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CONTENTS

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INVITED REVIEW

The expanding role of palliative care in critical illness: A narrative review

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ABSTRACT

Objective: To synthesize current evidence on the integration of palliative care into the care of critically ill patients, with a focus on models of delivery, symptom management, communication frameworks, ethical dimensions, and emerging trends in the field.

Materials and Methods: This narrative review was conducted through a structured literature search of PubMed, MEDLINE, and Cochrane databases using terms including 'palliative care,' 'intensive care unit,' 'critical illness,' 'goals of care,' and 'symptom management,' restricted to English-language articles published between 2000 and 2024. Articles were selected based on relevance to the review's core domains and methodological quality, prioritizing randomized controlled trials, systematic reviews, and consensus guidelines where available.

Results: Early and structured integration of palliative care in the ICU is associated with improved symptom control, reduced rates of post-intensive care syndrome in patients and families, decreased non-beneficial interventions, shorter ICU stays at end of life, and lower healthcare costs without increasing mortality. Structured communication interventions and validated trigger-based referral criteria demonstrate consistent benefit. Evidence is strongest in medical ICU and oncology populations; emerging data support application across neurocritical care, cardiac, and surgical ICUs.

Conclusion: As ICU populations continue to age and life-sustaining treatments grow more complex, integrating palliative care principles alongside intensive therapies is essential to providing high-quality, goal-concordant, and compassionate critical care globally.

Keywords: palliative care, intensive care unit, critical illness, goals of care, shared decision-making, symptom management, neurocritical care, cardiac intensive care, post-intensive care syndrome, end-of-life care

Introduction

Each year, between 5 and 6 million patients are admitted to ICUs in the United States alone, and in high-income countries an estimated 10-20% of all deaths occur in or shortly after an ICU stay (1,2). For many of these patients, the course of illness is neither brief nor predictable. They arrive in crisis, stabilize, deteriorate again, and may spend days or weeks in a state of profound physiological and existential uncertainty, sustained by technology, unable to communicate, dependent on surrogates who are themselves navigating grief and unfamiliar decisions (1,2). Technical excellence in organ support is necessary, but it is not enough. Meeting the full range of needs generated by critical illness requires something more: a parallel commitment to understanding what patients value, relieving what they suffer, and ensuring that the care delivered also reflects who they are, not only what their physiology demanded.

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Palliative care is specialized clinical care focused on improving quality of life for patients with serious illness and their families and care partners, delivered by a multidisciplinary team through symptom management, communication, and support for shared decision-making (3). Importantly, palliative care is not synonymous with hospice or end-of-life care; it is appropriate at any stage of serious illness and is designed to be delivered alongside curative or life-prolonging therapies. The World Health Organization (WHO) defines palliative care as an approach that "affirms life and regards dying as a normal process," neither hastening nor postponing death, and calls for its integration across all levels of the health system, including critical care (4,5) (Figure 1).

The need for this review is both clinical and contextual. While much of the foundational evidence for ICU palliative care integration has emerged from the United States, Canada, and Western Europe, settings with well-resourced palliative care infrastructure, specialist workforce pipelines, and specific insurance-based referral structures, the principles and evidence are increasingly relevant to health systems worldwide. In the Eastern Mediterranean and Middle Eastern region, palliative care programs are in varying stages of development, and intensivists often serve as the primary or sole providers of palliative support for critically ill patients (4,6). The integration models and communication frameworks discussed in this review must therefore be interpreted and adapted to local healthcare structures, cultural values, and available resources. Where possible, we highlight evidence that spans diverse healthcare contexts.

This narrative review synthesizes current evidence on the role of palliative care across ICU settings, focusing on the medical ICU (MICU), neurocritical care unit (NCCU), and cardiac ICU (CICU) as settings with distinct patient populations and palliative care demands. We examine models of integration, symptom management, serious illness communication, ethical dimensions, and emerging directions, with the goal of providing a practical and evidence-based framework for clinicians working in any critical care environment. While palliative care needs have grown across all ICU settings as patient populations age and treatment complexity increases, this review focuses specifically on three settings where the evidence base and clinical demands are particularly distinct: the MICU, the NCCU, and the CICU.

Defining palliative care in the ICU context

Critically-ill patients experience a profound and often underappreciated symptom burden. Studies using systematic assessment tools in ICU populations

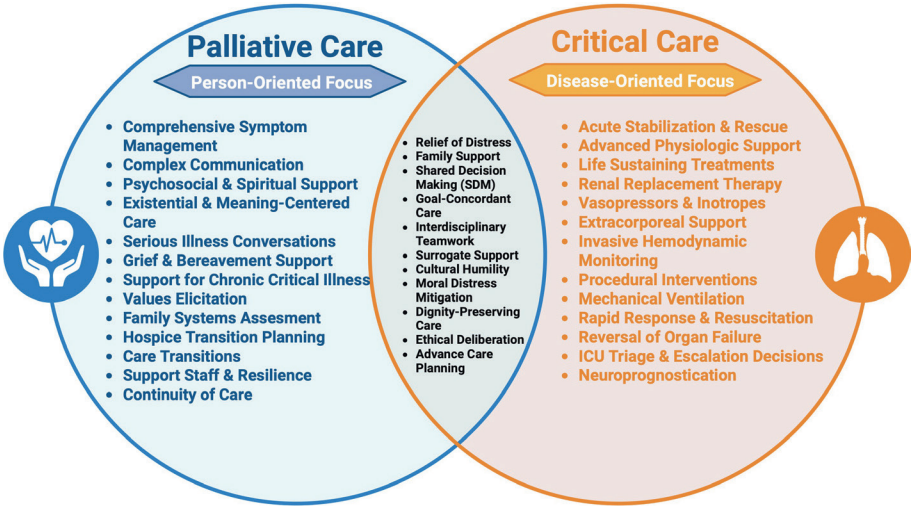

Figure 1. Intersection of critical care and palliative medicine

have documented that more than 50% of patients who are mechanically ventilated or have altered consciousness experience moderate-to-severe pain, and that dyspnea, anxiety, and agitation are present in the majority of patients at some point during their admission (7). Delirium affects 60-80% of patients who are mechanically ventilated and is independently associated with increased mortality, prolonged ICU stay, and long-term cognitive impairment (8,9). These symptoms are frequently undertreated, in part because patients are non-communicative and standard self-report instruments cannot be used.

What makes the ICU a distinct palliative care environment is not simply that patients are seriously ill - that is true in many settings. It is the convergence of features that defines the critical care context: patients are often unable to speak, so their suffering must be inferred and their values reconstructed from the people who love them. Families arrive in a state of shock, frequently without any prior conversation about what their loved one would want. Decisions that carry permanent consequences, whether to pursue tracheostomy, whether to continue mechanical ventilation, whether to withdraw life support, must sometimes be made within days or even hours, before anyone has had time to absorb what has happened. And clinicians are often simultaneously managing physiological crises and navigating the most important conversations of a family's life. Prognostic uncertainty exists across many serious illnesses, but in the ICU it lands differently: not as something to sit with over months of outpatient visits, but as something to act on now.

Three models of palliative care delivery have been described and studied in the ICU setting, and understanding the distinctions between them matters practically, because the right model for a given patient, clinician, or institution depends heavily on context (10). In the primary palliative care model, basic symptom assessment, comfort-focused care, and goals-of-care conversations are conducted by the ICU team itself. This is not a lesser form of palliative care; it is the foundation upon which specialist involvement builds, and in much of the world it represents the only palliative care critically ill patients will receive. In the integrated model, specialist palliative care clinicians work alongside ICU teams in a sustained, longitudinal way, attending rounds, co-facilitating family meetings, and providing continuity across a patient's ICU stay. In the consultative model, specialist teams are called upon for the most complex situations: refractory symptoms, protracted family conflict, requests to withdraw life-sustaining therapies, or ethical disputes that the primary team cannot resolve alone. These models are not mutually exclusive, and in the best-resourced settings they operate in concert. But even where specialist palliative care is limited, a primary care model grounded in communication skills and symptom awareness can meaningfully improve the experience of critically ill patients and their families (Figure 2).

Palliative care across ICU settings

The medical ICU (MICU)

The MICU has been the primary setting for palliative care integration research, and the evidence base here is the most robust. Patients admitted to the MICU frequently carry diagnoses of advanced malignancy, decompensated heart failure, respiratory failure, or sepsis, conditions with high short-term mortality, substantial symptom burden, and clinical trajectories that often shift rapidly toward end of life during the hospitalization itself.

Structured family meeting interventions have demonstrated the clearest and most consistent benefits in this population. The randomized trial by Carson and colleagues found that palliative care-led family meetings for patients with chronic critical illness significantly improved family members' emotional outcomes and reduced symptoms of PTSD at 90 days compared to usual care (11). Lilly and colleagues demonstrated in a prospective cohort study that a mandatory communication intervention in the MICU,

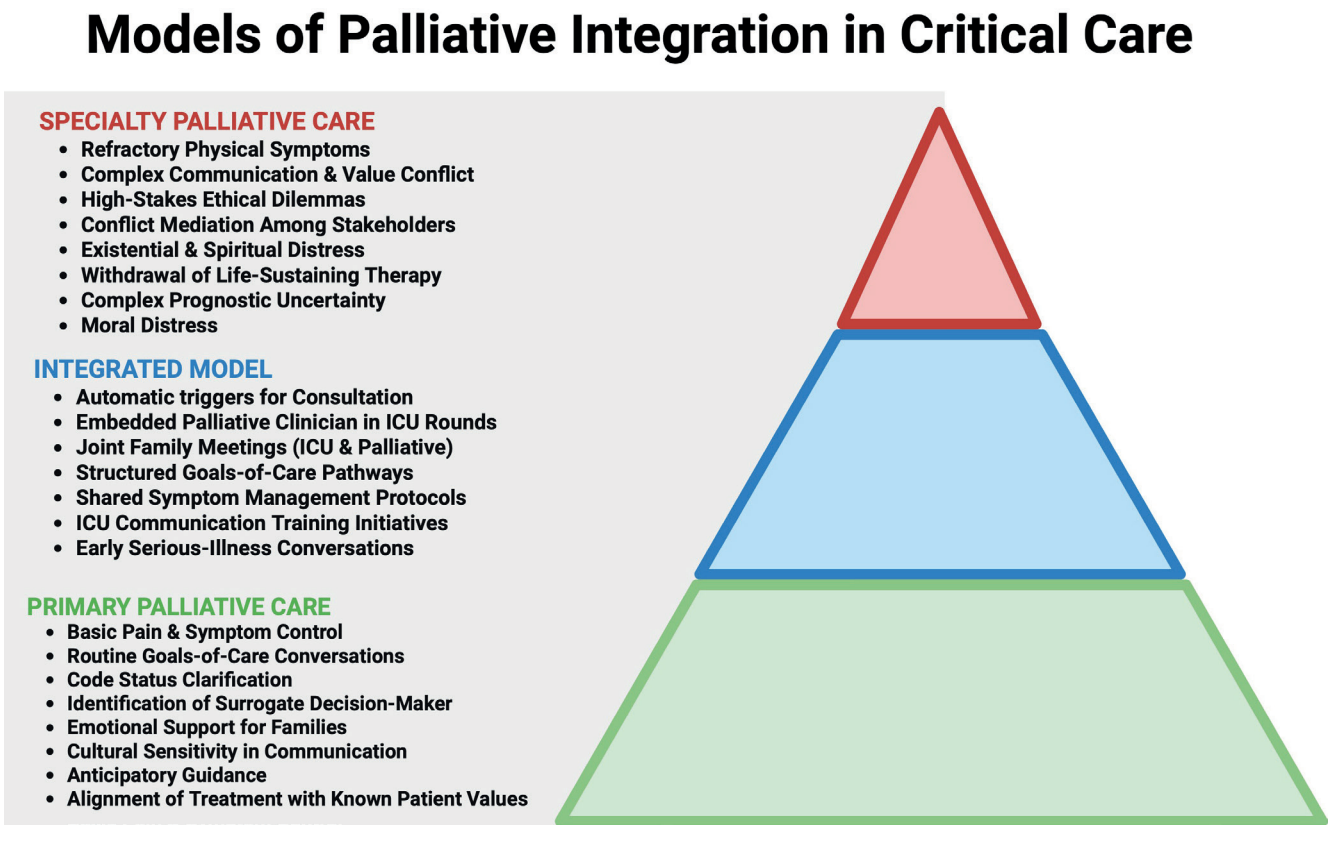

Figure 2. A three-tier model of palliative integration in critical care

consisting of structured family meetings within 72 hours of admission and palliative care involvement for high-risk patients, reduced ICU length of stay by more than 30% among patients who ultimately died, without increasing overall mortality (12). A systematic review by Khandelwal and colleagues similarly found that palliative care interventions and advance care planning in the ICU were associated with reductions in ICU length of stay for patients who died, again without increasing mortality, a finding that directly addresses the common concern that palliative involvement hastens death (13).

What makes the MICU population particularly distinct from a palliative care standpoint is the frequency with which patients arrive having never had a serious illness conversation, and the speed with which their condition can deteriorate to a point where those conversations become urgent. Many MICU patients are admitted with diagnoses that carry a high likelihood of in-hospital death, septic shock, acute respiratory failure, multi-organ failure, yet arrive without documented advance directives and with families who have had no opportunity to prepare. The palliative care imperative in the MICU is therefore one of compression: the work that ideally happens over months of outpatient serious illness conversations must be accomplished in days, in a family that is simultaneously in crisis. Trigger-based referral models, proactive family meetings, and structured communication frameworks are not supplementary to MICU care in this context, they are essential to ensuring that the care delivered in the final days of a patient's life reflects who that patient was, not simply what their physiology allowed.

The neurocritical care unit (NCCU)

Palliative care in the NCCU presents a distinct set of challenges that merit particular attention. Patients admitted with devastating neurological injuries including severe traumatic brain injury, malignant

hemispheric stroke, subarachnoid hemorrhage, or hypoxic-ischemic encephalopathy following cardiac arrest, face a clinical landscape defined not simply by prognostic uncertainty, but by the need to navigate irreversible, time-sensitive decisions in the absence of reliable long-term prognostic data.

Families in the NCCU are frequently under pressure, from the pace of the ICU environment, from uncertainty about what to hope for, and sometimes from clinical teams themselves, to make decisions about goals of care before reliable prognostic information is available. Current best practice in neurocritical care strongly cautions against early prognostication and early withdrawal decisions in the acute phase, recognizing that neurological recovery trajectories can be profoundly unpredictable in the first days following injury (14). The role of palliative care in the NCCU is therefore not to facilitate early decisions, but to help families and clinicians resist premature closure, holding space for uncertainty, clarifying patient values, and ensuring that any decisions made are anchored in what is known rather than what is feared. There is well-documented risk of premature mortality secondary to early withdrawal of life-sustaining treatment in this setting, often driven by pessimistic prognostication that does not account for the brain's capacity for recovery (14). Structured palliative involvement serves as a safeguard against this risk by centering patient values rather than clinician prognostic uncertainty in the decision-making process.

The integration of palliative care in the NCCU has been associated with improved documentation of goals of care, earlier clarification of treatment preferences, and a reduction in non-beneficial interventions at the end of life (15,16). Communication frameworks adapted to the NCCU context, emphasizing honest acknowledgment of uncertainty, the importance of patient values in guiding decisions, and the option to revisit initial decisions as the clinical picture evolves, are core to high-quality care in this setting.

What makes the NCCU population uniquely challenging from a palliative care standpoint is the intersection of three features that rarely converge so acutely in other settings: neurological injuries that may render patients permanently unable to participate in their own care, prognostic uncertainty that is genuine and not merely a function of limited information, and a decision-making timeline that is compressed by the biology of acute brain injury. A family navigating a loved one's devastating stroke is not simply dealing with a difficult prognosis, they are being asked to make irreversible decisions about a person whose neurological future cannot yet be known, often within days of an event that has upended everything they understood about that person's life. Palliative care in the NCCU exists to ensure that those decisions, whenever they are made, are made well, with full understanding of the uncertainty, grounded in patient values, and with the emotional and informational support families need to carry them forward.

