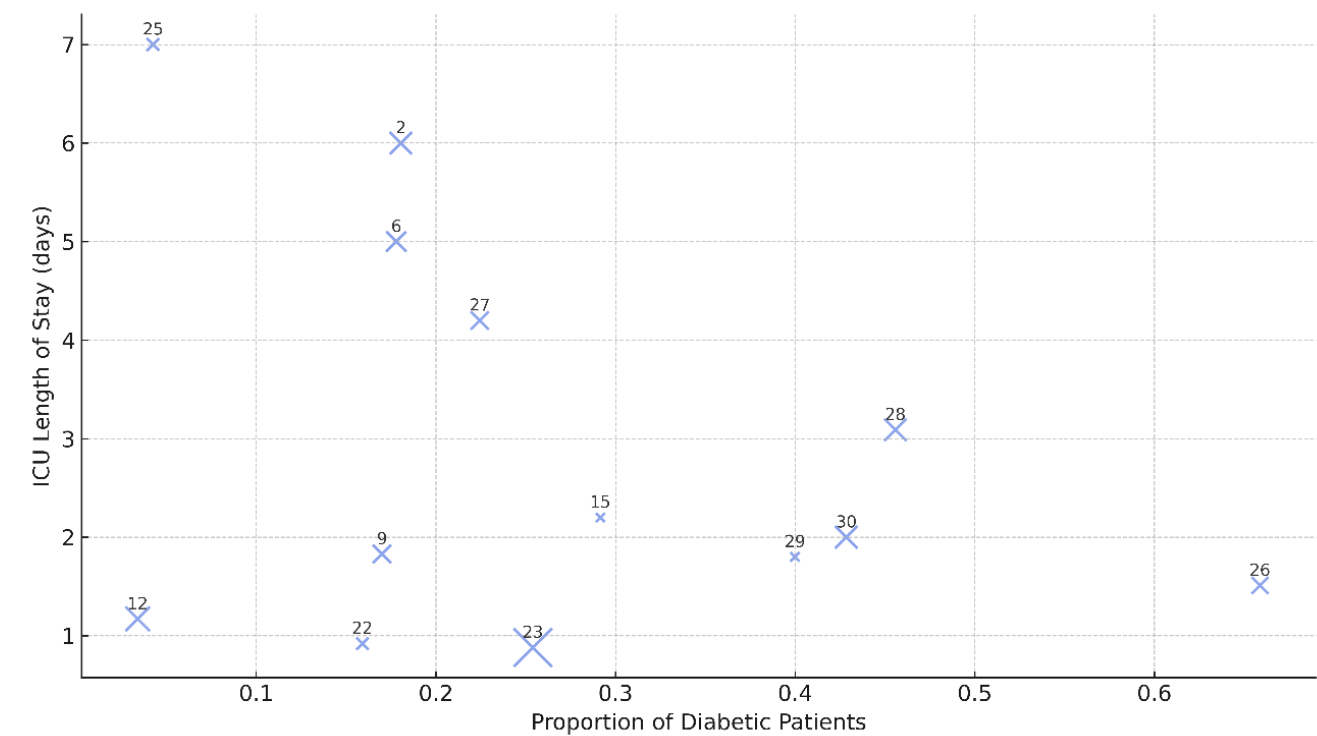
The 13 included studies were published between 2004 and 2024 and collectively enrolled 1588

patients. Sample sizes ranged from 24 to 433 participants. The studies reported on various types of cardiac surgery, including coronary-artery bypass grafting (CABG), valve replacement, and mixed cardiac procedures. The proportion of diabetic patients in the studies ranged from 3% to 66%.

Primary Analysis: ICU Length of Stay

The primary analysis examined the weighted correlation between the proportion of diabetic patients and ICU length of stay. The weighted correlation coefficient was -0.176 ($P=0.57$), with a mean ICU length of stay of 2.6 days, indicating a weak negative correlation that was not statistically significant.

Figure 1. Proportion of Diabetic Patients versus ICU Length of Stay.



Scatter plot illustrating the relationship between the proportion of diabetic patients in each study on the x axis and the corresponding mean ICU length of stay, in days, on the y axis. Each point represents one of the 13 included

studies. The size of each point is proportional to the total number of patients (N) in the respective study. Study codes are displayed above each data point for reference. Source: self-authored. ICU LOS denotes intensive care unit length of stay, DM diabetic patients, and N total number of patients.

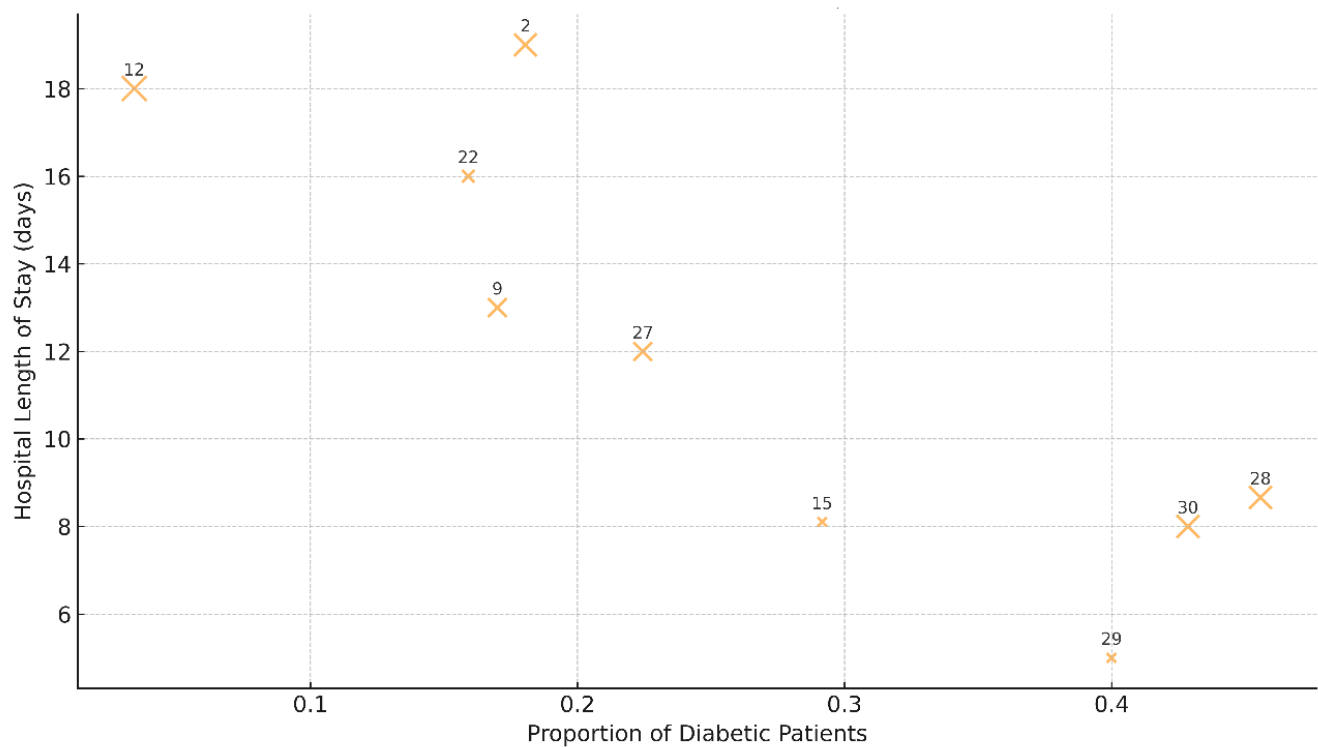
Secondary Analysis

Hospital Length of Stay

For the HLOS analysis, 9 studies with a total of 905 patients were included after those with missing data were excluded. The weighted mean HLOS was 13.1 days, and a weak but statistically significant negative correlation was found between the proportion of diabetic patients and HLOS (correlation coefficient, -0.255 ; $P=0.0020$). This

suggests that a higher proportion of diabetic patients was associated with shorter hospital stays. However, only 9 studies contributed data to this analysis, which limits the precision and robustness of the estimated association and warrants cautious interpretation. The WLS regression analysis showed a high proportion of explained variance ($R^2=0.768$; F statistic, 23.16; $P=0.002194$), but these results should be interpreted as exploratory given the small number of studies.

Figure 2. Proportion of Diabetic Patients versus Hospital Length of Stay.



Scatter plot illustrating the relationship between the proportion of diabetic patients and mean hospital length of stay (HLOS) across the included studies. Each data point represents one study. The x axis denotes the proportion of diabetic patients, and the y axis represents the corresponding mean HLOS, in days. The size of each point is

proportional to the total number of patients in the respective study (N). Study codes are labeled next to each point for identification. Source: self-authored on the basis of extracted data from included trials.

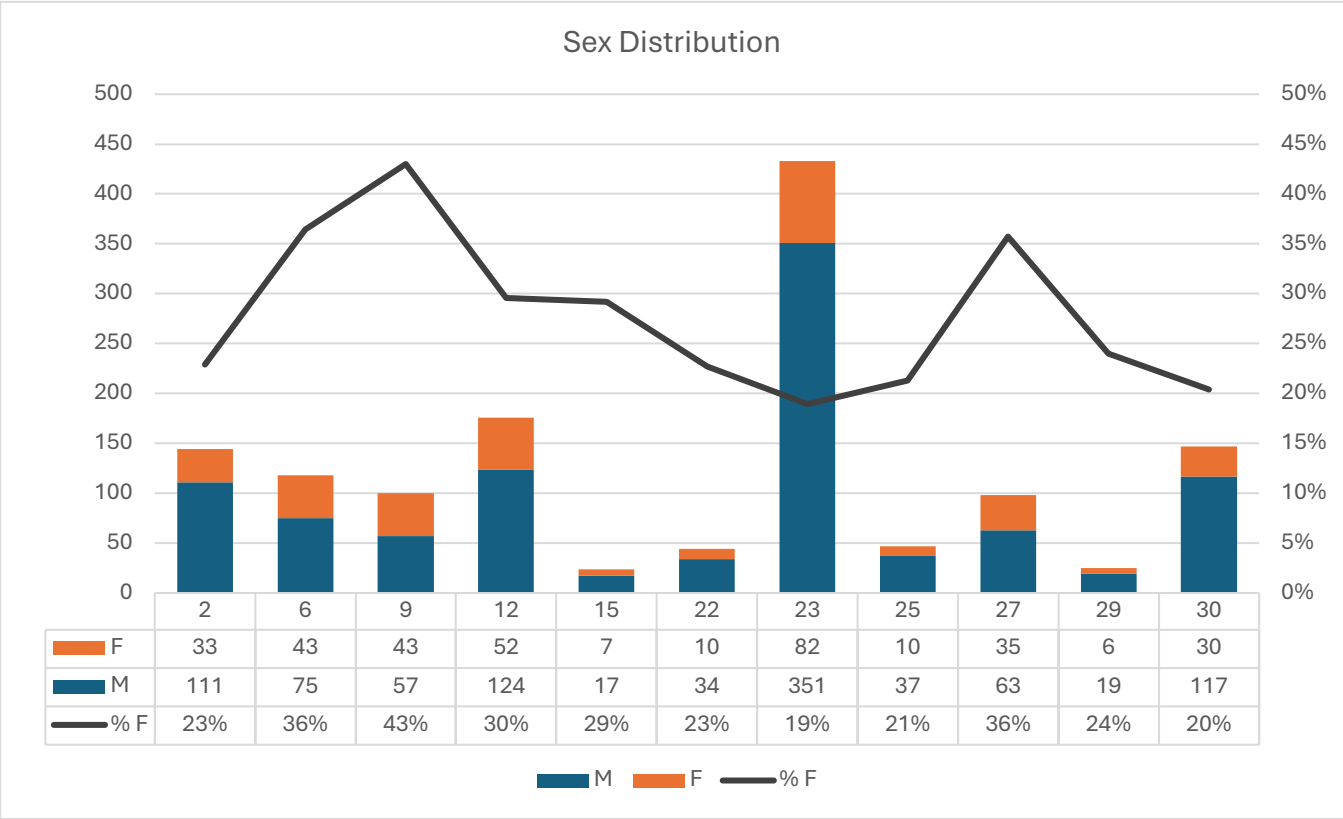
Mean Age

The age distribution across the studies was assessed with the weighted mean age. The weighted mean age was determined to be 64.7 years. To evaluate the effect of age on ICU length of stay, a WLS regression analysis was performed. The regression model included mean age as a predictor, weighted by the number of participants in each study. The regression analysis revealed that mean age did not have a statistically significant effect on ICU length of stay (coefficient, 0.065; P=0.51).