The cardiac ICU (CICU)

The CICU landscape has changed considerably over the past two decades. Where it once served primarily as a setting for managing acute myocardial infarction and arrhythmia, it now increasingly cares for patients with end-stage heart failure, cardiogenic shock, and complex structural disease, patients whose prognosis is often poor but whose trajectory is notoriously difficult to predict. Heart failure does not follow a clean downward decline; it moves in sudden drops and partial recoveries in ways that leave both clinicians and families uncertain about when, if ever, the time for comfort-focused care has arrived.

This prognostic complexity is compounded by the availability of mechanical cardiac support that can sustain life, sometimes indefinitely, without restoring meaningful function. A patient on veno-arterial extracorporeal membrane oxygenation (ECMO) or a durable left ventricular assist device may be alive in every measurable physiological sense while being unable to participate in any of the activities that gave their life meaning. Conversations about device deactivation are among the most ethically weighted in all of critical care: they require clinicians to navigate

questions of medical futility, patient autonomy, and the moral status of devices that patients may experience as extensions of themselves (17). Palliative care teams bring specific expertise to these conversations, and their involvement has been associated with improved patient and family satisfaction and reduced decisional conflict (17). Equally important is attention to symptom burden: dyspnea in advanced heart failure can be severe and is frequently under-treated in settings where the clinical focus is procedural. Addressing it is not peripheral to CICU care. It is part of it.

What distinguishes the CICU population from a palliative care standpoint is the particular cruelty of heart failure's trajectory combined with the false reassurance that mechanical support can create. Families of patients on ventricular assist devices or ECMO may believe, reasonably, that the presence of the technology means recovery remains possible, and clinicians in a procedurally oriented culture may be slow to initiate conversations that challenge that assumption. The result is that goals-of-care conversations in the CICU frequently happen too late, after patients have lost the capacity to participate in them, and after families have spent weeks or months emotionally committed to a trajectory of recovery that the clinical picture no longer supports (18). Palliative care integration in the CICU addresses this not by hastening difficult conversations, but by ensuring they happen while patients still have a voice, and by helping families understand that the question is not whether to fight for their loved one, but what their loved one would consider worth fighting for.

Symptom burden in the critically ill

One of the practical challenges of palliative care in the ICU is that the patients who most need symptom assessment are often those least able to report their symptoms. A patient on mechanical ventilation cannot say that she is in pain. A patient with delirium cannot reliably describe what he is experiencing. This is not a minor inconvenience, it is a fundamental clinical problem, and one that has driven the development of behavioral assessment tools specifically designed for the critical care environment. The Critical-Care Pain Observation Tool (CPOT) (19), the Richmond Agitation-Sedation Scale (RASS) (20), and the Confusion Assessment Method for the ICU (CAM-ICU) (21) represent validated, bedside-usable instruments that allow clinicians to systematically assess pain, sedation depth, and delirium in patients who cannot self-report (8). Embedded in the 2018 PADIS guidelines, these tools are now standard of care, but their consistent application in practice remains variable, and under-treatment of pain and delirium in the ICU remains a documented problem (8). Managing symptoms in the critically ill requires a different calculus than in other settings. Opioids, which carry well-founded concerns about respiratory depression in other contexts, are essential for managing dyspnea in patients transitioning to comfort-focused care, and evidence is clear that when appropriately titrated to symptom relief, they do not hasten death (8,22). Sedation must balance comfort against the cognitive costs of over-sedation. Delirium, which affects 60-80% of mechanically ventilated patients, demands non-pharmacological prevention strategies as a first line, reorientation, early mobility, sleep hygiene, because no pharmacological treatment has demonstrated reliable efficacy in reducing its incidence or duration (8). These are not straightforward clinical problems, and they require the kind of sustained, expert attention that palliative care teams are specifically trained to provide.

Beyond the patient, the symptom burden of critical illness extends to families and surrogate decision-makers. Up to 70% of family members of ICU patients experience clinically significant anxiety, and approximately one-third meet criteria for PTSD, depression, or complicated grief in the months following their loved one's ICU stay, a phenomenon now formally recognized as post-intensive care syndrome-family (PICS-F) (23-27). Structured communication, proactive family meetings, and anticipatory guidance about what to expect during and after the ICU course are core palliative competencies that have been shown to

reduce long-term psychological distress in surrogates (28). A randomized trial by Lautrette and colleagues demonstrated that a structured communication intervention, including a proactive family conference and a bereavement brochure, significantly reduced the proportion of family members who met PTSD criteria at 90 days following patient death in the ICU (28).

Shared decision-making and serious illness conversations

Serious illness conversations in the ICU involve high-stakes decisions about life-sustaining therapies under conditions of prognostic uncertainty. These conversations are among the most demanding in medicine: patients are frequently incapacitated, surrogate decision-makers may be meeting clinicians for the first time, and the decisions being made can be irreversible. Research documents that families of ICU patients frequently misunderstand prognosis, overestimate likelihood of recovery, and may not be aware of their loved one's previously expressed values and preferences (29,30). Clinicians, for their part, face well-documented challenges in communicating prognostic uncertainty clearly and in facilitating rather than directing decision-making.

Evidence supports the use of structured, patient- and family-centered conferences to align treatment plans with patient values and goals. The American College of Critical Care Medicine and the American Thoracic Society have published a joint policy statement on shared decision-making in the ICU, emphasizing that the goal is not to transfer decision-making burden entirely to families but to create a partnership in which clinical expertise and patient values are integrated into a collaborative plan (31). Palliative care teams bring specific expertise in facilitating these conversations, including training in eliciting patient values, delivering prognostic information clearly and with appropriate uncertainty, responding to emotional reactions, and supporting families in making decisions that reflect patient preferences rather than surrogate preferences alone.

The VALUE framework (Value family statements, Acknowledge emotions, Listen, Understand the patient as a person, and Elicit questions) is one of the most widely used structured communication tools in ICU family meetings, and has been associated with improvements in family-reported quality of communication and reductions in decisional conflict (28,31). Other evidence-based frameworks, including the Serious Illness Conversation Guide and the REMAP framework for reframing goals of care, have been adapted for critical care contexts and shown to improve the quality and completeness of goals-of-care documentation (32,33).

Early palliative involvement also reduces decisional conflict and improves the likelihood that care delivered in the ICU reflects patient preferences. Importantly, palliative care involvement does not hasten death: multiple studies, including those in MICU and oncology populations, have consistently demonstrated that early palliative involvement is associated with equivalent or improved survival compared to usual care, alongside meaningful improvements in quality of life and reductions in non-beneficial interventions (11,13,34).

Ethical dimensions and health system outcomes

The ethical tensions that arise in the ICU are not abstract, they emerge from real clinical situations, often in the middle of the night, when a patient's condition changes and the treatment path forward is no longer clear. Should a patient with severe hypoxic-ischemic encephalopathy receive a tracheostomy? Should ECMO be continued in a patient whose neurological injury now appears irreversible? When a surrogate's decision seems inconsistent with what the patient once expressed, how should the clinical team respond? These are the questions in which palliative care teams do some of their most important work, not by overriding clinical judgment, but by creating the conditions under which good

judgment can be exercised. The ethical framework underlying these conversations draws on principles of beneficence, non-maleficence, and autonomy, but these principles do not resolve ICU dilemmas by themselves (35,36). Beneficence in critical care requires asking not just 'can we sustain this person's life?' but 'does doing so serve their interests?' Non-maleficence demands a frank accounting of what aggressive treatment actually costs a patient who may not be able to recover. Autonomy, frequently exercised through surrogates in the ICU, requires that clinicians actively support decision-makers in understanding their role, substituted judgment, not personal preference. Palliative care teams are trained to hold all three principles in tension simultaneously, and their involvement has been shown to reduce ethical conflicts, improve advance directive documentation, and support clinicians in delivering care that is both rigorous and humane (35) (Figure 3).

The health system effects of palliative care integration in the ICU are well-documented. Early palliative involvement is consistently associated with reduced non-beneficial interventions, shorter ICU stays among patients nearing the end of life, fewer invasive procedures, and lower overall healthcare costs

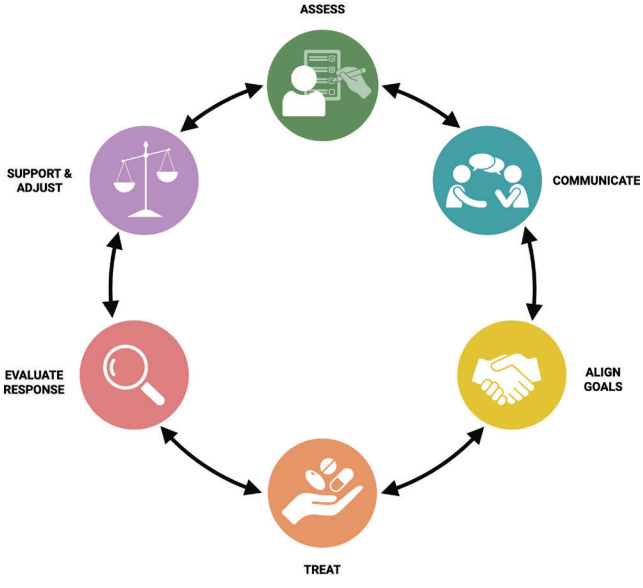

Figure 3. Dynamic decision-making cycle in the ICU

without an increase in mortality (12,13,37). Penrod and colleagues demonstrated in a large observational study that hospital-based palliative care consultation was associated with significant reductions in hospital costs, particularly in patients with high illness severity (37). Evidence supports the use of trigger criteria, including ICU stay duration greater than seven days, advanced malignancy, severe neurological injury, dependence on mechanical ventilation, and multi-organ failure, to systematically identify patients who would benefit from palliative care involvement (38). Trigger-based consultation models have been implemented in multiple ICU settings and shown to improve the timeliness of goals-of-care conversations and reduce non-beneficial treatment at the end of life (10,38). It should be noted, however, that trigger criteria vary across institutions, are not universally validated, and should be adapted to local clinical context and institutional resources rather than applied prescriptively (Figure 4).

Emerging trends and future directions

Palliative care in the ICU is not a static field. Several developments in recent years are reshaping how it is delivered, who has access to it, and how clinicians are trained to provide it, and they are worth noting not as abstract trends but as practical opportunities. Tele-palliative care has moved from a pandemic-era adaptation to a recognized delivery model. Palliative consultations conducted via videoconference have shown acceptability to patients and families and outcomes comparable to in-person consultation, particularly for goals-of-care conversations that do not require physical examination (39). For ICUs in rural or community hospital settings, and for health systems in countries where specialist palliative care teams are concentrated in major academic centers, this represents a meaningful expansion of access to expertise that was previously unavailable (39).

Equity in palliative care access is increasingly recognized as an urgent problem. In the United States, Black and Hispanic patients are significantly less likely

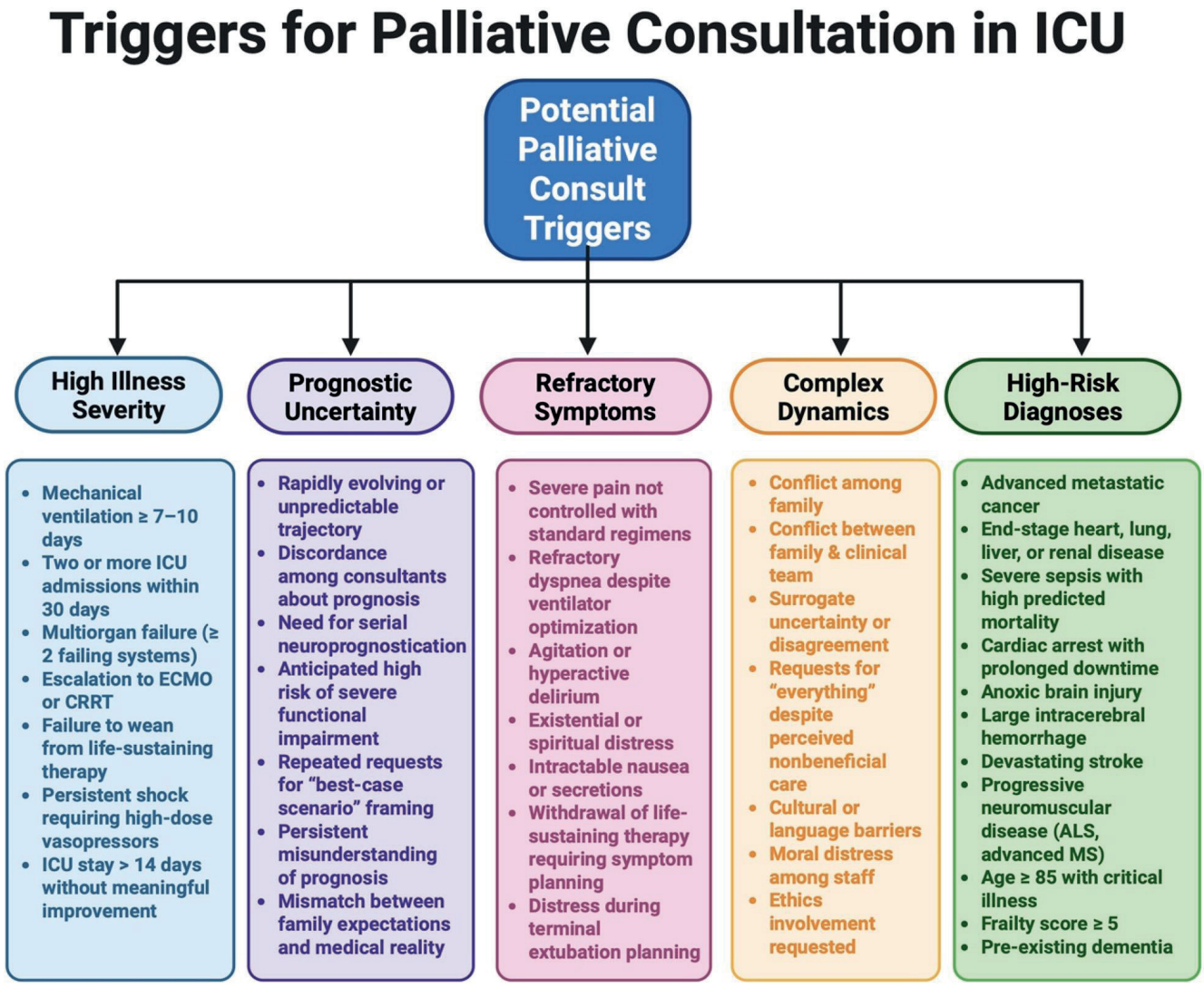

Figure 4. Clinical, prognostic, symptomatic, relational, and diagnostic triggers for specialty palliative care consultation in the ICU

Note: Trigger criteria presented are based on existing literature and institutional models. These criteria are not universally validated and should be adapted to local clinical context and institutional resources

to receive palliative care consultation and less likely to have documented advance directives, even after controlling for disease severity and insurance status (40,41). The reasons are multiple, historical distrust of the medical system, communication barriers, implicit bias in referral patterns, and structural underrepresentation of diverse populations in the palliative care workforce. Addressing these gaps requires more than expanding the number of palliative care teams; it requires training clinicians in culturally responsive communication and ensuring that serious illness conversations are conducted in patients' preferred languages with professional interpretation, not family members pressed into an impossible role.

Clinician training is evolving as well. Programs such as VitalTalk (42), the IPAL-ICU curriculum (43), and End-of-Life Nursing Education Consortium (ELNEC) critical care modules (44) have been developed and evaluated specifically for the ICU context. What they share is an emphasis on communication as a clinical skill, one that can be taught, practiced, and improved, rather than a personality trait that clinicians either

possess or do not. This framing matters: it means that the quality of serious illness conversations in the ICU is not fixed, and that investment in training has measurable returns for patients and families.