Sex Distribution

Sex-distribution differences across the studies were assessed. The total number of female participants was 351 (25.0%), and the total number of male participants was 1054 (75.0%). A weighted chi-square test revealed a chi-square statistic of 38.764, with a P value of less than 0.01, indicating a significant difference in sex distribution across the studies. This suggests that the variation in the proportion of female and male participants across the studies is nonrandom and should be considered when interpreting the results.

Figure 3. Sex Distribution across Included Studies.



Bars represent the absolute number of male (M) and female (F) participants in each study, and the line represents the percentage of female participants (%F). Numbers along the x axis correspond to study identification codes, which match the studies listed in Annex I. Source: self-authored. N denotes total number of patients, M number of male patients, F number of female patients, and ICU LOS intensive care unit length of stay.

BMI Analysis

The BMI analysis involved calculation of the weighted mean BMI, resulting in a value of 27.2 kg/m². A WLS regression analysis was conducted to understand the potential effect of BMI on ICU length of stay. The regression model included mean BMI as a predictor, weighted by the number of participants in each study. The regression analysis revealed that mean BMI did not have a statistically significant effect on ICU length of stay (coefficient, -0.20549; P=0.7657). The R² value was 0.021, indicating a very low proportion of variance in ICU length of stay explained by BMI.

Quality Assessment

The quality and risk of bias of the included studies were assessed with the Cochrane Risk of Bias 2 (ROB 2) tool. Overall, most included studies were judged to be at low risk of bias across all assessed domains. One study (Diab et al.¹²) was rated as having a moderate risk of bias due to protocol deviations, representing approximately 9% of the total pooled sample. No study was classified as having a high risk of bias.

Discussion

The primary objective of this systematic review was to determine the effect of diabetes on ICU and hospital length of stay after cardiac surgery with CPB. Our findings indicate that the proportion of diabetic patients within a study population does not significantly influence ICU length of stay, as

evidenced by the weak and nonsignificant negative correlation (weighted correlation coefficient, -0.176; P=0.57). This finding contrasts with the common paradigm that diabetes is associated with longer ICU stays after cardiac surgery,²⁵ suggesting that our analysis provides a new perspective on this relationship.

However, our secondary analysis revealed a statistically significant but weak negative correlation between the proportion of diabetic patients and HLOS, with a weighted correlation coefficient of -0.255 and a P value of 0.0020. This unexpected finding contrasts with the prevailing understanding that diabetes is generally associated with worse postoperative outcomes. Previous studies have commonly reported prolonged hospital stays among diabetic patients.⁸ One possible explanation is that study populations with a higher prevalence of diabetes may be managed with more standardized or intensive perioperative protocols, potentially influencing discharge practices. It is important to note that this secondary analysis was based on a small number of studies with available HLOS data. As emphasized by Button et al.,²⁶ analyses based on small sample sizes or limited numbers of studies are particularly prone to unstable effect estimates and reduced reproducibility. Accordingly, this finding should be interpreted cautiously and viewed as exploratory rather than confirmatory. Further research is needed to explore this hypothesis and identify the specific factors contributing to this outcome.

Although our analysis did not find significant effects of age or BMI on ICU length of stay, these factors

are well documented in the literature as important determinants of postoperative outcomes.^{27,28} In addition, our analysis revealed significant differences in sex distribution across studies, which may have influenced outcomes. In cardiac surgery populations, female patients have been shown to differ from male patients in baseline risk profiles, comorbidity burden, and physiological responses to CPB, including differences in body size, vascular anatomy, inflammatory response, and susceptibility to postoperative complications such as bleeding, renal dysfunction, and prolonged recovery. These sex-related factors may contribute to variability in ICU and hospital length of stay across studies.²⁹ Therefore, age, BMI, and sex distribution should continue to be considered in future studies to ensure a comprehensive understanding of factors influencing ICU length of stay.

Strengths and Limitations

This systematic review has several strengths, including a comprehensive search strategy, the use of multiple databases, and rigorous assessment of study quality. However, there are limitations that must be acknowledged. One included study was assessed as having a moderate risk of bias due to protocol deviations, accounting for approximately 9% of the total pooled data. Although this may slightly influence the reliability of the findings, the overall low risk of bias across the remaining studies supports the robustness of the primary conclusions. In addition, the exclusion of studies with missing data may have introduced selection bias, and the significant difference in sex distribution across the studies, as indicated by the weighted chi-square test, highlights the importance of considering sex as a variable in the analyses.

Therefore, although diabetes does not appear to significantly affect ICU length of stay, it may be

associated with shorter hospital stays after cardiac surgery with CPB. These findings underscore the need for further investigation into the specific care practices and management strategies that may benefit diabetic patients postoperatively. In addition, future research should aim to address these methodological limitations to provide more robust and reliable findings.

Another potential limitation is the heterogeneity in health care systems and postoperative care protocols across centers. Differences in institutional practices may influence outcomes such as ICU and hospital length of stay independently of diabetes status. As such, variations between single-center and multicenter studies may confound the observed associations.

Furthermore, institutional variability across studies, particularly between single-center and multicenter trials with differing perioperative protocols and health care delivery models, may have introduced confounding effects. These differences underscore the importance of accounting for interinstitutional variability when interpreting aggregate outcomes in systematic reviews.

An important limitation of this review is the lack of standardized definitions of diabetes mellitus across the included studies. Although a few studies described diabetic patients as having type 2 diabetes mellitus, most did not provide diagnostic criteria or clarify whether diabetes status was based on clinical history, pharmacologic treatment, or laboratory markers such as HbA1c. An important limitation of this review is the lack of standardized definitions of diabetes mellitus across the included studies. Although a few studies described diabetic patients as having type 2 diabetes mellitus, most did not provide diagnostic criteria or clarify whether diabetes status was based on clinical history, pharmacologic treatment, or laboratory markers such as HbA1c. This inconsistency limits the ability

to evaluate the impact of diabetes severity or control on postoperative outcomes. Additionally, no study provided data on glycemic control or stratified diabetic patients by disease severity. This heterogeneity limits the ability to assess how the metabolic status of patients may have influenced ICU or hospital length of stay.

The results of this systematic review help clarify discrepancies previously reported in the literature and may serve as a foundation for clinical practice and future research. Understanding how variation in diabetes prevalence across study populations correlates with ICU and hospital length of stay may inform the development of targeted interventions and contribute to optimizing perioperative care for diabetic patients. Moreover, the findings may support health policy decisions aimed at improving resource allocation and care delivery in cardiac surgery settings.

Conclusion

This systematic review used an ecological, study-level approach to examine whether variation in diabetes prevalence across cardiac surgery trials involving CPB is associated with differences in ICU and hospital length of stay. Across 13 studies, no significant association was observed between the proportion of diabetic patients and ICU length of stay. A weak inverse association was identified between diabetes prevalence and hospital length of stay; however, this finding was based on a small number of studies and should be interpreted cautiously.

These results should be viewed in light of important limitations, including the ecological design, the limited number of studies contributing hospital-length-of-stay data, missing outcome information, and heterogeneity in study populations and perioperative practices. Consequently, the observed association with hospital length of stay is

exploratory and hypothesis-generating rather than confirmatory.

Future research should prioritize adequately powered, patient-level analyses that account for diabetes severity, glycemic control, and perioperative management strategies to better clarify the relationship between diabetes and postoperative resource utilization after cardiac surgery.

Annex I. Systematic Review Table

COD	AUTHOR	YEAR	STUDY	N	DM	% DM	ICU LOS	HLOS	AGE	IMC	SEX F	SEX M
2	DIAB	2022	Cytokine Hemoadsorption During Cardiac Surgery Versus Standard Surgical Care for Infective Endocarditis (REMOVE)	144	26	18%	6,00	19	69	27,5	33	111
6	BARBA-NAVARRO	2017	The Effect of Spironolactone on Acute Kidney Injury After Cardiac Surgery	118	21	18%	5,00		54	26,8	43	75
9	RUJIROJINDAKUL	2014	Safety and efficacy of intensive intraoperative glycaemic control in cardiopulmonary bypass surgery	100	17	17%	1,83	13	54	23,3	43	57
12	HAASE	2013	Prophylactic Perioperative Sodium Bicarbonate to Prevent Acute Kidney Injury Following Open Heart Surgery	176	6	3%	1,17	18	64,6	27,5	52	124
15	MIRMOHAMMADSADEGHI	2020	Sleep Quality after Coronary Artery Bypass Graft Surgery: Comparing Pulsatile and Nonpulsatile Pump Flow	24	7	29%	2,20	8,1		25,3	7	17
22	BREUER	2006	Preoperative oral carbohydrate administration to ASA III-IV patients undergoing elective cardiac surgery	44	7	16%	0,92	16	64	27,5	10	34
23	VIDLUND	2012	GLUTAMICS-a randomized clinical trial on glutamate infusion in 861 patients undergoing surgery for acute coronary syndrome	433	110	25,4%	0,88		68	27	82	351
25	KNEZEVIC	2014	The effects of levosimendan on renal function early after heart transplantation: results from a pilot randomized trial	47	2	4%	7,00		49		10	37
26	SHER-I-MURTAZA	2012	Is there any benefit of preoperative oral trimetazidine in coronary artery bypass graft?	85	56	66%	1,51		54,8			
27	COGLIATI	2007	Fenoldopam Infusion for Renal Protection in High-Risk Cardiac Surgery Patients: A Randomized Clinical Study	98	22	22%	4,20	12	69,6		35	63
28	LAZAR	2007	Beneficial effects of complement inhibition with soluble complement receptor 1 (TP10) during cardiac surgery: Is there a sex difference?	147	67	46%	3,09	8,66	67,4			
29	COUTURE	2007	Milrinone enhances systolic, but not diastolic function during coronary artery bypass grafting surgery	25	10	40%	1,80	5	70		6	19
30	BURNS	2005	Perioperative N-acetylcysteine to prevent renal dysfunction in high-risk patients undergoing CABG surgery: A randomized controlled trial	147	63	43%	2,00	8	69.2	30	30	117
				1588	414	26%	2,64	13,10	64.7	27.2		

BMI denotes body-mass index, CABG coronary artery bypass grafting, DM diabetic patients, HLOS hospital length of stay, ICU intensive care unit, IMC body-mass index, and LOS length of stay.

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"Visus (Sight)" by Cornelis Cort (Artist, Netherlandish, 1533 – 1578), Hieronymus Cock (Publisher, Netherlandish, 1518 – 1570), and Frans Floris I (Artist After, Flemish, c. 1519 – 1570. 1561. Image courtesy of the National Gallery of Art.

Investigating the Need for Prehospital Education to Include Sex Differences in the Clinical Presentation of Stroke

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Keywords

stroke; emergency medical services; sex differences; prehospital education; stroke recognition

Abstract

Since Congress passed the National Institutes of Health Revitalization Act of 1993, a document that mandates the inclusion of women and minority groups in medical research, sex differences in the clinical presentations of diseases and responses to medication have emerged.¹ It has been found that women and men can present differently when experiencing a stroke, with women more often experiencing “atypical” or “nontraditional” signs and symptoms.^{2–8} Prehospital curriculum standards have not yet included this information for emergency medical technicians (EMTs) or paramedics. Further, prehospital provider education standards do not require competency in sex differences in epidemiology, physiology, pathophysiology, or pharmacology.^{9,10} Patients of EMS providers would likely benefit if their providers were aware of these sex differences, because previous research has found that women experiencing a stroke receive a lower quality of EMS care than men.¹¹ Early identification of stroke and timely notification to the nearest appropriate hospital can affect treatment decisions, and time to treatment can heavily influence functional outcomes.¹² Since there is robust evidence that the clinical presentation, quality of care, and health outcomes of stroke differ between men and women,

EMS education should include and emphasize these topics.