Finally, artificial intelligence and machine learning models are being developed to identify, earlier and more accurately, which ICU patients are at highest risk of death or prolonged functional dependence. The goal is to enable earlier, more proactive palliative engagement, to trigger a goals-of-care conversation before a family is in crisis rather than after. This is genuinely promising. Despite this, it does carry a real risk: a risk that algorithmic prognostication will substitute for individualized clinical judgment, that families will receive predictions rather than conversations, and that the quantification of prognosis will crowd out the human work of helping patients and families understand what the numbers mean for them. Used well, these tools can serve to extend clinical reach. However used poorly, they can reduce it.

Limitations

As a narrative review, the selection of literature reflects the authors' clinical expertise and is not exhaustive; findings should be interpreted with the understanding that this methodology carries an inherent risk of selection bias and does not capture the totality of available evidence.

Several additional limitations merit acknowledgment. First, the evidence base synthesized in this review is heavily weighted toward studies conducted in the United States, Canada, and Western Europe, where palliative care infrastructure, specialist workforce availability, and insurance-based referral structures may differ from other regions, and findings should therefore be adapted rather than directly applied to these contexts. Second, while this review addresses palliative care across the MICU, NCCU, and CICU, the evidence is uneven across settings, conclusions are strongest for medical ICU populations, and more high-quality research is needed in neurocritical and cardiac care environments before equivalent recommendations can be made. Third, several of the landmark trials informing this review were conducted 15-25 years ago, and advances in ICU technology, staffing models, and standard of care since that time may limit the direct applicability of their findings to contemporary critical care practice. Finally, as with any clinical literature, publication bias may have resulted in an overrepresentation of positive findings, and the true effect of palliative care integration across all ICU contexts may be more modest than the available evidence suggests.

Conclusion

Palliative care is not the endpoint of critical care, it is woven into its fabric. From the moment a patient arrives in the ICU, the questions that palliative care is designed to address are already present: What symptoms is this person experiencing? What do they value? What would patients want if they could speak for themselves? What do their family members and surrogate decision-makers need to navigate this crisis? The evidence reviewed here demonstrates consistently that structured, early integration of palliative care across ICU settings improves symptom management, supports families, reduces non-beneficial interventions, and aligns care with patient values, without hastening death.

The model for how this integration is delivered will vary by setting, resources, and culture. In high-resource academic centers, embedded multidisciplinary palliative care teams and trigger-based consultation protocols represent the standard of care. In settings with limited specialist workforce, the primary palliative care model, in which intensivists themselves deliver core palliative competencies, is both evidence-based and achievable. The goal is not to replicate any single system's approach but to ensure that every critically ill patient, wherever they are cared for, receives attention to their suffering, their values, and their dignity alongside attention to their physiology.

As ICU populations continue to age, as life-sustaining technologies advance, and as the complexity of critical illness increases, the integration of palliative care will only become more essential. Compassionate, goal-concordant, ethically grounded critical care is not a departure from excellence in intensive care medicine, it is its highest expression.

Ethical approval

This manuscript is a narrative review of published literature and does not involve human subjects, animal experiments, patient data, or clinical trials. Accordingly, ethics committee approval and informed consent were not required. No patient identifying information is included in this manuscript. The procedures described are consistent with the Helsinki Declaration of 1964, revised 2013.

Author contribution

Study conception and design: MQ; literature review: MQ; draft manuscript preparation: MQ; Critical review and revision: MQ, JRC, AKM. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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ORIGINAL RESEARCH

The impact of incidental endoscopic findings on PEG-related complications in critically ill patients

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ABSTRACT

Objective: This study investigated whether endoscopic abnormalities detected during percutaneous endoscopic gastrostomy placement are associated with complications in critically ill patients and whether these incidental findings predict adverse outcomes.

Materials and Methods: This retrospective cohort study included adult patients who underwent percutaneous endoscopic gastrostomy between January 2014 and January 2024 in the intensive care unit of a tertiary academic hospital. Demographic data, clinical features, endoscopic findings, biopsy results, and complications were recorded. Patients were grouped according to the presence or absence of complications, and statistical comparisons were performed.

Results: Eighty-seven critically ill patients were included. The median age was 69 years; 63.2% were male. Incidental endoscopic findings were observed in 39.1%, including esophagitis, gastritis, ulcers, and other mucosal abnormalities. Biopsies were obtained in 14.9% of patients and revealed chronic inflammation, intestinal metaplasia, or Helicobacter pylori. Complications occurred in 19.5%, with wound infection, bleeding, and leakage being most common. No statistically significant association was found between any endoscopic or histopathological findings and complication development.

Conclusion: Endoscopic and histopathological abnormalities were common but not predictive of complications. Percutaneous endoscopic gastrostomy can be safely performed without delay in the presence of mild to moderate mucosal changes. Systemic factors should guide risk assessment in critically ill patients.

Keywords: endoscopy, gastrointestinal, gastrostomy, percutaneous endoscopic, intensive care units

Introduction

Percutaneous endoscopic gastrostomy (PEG) is frequently employed in critically ill patients who are unable to maintain adequate oral intake due to neurological impairment, prolonged mechanical ventilation, or structural dysfunctions of the upper gastrointestinal tract. In the intensive care unit (ICU) setting, PEG serves as a reliable method to ensure safe and sustained enteral nutrition in patients requiring long-term feeding support (1).

Although PEG is considered a minimally invasive and generally safe procedure, it is not devoid of risks. Reported complication rates range from 4% to 30%, with major adverse events such as peritonitis, hemorrhage, and buried bumper syndrome occurring in a notable minority of patients (2,3). Additional retrospective analyses have shown that PEG can be safely performed in ICU patients, with complication rates comparable to those observed in general ward populations (4).

An underexplored aspect of PEG practice, particularly in ICU settings, is the presence and potential clinical relevance of incidental endoscopic findings discovered during PEG placement. These findings—

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such as esophagitis, erosions, ulcers, gastritis, bile reflux, or suspected neoplastic lesions—are not uncommon. One study reported incidental esophagitis in 14 patients, gastritis in 28, duodenal ulcers in 7, and gastric ulcers in 6 among those undergoing PEG placement, and speculated that such findings might sometimes warrant deferment of the procedure, although evidence remains limited (5). Another investigation focusing on neurologically impaired patients found a notable prevalence of mucosal abnormalities during endoscopic evaluation, including ulcers and esophagitis, highlighting the need for further research into their clinical significance (6).

This study aims to address these gaps by evaluating the incidence and types of PEG-related complications in ICU patients, examining the association between endoscopic findings and complication development, and analyzing baseline characteristics to identify potential risk factors. By providing a comprehensive and focused analysis in a critically ill population, this study provides novel insights that may guide future procedural strategies and improve outcomes in patients requiring long-term enteral nutrition.

Methods

Study design and setting

This was a retrospective, observational cohort study conducted in the intensive care unit of a tertiary care academic medical center. The study included adult patients who underwent PEG between January 2014 and January 2024. The institutional ethics committee approved the study protocol (Approval no: 2024000389)

Patient selection

Patients aged ≥18 years who underwent PEG during their ICU admission were eligible for inclusion. Patients with missing clinical or endoscopic data were excluded from the analysis. A total of 87 patients met the inclusion criteria and were included in the final analysis.

Data collection

Data were retrieved from the hospital's electronic medical records and included demographic characteristics such as age and sex, comorbid diseases, Charlson Comorbidity Index scores, ICU admission diagnoses, indications for PEG placement, and the timing of PEG insertion after ICU admission. Endoscopic findings and biopsy results during PEG placement were also recorded. PEG-related complications were identified based on clinical notes and procedure documentation.

Patients were categorized based on primary clinical indications into three groups: neurological, respiratory, and gastrointestinal. The neurological group included patients who underwent PEG due to stroke, traumatic brain injury, hypoxic-ischemic encephalopathy, prolonged disorders of consciousness, or neuromuscular diseases. The respiratory group comprised patients requiring prolonged mechanical ventilation, those with chronic respiratory failure (e.g., COPD), or patients with impaired oral intake associated with prolonged ventilatory support. Finally, the gastrointestinal group included patients presenting with swallowing dysfunction (dysphagia), structural esophageal or gastric disorders, or those requiring sustained nutritional support despite a functioning gastrointestinal system.

ICU admission diagnoses were categorized into ten predefined clinical groups reflecting the primary reason for ICU admission: respiratory, cardiovascular, neurological, trauma without surgery, PACU, sepsis/infection, metabolic/endocrine disturbances, renal indications, gastrointestinal causes, and toxicological causes.

Definitions

PEG-related complications were defined as any clinically documented event attributable to the PEG procedure, including wound infection, bleeding,

peristomal leakage, buried bumper syndrome, and fistula formation. Incidental endoscopic findings were defined as any unexpected mucosal or structural abnormality identified during PEG placement, not previously known or suspected.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics for Mac, version 28.0 (IBM Corp., Armonk, NY, USA) and Python (v3.10). Continuous variables were expressed as median and interquartile range (IQR) due to non-normal distribution, which was assessed using the Shapiro–Wilk test and visual inspection. Categorical variables were presented as numbers and percentages (n [%]).

Comparisons between patients with and without PEG-related complications were made using the Mann–Whitney U test for continuous variables and either the Chi-square test or Fisher's exact test for categorical variables, as appropriate. A two-tailed p-value <0.05 was considered statistically significant.

Results

A total of 87 patients who underwent PEG during their ICU stay were included in the analysis. The median age of the cohort was 69 years [IQR: 58–79], and 55 patients (63.2%) were male. The most frequently observed chronic conditions among all patients were atherosclerotic cardiovascular disease in 17 patients (19.5%), diabetes mellitus without end-organ damage in 12 (13.8%), dementia in 11 (12.6%), chronic pulmonary disease in 8 (9.2%), and prior stroke in 6 (6.9%). The median Charlson Comorbidity Index was 4 [IQR: 2–6], indicating a moderately comorbid population. The median time to PEG insertion after ICU admission was 20 days [IQR: 14–30].

The most common reasons for ICU admission were postoperative care in 40 patients (46.0%), neurologic conditions in 11 (12.6%), sepsis and infection in 11 (12.6%), and cardiovascular causes in 6 (6.9%). Neurological dysfunction was the leading indication for PEG placement, observed in 61 patients (70.1%), followed by respiratory failure in 21 (24.1%) and gastrointestinal causes in 5 (8.7%).

PEG-related complications were observed in 17 patients (19.5%). The most frequently encountered complications were wound infection in 9 patients (10.3%), bleeding in 8 (9.2%), and peristomal leakage in 8 (9.2%). Less common complications included buried bumper syndrome in 2 patients (2.3%) and fistula formation in 1 (1.1%). Patients were categorized into two groups based on the presence or absence of complications, and their baseline characteristics were compared. No statistically significant differences were found between the two groups in terms of age, sex, CCI score, PEG indication, or ICU admission reason, indicating that the groups were comparable at baseline. A detailed comparison of demographic and clinical characteristics between groups is provided in Table 1.

Endoscopic evaluation revealed incidental findings in 34 patients (39.1%) during PEG placement. Esophageal abnormalities were observed in 13 patients (14.9%), including esophagitis in 9 (10.3%), tumor-like lesions in 2 (2.3%), and tracheoesophageal fistula in 1 (1.1%). Gastric findings were present in 28 patients (32.2%) and included erosions in 11 (12.6%), pangastritis in 10 (11.5%), gastric ulcers in 5 (5.7%), LES laxity in 4 (4.6%), bile reflux in 1 (1.1%), and an intragastric balloon in 1 (1.1%).

When compared between patients with and without PEG-related complications, none of the individual endoscopic findings showed a statistically significant association with complication development ($p>0.05$ for all). Notably, pangastritis and mucosal erosions appeared numerically more frequent in the complication group; however, these differences did not reach statistical significance. A detailed comparison of endoscopic findings and complication status is provided in Table 2.

Endoscopic biopsy was performed in 13 patients (14.9%) during PEG placement. Of these, 11 patients

Table 1. Baseline Demographic and Clinical Characteristics of Patients by PEG-Related Complication Status.

	Total	Complication		P-Value
		Yes	No	
General Patient Characteristics				
Age (years), median [IQR]	69 [58-79]	70 [62-80]	68 [56–77]	0.406
Male sex, n (%)	55 (63.2%)	14 (25.5%)	41 (74.5%)	0.522
CCI, median [IQR]	4 [2-6]	5 [3–7]	4 [2–5]	0.346
PEG insertion day, median [IQR]	20 [14–30]	20 [13–35]	20.5 [14–27]	0.944
ICU Admission Indication, n (%)				
Post-operative	40 (46.0%)	14 (35.0%)	26 (65.0%)	0.291
Sepsis/Infection	12 (13.8%)	3 (25.0%)	9 (75.0%)	
Multi-trauma	11 (12.6%)	3 (27.3%)	8 (72.7%)	
Neurological	11 (12.6%)	4 (36.4%)	7 (63.6%)	
Cardiovascular	6 (6.9%)	0 (0.0%)	6 (100%)	
Respiratory	5 (5.7%)	0 (0.0%)	5 (100%)	
Toxicological	1 (1.1%)	0 (0.0%)	1 (100%)	
Metabolic/Endocrine	1 (1.1%)	1 (100%)	0 (0.0%)	
PEG Indication, n (%)				
Neurological	61 (70.1%)	15 (24.6%)	46 (75.4%)	0.423
Respiratory	21 (24.1%)	8 (38.1%)	13 (61.9%)	
Gastrointestinal	5 (8.7%)	2 (40%)	3 (60%)	

Values are presented as median [IQR] for continuous variables and number (%) for categorical variables. Percentages in the "Total" column are calculated out of the total cohort (n=87), while percentages in the "Complication (Yes)" and "Complication (No)" columns are calculated within each row. P-values were calculated using the Mann–Whitney U test for continuous variables and the Chi-square test for categorical variables, as appropriate.
CCI, Charlson Comorbidity Index; ICU, Intensive Care Unit; PEG, Percutaneous Endoscopic Gastrostomy.

Table 2. Comparison of Incidental Endoscopic Findings Between Patients With and Without PEG-Related Complications.

	Total	Complication		P-Value
		Yes	No	
Incidental Finding, n (%)	34 (39.1%)	11 (32.4%)	23 (67.6%)	0.550
Esophageal Finding, n (%)	13 (14.9%)	6 (46.2%)	7 (53.8%)	0.132
Esophagitis	9 (10.3%)	4 (44.4%)	5 (55.6%)	0.271
Tracheoesophageal fistula	1 (1.1%)	0 (0.0%)	1 (100.0%)	1.000
Tumor-like Lession, n (%)	2 (2.3%)	1 (50%)	1 (50%)	0.495
Ulcer, n (%)	1 (1.1%)	1 (100%)	0 (0.0%)	0.287
Gastric Finding, n (%)	28 (32.2%)	8 (28.6%)	20 (71.4%)	0.981
Erosion	11 (12.6%)	4 (36.4%)	7 (63.6%)	0.550
Pangastritis	10 (11.5%)	5 (50.0%)	5 (50.0%)	0.114
Ulcer	5 (5.7%)	2 (40.0%)	3 (60.0%)	0.566
LES Laxity	4 (4.6%)	1 (25.0%)	3 (75.0%)	1.000
Bile Reflux	1 (1.1%)	0 (0.0%)	1 (100.0%)	1.000
Intragastric Balloon	1 (1.1%)	0 (0.0%)	1 (100.0%)	1.000

Values are presented as number (%). Percentages in the "Total" column are calculated out of the total cohort (n=87), while percentages in the "Complication (Yes)" and "Complication (No)" *columns are calculated within each row. P-values were calculated using the Chi-square or Fisher's exact test, as appropriate.*
LES, Lower Esophageal Sphincter.

Table 3. Histopathologic Findings in Patients Who Underwent Endoscopic Biopsy During PEG Placement.

	Total	Complication		P-Value
		Yes	No	
Biopsy Taken, n (%)	13 (14.9%)	2 (15.4%)	11 (84.6%)	0.249
Histologically Normal	1 (1.1%)	0 (0.0%)	1 (100.0%)	1.000
Chronic Inflammation	11 (12.6%)	2 (18.2%)	9 (81.8%)	0.408
Intestinal Metaplasia	3 (3.4%)	1 (33.3%)	2 (66.7%)	0.858
Helicobacter Pylori Positive	5 (5.7%)	2 (40.0%)	3 (60.0%)	0.566

Values are presented as number (%). Percentages in the "Total" column are based on the total cohort (n=87), while percentages in the "Complication (Yes)" and "Complication (No)" columns are calculated within each row. P-values were calculated using Fisher's exact test.

(12.6%) had findings of chronic inflammation, 3 (3.4%) had intestinal metaplasia, and 5 (5.7%) tested positive for *Helicobacter pylori*. Only one patient had a histologically normal biopsy result.

When compared according to complication status, none of the histopathologic findings showed a statistically significant difference between patients with and without PEG-related complications ($p>0.05$ for all comparisons). A summary of the biopsy results and complication distribution is shown in Table 3.

Overall, although various mucosal and histopathologic abnormalities were identified during PEG placement, none were independently associated with an increased risk of PEG-related complications. These findings suggest that the presence of incidental or histopathologic abnormalities alone may not be sufficient to predict the occurrence of complications in critically ill patients undergoing PEG.

Discussion

In this retrospective cohort study, we evaluated the association between incidental endoscopic findings during PEG placement and the subsequent development of PEG-related complications in critically ill patients. Among the 87 patients included, incidental findings were observed in 39.1% during endoscopic evaluation. However, none of these findings, nor histopathological abnormalities demonstrated a statistically significant association with the development of PEG-related complications.

PEG is a commonly performed procedure to ensure long-term enteral nutrition in critically ill or neurologically impaired patients. Despite its benefits, PEG is associated with complications such as wound infection, bleeding, leakage, and buried bumper syndrome, with reported rates ranging between 10% and 35% (7,8).

During PEG placement, incidental endoscopic findings—such as esophagitis, gastritis, and ulcers—are frequently encountered across various patient populations. Among neurologically impaired patients specifically, a significant proportion have been found to exhibit incidental mucosal abnormalities during endoscopic evaluation (6). However, the clinical relevance of these findings regarding PEG-related complications remains unclear. In our study, although nearly 40% of patients had endoscopic or histopathologic abnormalities, these were not statistically associated with increased complications. This observation is consistent with other studies suggesting that mucosal lesions observed during PEG are often benign and do not necessitate deferral of the procedure (4,6).

Interestingly, systemic inflammatory status may be a more accurate predictor of complications than local mucosal pathology. For example, the C-reactive protein to albumin ratio (CAR) has been shown to correlate with both early mortality and complication risk following PEG placement (9). Additionally, studies have emphasized that peristomal infections following PEG are more strongly associated with systemic

patient factors such as frailty and immune compromise, rather than localized mucosal abnormalities identified during the procedure (10). These observations support the notion that mild to moderate mucosal changes do not independently predict adverse outcomes, particularly when acid suppression therapy is routinely administered in ICU settings.

Our study is distinct from previous works in several key ways. Most existing literature on PEG placement has focused on general patient populations or specific surgical settings, with limited attention paid to critically ill patients in ICUs. The ICU population presents unique challenges, including severe comorbidities, altered physiology, and higher risk of complications. Furthermore, while incidental endoscopic findings such as esophagitis, gastritis, and ulcers are frequently observed during PEG placement, their clinical relevance in the ICU context remains largely unexplored. Our study specifically addresses this gap by evaluating the impact of these incidental findings on the development of PEG-related complications in critically ill ICU patients, a population that is often underrepresented in existing studies. Additionally, while previous studies have focused on PEG complications in general or surgical ICU settings, our research uniquely combines the exploration of incidental endoscopic findings with detailed analyses of baseline patient characteristics and complication outcomes. This approach allows us to provide a more comprehensive understanding of the role of endoscopic findings in predicting post-PEG complications, which has been inadequately addressed in prior literature. Taken together, these findings suggest that although incidental endoscopic abnormalities are prevalent among critically ill patients undergoing PEG, they do not independently predict procedural complications. Routine detection of such findings should prompt clinical awareness but does not necessarily mandate postponement or alteration of PEG placement strategies.

Our study's strengths include the simultaneous analysis of endoscopic and histopathologic data and a focus on a critically ill ICU population. However, limitations such as retrospective design, small sample size, and lack of long-term follow-up restrict broader generalizability. Moreover, uniform administration of PPIs may have diminished the potential impact of local lesions on complications.

Clinically, our findings suggest that routine endoscopic abnormalities—unless suggestive of severe pathology—should not delay PEG. Biopsies performed for incidental lesions may still have long-term prognostic value (e.g., for *H. pylori* or metaplasia), but their relevance to immediate post-procedural safety appears limited. Future prospective, multicenter studies with larger samples are needed to refine risk stratification protocols and validate these observations.

Conclusion

Incidental endoscopic and histopathologic findings are common during PEG placement in critically ill patients but do not independently increase the risk of complications. PEG can be safely performed without deferral in the presence of mild to moderate mucosal abnormalities, while systemic factors should remain the primary focus for risk assessment.

Ethical approval

This study has been approved by the Ondokuz Mayıs University Clinical Research Ethics Committee (approval date: 10.09.2024, number: 2024000389). Informed consent was not obtained due to the retrospective design of the study.

Author contribution

Study conception and design: ÖYÇ, NÜA; data collection: Mİ, TSA; analysis and interpretation of results: ÖYÇ, NÜA, FÜ, TSA; draft manuscript preparation: ÖYÇ, NÜA, Mİ, FÜ. The author(s) reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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ORIGINAL RESEARCH

Prognostic value of Charlson comorbidity index, ASA status, and APACHE-II score in predicting in-hospital mortality in critically ill geriatric hip fracture patients

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ABSTRACT

Objective: This study aimed to investigate the prognostic value of the Charlson comorbidity index (CCI), American Society of Anesthesiologists (ASA) status, and Acute Physiology and Chronic Disease Evaluation II (APACHE-II) score in critically ill geriatric hip fracture patients followed in the surgical intensive care unit (SICU).

Materials and Methods: Critical geriatric hip fracture patients who underwent surgery and were followed in the SICU between January 2022 and December 2023 were evaluated retrospectively. The performance of CCI, ASA status, and APACHE-II scores in predicting in-hospital mortality was investigated.

Results: The study included 137 patients, and 66.4% (n=91) were female. ASA IV status, APACHE-II, CCI score, and the number of patients with coronary vascular disease/heart failure were significantly higher in the mortality group (p=0.003, p<0.001, p<0.001, and 0.010, respectively). Mean Glasgow Coma Scale and serum albumin levels at SICU admission were significantly lower in the mortality group (p=0.008 and p=0.006, respectively). ASA status, APACHE-II, and CCI scores were independent predictors of mortality (p=0.002, p=0.022, and p=0.034, respectively). In ROC curve analysis, the area under the curve (AUC) for APACHE-II was 0.803 (95% CI, 0.697-0.908), AUC for CCI was 0.742 (95% CI, 0.598-0.886), and AUC for ASA status was 0.614 (0.458-0.769).

Conclusions: CCI, ASA status, and APACHE-II scores independently predict in-hospital mortality in patients with critical hip fractures. It has prognostic value in predicting mortality and is listed from highest to lowest as APACHE-II, CCI, and ASA status.

Keywords: hip fracture, Charlson comorbidity index, ASA, APACHE-II, in-hospital mortality

Introduction

Hip fractures are a leading cause of morbidity and mortality in the geriatric population (≥65 years). It is also among the top 10 causes of disability-adjusted life years lost for older adults (1). The proportion of the geriatric population is increasing rapidly in developed and developing countries due to increasing life expectancy and decreasing birth rates. According to the 2022 data from the Turkish Statistical Institute, the proportion of the geriatric population (≥ 65 years) in Turkey has increased to 9.9% (2). Visual and hearing impairments, decreased muscle strength and activity, decreased bone density and joint flexibility, decreased motor and cognitive functions, comorbidities, and polypharmacy in the geriatric population increase the risk of trauma (3). The most common mechanism of traumatic injury in geriatric patients is falls from ground level, and hip fractures occur frequently (4-6). The mortality rate in patients with hip fractures within

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the first year was reported as 21.9% in women and 32.5% in men (7). Deaths following hip fractures in the geriatric population are often due to cardiovascular and respiratory complications. Mortality rates increase in patients who develop pneumonia, pulmonary embolism, arrhythmias, and acute cardiovascular collapse. Critical geriatric hip fracture patients are frequently monitored in the intensive care unit (ICU) in the early postoperative period.

Prognostic scoring systems help predict mortality and plan aggressive treatment in critically ill patients followed in the ICU. Anesthesiologists frequently use the American Society of Anesthesiologists (ASA) status to determine preoperative physical status. However, the Acute Physiology and Chronic Disease Evaluation-II (APACHE-II) score helps predict mortality in patients admitted to the ICU. Scoring systems such as the Glasgow coma scale (GCS) and the revised trauma score, specific to trauma patients, have been reported to have prognostic value in critical trauma patients (6). Charlson comorbidity index (CCI) is a scoring system with prognostic value that considers patients' age and chronic diseases. CCI has prognostic value in various clinical conditions and helps predict 30-day and 1-year mortality in patients with hip fractures (8-10).

This study compared the performances of CCI, ASA status, and APACHE-II scores in predicting in-hospital mortality in critically ill geriatric hip fracture patients who were followed up and treated postoperatively in a tertiary hospital's surgical ICU (SICU).

Materials and Methods

This comprehensive retrospective observational study was conducted according to the principles of the Declaration of Helsinki. It was initiated after approval from the Clinical Research Ethics Committee of University of Health Sciences, Istanbul Kanuni Sultan Süleyman Training and Research Hospital (date: 08.05.2024, KAEK/2024.05.89). The study included patients who underwent surgery for geriatric hip fractures at the University of Health Sciences, Istanbul Kanuni Sultan Süleyman Training and Research Hospital between January 2021 and December 2023 and were followed up in the SICU during the postoperative period. Patient data were accessed through the hospital information system and patient files.

Inclusion criteria: Patients aged 65 years and older who underwent surgery due to geriatric hip fracture and were followed up in the SICU postoperatively. Exclusion criteria: (1) trauma to another extremity or body part in addition to hip fracture; (2) viral and bacterial infection within the last month; (3) deterioration and admission to the SICU while being followed up in the inpatient service postoperatively, (4) intraoperative cardiovascular arrest (5) missing data.

Our hospital, a tertiary healthcare institution, provides postoperative surgical intensive care unit (SICU) care with eight beds. Geriatric hip fracture patients with ASA III status or higher who are at high risk for cardiac, respiratory, or other systemic conditions are monitored in the SICU postoperatively. Patients who are not at high risk but who exhibit hemodynamic instability, cardiac, or respiratory failure during the perioperative period are also monitored in the SICU at the discretion of the anesthesiologist. The current study did not standardize SICU admission criteria. Patients deemed high risk during the preanesthetic visit or those identified as having hemodynamic instability during the intraoperative period and requiring close monitoring were admitted to the SICU.

The data collected, including demographic data, ASA status, comorbidities, CCI, Glasgow Coma Scale (GCS) and Acute Physiology and Chronic Disease Evaluation-II (APACHE-II) scores at the time of admission to SICU, anesthesia methods, SICU and hospital stay, hemoglobin and albumin levels at admission, and in-hospital mortality, is of utmost importance in understanding critical care outcomes. These findings were then categorized into a survivor group and a mortality group based on in-hospital mortality, a significant factor in critical care outcomes.

Charlson comorbidity index (CCI)

Charlson et al. developed the Charlson Comorbidity Index in 1987 to classify comorbidities that may affect the risk of death. The CCI is the most widely used comorbidity index to determine survival (1 year and 10 years) in patients with comorbidities (8). Each comorbidity is scored 1, 2, 3, or 6. The scores are added to provide a total score to predict mortality. As the CCI score increases, the patient's mortality risk increases.

Comorbid diseases and corresponding scores in the CCI are listed below:

1 points each: Cerebrovascular disease, chronic lung disease, congestive heart failure, dementia, diabetes (under control), liver disease (mild), myocardial infarction, peptic ulcer disease, peripheral vascular disease, rheumatologic disease.

2 points each: Diabetes (uncontrolled, end organ damage present), hemiplegia and paraplegia, kidney disease, leukemia, lymphoma, malignancy (localized).

3 points each: Moderate or severe liver disease

6 points each: AIDS, metastatic malignancy

The following points are added to the CCI score of patients aged 50 and over:

Age 50 to 59: +1 point added

Age 60 to 69: +2 points added

Age 70 to 79: +3 points added

Age 80 and above: +4 points added.

The study's primary objective was to compare the performance of CCI, ASA status, and APACHE-II scores in predicting in-hospital mortality in patients with geriatric hip fractures who were followed in the SICU. The sample size was not determined in this retrospective cohort study, and all patients who met the inclusion and exclusion criteria during the study's two years were included.

Statistical analysis

All analyses were performed using SPSS v27.0 software (SPSS Inc., Chicago, USA). The conformity of the data to normal distribution was evaluated using the Shapiro-Wilks test, histogram, skewness, and kurtosis. Descriptive statistics were expressed as number of patients, percentage, and median (interquartile range = Q1-Q3). Mann-Whitney U test and independent samples t-test were used in the analysis of quantitative data. Qualitative data were analyzed using the Pearson chi-square test and Fisher exact test. Multivariate logistic regression analysis was performed to determine independent predictors that effectively predict mortality. Receiver operating characteristics (ROC) curve analysis was performed to determine the prognostic value of CCI, ASA status, and APACHE-II score. Statistical significance was set at $p < 0.05$.