Methodology

This integrative review identified appropriate articles through a PubMed search from June 1, 2024, through August 14, 2024, with the keywords “sex and gender differences,” “sex and gender differences in the clinical presentation of,” “stroke,” “pathophysiology,” “anatomy,” “differences in stroke clinical presentation of transgender individuals,” “EMS recognition of stroke,” and “time to treatment and outcome.” The PubMed search did not include “chromosomal anomalies,” because this information lies outside the scope of EMS provider education standards.⁹ A total of 49 articles were assessed and considered relevant if they were published after the year 2000 and addressed one or more of the following questions:

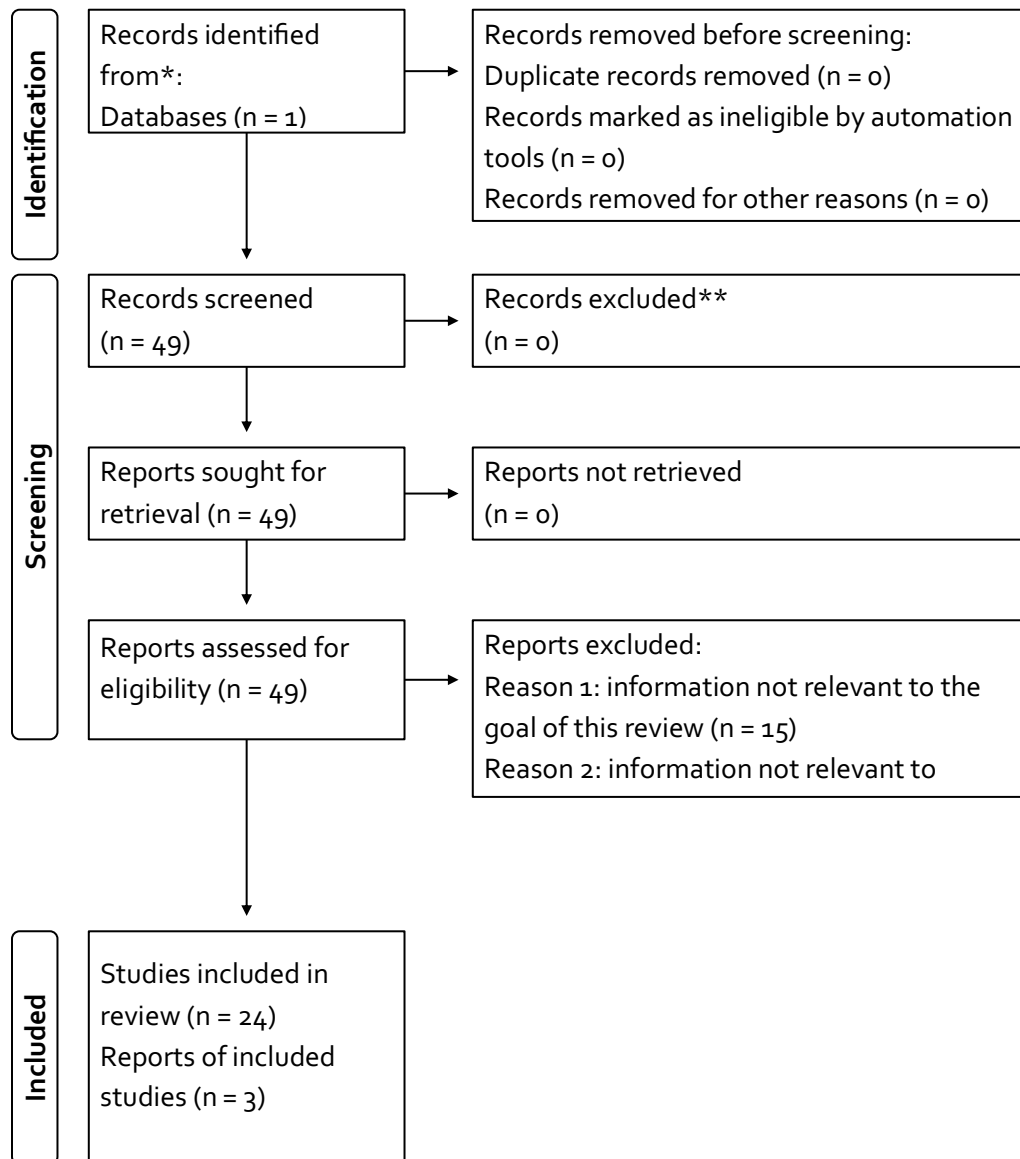
- Are there sex differences in the clinical presentation of stroke? If so, which sexes are included in these studies?
- Do men’s and women’s hormonal differences affect the development of stroke? Do sex differences in anatomy or physiology differ in the pathogenesis of stroke? Are there sex differences in risk factors for stroke?

- Is there an association between time to treatment for stroke and functional outcomes or mortality? How does EMS play a role in a patient's functional outcome?
- How accurate is EMS recognition of stroke?

- Is there a difference in the quality of EMS care between male and female patients?

Figure 1 describes the screening process for the reviewed articles.

Figure 1. Identification of Studies through Database Searching.



Sex and Gender

A person's chromosomal makeup of XX (female) or XY (male) defines one's sex. Other chromosomal anomalies exist, such as XXY (Klinefelter's syndrome) or X (Turner's syndrome). Gender is defined as a person's chosen identification and how they express themselves. Gender includes categories such as man, woman, transgender man or woman, or nonbinary, as well as others. The reviewed studies placed patients into binary categories of "male" or "female." None of the reviewed studies included individuals with chromosomal anomalies or transgender individuals. Therefore, this paper will focus on the differences between males and females.

Stroke

Signs and Symptoms

EMS providers commonly care for patients with stroke-like signs and symptoms. A stroke can present with focal or nonfocal symptoms, or both. Focal symptoms result from a lesion in the central nervous system, spinal cord, or nerve that then affects a specific area of the body. Examples of focal symptoms include unilateral muscle weakness, vertigo, and dysarthria. Nonfocal symptoms affect the body in a nonspecific manner and do not correspond to a particular area of the brain. Examples of nonfocal symptoms include fatigue, dizziness, and headache. Previous research has found differences in how women and men might present with any type of stroke.⁴⁻⁷ One difference is that women more commonly present with nonfocal

symptoms than men.⁴⁻⁷ Specifically, these nonfocal symptoms include changes in level of consciousness and mental status, headaches or migraines, and pain.⁴⁻⁷ Women also more often present with coma or stupor.⁴ In the prehospital setting, these nonfocal symptoms alone can warrant a long list of differential diagnoses and complicate the prehospital provider's impression of the patient's condition.

Although women more often present with nonfocal symptoms, focal symptoms, in general, affect women and men at comparable rates. Certain focal symptoms, such as lightheadedness, gait disturbance, imbalance, ataxia, and aphasia, affect women and men similarly.⁴ In contrast, other symptoms disproportionately affect one sex over the other. Women more commonly present with dysarthria and vertigo, and men more commonly present with paresis or hemiparesis, diplopia, and focal visual disturbances.⁴ Figure 2 displays the similarities and differences among these signs and symptoms. Last, women and men tend to experience a similar number of symptoms, because a systematic review and meta-analysis by Ali et al. found that both sexes experienced a mean of three symptoms.⁴ These differences highlight that, although women and men both display nonfocal and focal symptoms, certain symptoms may be more common in one sex than the other. EMS providers should receive up-to-date information on these trends in clinical presentation, with an emphasis on women's more common presentation with nonfocal symptoms and appropriate management.

Figure 2. Signs and Symptoms Categorized According to Sex.

Signs and Symptoms Categorized by Sex

Signs/symptoms more common in males	Similar signs/symptoms in males and females	Signs/symptoms more common in females
Focal – Paresis – Hemiparesis – Diplopia – Focal visual disturbances	Focal – Lightheadedness – Gait disturbance – Ataxia – Aphasia	Nonfocal – Change in level of consciousness – Fatigue – Dizziness – Headache Focal – Dysarthria – Vertigo

Pathophysiology

There are several underlying differences in stroke risks and pathophysiology between women and men. Annually, more women have strokes than men.^{13,14} It is thought that women’s longer life span partially contributes to the discrepancy in incidence.¹³ In addition, it has been shown that female sex is a risk factor for stroke in patients with atrial fibrillation.¹⁴ Proposed reasoning for this increased risk in women with atrial fibrillation is that they have more coexisting conditions than men.¹⁵ However, more research is needed to determine whether female sex alone presents an increased risk or whether increased age and coexisting conditions fully account for this discrepancy.

Women and men also tend to experience different types of strokes. Women more commonly experience either subarachnoid hemorrhage (SAH), cardioembolic stroke, or a larger territorial infarct.^{4,16} Since a greater proportion of women have atrial fibrillation, it makes sense that women

also have an increased risk of cardioembolic stroke. Meanwhile, men more often experience a stroke due to small-vessel disease or lacunar infarcts.^{8,16} Differences in risk factors and the types of infarcts may partly account for the differences in clinical presentation. However, more research is needed to explore the relationship between symptoms and stroke types. Nonfocal symptoms can arise from injury to any area of the brain, so it is unclear why women more often present with these symptoms. Nonetheless, including pathophysiologic differences in the prehospital curriculum could bolster prehospital providers’ understanding of the clinical differences they may encounter.

Clinical Assessment and Implications

To assess whether a patient is experiencing a stroke, prehospital providers are taught one or more nationally recognized prehospital stroke scales. These include the Cincinnati and FAST-ED stroke scales. The Cincinnati Prehospital Stroke Scale assesses facial asymmetry, arm drift, and

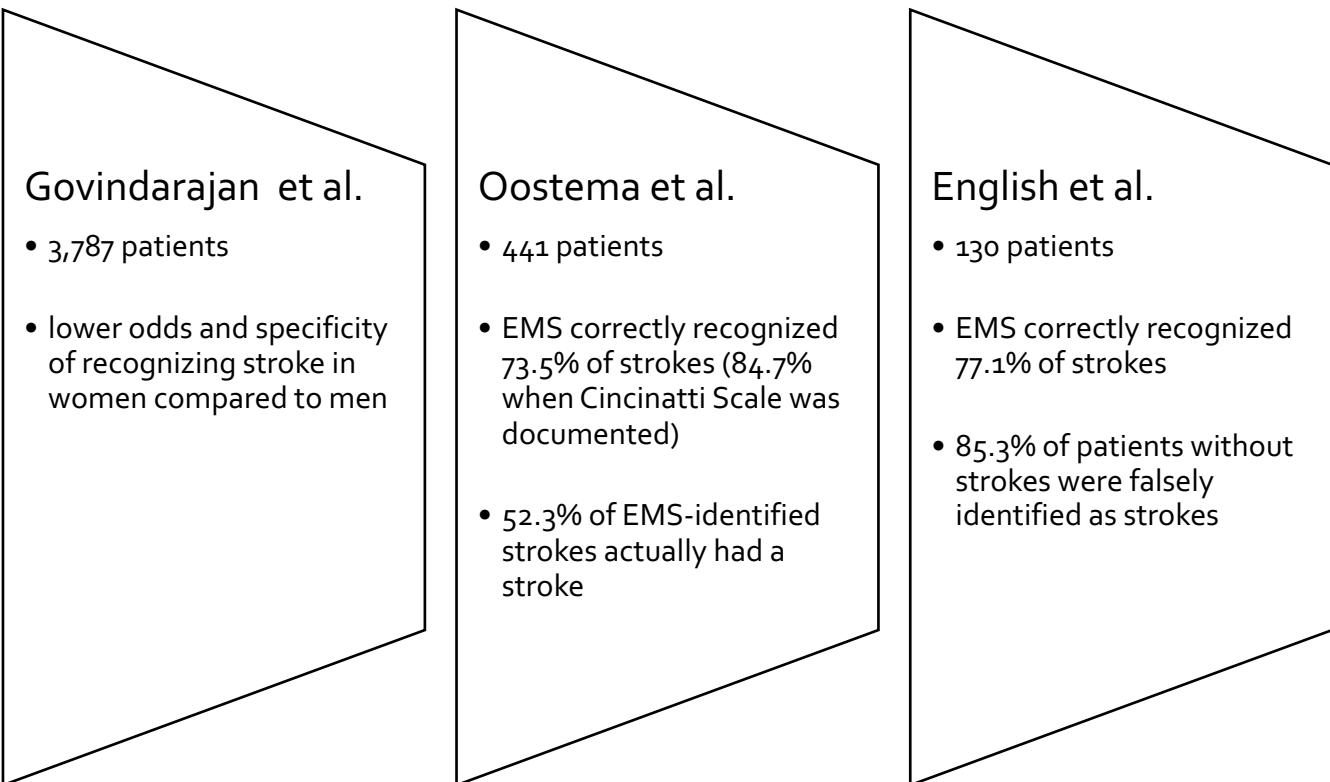
speech, and the FAST-ED Prehospital Stroke Scale assesses facial asymmetry, arm weakness, speech, time when the patient was last seen normal, eye deviation, and whether the patient recognizes weakness in the upper extremity.^{17,18} When a patient has a positive stroke scale, EMS providers are taught to call in a stroke alert and transport the patient to the nearest stroke center. Notably, these stroke scales assess focal symptoms. Since more women have nonfocal symptoms, it is possible that more women may be experiencing a stroke but may not have a positive stroke scale. Subsequently, more women may not be transported with appropriate priority or to an appropriate stroke center. It is worth educating prehospital providers that both women and men may not have a positive stroke scale because of the possibility of a stroke manifesting with nonfocal symptoms. On the basis of the severity of nonfocal symptoms, the scene where the patient was found, and the patient's history, the provider should assign appropriate priority so that the patient arrives at the emergency department with the necessary resources already prepared.