Results

Between June 2021 and December 2023, 137 patients aged 65 years and older who underwent surgery (hemiarthroplasty and proximal femoral nail) due to hip fracture and were followed up in the SICU after surgery were included in the study (Figure 1). The mean age in the entire population was 79.1±8.4 years, and 66.4% (n=91) were female. Age, gender, and BMI did not differ significantly between the groups (p=0.692, p=0.113, and p=0.786, respectively). The mean GCS scores on admission to the SICU were significantly lower in the mortality group (11.7±2.7 vs. 13.7±1.5, p=0.008). The number of ASA IV patients was significantly higher in the mortality group (27.8% vs. 5%, p=0.003). The mean APACHE-II score at admission to the SICU was significantly higher in the mortality group than in the survival group (20.1±6.4 vs. 13.9±4.3, p<0.001). CCI was significantly higher in the mortality group (5.9±1.4 vs. 4.8±1.2, p<0.001). Spinal anesthesia was performed in 84.7% (n=116) of geriatric hip fracture patients, and the type of anesthesia did not differ significantly between the groups (p=0.211). At admission to the SICU, the mean

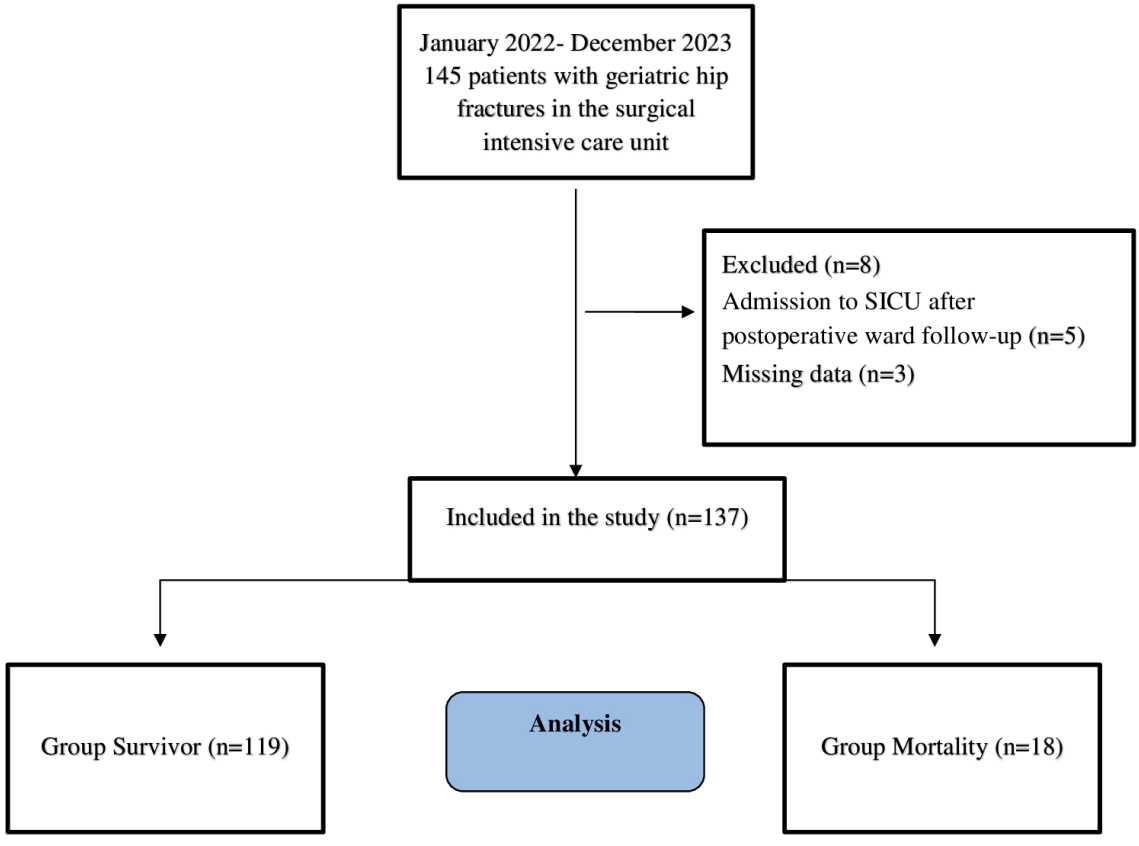

Figure 1. Flow chart of the study

hemoglobin values were lower in the mortality group, but no significant difference was observed (p=0.056). The mean ICU stay for the entire population was 4.1±6.5 days, and the mean hospital stay was 7.7±6.7 days. The in-hospital mortality rate for the entire population was 13.1% (Table 1).

The most common comorbidities were hypertension in 67.9% (n=93) of the entire population, CVD/HF in 34.3% (n=47), and diabetes in 29.9% (n=41). In the mortality group, only CVD/HF (61.1% vs. 30.2%, p=0.010) was significantly higher than in the survivor group (Table 2).

After univariate analysis, multivariate analysis was performed. The risk ratio and 95% confidence interval were reported for each significant variable in multivariate analysis. ASA, APACHE-II, CCI, and GKS scores were found to be independent predictors of mortality (p=0.002, p=0.022, p=0.034, and p=0.002, respectively) (Table 3).

When the prognostic values of the scores in predicting mortality were evaluated with ROC curve analysis, the cut-off value of the ASA score was ≥ 3.5, and the area under the curve (AUC) = 0.614 (95% CI, 0.458-0.769). The cut-off value of the APACHE-II score was ≥ 17.5 and AUC= 0.803 (95% CI, 0.697-0.908), and the cut-off value of CCI was ≥ 6.5 and AUC= 0.742 (95% CI, 0.598-0.886). The mortality prediction performances were determined based on the APACHE-II score, CCI, and ASA status, from highest to lowest. (Figure 2, Table 4).

Table 1. Clinical characteristics.

Variable	All population (n=137)	Survivor (n=119)	Mortality (n=18)	p-value
Age (years)				0.692
Mean ± S.D	79.1±8.4	78.9±8.3	79.8±8.9	
Median (Q1-Q3)	79 (73-85)	78 (73-85)	79 (72-88)	
Age (range)				0.559
65-74	46 (33.6)	40 (33.6)	6 (33.3)	
75-84	51 (37.2)	46 (38.7)	5 (27.8)	
≥ 85	40 (29.2)	33 (27.7)	7 (38.9)	
Sex, n (%)				0.113
Female	91 (66.4)	82 (68.9)	9 (50)	
Male	46 (33.6)	37 (31.1)	9 (50)	
Body mass index				0.786
Mean±S.D	26.6±4.7	26.6±4.8	26.2±4.2	
Median (Q1-Q3)	25.7 (23.5-29.3)	25.7 (23.6-29.3)	25.3 (23.4-29.7)	
GCS				**0.008**
Mean ± S.D	13.4±1.8	13.7±1.5	11.7±2.7	
Median (Q1-Q3)	14 (12-15)	14 (13-15)	11 (9-15)	
ASA status				**0.003**
II	20 (14.6)	19 (16)	1 (5.6)	
III	106 (77.4)	94 (79)	12 (66.7)	
IV	11 (8)	6 (5)	5 (27.8)	
APACHE-II				**<0.001**
Mean ± S.D	14.7±5.1	13.9±4.3	20.1±6.4	
Median (Q1-Q3)	14 (12-17)	13 (11-15)	20 (14-22)	
CCI				**<0.001**
Mean±S.D	4.9±1.3	4.8±1.2	5.9±1.4	
Median (Q1-Q3)	5 (4-6)	5 (4-5)	7 (5-7)	
Anesthesia type				0.211
Spinal	116 (84.7)	103 (86.6)	13 (72.2)	
Spinal+Epidural	11 (8)	9 (7.6)	2 (11.1)	
General	10 (7.3)	7 (5.9)	3 (16.7)	
Hemoglobin (g/dL)				0.056
Mean±S.D	10.4±1.6	10.4±1.7	9.9±1.3	
Median (Q1-Q3)	10.4 (9.3-11.2)	10.5 (9.4-11.2)	9.7 (9.2-10.2)	
Albumin (g/dL)				**0.006**
Mean±S.D	3.0±0.5	3.0±0.5	2.7±0.5	
Median (Q1-Q3)	3.1 (2.7-3.4)	3.1 (2.7-3.4)	2.7 (2.5-3.1)	
Length of stay in SICU (days)				**<0.001**
Mean±S.D	4.1±6.5	2.8±4.1	12.7±11.4	
Median (Q1-Q3)	2 (1-4)	2 (1-3)	10 (4-19)	
Length of stay in hospital (days)				**<0.001**
Mean±S.D	7.7±6.7	6.3±4.4	17.1±10.9	
Median (Q1-Q3)	6 (5-8)	6 (4-7)	15 (8-22)	

GCS: Glasgow Coma Scale, ASA: American Society of Anesthesiologist, APACHE-II: Acute Physiology and Chronic Health Assessment-II, CCI: Charlson Comorbidity Index, SICU: Surgical Intensive Care Unit.

Table 2. Comorbidities in geriatric hip fracture patients.

Comorbidity, n (%)	All population (n=137)	Survivor (n=119)	Mortality (n=18)	p-value
Hypertension	93 (67.9)	79 (66.4)	14 (77.8)	0.335
CVD/HF	47 (34.3)	36 (30.3)	11 (61.1)	**0.010**
Diabetes	41 (29.9)	32 (26.9)	9 (50)	0.056
Stroke	21 (15.3)	18 (15.1)	3 (16.7)	0.866
Asthma /COPD	16 (11.7)	14 (11.8)	2 (11.1)	1.000
Chronic renal failure	14 (10.2)	10 (8.4)	4 (22.2)	0.090

CVD/HF: Coronary vascular disease/heart failure, COPD: Chronic obstructive pulmonary Disease.

Table 3. Multivariate logistic regression analysis.

	Odds Ratio	95% CI (min-max)	p-value
ASA status	0.047	0.007-0.328	0.002
APACHE-II	1.149	1.020-1.295	0.022
CCI	1.922	1.049-3.522	0.034
GCS	0.534	0.361-0.789	0.002
Albumin	0.416	0.088-1.955	0.266
CVD/HF	3.199	0.685-14.940	0.139

ASA: American society of anesthesiologist, APACHE-II: Acute Physiology and Chronic Health Assessment-II, CCI: Charlson Comorbidity Index, GCS: Glasgow coma scale, CVD/HF: Coronary vascular disease/heart failure.

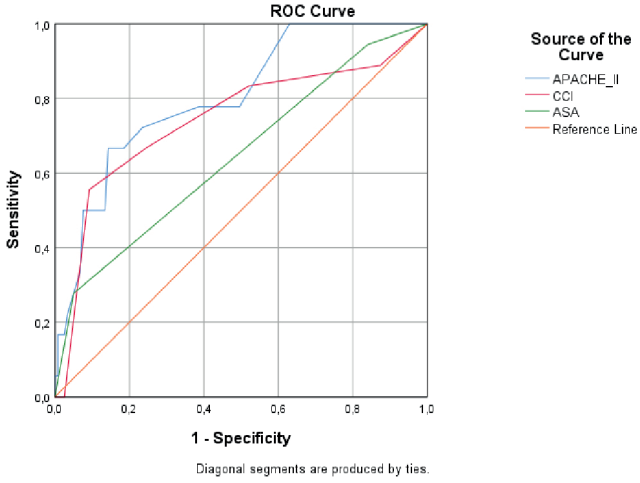

Figure 2. ROC curve for prognostic scores

Receiver operating characteristics curve analyses of prognostic scores in geriatric hip fracture patients. The AUCs of APACHE-II was 0.803 (95% CI, 0.697-0.908), AUCs of CCI was 0.742 (95% CI, 0.598-0.886), and AUCs of ASA status was 0.614 (95% CI, 0.458-0.769).

AUC: area under the curve, CI: confidence intervals, APACHE-II: Acute Physiology and Chronic Health Assessment-II, CCI: Charlson Comorbidity Index, ASA: American society of Anesthesiologist

Discussion

In this study conducted in a tertiary healthcare institution, low GCS scores, high ASA status and APACHE-II scores, and CCI were found to be associated with mortality in patients who underwent surgery due to geriatric hip fracture and were followed up in the SICU in the postoperative period. Comorbid diseases were not independent predictors of mortality. ASA status, APACHE-II, CCI, and GCS were determined to be independent predictors of mortality. In patients with geriatric hip fracture, the scores that performed best in predicting in-hospital mortality were APACHE-II (AUC=0.803), CCI (0.742), and ASA status (0.614), from highest to lowest.

Low-energy traumas, such as falls from the same level, are frequently seen in the geriatric population and mostly cause hip fractures (proximal femur fractures) (11). Approximately 30% of adults aged 60 and over fall annually (12). It has been reported that more than 1.5 million people are affected by hip fractures globally each year and that the highest mortality is seen within the first 30 days (13). Many parameters,

Table 4. Mortality prediction performance of ASA status, APACHE-II and CCI score.

	Cut-off	Sensitivity	Specificity	AUC (95% CI)
ASA status	3.5	0.278	0.950	0.614 (0.458-0.769)
APACHE-II	17.5	0.667	0.857	0.803 (0.697-0.908)
CCI	6.5	0.556	0.908	0.742 (0.598-0.886)

AUC: Area Under Curve, CI: Confidence interval, ASA: American society of anesthesiologist, APACHE-II: Acute Physiology and Chronic Health Assessment-II, CCI: Charlson Comorbidity Index,

such as type of injury, type of operation and surgical technique, early postoperative mobilization, postoperative cognitive impairment, and delirium, are associated with morbidity and mortality in the geriatric population. A meta-analysis reported that the female gender ratio was higher than male in patients with hip fractures and was determined as 61%-87.7% (14). Although it was reported that mortality was significantly higher in males, there are also studies reporting that gender does not affect mortality (15,16). The in-hospital mortality rate for geriatric hip fractures has been reported to be between 4-12% (17). It has been stated that the mortality risk is highest in the first 4 weeks after the fracture (15). In another study, it was stated that the in-hospital mortality rate for geriatric hip fractures was determined to be 32%. The authors reported that the high mortality rate may be due to the study's inclusion of COVID-19-positive patients (18). In the current study, the in-hospital mortality rate in geriatric hip fractures was found to be 13.1%. Although the female gender ratio was high in the literature, gender did not significantly affect in-hospital mortality.

Various comorbidities such as hypertension, coronary artery disease, and diabetes are frequently encountered in the geriatric population. Increased comorbidities increase perioperative morbidity and mortality. Previous myocardial infarction and congestive heart failure have been reported to be predictors of mortality in the geriatric population (19). The ASA Physical Status Classification System classifies patients into six classes based on their current health status, including underlying medical conditions that may affect anesthesia. Patients with higher ASA status are associated with increased perioperative complications and mortality. Similarly, higher CCI scores have been associated with short- and long-term mortality in patients with hip fractures. (19,20). Haugan et al. reported that CCI and ASA scores have similar prognostic value in predicting mortality in patients with geriatric hip fractures (20). Hasan et al. found that the risk of developing postoperative complications in patients with high CCI scores was 1.45 times higher than in patients with low CCI scores (15). The authors also reported that the probability of developing postoperative complications in patients with higher ASA status was 1.77 times higher than in patients with low ASA status. Lakomkin et al. examined the relationship between CCI and postoperative side effects in repeat hip surgery. They stated that high CCI scores were associated with major complications. The authors also reported that CCI was significantly associated with mortality after surgery (21). In our study, coronary vascular disease/ heart failure was found to be significantly higher in the mortality group. However, multivariate regression analysis determined that it was not an independent predictor of mortality. In addition, high ASA status and CCI were found to be independent predictors of mortality in hip fracture patients in the postoperative SICU. The predictive performance of CCI (>6) was found to be superior to the ASA score (>3) in predicting in-hospital mortality (AUC 0.742 vs. 0.614). However, complications other than in-hospital mortality were not evaluated in our study. CCI score provides more detailed scoring than the ASA classification. Health status and lifestyle factors such as smoking and obesity may be associated with mortality. However, they are not taken into account in CCI, while they are taken into account in ASA status. Accurate calculation of CCI score requires a comprehensive review of

medical records. However, the superiority of CCI over ASA is more helpful in predicting in-hospital mortality.

The APACHE II score is a widely used, reliable, and easily administered tool for predicting mortality risk in patients monitored in the ICU based on their physiological values in the first 24 hours. The APACHE-II score evaluates 12 physiological parameters, as well as the patient's age and previous health status. The maximum score is 71, with higher scores indicating a poor prognosis. The APACHE-II score is not a trauma-specific scoring system. It has been reported to be prognostic in predicting mortality in various patient groups monitored in the ICU. Furthermore, it has also been reported to help determine the prognosis in trauma patients (22-24). To our knowledge, the predictive performance of APACHE-II, which is routinely recorded in postoperative hip fracture patients followed in SICU, and CCI and ASA status in predicting mortality has not been compared. In our study, the predictive performance of the APACHE-II score was superior to both CCI and ASA status. The detailed structure of the APACHE-II score, which includes 12 physiological parameters, patient age, and surgical history, effectively prevented this situation from arising. However, CCI also has an acceptable prognostic value.

Other surgical and anesthesia-related conditions may affect mortality in patients with hip fractures. Some opinions state that the type of anesthesia does not affect mortality (4,18,25). In our study, however, it was determined that the type of anesthesia did not affect in-hospital mortality. Although it has been reported that the time from the fracture to the operation also affects mortality in hip fractures, there is no generally accepted opinion. It has been stated that in-hospital mortality increases in cases where the time from the fracture to the operation is more than 48 hours (26). Another study reported that delaying hip fracture surgery for up to four days did not increase mortality; however, mortality increased significantly with a delay of more than four days (27). In the current study, the time between the onset of hip fractures and the time until surgery was not evaluated because we did not have reliable data on this subject.