Recognition of stroke in the prehospital setting is important because previous research has found that, after a stroke, time to treatment can affect functional outcomes. A patient's functional outcome tends to decrease as time to endovascular therapy, a common stroke treatment, increases.¹² Further, longer times from symptom onset to reperfusion are associated with increased mortality.^{12,19} Multiple studies have found that women have worse functional outcomes and greater mortality than men.^{11,16} However, the demographics between women and men differ. At stroke onset, women are typically older and live alone.²⁰ It is thought that older age and living alone

greatly contribute to women experiencing longer delays to treatment and more severe symptoms.²⁰ EMS providers should be aware of these social factors so that they may remain suspicious of stroke or other life-threatening conditions for patients with these demographics and presentation.

EMS recognition of strokes is not completely accurate. The sensitivity of EMS recognition of stroke varies. Govindarajan et al. found that EMS had lower odds of correctly recognizing stroke in women than in men; one study from southwestern Michigan found that EMS correctly suspected 73.5% of strokes; and English et al. found that their EMS system at the Mayo Clinic correctly identified 77.1% of strokes.²¹⁻²³ EMS sensitivity for stroke recognition likely varies because of study differences and EMS provider education, training, and experience. However, conducting a proper prehospital stroke scale may be associated with correctly identifying strokes, because Oostema et al. found that EMS stroke recognition was highest when the Cincinnati Prehospital Stroke Scale was documented.²² Details of these studies can be found in Figure 3. Among the missed strokes, EMS commonly listed general weakness and altered mental status as their clinical impression.²² Since these nonfocal symptoms have many causes, it is difficult for providers to identify a stroke that presents in this fashion in the absence of focal symptoms. In addition, research has shown that EMS recognition of stroke improves after a stroke training module.²⁴ Therefore, a continuing education course that covers focal and nonfocal symptoms, trends seen in men's and women's stroke presentations, and proper stroke protocols may help improve the sensitivity of EMS stroke recognition.

Figure 3. EMS Recognition of Stroke Among Three Studies.



Care Disparities

There is a discrepancy in EMS providers' delivery of appropriate care to women and men, which should be provided equally. Using national EMS data from 2019 and 2020, Dylla et al. assessed Advanced Life Support providers' compliance with American Stroke Association recommendations; criteria for compliance included eight metrics: documenting stroke scale, hospital prenotification, obtaining blood glucose level, giving oxygen only when oxygen saturation fell below 94%, obtaining a 12-lead electrocardiogram, documenting last known well since symptom onset, having a less than 90-second call-to-dispatch time, and having a less than 15-minute on-scene time.¹¹ These actions play an important role in caring for and transporting a

patient with stroke-like symptoms. Dylla et al. found that EMS providers met all eight criteria in 0.39% of cases.¹¹ A significant proportion of providers caring for male patients met six or more criteria and therefore had greater compliance than providers who cared for female patients.¹¹ Dylla et al.'s study exposes the need to improve EMS training and reduce provider bias nationwide.¹¹ It seems appropriate to structure a continuing education course that refreshes providers on stroke symptoms and protocols and brings awareness to statistics showing sex bias. In addition, current EMS certification classes should consider sharing the statistics regarding gender bias. However, deep-rooted gender bias poses a challenge that will likely take years or generations to resolve. Education could serve as a platform to promote a culture within EMS that frowns on sex bias.

Conclusion

On the basis of evidence of sex disparities in functional outcomes and quality of care, sex differences in the clinical presentation of stroke should be incorporated into the EMS curriculum. The goal of this education is to improve understanding that stroke can present in lesser-known ways and potentially improve EMS stroke recognition. Current providers may be educated through continuing education classes, and future EMS providers could obtain this knowledge through their initial certification. The curriculum should include an overview of stroke pathophysiology, sex differences related to anatomy and physiology, and evidence-based sex differences in the clinical presentation of stroke. History taking should also be reviewed, because certain information, such as the last time the patient was asymptomatic, can help hospital clinicians make treatment decisions. In addition, the curriculum should review the various nationally recognized stroke scales, because there is evidence that documenting these scales helps improve EMS recognition of stroke patients. The education should emphasize that strokes can present with focal or nonfocal symptoms, or both, and that it is important to include stroke in the differential diagnosis when gathering information from the scene.

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More research is needed to explore the relationship among sex differences in anatomy, physiology, risk factors for stroke, and sex differences in clinical presentation. Since women more commonly present with nonfocal symptoms, one future direction could investigate whether these symptoms correlate with the specific types of strokes these women experience. If there are trends in nonfocal symptom presentation and type of stroke, then providers may arrive at a stroke diagnosis more quickly and improve functional outcomes.

Although current research focuses on sex differences related to biological males and females, more research is needed to address whether there are differences in clinical presentations among individuals receiving hormone-replacement therapy, those identifying as transgender, or those with chromosomal disorders. This type of research would broaden providers' awareness if there were differences in clinical presentation among various sexes and genders. With increased awareness of how stroke can present differently across sexes, this education could decrease knowledge gaps and potentially improve quality-of-care discrepancies for all patient populations.

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"Plate Number 535. Movement of the hand, beating time" by Eadweard Muybridge (Artist, American, born England, 1830 – 1904). 1887. Image courtesy of the National Gallery of Art.

Neurological and Cerebrospinal Fluid Accumulation Effects of Noncobalt Metal Ions from Joint Implants: Cognition, Peripheral Neuropathy, and Movement Disorders

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Keywords

joint arthroplasty; metal ions; cerebrospinal fluid; neurotoxicity; implant-related complications

Introduction

Joint arthroplasty remains one of the most impactful interventions in orthopedic surgery, enabling pain relief and restoration of mobility for millions of patients annually. With improvements in implant materials and surgical technique, and with patient demographics expanding to include younger, more active individuals, long-term systemic consequences of implant wear and corrosion are coming under increasing scrutiny. Historically, the primary concern centered on cobalt and chromium ions released from metal-on-metal hip designs and their systemic toxicity. However, emerging evidence indicates that noncobalt metal ions, including titanium (Ti), niobium (Nb), zirconium (Zr), and vanadium (V), may also accumulate in systemic circulation and in the cerebrospinal fluid (CSF), raising the possibility of neurologic sequelae such as cognitive impairment, peripheral neuropathy, and movement disorders.

This review synthesizes current mechanistic and clinical evidence regarding noncobalt metal ion exposure from joint implants and its potential neurologic implications. We begin by delineating the background and rising interest in this field, then describe mechanisms of ion release and neurologic targeting, summarize current evidence, including

functional outcomes, discuss clinical implications and application in practice, highlight limitations of existing data, and close with future directions and concluding remarks. The rationale for this comprehensive review lies at the intersection of orthopedic biomaterials science, neurotoxicology, and clinical neurology; as patients live longer with implants, neurologic health must become part of the outcome equation.

Methods

This narrative review was conducted with a targeted search of PubMed/MEDLINE, Scopus, and Google Scholar to identify mechanistic, translational, and clinical studies evaluating metal ion release from orthopedic implants and associated neurologic outcomes. Search terms included combinations of joint arthroplasty, metal ions, titanium, niobium, zirconium, cerebrospinal fluid, neurologic toxicity, cognition, peripheral neuropathy, and movement disorders. The search included English-language publications from January 2000 through October 2025. Reference lists of relevant articles were manually screened to identify additional studies. The final literature search was completed on October 15, 2025.

Implant-Derived Metal Ion Exposure

Metallic joint implants, including total hip, knee, and shoulder arthroplasties, are subject to mechanical wear, micromotion at modular junctions, and electrochemical corrosion in vivo, leading to the release of metal particles and ions.^{1,3} Although Ti-based alloys — for example, Ti-6Al-4V and Ti-Nb — and Zr-coated components were long thought to be biologically inert, more recent work has shown that, under certain mechanical or electrochemical conditions, ionic release still occurs.^{4,15} The vast majority of early literature focused on cobalt-chromium alloy corrosion and what has been termed “arthroprosthetic cobaltism,” associated with systemic cardiovascular, thyroid, auditory, and neurologic consequences. However, the field has begun to shift as newer implant designs emphasize modularity, mixed alloys, and increased lifespans, all factors that may increase cumulative systemic exposure even in “noncobalt” systems.

A landmark cross-sectional study by Rakow et al. demonstrated that patients with large joint replacements exhibited significantly higher whole-blood levels of Ti, Nb, and Zr and measurable elevations of these ions in CSF, as compared with matched controls.⁵ This finding directly indicates that implant-derived ions cross neural barriers and accumulate in compartments historically less considered. The rising interest in neurologic endpoints of implant exposure is driven by several converging trends: younger and more active recipients, more modular implant designs with the potential for fretting and corrosion, heightened analytic capability of low-level CSF ion detection, and the recognition that neurologic dysfunction — involving cognition, peripheral nerves, and movement — may manifest insidiously and be misattributed to aging or coexisting disease. Hence, the rationale for this review is to bring together mechanistic, exposure, and outcome evidence regarding noncobalt metal ions and neurologic

health in arthroplasty patients, thereby informing orthopedic and neurology practitioners alike.

Mechanisms of Neurologic Exposure and Injury

Ion Release and Accumulation

Release of metal ions and particles from joint implants results from mechanical wear at articulation surfaces, fretting and corrosion at modular junctions — such as head-neck tapers and dual-modular necks — and electrochemical degradation of alloy surfaces in vivo. Szczesny et al. provided a detailed overview of electrochemical processes in orthopedic metals such as Ti, Cr, Co, Ni, V, and Al, highlighting how metal-protein interactions may form antigenic complexes and drive inflammatory responses rather than simply inert corrosion.³ Kim et al. reviewed Ti toxicity and showed that Ti particles deposit systemically and can reach remote organs, including neural tissues.¹ Abd-Elaziem et al. further described how Ti-Nb alloys and composites, although engineered for improved biocompatibility, can still undergo ionic release under certain conditions.⁴

Once in the circulation, metal ions — for example, Ti^{2+} , Nb^{5+} , Zr^{4+} , and V^{3+}/V^{5+} — may cross the endothelial blood-brain barrier (BBB) or the blood-CSF barrier, possibly through metal transporters such as DMT1 or through barrier disruption by oxidative stress.¹¹ In the NeuroWear study, Rakow et al. demonstrated that patients with implants had significantly higher Ti, Nb, and Zr in CSF than controls; for example, median Ti was 0.75 μg per liter versus 0.57 μg per liter in controls, thereby confirming that neural barrier penetration occurs.⁵ The study also observed a strong correlation for cobalt ($r=0.82$ between blood and CSF), suggesting a more direct transport mechanism, but weaker correlations for Nb and Zr, suggesting that accumulation may depend on serum elevation first.⁵

Neurologic Targets: Cognition, Peripheral Neuropathy, and Movement Disorders

Within neural tissues, metal ions may exert toxicity through multiple overlapping mechanisms. These include oxidative stress and reactive oxygen species (ROS) generation, leading to mitochondrial dysfunction, glial activation, and neuronal injury.¹¹ For instance, TiO₂ nanoparticles in vitro induced paracellular leakiness in human BBB models and proinflammatory cytokine up-regulation (interleukin-1 and interleukin-6) in endothelial cells, implicating barrier disruption and neuroinflammation.¹¹ Venkatraman et al. described a case of spasticity after bilateral hip arthroplasty with elevated cobalt levels; after revision, improvement occurred, thereby demonstrating reversibility of neurologic injury if caught early.⁹ Moretti et al. reported severe peripheral neuropathy in the context of failed hip arthroplasty. Although these reports emphasize cobalt and chromium, the biologic mechanism is transferable to other metal ions capable of neural penetration.

Cognitive impairment is another recognized target: Green et al. found a mean Mini-Mental State Examination (MMSE) score of 24.2 and a Beck Depression Inventory (BDI) score of 27.6 among 10 patients with metal-on-metal hip failure and elevated Co and Cr, reflecting memory, attention, and mood impairments.¹⁰ A more recent study by Beba et al. examined correlations between blood metal concentration, including Ti, and cognitive and neuroimaging outcomes among 113 patients with total joint arthroplasty, finding associations between elevated metal levels and neuroimaging markers, though not yet cognitive scores.¹⁷ With respect to movement disorders, Clark et al. demonstrated subtle brain structural alterations involving the basal ganglia and optic pathways in patients 8 years after metal-on-metal hip

replacement, raising concern for long-term neuromotor sequelae.²⁰

Timing of Exposure and Clinical Effect

Although ion release begins soon after implantation, the latency to neurologic manifestations is heterogeneous and likely influenced by cumulative exposure, patient clearance through renal and hepatic function, age, vascular risk, and implant design. In the NeuroWear cohort, some CSF accumulation of Ti, Nb, and Zr was observed after implants had been in situ for less than 10 years.⁵ In the cobalt literature, case reports often emerge 2 to 4 years after implantation when serum cobalt levels exceed 7 to 10 µg per liter.⁹ The implication is that neurologic injury is likely a multiphase process: initial systemic exposure, accumulation, barrier penetration, neuronal injury, and clinical manifestation. Thus, long-term surveillance is essential, especially in younger, more active recipients.

Current Evidence

Randomized Trial Findings

To date, no randomized, controlled trials have been conducted with neurologic endpoints specifically in arthroplasty patients stratified according to noncobalt metal ion exposure. The lack of randomized, controlled trials with cognition, neuropathy, or movement disorder as primary outcomes remains a critical gap in the literature.

Cohort and Registry Data

The NeuroWear study by Rakow et al. stands as the first large-scale, cross-sectional human study measuring a broad panel of arthroplasty-relevant metals in blood and CSF, showing elevated Ti, Nb, and Zr in implant patients as compared with controls.⁵ Among registry and cohort analyses, Tamagawa et al. studied 59 patients with CoCr rods and 29 with Ti alloy rods in scoliosis surgery and

found mild elevation of Ti levels versus controls, though no clinical neurologic correlation was established.¹⁶ Crutsen et al., in a systematic review of 62 cases of prosthetic hip–associated cobalt toxicity (PHACT), reported cognitive or memory dysfunction in 25.8% and paresthesia in 21%.⁶ Although these data are cobalt-centric, they highlight the broader paradigm of implant-derived neurologic risks. Other mechanistic reviews include Kim et al. cataloguing Ti toxicity, Shelly et al. showing Ti nanoparticle neurotoxicity, and Szczęsny et al. detailing metal–protein interactions triggering inflammation.^{1,3,11}

Evidence and Functional and Patient-Reported Outcomes

Functional neurologic outcomes such as cognitive testing, nerve conduction studies, and movement disorder scales remain poorly represented in the arthroplasty literature. Among the few studies, Green et al. documented neuropsychiatric deficits in patients with metal-on-metal implants.¹⁰ Beba et al. found associations between blood Ti, Co, and Cr levels and neuroimaging markers but not yet cognitive performance.¹⁷ Clark et al. found subtle structural brain changes in patients with metal-on-metal implants.²⁰ The critical deficiency remains the absence of large longitudinal cohorts linking noncobalt ion levels, including Ti, Nb, and Zr, to validated neurologic endpoints with patient-reported outcomes and functional testing.

Clinical Applications

Patient-Selection Considerations

From a combined orthopedic–neurology viewpoint, certain patient profiles warrant particular attention. Patients with preexisting neurologic conditions, such as mild cognitive impairment, peripheral neuropathy, or a movement disorder; renal or hepatic impairment, which may reduce clearance of metal ions; younger age at implantation, with long-

term exposure potential; and high activity levels may represent higher-risk groups. In these patients, implant-design decisions — such as favoring ceramic heads, monoblock stems, fewer modular junctions, or nonmixed alloy tapers — may mitigate long-term exposure risk. Preoperative baseline neurologic screening, including cognitive assessment, peripheral nerve examination, and movement screening, may provide a reference for later surveillance.

Integration into Practice, Technical Pearls, and Safety Profile

Preoperative patient counseling should routinely include discussion of systemic risks of metal-ion release, including potential neurologic sequelae, albeit rare. Intraoperative technique remains critical: ensuring optimal component alignment, minimizing modular interfaces, avoiding mixed-alloy combinations, and selecting lower-wear bearing pairings can reduce ion release. Postoperatively, high-risk patients may benefit from periodic whole-blood metal ion measurement, including Ti, Nb, and Zr if available, and baseline and serial neurologic screening — for example, MoCA, neuropathy symptom inventory, and tremor or ataxia assessment. However, specific thresholds and monitoring intervals for noncobalt ions, such as titanium, niobium, and zirconium, are not currently standardized, and such surveillance should be considered precautionary pending longitudinal outcome data linking exposure levels to neurologic endpoints. In symptomatic patients with new-onset neuropathy, tremor, or cognitive decline and elevated ion levels, referral to neurology and consideration of CSF sampling may be appropriate. Although the overall safety profile of modern implants remains favorable, recognition that neurologic injury may present years after implantation must inform long-term monitoring strategies.

Limitations of Current Data

Despite growing interest, the evidence base has significant limitations. First, the number of neurologic-endpoint studies is very small; most data derive from case reports or small series.⁹ Second, heterogeneity in implant types — hip, knee, and shoulder — materials, including Ti, Nb, Zr, Co, and Cr, measurement protocols, including which ion, which matrix, and timing, and neurologic outcome definitions, including cognition, neuropathy, and movement, make comparison and meta-analysis difficult. Third, follow-up durations are generally short, often under 10 years, whereas neurologic injury may manifest only decades later.²⁰ Fourth, coexisting conditions, including aging, vascular disease, diabetes, and neurodegenerative disorders, complicate attribution of neurologic findings to implant-derived metal exposure. Fifth, a predominance of cobalt–chromium-centric literature limits direct extrapolation to newer Ti, Nb, and Zr exposures; true threshold “safe” levels are unknown. Lastly, there are no randomized, controlled trials or large prospective neurologic outcome cohorts, and no consensus on monitoring or revision thresholds. In addition, no consensus exists regarding safe exposure thresholds or optimal surveillance intervals for noncobalt metal ions, limiting translation into standardized clinical guidelines.

Future Directions

To advance the field, several key initiatives are warranted. Prospective longitudinal cohort studies of arthroplasty patients stratified according to implant material and measured metal-ion exposures (Ti, Nb, Zr, and V), with repeat neurologic assessments, including cognitive tests, nerve conduction studies, and movement disorder scales, are essential to define dose–response relationships and thresholds. The development of standardized neurologic outcome batteries in arthroplasty

populations — for example, MoCA, nerve conduction, and tremor or ataxia scales — would facilitate comparability across studies. Translational studies linking human exposure, including ion levels in blood and CSF, to biomarkers of neurologic injury, such as neurofilament light chain, glial fibrillary acidic protein, and MRI white-matter changes, are needed to move from exposure to injury to clinical effect. Materials-science research should continue progressing toward implants with ultralow ion release — for example, TiSiN or ZrN coatings — and long-term neurologic outcome data in such cohorts are needed. Clinical guidelines and surveillance protocols developed jointly by orthopedic, neurology, and toxicology societies should outline patient-risk stratification, monitoring intervals, revision considerations, and neurologic referral criteria. Finally, given the very large number of joint arthroplasties performed globally, modeling studies estimating the public health burden of subtle neurologic decline linked to long-term metal ion exposure will inform cost–benefit analyses of surveillance and prevention strategies.

Conclusion

Joint arthroplasty continues to be transformative in the management of end-stage joint disease. However, the field must evolve to consider not only mechanical and implant-survival outcomes but systemic neurologic health. There is strong mechanistic plausibility and emerging exposure data indicating that metal ions from implants, including noncobalt species such as titanium, niobium, and zirconium, can cross neural barriers and accumulate in CSF.⁵ Case reports and cohort data document cognitive impairment, peripheral neuropathy, and movement disorders in the context of metal-ion exposure.^{9,10,17} In current practice, orthopedic surgeons and neurologists should be cognizant of these possibilities, particularly for younger patients, those with long-life implants, modular designs, or preexisting neurologic

vulnerability. Key unanswered questions remain: What is the safe threshold for noncobalt ion exposure? What is the latency and cumulative dose–effect curve? Can early monitoring and revision prevent neurologic injury? How will next-generation implant materials alter neurologic risk?

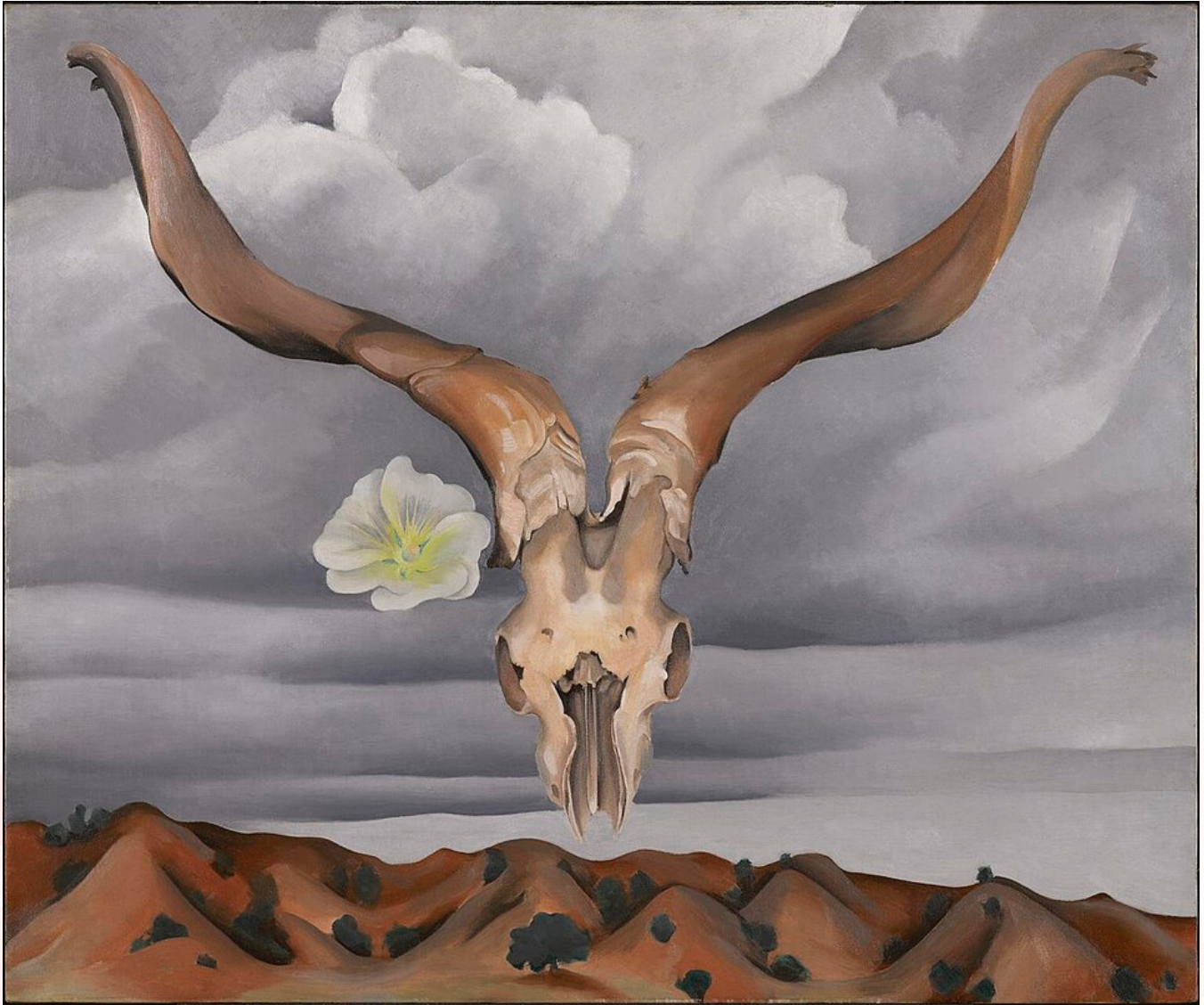
By bridging biomaterials science, orthopedic surgery, and neurology, the next frontier of

arthroplasty may lie as much in neurodefense as in joint restoration. With the adoption of implants with minimal ion release, systematic neurologic surveillance of high-risk patients, and rigorous epidemiologic and mechanistic research, joint replacement can continue to restore mobility while also safeguarding neurologic health over the patient's lifetime.