Malnutrition is common in geriatric patients with hip fractures. Malnutrition has been reported to increase comorbidities, increase healthcare costs, and lead to increased mortality rates (28). Serum albumin levels are used to determine malnutrition in the geriatric population. Albumin, a negative atrial phase protein, has been reported to help predict mortality in patients with traumatic brain injury and polytrauma (29). The prognostic nutritional index (PNI) is a marker derived from serum albumin levels. It has been reported to have prognostic value in geriatric hip fracture patients. Both PNI and CCI have been reported in the literature to be independent predictors of mortality in geriatric patients with hip fractures (30). In the current study, serum albumin levels at the time of SICU admission were significantly lower in the mortality group. However, hypoalbuminemia was not found to be an independent predictor of mortality. Since the aim of the study was not to determine the prognostic value of PNI, it was not evaluated.

Study limitations

The study has several limitations. First, it is a retrospective observational study. Second, it included patients with critical hip fractures from a single institution. This may make it difficult to generalize the results to a larger population. Third, in-hospital mortality was the primary outcome of the study. Long-term mortality was not assessed. Furthermore, the mortality group consisted of a small number of patients (n=18). The small size of the mortality group may have affected the validity of the ROC analyses. Fourth, the time to surgery in patients with hip fractures is crucial for both morbidity and mortality. We were unable to assess this timeframe in the current study because we did not have access to these specific timeframes. Fifth, complications that occurred during the patients' SICU follow-up were not evaluated.

Conclusion

In conclusion, hip fractures resulting from low-energy trauma in the geriatric population are significant causes of morbidity and mortality. CCI, ASA status, and APACHE-II score were found to be independent predictors of mortality in critically ill geriatric patients with frequent comorbidities. The prognostic values of the scores in in-hospital mortality are listed from highest to lowest according to APACHE-II, CCI, and ASA status. All three scores have acceptable prognostic value in identifying critically ill patients within the first month when mortality rates are high in critical geriatric hip fracture patients.

Ethical approval

This study has been approved by the University of Health Sciences, Istanbul Kanuni Sultan Süleyman Training and Research Hospital Clinical Trials Review Board and Ethics Committee (approval date: 08.05.2024, number: KAEK/2024.05.89). Written informed consent was obtained from the participants.

Author contribution

Study conception and design: KA, ASŞ; data collection: KA; analysis and interpretation of results: KA; draft manuscript preparation: KA, ASŞ. The author(s) reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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ORIGINAL RESEARCH

Intentional drug overdose in the intensive care unit: A three-year retrospective cohort on polypharmacy and length of stay

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ABSTRACT

Aims: Intentional drug overdose is a leading cause of poisoning-related intensive care admissions and a major concern in clinical toxicology and public health. Identifying toxicological patterns, demographic features, and associated outcomes is essential to guide prevention and optimize early management.

Methods: We conducted a retrospective analysis of toxicological profiles, psychiatric history, and clinical outcomes among patients admitted to the intensive care unit after intentional drug overdose. Data collected included demographics, psychiatric comorbidities, ingested drug classes, length of stay in the intensive care unit, need for mechanical ventilation, and mortality. Patients were categorized as single- or multiple-drug ingestion, and groups were compared using appropriate statistical tests.

Results: Among 229 patients (57.2% female; 59.1% aged 18–33 years), antidepressants (20.9%) and analgesics (17.3%) were the most frequent agents. Multiple-drug ingestion occurred in 65.9% and was associated with a longer intensive care unit stay (2.31 ± 2.61 vs. 1.60 ± 0.83 days; P = 0.0088). Mechanical ventilation was required in 3.1%, and mortality was 0.3%.

Conclusion: Intentional overdose predominantly affects young adults and often involves multiple-drug ingestion (acute polypharmacy). Although critical outcomes were rare, polypharmacy correlated with prolonged intensive care unit stay, supporting prevention efforts and targeted psychiatric follow-up.

Keywords: drug overdose, poisoning, intensive care units, length of stay, respiration, artificial, suicide, attempted

Introduction

Poisoning is a potentially life-threatening condition resulting from intentional or unintentional exposure to toxic agents. Such exposure may occur through suicidal ingestion of drugs or chemicals, accidental overdose, or inadvertent contact with environmental toxins. Clinical severity—and the attendant risks of morbidity and mortality—varies with patient age, the type and amount of substance ingested, and the time to presentation for medical care (1).

Drug ingestion is the most common method in suicide attempts presenting to emergency departments, with several reports noting rates exceeding 50% (2). Antidepressants and analgesics are among the pharmacologic agents most frequently implicated in these attempts (3).

Reported ICU admission rates for patients presenting with acute drug poisoning range from 3% to 40% (4).

Depending on the pharmacologic properties and dose of the ingested agent, respiratory failure may ensue, necessitating mechanical ventilation; prolonged ventilatory support can, in turn, increase ICU length of stay and mortality risk (5).

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In this study, we retrospectively analyzed the demographics, ingestion patterns, need for mechanical ventilation, and mortality among patients admitted to the ICU after intentional drug overdose. We hypothesized that multiple-drug ingestion would be associated with a longer ICU stay and a higher risk of complications compared with single-drug ingestion.

Methods

We performed a retrospective chart review of adults admitted to the ICU for intentional drug ingestion between January 1, 2022 and January 1, 2025 (n = 229). Intentional ingestion was defined as self-reported or clinically documented consumption for self-harm/suicide, classified on the basis of emergency department (ED) notes and/or psychiatric consultation. Exclusions were recreational use, accidental overdose/medication error, unclear intent, incomplete records, or an indeterminate etiology of intoxication.

Ethical approval

This retrospective study was approved by the institutional ethics committee (Approval No: 2024/2-06) and conducted in accordance with the principles of the Declaration of Helsinki. Because only de-identified patient data were used, the requirement for informed consent was waived.

Outcomes

In this study, we used the term "multiple-drug ingestion" to denote the intentional ingestion of two or more pharmacologically distinct agents during a single suicide attempt. Although the term "polypharmacy" is classically defined as the chronic use of five or more medications, we adopted this terminology in a broader, descriptive sense to reflect acute exposure to multiple substances, consistent with prior toxicology literature. For clarity, we primarily use the term 'multiple-drug ingestion' for acute co-ingestion; 'polypharmacy' is used in a descriptive sense to refer to the same acute exposure context.

The primary outcome was ICU length of stay (LOS). Secondary outcomes included the need for mechanical ventilation, in-hospital mortality, and complications (e.g., renal replacement therapy). Explanatory variables comprised age, sex, psychiatric history, and ingested drug classes. Because only seven patients required mechanical ventilation and one patient died, multivariable logistic regression was underpowered; therefore, we conducted descriptive comparisons (e.g., by psychiatric diagnosis, polypharmacy, and drug type) between ventilated and non-ventilated patients.

Data collection and quality control

Two physicians with ICU/toxicology experience independently abstracted data using predefined criteria after standardized training. Inter-rater reliability was assessed in a random 10% sample, and discrepancies were resolved by consensus. Records missing critical variables (drug type, ICU duration, or outcomes) were excluded. This methodological framework follows established recommendations for rigorous retrospective chart review and is intended to enhance reproducibility and internal validity (6).

Psychiatric consultation notes were available for all patients admitted to the ICU and were systematically reviewed to extract information on psychiatric diagnoses, prior suicide attempts, substance use disorders, and post-discharge follow-up recommendations.

Toxicology

Confirmation of intent and substances relied primarily on clinical documentation. Urine toxicology was available in 56 of 229 patients (24.45%); among these, 52 of 56 (92.86%) were concordant with the reported agents (e.g., benzodiazepines, opioids, antidepressants, amphetamines, barbiturates), supporting the overall reliability of the data.

Urine toxicology screening was performed using a qualitative immunoassay panel capable of detecting common drug classes, including benzodiazepines, opioids, amphetamines, barbiturates, cocaine metabolites, and tricyclic antidepressants. Confirmatory testing by gas chromatography–mass spectrometry was not routinely available. Toxicology testing was ordered at the discretion of the treating physician and was not systematically performed in all patients.

ICU admission and treatment

According to institutional guidelines, ICU admission was recommended for patients evaluated by the ED physician or intensivist who met any of the following criteria: Glasgow Coma Scale (GCS) ≤ 12, respiratory rate < 10/min or oxygen saturation < 90% on room air, systolic blood pressure < 90 mmHg, clinically significant arrhythmias, severe metabolic acidosis (pH < 7.25), seizures, need for airway protection, ingestion of known high-risk agents (e.g., tricyclic antidepressants, opioids, organophosphates), or high imminent suicide risk as determined by psychiatric evaluation. Management followed standardized practices: gastric lavage (≤1 hour with a protected airway), activated charcoal (within 1–2 hours when not contraindicated), dialysis/hemofiltration for severe or dialyzable intoxications, mechanical ventilation for GCS ≤ 8 or respiratory failure, and antidotal therapy (e.g., naloxone, flumazenil) when indicated.

Gastric lavage was considered only within the first hour after ingestion and exclusively in patients with a protected airway, and it was contraindicated in caustic or hydrocarbon ingestion. Activated charcoal was administered within 1–2 hours when patients were alert or intubated and when bowel obstruction, ileus, or high aspiration risk was absent. Renal replacement therapy was reserved for severe intoxications involving dialyzable substances (e.g., lithium, methanol, ethylene glycol) or refractory metabolic derangements. Mechanical ventilation was initiated for GCS ≤ 8, respiratory failure, or loss of airway reflexes. Antidotal therapy (e.g., naloxone for opioids, flumazenil for benzodiazepines) was used selectively, with flumazenil avoided in patients with chronic benzodiazepine use or suspected mixed overdoses.

Statistical analysis

Because this was a retrospective chart review, no formal sample size calculation was performed; all eligible patients admitted during the study period were included. Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 24.0 (IBM Corp., Armonk, NY, USA). Categorical variables were summarized as counts and percentages; continuous variables (e.g., laboratory parameters, length of stay) as mean ± standard deviation (SD). Group comparisons for categorical variables used Fisher's exact or X^2 tests, as appropriate. Owing to non-normal distributions, differences in continuous variables between groups were assessed with the Mann–Whitney U test. Given the low frequency of certain outcomes (e.g., mechanical ventilation, mortality), inferences for these endpoints were interpreted with caution and considered exploratory rather than confirmatory. Statistical significance was set at $P < 0.05$. For sparse endpoints (e.g., mechanical ventilation, hemofiltration, mortality), proportions and exact 95% confidence intervals were calculated using the Clopper–Pearson method, prioritizing precision over model-based inference.

Results

Of the 229 patients included in the study, 131 (57.20%) were female and 98 (42.80%) were male. All met the inclusion criteria for intentional ingestion as defined in the *Methods*. Among those with available toxicology screening (n = 56), 92.80% had results consistent with their reported ingestion.

The majority of patients were young adults, with 59.10% aged between 18 and 33 years. Regarding seasonal distribution, admissions were most frequent during the summer months (31.40%, n = 72), followed by spring (23.60%, n = 54), autumn (23.10%, n = 53), and winter (21.80%, n = 50).

When admission times were analyzed, the highest frequency occurred between 20:00 and 04:00 (n = 88, 38.40%), followed by 14:00–20:00 (24.50%), 04:00–08:00 (21.00%), and 08:00–14:00 (16.20%) (Table 1).

There were no statistically significant differences between sexes with respect to age, season, or time of admission. However, a documented psychiatric diagnosis was significantly more common in males (27.55%) than in females (9.16%) ($P < 0.05$) (Table 2).

The most frequently implicated agents in suicide attempts were antidepressants (20.88%; n = 52), analgesics (17.27%; n = 43), and antipsychotics (11.24%; n = 28), followed by alcohol co-ingestion (13.65%; n = 34), which was recorded as a concomitant intoxicant rather than a medication, antibiotics (8.84%; n = 22), over-the-counter cold and flu preparations (multi-ingredient) (7.63%; n = 19), and illicit substances (4.82%; n = 12). Less commonly involved were pesticides (2.41%), antiepileptics (2.81%), and various other agents (Table 3).

Table 1. Descriptive characteristics of the patients (N = 229)

		n (%)
Gender	Female	131 (57.21%)
	Male	98 (42.79%)
Age	18-25 years	69 (30.13%)
	26-33 years	67 (29.26%)
	34-41 years	39 (17.03%)
	≥42 years	54 (23.58%)
Psychiatric diagnosis	Yes	39 (17.03%)
Chronic disease	Yes	26 (11.35%)
Season of attempt	Spring	54 (23.58%)
	Summer	72 (31.44%)
	Autumn	53 (23.14%)
	Winter	50 (21.83%)
Time of attempt	08:00–14:00	37 (16.16%)
	14:00–20:00	56 (24.45%)
	20:00–04:00	88 (38.43%)
	04:00–08:00	48 (20.96%)
Pregnancy	Yes	6 (2.62%)
Multiple suicide attempts	Yes	18 (7.86%)
Alcohol or substance abuse	Yes	21 (9.17%)

Presented as frequency (n) and percentage (%).

Of the patients, 65.94% (n = 151) ingested multiple drugs, while 34.06% (n = 78) took a single medication (Table 4).

Seven patients (3.1%, 95% CI: 1.3–6.2) required mechanical ventilation—four in the single-drug group and three in the multiple-drug group—with no statistically significant between-group difference ($P = 0.233$). Hemofiltration was administered to two patients in the multiple-drug group (1.30%, 95% CI: 0.2–4.7) and to none in the single-drug group (95% CI: 0.0–4.6) (Table 5).

Only one patient (0.33%) died during the study period—a 33-year-old man who developed respiratory failure following benzodiazepine overdose and required intubation. Although no sex-based mortality comparisons can be inferred from a single event, this finding is directionally consistent with prior evidence that completed suicides are more common in men.

No statistically significant differences were observed between the single- and multiple-drug groups in AST (median: 21 vs. 22), ALT (16 vs. 20), urea (22 vs. 21), or creatinine (0.80 vs. 0.70) ($P > 0.05$). CK levels were likewise similar (median: 114.5 vs. 125), although the maximum CK reached 1023 mg/dL in the multiple-drug group. Arterial blood gas analysis showed pH values within normal ranges in both groups; however, marked metabolic acidosis was identified in three intubated patients, which is clinically noteworthy (Table 6). The distribution of patients according to the number of ingested drugs is summarized in Table 7.

As shown in Figure 1, ICU length of stay was significantly longer in the multiple-drug group. The mean ICU stay was 1.60 ± 0.83 days (median, 1; range, 1–4) for single-drug ingestion and 2.31 ± 2.61 days (median, 2; range, 1–16) for multiple-drug ingestion, with the difference reaching statistical significance ($P = 0.0088$).

Table 2. Comparison of clinical and demographic features by gender (N = 229)

		Female (n=131) n (%)	Male (n=98) n (%)	P-value
Psychiatric diagnosis	Yes	12 (9.16%)	27 (27.55%)	$P_1 < 0.05$*
Chronic disease	Yes	12 (9.16%)	14 (14.28%)	P = 0.293
Season of attempt	Spring	32 (24.42%)	22 (22.44%)	P = 0.840
	Summer	43 (32.82%)	29 (29.59%)	
	Autumn	30 (22.90%)	23 (23.46%)	
	Winter	26 (19.84%)	24 (24.48%)	
Time of attempt	08:00–14:00	21 (16.03%)	16 (16.32%)	P = 0.952
	14:00–20:00	35 (26.71%)	21 (21.42%)	
	20:00–04:00	46 (35.11%)	32 (32.65%)	
	04:00–08:00	29 (22.13%)	19 (19.38%)	
Age	18–25 years	41 (31.29%)	28 (28.57%)	P = 0.843
	26–33 years	36 (27.48%)	31 (31.63%)	
	34–41 years	24 (18.32%)	15 (15.30%)	
	≥42 years	30 (22.90%)	24 (24.48%)	

*Statistical analysis was performed using Fisher's Exact Test. Values with *P < 0.05 were considered statistically significant.*

Table 3. Distribution of ingested drug groups and concomitant intoxicants (N = 229)

	n
Antidepressant	52 (20.88%)
Analgesic	43 (17.27%)
Alcohol	34 (13.65%)
Antipsychotic	28 (11.24%)
Antibiotic	22 (8.84%)
Cold and flu preparations (multi-ingredient, OTC)	19 (7.63%)
Illicit substances	12 (4.82%)
Antiepileptic	7 (2.81%)
Others (e.g., antihypertensives, antiarrhythmics) and pesticides	26 (10.44%)

Presented as frequency (n) and percentage (%).
Alcohol was recorded as a concomitant intoxicant rather than a medication.

Table 4. Overall clinical outcomes of the patients (N = 229)

		n
Drugs	Single	78 (34.06%)
	Multiple	151 (65.94%)
Mechanical ventilation support	Yes	7 (3.06%)
Hemofiltration support	Yes	2 (0.87%)
Mortality	Yes	1 (0.33%)

Values are presented as frequency and percentage.

Discussion

The predominance of antidepressants and analgesics is consistent with pathophysiologic mechanisms that often necessitate ICU care: tricyclics can produce QRS widening and metabolic acidosis, whereas benzodiazepines depress respiratory drive—findings that align with our small but clinically relevant rate of mechanical ventilation. The limited acid–base disturbances observed likewise fit these expectations. Whether intentional or accidental, intoxication disrupts physiological homeostasis and is frequently managed in EDs and ICUs, imposing a substantial burden on healthcare systems and carrying a nontrivial risk of mortality (7).

Numerous studies have shown that the primary cause of intoxication is suicide attempts. Investigations by Tüfek et al. (8), Muhammedoğlu et al. (9), and Lee et al. (10) similarly demonstrated that drug-related poisonings most often result from suicidal intent.

Our findings are consistent with the literature regarding age and sex distribution. Multiple studies have reported that intoxication cases occur more frequently among

Table 5. Clinical outcomes by number of ingested drugs

	Single drug (n=78)	Multiple drugs (n=151)	P-value
Mechanical ventilation support	4 (5.10%, 95% CI: 1.4–12.6)	3 (2.0%, 95% CI: 0.4–5.7)	P = 0.233
Hemofiltration support	0 (0.0%, 95% CI: 0.0–4.6)	2 (1.30%, 95% CI: 0.2–4.7)	P = 0.549

Note: Fisher's Exact Test was used for comparisons (N=78/N=151). P < 0.05 was considered statistically significant. Percentages are presented with 95% confidence intervals (Clopper–Pearson method).

Table 6. Comparison of biochemical parameters by drug intake type

Biochemical parameter	Single drug Mean ± SD; Median (range)	Multiple drugs Mean ± SD; Median (range)	P-value
AST (U/L)	26.13±13.59 21 (13-78)	28.35±28.70 22 (10-246)	P = 0.712
ALT (U/L)	27.13±37.26 16 (3-206)	27.29±37.35 20 (7-270)	P = 0.275
Urea (mg/dL)	23.87±8.77 22 (9-51)	25.44±8.54 21 (13-70)	P = 0.424
Creatinine (mg/dL)	0.84±0.29 0.80 (0.48-1.66)	0.80±0.35 0.70 (0.26-1.76)	P = 0.476
CK (U/L)	149.93±106.41 114.5 (38-535)	152.34±167.47 125 (26-1023)	P = 0.223
Prothrombin time (PT), (sec)	11.67±1.32 11.25 (10-15.1)	12±1.21 12 (10.3-13.9)	P = 0.663
pH (Arterial blood gas)	7.34±0.06 7.31 (7.27-7.50)	7.34±0.16 7.34 (7.08-7.68)	P = 0.918
Lactate (mmol/L)	1.74±1.19 1 (0.7-5.4)	1.88±1.85 1 (0.4-8.9)	P = 0.941

Mann–Whitney U test was used. P < 0.05 was considered statistically significant.

Table 7. Number of ingested drugs per patient (N = 229)

Number of drugs ingested	n (%)
1 drug	78 (34.06%)
2 drugs	54 (23.58%)
3 drugs	61 (26.64%)
4 drugs	20 (8.73%)
≥5 drugs	16 (6.99%)
Total	229 (100%)

Multiple-drug ingestion was defined as the intentional ingestion of two or more pharmacologically distinct agents during a single suicide attempt.

young women (11,12) —a pattern also observed in our cohort. Notably, the only fatal case involved a male patient, aligning with prior evidence that completed suicides are more common in men (13).

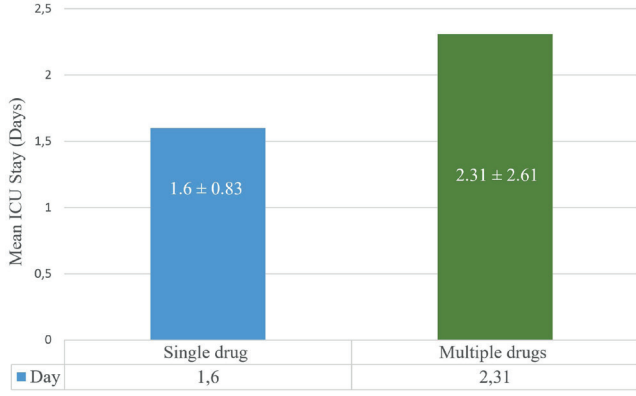

Figure 1. Length of stay by type of drug intake

Length of ICU stay (days):

- Single drug: 1.6 ± 0.83; median (range): 1 (1–4)
- Multiple drugs: 2.31 ± 2.61; median (range): 2 (1–16)
- P = 0.0088*
- Mann–Whitney U Test. Values presented as mean ± standard deviation and median (min–max).

A total of 26 patients had chronic illnesses. The reduced quality of life and increased psychological burden in such individuals may contribute to a higher risk of suicide. In line with prior ICU series, antidepressant-related intoxications were common in our cohort (14). In the study by Yeşiler et al. (15), more than one-third of cases carried a psychiatric diagnosis, and other reports similarly note high rates of depression and alcohol use disorder in comparable populations. Totoz et al. (16) and Wilcox et al. (17) likewise emphasized that most individuals who attempted suicide had a history of antidepressant use or a diagnosed psychiatric disorder. In our cohort, the overall prevalence of psychiatric disorders was 17.03%, increasing to 27.55% among male patients.

Suicide attempts during pregnancy and the postpartum period warrant particular attention. In our cohort, six patients were pregnant and twelve had a pregnancy within the preceding year, underscoring the psychological vulnerability of these stages. Enhanced psychosocial support during pregnancy and the postpartum period is therefore recommended.

A prior history of suicide attempts is a strong predictor of future self-harm (18). Structured interventions such as Safety Planning with follow-up can reduce subsequent suicidal behavior (19). In our study, 18 patients had a documented history of previous attempts, reinforcing the need for rigorous psychiatric follow-up after an initial event.

Although seasonal patterns vary across studies, our data showed a predominance in summer months, consistent with national statistics (20).

Approximately one-third of cases occurred during nighttime hours (20:00–04:00), when individuals are typically at home. This pattern suggests that attempts may not occur in isolation but rather in the presence of others.

Suicide attempts involving drug ingestion are well documented in the literature (2,3,9,15). The most frequently implicated classes are antidepressants and analgesics, likely reflecting their widespread use in the community and the ease of obtaining many such medications without a prescription. The ready availability of these agents in households may facilitate their use during psychological crises.

Although less commonly encountered, agents such as pesticides, antiepileptics, and over-the-counter multi-ingredient cold and flu preparations can also produce severe toxic effects. Clinicians should therefore remain vigilant not only for the most frequently used drugs but for all potentially harmful substances.

The reported rate of multiple-drug ingestion is high in the literature, and in our cohort it was 65.94% (21). This pattern may reflect both over-the-counter availability and the presence of multiple medications in households due to chronic disease. Restricting access to non-prescription drugs could help prevent such cases.

Reported ICU length of stay in the literature ranges from 1.7 to 2.5 days (18). In our study, LOS was 1.6 days in the single-drug group and 2.3 days in the multiple-drug group. This difference likely reflects the greater clinical complexity associated with polypharmacy.

Although the rate of mechanical ventilation was relatively low (3.06%), it falls within the range reported in prior studies (typically 3–20%). The lack of a statistically significant difference between groups likely reflects limited subgroup sample sizes. Larger studies are needed to more robustly evaluate these infrequent yet clinically critical outcomes.

Although the absolute numbers of mechanical ventilation and mortality were low, this pattern reflects the real-world epidemiology of drug intoxication in ICU settings. Reporting these outcomes—even in small numbers—adds to the cumulative evidence on patient profiles, risks, and clinical trajectories. Moreover, the concordance of our results with national registry data and prior literature supports their relevance despite limited statistical power.

Only two patients required hemofiltration, and there was a single fatality (0.33%). These findings support

the notion that early admission and timely intervention can reduce mortality. Nevertheless, the multiorgan failure observed in the deceased patient underscores the potential severity of intoxication.

Reported mortality rates range from 0.92% to 4.20% (10). In our cohort, there was a single fatality—a male patient who developed multiorgan failure following benzodiazepine intoxication. All other intubated patients recovered and were discharged after treatment.

Morbidity and mortality in intoxication depend on multiple factors, including the type and dose of the toxic agent, pharmacokinetic properties, co-ingestion of other substances, baseline comorbid conditions, age, timeliness of medical intervention, adequacy of airway protection, and the development of complications such as metabolic acidosis, arrhythmias, or multiorgan failure (22). Accurate interpretation of biochemical and blood gas parameters is essential for the early detection of organ dysfunction. For example, tricyclic antidepressants can precipitate severe metabolic acidosis (23). Although our study did not identify significant between-group differences in routine biochemical measures, patients who required intubation exhibited notable laboratory derangements.

Most ICU admissions for intentional drug ingestion involved young women, with presentations clustering in the summer months and during nighttime hours. Antidepressants and analgesics were the most frequently implicated agents. Polypharmacy was associated with a longer ICU length of stay, whereas complication and mortality rates were low but not negligible. The predominance of these drug classes is consistent with established toxicodynamic risks—cardiotoxicity, metabolic acidosis, and central nervous system depression—which justify ICU-level monitoring in selected cases. These patterns should inform both clinical management and prevention. From a public health standpoint, safe prescribing, prudent regulation of over-the-counter access, secure home storage, pharmacy counseling for high-risk households, and early psychiatric follow-up may help reduce preventable overdose-related ICU admissions, particularly given the observed summer and nighttime clustering.

Limitations and future directions

This retrospective, single-center design relies on the accuracy of clinical documentation and limits generalizability. Although intent was classified using clinical records and psychiatric evaluation, misclassification is possible because toxicology screening was not universally available. Cases missing key variables (e.g., dose, duration of intoxication, comorbidities) were excluded, which may have introduced selection bias. The very low rates of critical outcomes (mechanical ventilation, 3.06%; mortality, 0.33%) constrained inferential analyses and rendered subgroup comparisons underpowered; consequently, multivariable adjustment for confounders was not feasible. Important determinants such as socioeconomic status, education, and prior psychiatric treatment were not captured. For rare outcomes, we report proportions with exact 95% confidence intervals to convey precision. Larger, multicenter prospective studies are needed to validate these findings and inform prevention strategies.

Conclusions

Intentional overdoses admitted to the ICU predominantly involved young adults and frequently featured polypharmacy. Although mortality and the need for mechanical ventilation were uncommon, polypharmacy was associated with a longer ICU stay, underscoring the need for targeted prevention and post-discharge psychiatric follow-up. Larger, multicenter prospective studies are warranted to confirm these observations.

From an intensive care perspective, our findings indicate that patients with multiple-drug ingestion constitute a higher-risk subgroup characterized by prolonged ICU length of stay and greater clinical complexity. Early identification of co-ingestion, structured toxicological screening, and anticipatory monitoring for respiratory

and metabolic complications may facilitate more efficient resource utilization and earlier escalation of care when indicated. These results support the integration of standardized overdose pathways and mandatory psychiatric consultation into ICU protocols for intentional intoxication.

Ethical approval

This study has been approved by the Ethics Committee of Elazığ Fethi Sekin City Hospital (approval date: 24.10.2024, number: 2024/2-06). The requirement for informed consent was waived due to the retrospective design of the study.

Author contribution

Study conception and design: SŞK; data collection: SŞK, OKB; analysis and interpretation of results: SŞK, SFÖ; draft manuscript preparation: SŞK; critical revision of the manuscript: OKB, SFÖ. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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ORIGINAL RESEARCH

Arterial pH at hospital admission and its relationship with early mortality in post-cardiac arrest patients

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ABSTRACT

Objective: To evaluate the prognostic value of arterial pH at ICU admission for short-term survival after cardiac arrest.

Materials and Methods: This single-center observational study included 60 adults (≥18 years) admitted to the ICU between May 2024 and June 2025 after successful resuscitation with return of spontaneous circulation (ROSC). Clinical, demographic, and laboratory data were collected. Survivors and non-survivors at day 7 were compared using logistic regression and ROC analyses to determine independent predictors of mortality.

Results: The mean age was 61 ± 17 years, and 43% of patients were women. Seven-day mortality was 51.7%. Non-survivors were older and had higher APACHE II scores, lactate and procalcitonin levels, longer CPR-to-ROSC intervals, lower arterial pH values, and shorter ICU stays (all $p < 0.05$). In multivariable logistic regression analysis, age, higher APACHE II score, elevated procalcitonin levels, and lower arterial pH were independently associated with 7-day mortality. Lower arterial pH remained significantly associated with mortality (OR: 1.53; 95% CI: 0.93–2.86; $p = 0.044$). ROC analysis yielded an AUC of 0.668, with an optimal pH cut-off value of 7.13 (sensitivity 61.3%, specificity 75.9%).

Conclusion: Lower arterial pH at ICU admission independently predicts 7-day mortality after cardiac arrest, emphasizing the importance of early recognition and correction of acidosis in post-resuscitation care

Keywords: arterial blood gas, heart arrest, cardiopulmonary resuscitation, return of spontaneous circulation, critical care

Introduction

Despite substantial advancements in the management and care of cardiovascular conditions, sudden cardiac arrest (SCA) remains a formidable issue in both clinical cardiology and broader public health. Current estimates suggest that SCA contributes to approximately 15–20% of all deaths globally (1). Elevated mortality rates are noted not only in out-of-hospital cardiac arrest (OHCA) cases but also pose a significant challenge in in-hospital cardiac arrest (IHCA) scenarios. In the United States, the combined annual incidence of cardiac arrests including both OHCA and IHCA is estimated to range from 350,000 to 750,000 cases. Even with effective resuscitation and the restoration of spontaneous circulation (ROSC), the percentage of patients discharged alive from the hospital remains relatively low, estimated at approximately 18% (2). Although survival rates for in-hospital cardiac arrest in the United States demonstrated a marked improvement between 2000 and 2010, subsequent data indicate that these gains have plateaued, with current rates stabilizing around 25% in the years following 2010 (3). The fundamental goal of cardiopulmonary resuscitation (CPR) is to reestablish sufficient perfusion and oxygen delivery

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to vital organs—particularly the myocardium and brain—thereby sustaining cellular metabolism until spontaneous circulation is restored. Among the most critical factors influencing survival in these patients is the timely administration of high-quality, effective CPR (4). A range of clinical parameters has been recognized for their prognostic significance following cardiac arrest. These include the nature of the initial cardiac rhythm, patient age, existing comorbidities, both the duration and effectiveness of CPR efforts, the implementation of targeted temperature management when indicated, and various pre-arrest hematologic and biochemical indicators. Current investigations continue to examine brain biomarkers and other factors that may predict survival and favorable neurological outcomes in patients who achieve ROSC after resuscitation (5). This research examined the predictive significance of arterial pH levels—a biochemical marker of acid–base imbalance—on 7-day mortality in patients who underwent CPR and were thereafter admitted to the critical care unit (ICU).