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"Ram's Head, White Hollyhock – Hills" by Georgia O'Keeffe (Painter, American, 1887 - 1986). 1935. Image available in the Public Domain.

Non-Inferiority Analysis of Levonorgestrel IUD versus Oral Levonorgestrel for Emergency Contraception: A Systematic Review and Meta-Analysis

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Keywords

emergency contraception;
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intrauterine device;
pregnancy prevention;
levonorgestrel

Abstract

Introduction: Emergency contraception (EC) is a critical component of reproductive health care, with currently approved oral options including levonorgestrel (LNG) and ulipristal acetate. Although effective, oral EC methods demonstrate reduced efficacy with increasing time since intercourse and higher body-mass index (BMI). In contrast, intrauterine devices (IUDs), particularly the copper IUD, provide highly effective EC. Emerging evidence suggests that the levonorgestrel IUD may also be a noninferior option. This systematic review and meta-analysis examined the comparative efficacy of the LNG-IUD versus oral LNG for EC.

Methods: Following PRISMA guidelines, PubMed, Scopus, Medline, and ClinicalTrials.gov were searched through December 2024. Five studies involving 920 participants met inclusion criteria and were evaluated for risk of bias with the Mixed Methods Appraisal Tool (MMAT). Using a random-effects meta-analysis, we estimated pooled pregnancy proportions with 95% confidence

intervals, assessed heterogeneity and publication bias, and conducted a noninferiority test with a 1% margin to compare the effectiveness of the levonorgestrel IUD versus oral levonorgestrel for EC.

Results: This study found an overall pregnancy proportion of 1% or less, with no significant differences among LNG-IUD, oral LNG, and copper IUD groups. Noninferiority testing demonstrated that the LNG-IUD was noninferior to oral LNG, as the upper bound of the pooled difference (0.008) remained below the 1% margin.

Conclusion: Despite limited direct comparison studies requiring subgroup formation, these findings indicate that the LNG-IUD does not confer a clinically meaningful increase in pregnancy risk as compared with oral LNG when used for EC. The findings suggest that the LNG-IUD could be a promising alternative to oral LNG for EC, offering both immediate and long-term contraception. Further large-scale, direct comparative studies are warranted to expand EC options for women.

Introduction

Emergency contraception (EC) is a critical yet often underrecognized component of women's reproductive health care, serving as an essential safeguard against unintended pregnancy after unprotected or inadequately protected intercourse.¹ The United States Food and Drug Administration (FDA) currently approves two oral EC methods: a progestin-only formulation containing levonorgestrel (LNG), administered either as a single 1.5-mg dose or as two 0.75-mg doses 12 hours apart, and the selective progesterone-receptor modulator ulipristal acetate (UPA), administered at a 30-mg dose.² Although both methods are widely used, it is important to note that neither method is 100% effective.^{3,4}

Oral LNG EC is most effective when taken as soon as possible, ideally within 72 hours after intercourse.⁵ However, its efficacy declines over time, particularly in individuals with a higher body-mass index (BMI).⁶ In contrast, UPA maintains effectiveness for up to 120 hours and demonstrates superior performance in women with elevated BMI, making it the more reliable oral EC option in these circumstances.³

Intrauterine devices (IUDs) can also serve as EC. Although no IUD currently holds FDA approval for this indication, the copper T380A IUD is widely regarded as the most effective nonoral EC option when inserted within 5 days after intercourse, with pregnancy rates of 0.2% or less.^{7,8} Observational studies further demonstrate that individuals who used the copper IUD for EC had significantly lower pregnancy rates at 1 year than those who used oral LNG for EC.⁹ Despite this strong evidence and support by the American College of Obstetricians and Gynecologists (ACOG), the copper IUD has not yet become the clinical standard for EC.^{1,10-14}

The LNG-IUD, a well-established method of long-standing contraception, has recently gained attention as a potential option for EC.¹⁵ Available in

formulations ranging from 13.5 mg to 52 mg, it provides 3 to 8 years of highly effective pregnancy prevention, with efficacy rates of 99.2 to 99.6%.^{16,17} In terms of EC, a recent randomized noninferiority trial published in the *New England Journal of Medicine* reported a 1-month pregnancy rate of 0.3% with the LNG-IUD as compared with 0% with the copper IUD when inserted within 5 days after intercourse, demonstrating noninferiority of the LNG device.¹⁸ Notably, the effectiveness of the LNG-IUD did not vary according to BMI, which may offer an advantage over oral EC methods.¹⁸ Additional data from a 2023 Cochrane review similarly suggested that progestin-containing IUDs may be an effective EC method, though more long-term safety and implementation data are needed because limited data are available.¹⁹ Unlike oral levonorgestrel, which acts primarily through systemic absorption to delay or inhibit ovulation in a time-dependent manner, the LNG-IUD delivers continuous intrauterine hormone exposure that induces profound local endometrial suppression, alters cervical mucus, and impairs implantation-related processes, providing a biologically distinct mechanism for emergency contraception.

Despite this evidence, the LNG-IUD remains off-label for EC. It offers several advantages over oral forms, including immediate long-term contraceptive benefit, reduction in menstrual symptoms, and more consistent efficacy across BMI categories.¹⁸ This review aims to gather the current evidence for comparative effectiveness of the LNG-IUD and the LNG pill as EC, hypothesizing that the LNG-IUD is noninferior to oral LNG in pregnancy prevention.

Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The research question was formulated

according to Population, Intervention, Comparison, Outcome, and Timeframe (PICOT) criteria.²⁰

Table 1. Population, intervention, comparison, outcome, and timeframe criteria for inclusion of studies in this systematic review.

Parameter	Inclusion criteria
Population	Women of reproductive age
Intervention	LNG-IUD as emergency contraception; case-control studies, case studies, or randomized, controlled trials
Comparison	Oral LNG as emergency contraception; case-control studies, case studies, or randomized, controlled trials
Outcomes	Effectiveness of emergency contraception (pregnancy outcomes)
Timeframe	Published before December 16, 2024

LNG denotes levonorgestrel, and IUD intrauterine device.

Sources

A literature search was conducted up to December 16, 2024, with PubMed, Scopus, Medline (Ovid), and ClinicalTrials.gov to identify peer-reviewed English-language articles on the effectiveness of oral LNG and the LNG-IUD as EC. Keywords and MeSH terms (Appendix 1) guided the search. Rayyan²¹ and Zotero were used for screening and organization. The accuracy of the search was verified by confirming inclusion of three known relevant articles.

Study Selection

Articles that met all PICOT criteria (Table 1) were included if they involved human patients of reproductive age using oral LNG or the LNG-IUD as EC and if they were randomized, controlled trials, case studies, or case-control studies. The wide range of article types was included because of the limited number of studies reported on this topic. Exclusion criteria included incorrect predictor variables, altered timing of drug administration based on ovulation, irrelevant outcomes, lack of original data,

inappropriate population, non-English language, or unsuitable study design.

After duplicates were removed in Zotero by A. Blankenstein, article abstracts were screened in Rayyan by A. Blankenstein, C. Crow, J. Currier, E. Hock, B. Liyanage, and E. Williams, with each article reviewed by at least two screeners. All screeners were given inclusion and exclusion criteria. Discrepancies were resolved by group discussion. Full-text screening and data extraction were then completed by the same team.

Assessment of Risk of Bias

To evaluate the risk of bias in each study included in the full-text reviews, two authors independently assessed one article with the Mixed Methods Appraisal Tool (MMAT), version 2018.²² This tool is specifically designed to assess the risk of bias in studies with different designs included in a single systematic review. The MMAT table for each article is displayed in Table 2. In addition, specific questions addressed for MMAT assessment are included in Appendix 2.

Table 2. MMAT assessment for risk of bias.

Study type	Authors (Year)	S1	S2	2.1	2.2	2.3	2.4	2.5
Quantitative Randomized Controlled Trials		S1	S2	2.1	2.2	2.3	2.4	2.5
Phase II/III Studies	Turok D.K., et al. (2021) [18]	Y	Y	Y	Y	Y	N	Y
Open Label Studies	Planned Parenthood (2024) [23]	Y	Y	Y	Y	N	N	Y
Quantitative Non-Randomized		S1	S2	3.1	3.2	3.3	3.4	3.5
Observational Studies	Turok D.K., et al. (2010) [14]	Y	Y	N	Y	Y	Y	Y
Observational Studies	Elnasar I., et al. (2021) [24]	Y	Y	N	Y	Y	Y	Y
Observational Studies	Turok D.K., et al. (2013) [9]	Y	Y	Y	Y	Y	Y	N

Risk-of-bias assessment for studies evaluating LNG-IUD versus oral LNG for emergency contraception, including studies conducted across multiple international settings and published through December 2024. A “Y” indicates “Yes” for a given MMAT criterion, and an “N” indicates “No.” Overall, the included studies demonstrated low risk of bias, with most meeting key indicators of strong methodological quality.

Risk-of-bias assessment for studies evaluating LNG-IUD versus oral LNG for emergency contraception, including studies conducted across multiple international settings and published through December 2024. A “Y” indicates “Yes” for a given MMAT criterion, and an “N” indicates “No.” Overall, the included studies demonstrated low risk of bias, with most meeting key indicators of strong methodological quality.

Meta-Analysis

Statistical analyses were conducted with the metafor package in R software, version 4.5.1. Meta-analysis used random-effects models for the pregnancy proportion, because heterogeneity was significant in the fixed-effects models (Q test, 25.4725; P=0.0013). Weighted estimates of proportion with 95% confidence intervals were reported in the forest plot to evaluate the efficacy of the levonorgestrel intrauterine device and oral levonorgestrel for contraception. I² estimated the percentage of total variability in the observed effect sizes that could be attributed to heterogeneity and estimated the amount of heterogeneity. Funnel

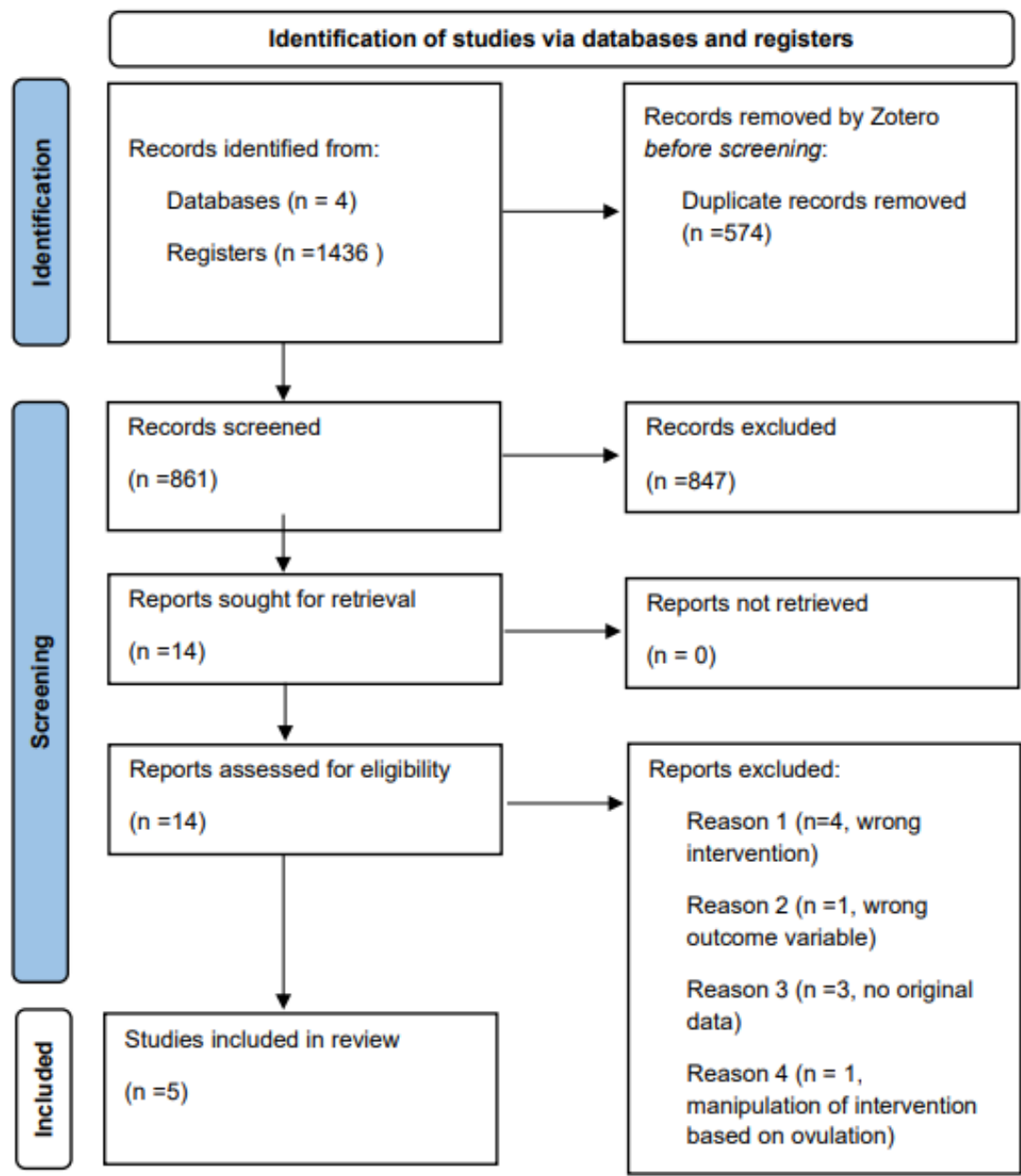
plots, tests for funnel-plot asymmetry, and limit estimates were used to identify bias. A noninferiority test based on a margin of 1% was conducted. All analytical results were considered significant when P values were 0.05 or less.

Results

Study Selection

A total of 1433 articles were retrieved from PubMed, Scopus, Medline (Ovid), and ClinicalTrials.gov. After 574 duplicates were removed, 859 articles remained and were screened with PICOT criteria. Fourteen articles underwent full-text review; four were excluded for wrong intervention, one for reporting the wrong outcome variable, three for lacking original data, and one for manipulation of intervention timing based on ovulation. Ultimately, five studies met inclusion criteria and were incorporated into the meta-analysis. A detailed overview of the study-selection process is illustrated in the PRISMA flow diagram (Figure 1). Appendix 3 includes demographic characteristics of individual studies.

Figure 1. PRISMA 2020 flow diagram outlining study selection for the systematic review and meta-analysis of LNG-IUD versus oral LNG for emergency contraception, including studies published through December 2024.



Study Characteristics

A total of 5 studies involving 920 participants were included in the meta-analysis to indirectly compare

pregnancy rates between the LNG-IUD and LNG pill as EC. Three prospective observational studies that compared oral LNG with the copper IUD were included. The other two studies were randomized,

controlled trials, one of which examined the LNG-IUD alone and one of which compared it with the copper IUD as EC.

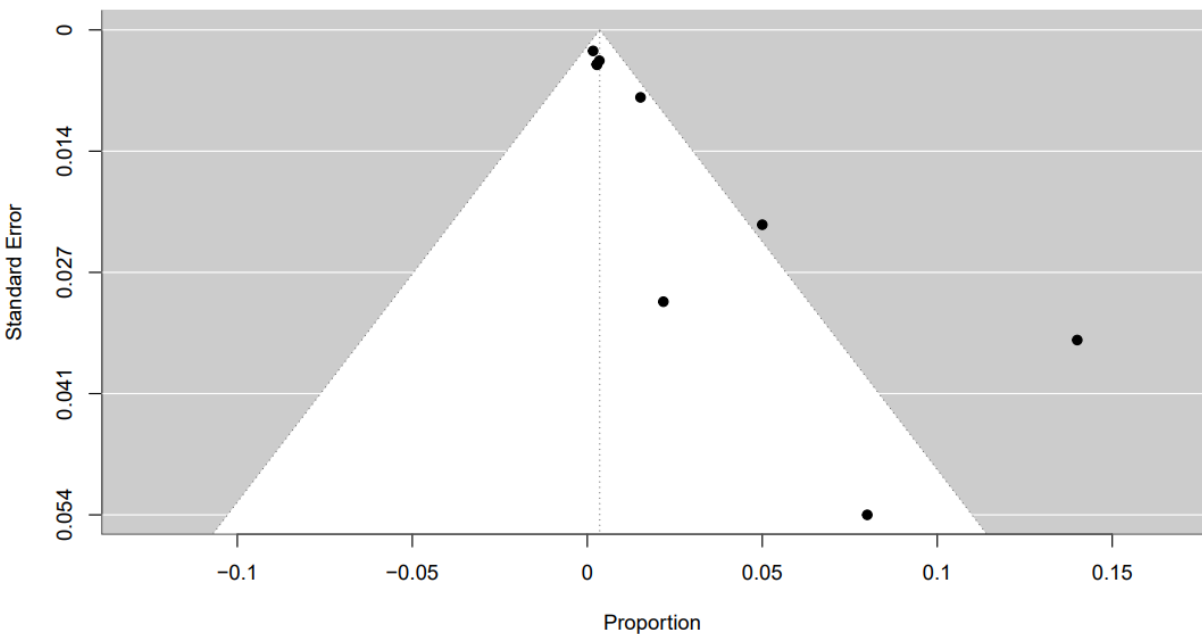
From our subgroups of the LNG-IUD and oral LNG as EC, 461 participants received oral LNG and 459 received the LNG-IUD. All participants were female, with a mean age of 24.8 years. Two studies did not report race; among those that did, most participants identified as White (n=318, 34.6%), followed by Hispanic (n=119, 12.9%), African American (n=118, 12.8%), and Asian (n=3, <1%).

Risk-of-Bias Assessment

To evaluate the quality of the included studies, a risk-of-bias assessment was conducted. Each of the 5 studies had relatively low bias. A table using the MMAT criteria can be seen in Table 2. Weaknesses were evident in the target-population category, because participants in most studies were limited to

a particular location or by other reproductive characteristics, such as multiparity. In addition, the randomized, controlled trials were not blinded, lowering their risk-of-bias scores. A funnel plot and funnel-plot asymmetry test were also conducted to further assess bias (Figure 2). The funnel plot for transformed proportion showed apparent asymmetry, which was supported by the test for funnel-plot asymmetry ($P=0.0001$). This may be an indication of publication bias. However, there may be reasons other than publication bias that could lead to asymmetry in the funnel plot. A nonsignificant coefficient (0.0025; 95% CI, -0.0007 to 0.0057) implied no pattern of publication bias. We minimized publication bias by following PRISMA guidelines to explore databases systematically. However, we were unable to adequately explain the other type of bias causing the funnel-plot asymmetry for the proportion of pregnancy.

Figure 2. Funnel plot of transformed pregnancy proportions from all study arms included in the systematic review and meta-analysis of LNG-IUD versus oral LNG for emergency contraception, incorporating studies published through December 2024. The plot is used to assess potential publication bias. Visual inspection suggests asymmetry, supported by a significant test for funnel-plot asymmetry ($P=0.0001$).

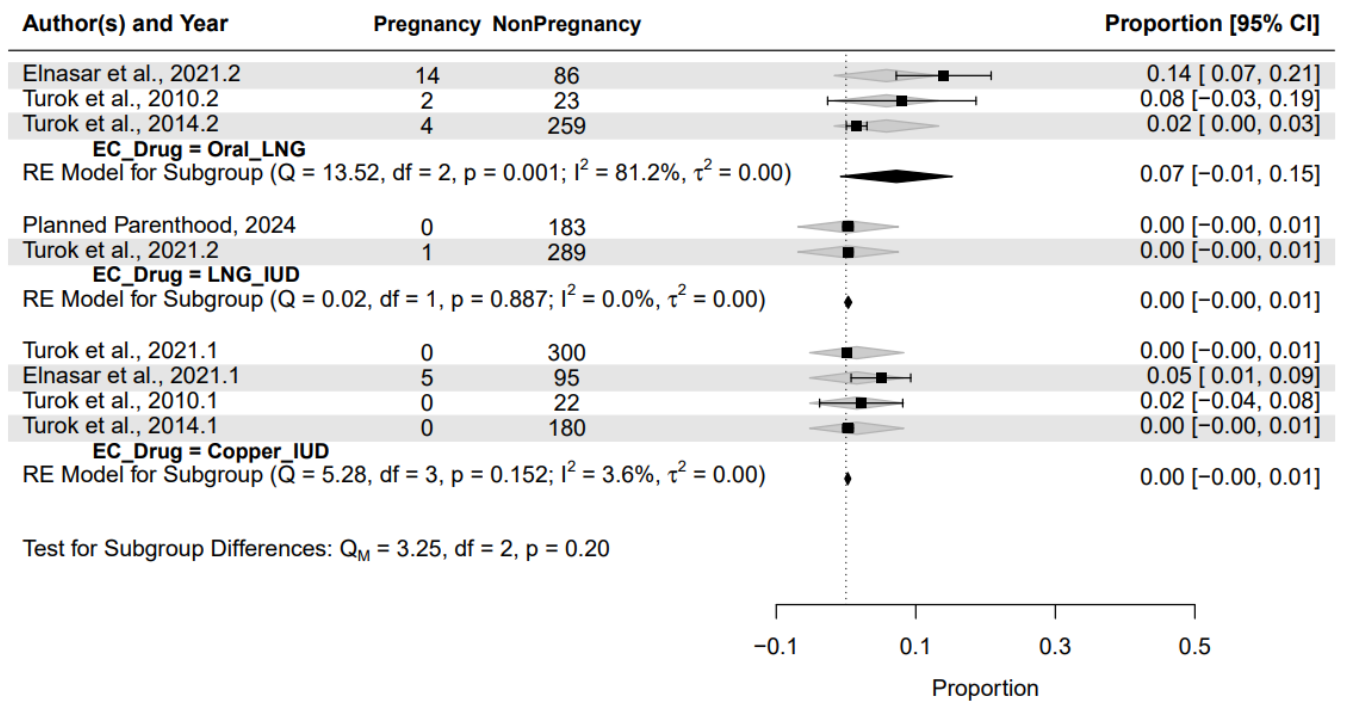


Forest Plot

A random-effects model estimated the proportion of pregnancy at 1% or lower (95% CI, <0.01 to 0.01) (Figure 3). The subgroup for the LNG-IUD's proportion of pregnancy was 0.00 (95% CI, -0.00 to 0.01), indicating that the probability of pregnancy in this group was less than 1%. The oral LNG subgroup

proportion of pregnancy was 0.07 (95% CI, -0.01 to 0.15), indicating that the probability of pregnancy in this group was less than 15%. Last, the copper IUD subgroup had a probability of 0.00 (95% CI, -0.00 to 0.01), also indicating that the probability of pregnancy was less than 1% in this group. The results showed no significant difference among the three subgroups for pregnancy rate ($P=0.20$).

Figure 3. Forest plot summarizing pregnancy event proportions from six study arms across three predefined subgroups in the systematic review and meta-analysis of LNG-IUD versus oral LNG for emergency contraception, incorporating studies conducted across various settings and published through December 2024. Each study contributes its number of events, total sample size, and corresponding proportion with 95% confidence intervals.



Noninferiority Testing

The noninferiority test comparing the LNG-IUD with oral LNG resulted in a pooled difference in pregnancy rates of -0.055, with a 95% confidence interval of -0.117 to 0.008. Because the upper

boundary of 0.008 is below the noninferiority margin of 1%, the LNG-IUD met criteria for noninferiority.

Synthesis of Findings

A random-effects model estimated an overall pregnancy proportion of 1% or less, with no significant differences among the LNG-IUD, oral LNG, and copper IUD subgroups ($P=0.20$). Both the LNG-IUD and copper IUD showed pregnancy proportions under 1%, whereas oral LNG demonstrated a higher but still low estimated proportion (<15%). Noninferiority testing further showed that the LNG-IUD was noninferior to oral LNG, as the upper bound of the pooled difference in pregnancy rates (0.008) remained below the predefined 1% noninferiority margin. Overall, these results indicate that the LNG-IUD does not result in a clinically important increase in pregnancy risk as compared with oral LNG when used for emergency contraception.

Discussion

Main Findings

This systematic review and meta-analysis provides an overview of the comparative efficacy of the LNG-IUD versus oral LNG as EC methods, summarizing the current evidence in this emerging field. Owing to the limited availability of studies directly comparing the LNG-IUD with oral LNG EC, studies that compared copper IUDs with the LNG-IUD and oral LNG as EC were used for subgroup formation. This review found no significant difference in the proportion of pregnancies between the LNG-IUD and oral LNG for EC ($P=0.20$), supporting the LNG-IUD as a viable EC option. In addition, noninferiority testing revealed the LNG-IUD as a noninferior option to oral LNG, because the upper bound of the difference in pregnancy rates was less than 1%.

Strengths and Limitations

The oral LNG pill and ulipristal acetate are currently the only FDA-approved forms of EC.² However, the copper IUD is traditionally regarded as the most effective EC method.¹⁴ Despite its high efficacy, copper IUD insertion is often associated with side

effects such as heavier menstrual bleeding, increased cramping, and back pain.^{25,26} In contrast, the LNG-IUD is generally associated with lighter periods or amenorrhea, which may increase its acceptability among some patients.^{25,26}

The LNG-IUD additionally offers the dual benefit of providing both immediate EC and long-term reproductive control, positioning it as a convenient, singular solution for women not seeking pregnancy.¹⁴ Although the oral LNG EC pill remains widely accessible and convenient, its efficacy is lower than that of IUD-based methods, particularly when administered later within the 72-hour window.²⁷ This discrepancy highlights the importance of careful clinical decision making and patient counseling. Our analysis contributes emerging evidence supporting the LNG-IUD as a viable EC option. However, the lack of direct comparative studies between the LNG-IUD and oral LNG highlights a critical gap in the literature, limiting definitive conclusions about their relative effectiveness.

A key strength of this meta-analysis is the inclusion of both randomized and nonrandomized trials comparing LNG and copper-based methods, providing a comprehensive and balanced evaluation. Adhering to PRISMA guidelines ensured methodologic rigor, whereas broad search strategies across multiple databases minimized the likelihood of missing relevant studies. The efficacy of contraceptive methods was evaluated with validated statistical and graphical techniques, enhancing the credibility of the findings. In addition, the use of robust statistical methods — including random-effects modeling with heterogeneity assessment (I^2 , τ^2 , and Q test), weighted proportion estimates with 95% confidence intervals, moderator analyses, funnel-plot diagnostics, tests for asymmetry, and noninferiority testing conducted through the metafor package in R software, version

4.5.1 — further strengthened the analytic rigor and reliability of the results.

Several limitations were identified. The funnel plot demonstrated apparent asymmetry, and the test for funnel-plot asymmetry yielded a P value of 0.0001, suggesting potential publication bias. Although PRISMA guidelines were rigorously followed, multiple sources of bias may still have been introduced. Few studies directly compared the LNG-IUD with oral LNG, resulting in reliance on indirect comparisons that may increase variability. The number of LNG-IUD studies was limited, and the included studies varied in design, sample size, and methodology, which constrains overall generalizability. Across studies, participant populations were geographically restricted, primarily to North America and Egypt, and demographically narrow, consisting predominantly of young, reproductive-aged women, with limited racial and ethnic diversity reported and minimal information on socioeconomic or educational background. Where race was reported in most studies, samples were largely White. These population characteristics limit the applicability of findings to more diverse populations, including older reproductive-aged individuals and those from underrepresented racial, socioeconomic, and

geographic groups. The lack of control for demographic and socioeconomic variables may have further contributed to bias and limited the robustness of the results.

Conclusion

These findings support the potential of the LNG-IUD as an effective method of EC, demonstrating the LNG-IUD as a noninferior option to oral LNG. Although the LNG-IUD is not currently approved by the FDA for use as EC, it represents a promising option offering both immediate and sustained contraceptive benefits. In addition, increasing emergency contraception options can lead to increased availability for patients. Future research should prioritize randomized, controlled trials with extended follow-up periods to directly compare the LNG-IUD and oral LNG in terms of EC effectiveness and long-term outcomes. Expanding the range of available EC methods may substantially enhance reproductive health care for women by accommodating the diverse needs and preferences of patients. In current practice, clinicians should continue to balance benefits, patient values, and resource availability when determining the most appropriate EC method.

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Supplemental

Appendix 1. Databases and Search Terms.

Database	Search Terms
PubMed	("Contraception, Postcoital"[Mesh] OR emergenc*[tiab] OR postcoital[tiab] OR "post-coital"[tiab] OR "post coital"[tiab]) AND ("Levonorgestrel"[Mesh] OR Levonorgestrel[tiab] OR "I-Norgestrel"[tiab] OR "I Norgestrel"[tiab] OR "D-Norgestrel"[tiab] OR "D Norgestrel"[tiab] OR Microval[tiab] OR Microlut[tiab] OR Mirena[tiab] OR Norgeston[tiab] OR "Norplant-2"[tiab] OR "Norplant 2"[tiab] OR Norplant2[tiab] OR NorLevo[tiab] OR Norplant[tiab] OR Vikela[tiab] OR Cerazet[tiab] OR Capronor[tiab] OR "ulipristal acetate"[tiab] OR "Plan B"[tiab]) AND ("Intrauterine Devices"[Mesh] OR "Intrauterine Devices, Medicated"[Mesh] OR intrauterine[tiab] OR IUD[tiab]) AND ("Contraceptives, Oral"[Mesh] OR oral*[tiab] OR pill*[tiab])
Scopus	(INDEXTERMS("Contraception, Postcoital") OR TITLE-ABS(emergenc*) OR TITLE-ABS(postcoital) OR TITLE-ABS(post-coital) OR TITLE-ABS("post coital")) AND (INDEXTERMS(Levonorgestrel) OR TITLE-ABS(Levonorgestrel) OR TITLE-ABS(I-Norgestrel) OR TITLE-ABS("I Norgestrel") OR TITLE-ABS(D-Norgestrel) OR TITLE-ABS("D Norgestrel") OR TITLE-ABS(Microval) OR TITLE-ABS(Microlut) OR TITLE-ABS(Mirena) OR TITLE-ABS(Norgeston) OR TITLE-ABS(Norplant-2) OR TITLE-ABS("Norplant 2") OR TITLE-ABS(Norplant2) OR TITLE-ABS(NorLevo) OR TITLE-ABS(Norplant) OR TITLE-ABS(Vikela) OR TITLE-ABS(Cerazet) OR TITLE-ABS(Capronor) OR TITLE-ABS("ulipristal acetate") OR TITLE-ABS("Plan B")) AND (INDEXTERMS("Intrauterine Devices") OR INDEXTERMS("Intrauterine Devices, Medicated") OR TITLE-ABS(intrauterine) OR TITLE-ABS(IUD)) AND (INDEXTERMS("Contraceptives, Oral") OR TITLE-ABS(oral*) OR TITLE-ABS(pill*))
Medline (Ovid)	(exp "Contraception, Postcoital"/ OR emergenc*.tw. OR postcoital.tw. OR post-coital.tw. OR "post coital".tw.) AND (exp Levonorgestrel/ OR Levonorgestrel.tw. OR I-Norgestrel.tw. OR "I Norgestrel".tw. OR D-Norgestrel.tw. OR "D Norgestrel".tw. OR Microval.tw. OR Microlut.tw. OR Mirena.tw. OR Norgeston.tw. OR Norplant-2.tw. OR "Norplant 2".tw. OR Norplant2.tw. OR NorLevo.tw. OR Norplant.tw. OR Vikela.tw. OR Cerazet.tw. OR Capronor.tw. OR "ulipristal acetate".tw. OR "Plan B".tw.) AND (exp "Intrauterine Devices"/ OR exp "Intrauterine Devices, Medicated"/ OR intrauterine.tw. OR IUD.tw.) AND (exp "Contraceptives, Oral"/ OR oral*.tw. OR pill*.tw.)

Database	Search Terms
ClinicalTrials.gov	((("Emergency Contraception" OR "Postcoital Contraception" OR emergenc* OR postcoital OR "post-coital" OR "post coital") AND ("Levonorgestrel" OR "LNG" OR "LNG-IUD" OR "Levonorgestrel IUD" OR "Levonorgestrel Intrauterine Device" OR "Mirena" OR "Kyleena" OR "Skyla" OR "Jaydess" OR "Norplant" OR "NorLevo" OR "Plan B" OR "ulipristal acetate") AND ("Intrauterine Device" OR "IUD" OR "Medicated IUD" OR "Copper IUD" OR "Hormonal IUD" OR "Oral Contraceptive" OR "Oral Levonorgestrel" OR "Oral Contraceptive Pill"))

Appendix 2. MMAT Questions Assessing Bias.

Category	Assessment Question
Screening questions	Are there clear research questions?
Screening questions	Do the collected data allow the research questions to be addressed?
Quantitative randomized controlled trials	2.1. Is randomization appropriately performed?
Quantitative randomized controlled trials	2.2. Are the groups comparable at baseline?
Quantitative randomized controlled trials	2.3. Are there complete outcome data?
Quantitative randomized controlled trials	2.4. Are outcome assessors blinded to the intervention provided?
Quantitative randomized controlled trials	2.5. Did the participants adhere to the assigned intervention?
Quantitative non-randomized studies	3.1. Are the participants representative of the target population?
Quantitative non-randomized studies	3.2. Are measurements appropriate regarding both the outcome and intervention (or exposure)?
Quantitative non-randomized studies	3.3. Are there complete outcome data?
Quantitative non-randomized studies	3.4. Are the confounders accounted for in the design and analysis?
Quantitative non-randomized studies	3.5. During the study period, is the intervention administered (or exposure occurred) as intended?

Risk of bias was assessed by 2 independent reviewers with “Yes” or “No” responses to the provided questions based on study design/category. If there was uncertainty, the question was provided with the article to a third author for confirmation of “Yes/No” response.

Appendix 3. Study Characteristics.

Title	Authors (Year)	Study Design	EC Used and Timing	Geography	Sample Size	Mean Age (years)	Unprotected Intercourse Timing	Race and Ethnicity
A pilot study of the Copper T380A IUD and oral levonorgestrel for emergency contraception	Turok D.K., et al (2010)	Prospective Observational Study	Oral LNG vs Copper IUD 1 and 6 months	Utah	Oral LNG: 34 Copper IUD: 23	Oral LNG: 23 Copper IUD: 24.7	< 120 hours	Oral LNG: White (20), Hispanic (11), Asian (3) Copper IUD: White (15), Hispanic (6), Asian (1), Hawaiian (1)
Intrauterine Device Versus Levonorgestrel As Emergency Contraception. Observational Study	Elnasar, I., et al, (2021)	Prospective Observational Study	Oral LNG vs Copper IUD 3 months	Egypt	Oral LNG: 100 Copper IUD: 100	Oral LNG: 27 Copper IUD: 26.7	< 120 hours	Not reported
Emergency contraception with a copper IUD or oral levonorgestrel: an observational study of 1 year pregnancy rates	Turok, D.K., et al (2013)	Prospective Observational Study	Oral LNG vs Copper IUD 1 year	Utah	Oral LNG: 327 Copper IUD: 215	Oral LNG: 22 Copper IUD: 23.1	< 120 hours	Oral LNG: White (212), Hispanic (68) Copper IUD: White (144), Hispanic (36)
Levonorgestrel Intrauterine System For Emergency Contraception (LIFE)	Planned Parenthood (2024)	Randomized Controlled Trial	LNG IUD vs Ulipristal Acetate 5–6 weeks	United States	LNG IUD: 183 Ulipristal Acetate: 73	LNG IUD: 27.7 Ulipristal Acetate: 27.1	< 120 hours	LNG IUD: African American (66), White (93), Other (23), Hispanic (168) Ulipristal Acetate: African American (40), White (26), Other (7), Hispanic (68)

Title	Authors (Year)	Study Design	EC Used and Timing	Geography	Sample Size	Mean Age (years)	Unprotected Intercourse Timing	Race and Ethnicity
Levonorgestrel vs. Copper Intrauterine Devices for Emergency Contraception	Turok, D.K., et al (2021)	Randomized Controlled Trial	Copper IUD vs LNG IUD 1 month	Utah	Copper IUD: 321 LNG IUD: 317	Copper IUD: 23.9 LNG IUD: 24	< 120 hours	Copper IUD: White (190), Hispanic (98), African American (12), Other (29) LNG IUD: White (179), Hispanic (108), African American (12), Other (28)

UPI denotes unprotected intercourse.

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