Materials and Methods

This retrospective study was conducted in the intensive care unit of a tertiary medical center between May 2024 and June 2025. Adults (≥18 years) who experienced cardiac arrest, achieved return of ROSC, and remained in the ICU for at least 24 hours were included (n = 60). Data were extracted from electronic hospital records and medical charts, including age, sex, Glasgow Coma Scale after ROSC, APACHE II and SOFA scores, comorbidities, ICU stay length, mechanical ventilation duration, witnessed status, arrest location, collapse-to-ROSC interval, and need for sedation, renal replacement therapy, transfusion, or arrhythmia management. Laboratory parameters white blood cell count, hemoglobin, CRP, procalcitonin, arterial pH, lactate, bicarbonate, pCO_2, albumin, creatinine, BUN, liver enzymes, and electrolytes were recorded. The primary endpoint was 7-day all-cause mortality. Ethical approval was obtained from the Institutional Review Board (Ref: 645; September 19, 2025), and informed consent was waived due to the study's retrospective design.

Statistical analysis

Data were analyzed using SPSS version 22.0. Normality was assessed with the Shapiro–Wilk test. Continuous variables were expressed as mean ± standard deviation or median (interquartile range) as appropriate, and compared using the Student's *t*-test or Mann–Whitney *U* test. Categorical variables were analyzed with the chi-square or Fisher's exact test, depending on expected cell counts. Factors associated with 7-day mortality were evaluated by logistic regression, and the predictive value of arterial pH was examined using ROC analysis. The optimal cut-off value for arterial pH was determined using the Youden index. A two-tailed p value < 0.05 was considered statistically significant.

Results

Sixty patients met the inclusion criteria; 26 (43%) were female, and the mean age was 61 ± 17 years. The 7-day mortality rate was 51.7%. Median ICU stay was 5 days (IQR: 2–11). At admission, the mean APACHE II and median SOFA scores were 25 ± 6 and 10 (IQR: 8–12), respectively.

The underlying causes of cardiac arrest included acute coronary syndrome, malignant arrhythmias, pulmonary embolism, and respiratory arrest. Among these, acute coronary syndrome and arrhythmic causes constituted the most frequent etiologies, followed by pulmonary embolism and respiratory arrest. Patients with trauma-related cardiac arrest were not included in the study cohort.

Cardiac arrest occurred in-hospital in 17 patients (28%) and out-of-hospital in 43 (72%); 21 cases (35%) were witnessed. The median time from arrest to ROSC was 20 minutes (IQR: 15–40). Sedation was used in 46 patients (77%), blood product transfusion in 22 (37%), and arrhythmias occurred in 37 (62%).

Common comorbidities were hypertension (43%), diabetes mellitus (35%), coronary artery disease (32%), COPD (27%), chronic kidney disease (23%), and heart failure (22%). Cerebrovascular disease and atrial fibrillation were each observed in 3 patients (5%). Post-ROSC neurological assessment showed a median GCS of 3 (IQR: 3–4), and 16 patients (27%) required renal replacement therapy.

On admission, median lactate was 8 mmol/L (IQR: 5–12), arterial pH 7.16 (IQR: 6.9–7.26), pCO_2 42 mmHg (IQR: 31–59), and HCO_3 15 mmol/L (IQR: 6–15).

Non-survivors were older (67 ± 14 vs. 54 ± 17 years; $p = 0.002$) and had higher APACHE II scores (28 ± 5 vs. 22 ± 6; $p = 0.001$), lactate (10 [3–22] vs. 6 [1–18] mmol/L; $p = 0.005$), and procalcitonin levels (9 [0.04–25] vs. 1.9 [0.1–100] ng/mL; $p = 0.001$). CPR-to-ROSC time was longer in non-survivors (30 [10–60] vs. 15 [5–60] min; $p = 0.003$).

Arterial pH was lower in non-survivors (7.09 [6.5–7.35] vs. 7.22 [6.8–7.41]; $p = 0.025$), who also had shorter ICU stays (4 [2–7] vs. 11 [2–139] days; $p = 0.001$). No significant differences were observed in gender, SOFA score, renal replacement therapy, sedation use, GCS, transfusion, WBC, CRP, albumin, hemoglobin, electrolytes, or comorbidity profiles (all $p > 0.05$). Table 1 summarizes the main findings.

In multivariable logistic regression analysis, age, APACHE II score, procalcitonin levels, and arterial pH were independently associated with 7-day mortality. (Table 2). Among these variables, lower arterial pH

Table 1. Demographic and clinical characteristics of the patients

Variables	Total (n = 60)	Survivors on 7 day (n = 29)	Non-survivors on 7 day (n = 31)	p
Age, (y)	61±17	54±17	67±14	**0.002**
Male, n(%)	34 (57)	19 (64.5)	15 (48)	0.181
APACHE II score	25±6	22±6	28±5	**0.001**
SOFA score	10 (8-12)	10 (8-12)	11 (10-12)	0.06
IHCA, n(%)	17 (28)	9 (29)	8 (28)	0.901
WBC (10^3/µL)	14 (11-24)	13 (6-33)	14 (11-24)	0.446
Lactate (mmol/L)	8 (5-12)	6 (1-18)	10 (3-22)	**0.005**
CRP (mg/dL)	28 (6-121)	20 (2-300)	40 (2-300)	0.069
pH	7.16 (6.9-7.26)	7.22 (6.8-7.41)	7.09 (6.5-7.35)	**0.025**
HCO_3 (mEq/L)	15 (6-15)	16 (4-29)	15 (1-27)	0.135
PCO_2 (mmHg)	42 (31-59)	38 (17-85)	47 (16-90)	0.314
Hemoglobin (g/dL)	13±3	13±3	12±4	0.414
Sodium (mmol/L)	138±6	139±5	137±6	0.351
Potassium (mmol/L)	4.5±0.9	4.3±1	4.7±0.9	0.107
Chloride (mmol/L)	106±7	107±6	105±8	0.275
Urea (mg/dL)	49 (39-82)	44 (21-157)	56 (17-206)	0.307
Creatinine (mg/dL)	1.2 (1.1-1.8)	1.2 (0.7-4.2)	1.2 (0.6-5.4)	0.657
AST (U/L)	180 (67-478)	178 (19-928)	181 (14-4001)	0.564
ALT (U/L)	130 (40-349)	177 (11-933)	127 (9-2786)	0.842
Procalcitonin (ng/ml)		1.9 (0.1-100)	9 (0.04-25)	**0.001**
CPR-to-ROSC time (min)		15 (5-60)	30 (10-60)	**0.003**
LOS in ICU, days	5 (2-11)	11 (2-139)	4 (2-7)	**0.001**

AF: Atrial fibrillation, ALT: Alanine aminotransferase, APACHE II: Acute physiologic and chronic health evaluation, AST: Aspartate transaminase, CAD: Coronary artery disease, CHF: Congestive heart failure, COPD: Chronic obstructive pulmonary disease, CRF: Chronic renal failure, CRP: C-reactive protein, CVD: Cerebrovascular disease, DM: Diabetes mellitus, GCS: Glasgow coma scale, HTN: Hypertension, ICU: Intensive care unit, IHCA: In-hospital cardiac arrest, LOS: Length of stay, n: Number, p: Probability, PCT: Procalcitonin, ROSC: Return of spontaneous circulation, SOFA: Sequential organ failure assessment, WBC: White blood cell, y: Year.

Table 2. Multivariable binary logistic regression modeling of parameters for 7 day mortality

Variables	OR	%95 CI	p
Age	0.913	0.850-0.981	0.013
APACHE II score	0.781	0.620-0.985	0.037
Lactate	0.882	0.637-1.221	0.447
Procalcitonin	0.841	0.724-0.977	0.024
pH	1.533	0.927-2.863	0.044

APACHE II: Acute physiologic and chronic health evaluation, CI: Confidence interval, OR: Odds ratio, p: Probability.

remained significantly associated with mortality (OR 1.53; 95% CI 0.93–2.86; p = 0.044). ROC analysis demonstrated an AUC of 0.668 (95% CI 0.53–0.81; p = 0.026), with an optimal cut-off value of 7.13, yielding a sensitivity of 61.3% and a specificity of 75.9% (Figure 1).

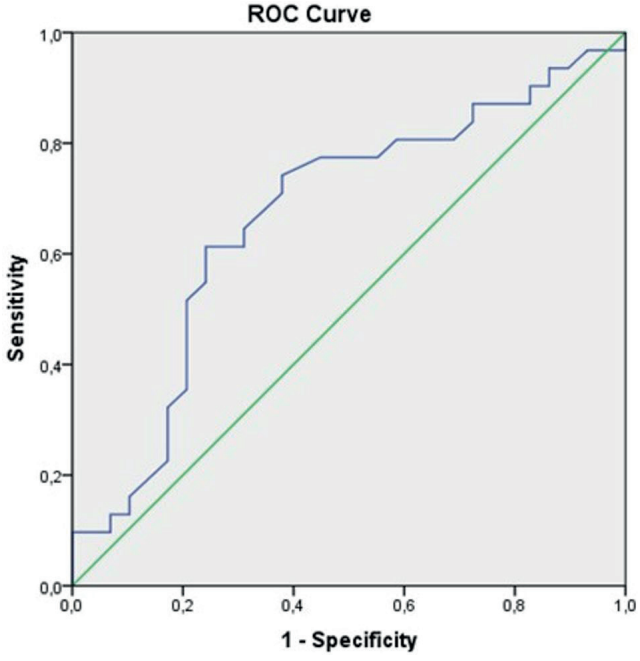

Figure 1. Receiver operating characteristic (ROC) curve demonstrating the predictive performance of arterial pH for 7-day mortality in post-cardiac arrest patients

The area under the curve (AUC) was 0.668 (95% CI, 0.53–0.81; p = 0.026), indicating moderate discriminative ability. The optimal cut-off value of arterial pH was 7.13, corresponding to 61.3% sensitivity and 75.9% specificity for predicting early mortality.

Discussion

Cardiac arrest remains a condition with high mortality, and effective cardiopulmonary resuscitation is essential to achieve return of spontaneous circulation (ROSC) as early as possible and to improve neurological outcomes. Following cardiac arrest, tissue hypoperfusion and hypoxia lead to increased anaerobic metabolism and lactate production, resulting in metabolic acidosis (4). In addition, impaired ventilation and gas exchange during and after resuscitation may contribute to concomitant respiratory acidosis.

This investigation focused on analyzing the association between arterial pH levels and 7-day mortality among patients receiving post-CPR care in a tertiary ICU, independent of underlying etiology. Despite intensive care efforts, pre-ICU cardiac arrest is associated with a markedly elevated mortality rate, often exceeding 90%. Analysis of these cases indicates that younger patients exhibit improved survival outcomes, particularly when timely and appropriate interventions are administered by trained medical personnel (6). Survival trends among patients who experienced non-cardiac arrest etiologies revealed that the majority of fatalities occurred within the first 48 hours following ICU admission. In this period, patient-based aggressive treatment that does not create a serious burden on the patient's hemodynamic status is of great importance in terms of prognosis. Among the patients we included in the study, the deceased patient group had higher age, the median time from arrest to ROSC, lactate,

procalcitonin and APACHE II score, while the LOS in ICU and pH value was lower. Although several clinical and biochemical variables were associated with early mortality, multivariable analysis demonstrated that arterial pH remained independently associated with 7-day mortality, alongside established predictors such as age, APACHE II score, and procalcitonin levels. In our cohort, patients who died had significantly higher age, lactate, APACHE II, and procalcitonin levels compared with survivors, findings that are in line with previously published studies (7-10). The prognosis of patients may be affected by the acidosis due to refractory shock that occurs in this post-CPR patient group whose management and treatment are already difficult (11). While acidosis is defined as a blood pH below 7.35, in cases of severe acidosis (pH < 7.2), different clinical outcomes such as vasodilation, decrease in myocardial contractile function and mean arterial pressure values, decreased response to vasopressor agents, microcirculatory deregulation, arrhythmia, potassium imbalance and mental instability can be observed (12). When the 30-day mortality rates of patients with severe acidosis were examined, values as high as 74.8%, 68% and 83% were observed in different studies (13,14). In our study, based on the ROC curve for pH value, a cut-off value of 7.13 was obtained. Although differences in HCO_3 and pCO_2 levels did not reach statistical significance, non-survivors exhibited higher pCO_2 levels and markedly elevated lactate concentrations, supporting the presence of combined metabolic and respiratory acid–base disturbances in the early post-resuscitation period. Lactate concentrations were notably elevated in patients who did not survive, compared to those who were discharged alive. This finding further supports the contribution of metabolic acidosis due to tissue hypoperfusion in early post-resuscitation mortality. Accumulated anions due to acute renal failure, which is common in post-CPR patients may also cause significant changes in pH (15,16). Jamme et al. showed that pH and HCO_3 had a significant effect on mortality, while pCO_2 had no effect in their study on 826 patients diagnosed with IHCA (11). Shin et al. In their evaluation of OHCA cases, the authors reported that pH, pCO_2, HCO_3, and lactate levels exhibited statistically significant differences between non-survivors and survivors (17). Kim et al. showed that pH, PaCO2 and lactate levels differed significantly between a sustained ROSC and a non-ROSC group among patients with OHCA but did not show a significant association between pH and survival (18). Trepa et al. showed that among 60 patients with proven coronary artery disease who underwent OHCA, pH was significantly lower in those who died than in those who survived (19). In a systematic review and meta-analysis including 4077 OHCA patients, a pH value of 7.22 was associated with favorable survival outcomes (16). In our study, the median pH value in the survivors group was 7.22 (6.8-7.41). However, the threshold value for mortality in the ROC curve was 7.13 for pH, with a sensitivity of 61.3% and a specificity of 75.9%.

Limitations

This study was performed at a single medical center, potentially restricting the applicability of its results to broader populations. The study cohort included a heterogeneous patient population, comprising individuals with a range of underlying conditions such as cardiac, cardiothoracic, neurosurgical, trauma-related, pulmonary, and post-operative diagnoses.

Furthermore, the retrospective study design and relatively small sample size introduce inherent risks of selection and information bias that could not be entirely eliminated. As a result of the retrospective methodology, certain clinical variables potentially affecting both short- and long-term outcomes in post-cardiac arrest patients particularly those related to CPR quality, neurological status, and post-resuscitation interventions were not available for analysis and may have influenced the statistical interpretations.

Conclusions

The findings of this study reinforce the association between acid–base disturbances and increased short-term mortality in patients who undergo cardiopulmonary resuscitation. Lower arterial pH values observed among non-survivors likely reflect the combined impact of metabolic (predominantly lactic) and respiratory acidosis in the early post-resuscitation period. Rather than representing an isolated abnormality, arterial pH serves as an integrative marker of systemic hypoperfusion and impaired ventilation following cardiac arrest. These findings underscore the importance of comprehensive acid–base assessment and close monitoring during post-resuscitation care. Early recognition and management of acidosis may contribute to improved outcomes in this vulnerable patient population.

Ethical approval

This study has been approved by the Clinical Research Ethics Committee of Gazi Yaşargil Training and Research Hospital (approval date: 19.09.2025, number: 645). Written informed consent was waived due to the retrospective nature of the study.

Author contribution

Study conception and design: AD, SY; Data collection: AD, MC; Analysis and interpretation of results: AD, BSK; Draft manuscript preparation: AD; Critical revision of the manuscript: SY, MC, BSK. The authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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CASE REPORT

Therapeutic plasma exchange in the treatment of complicated Plasmodium falciparum malaria and invasive aspergillus fumigatus coinfection: A case report

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ABSTRACT

Objective: A rare case of coinfection of Plasmodium falciparum and Aspergillus Fumigatus from travel to Tanzania is presented in this report.

Methods: A-43-year-old, Turkish male patient who travelled to Tanzania for business without any malaria prophylaxis was admitted to hospital with high fever (39.5 degrees C), weakness, nausea and vomiting and dyspnea when returned to Turkey. The patient had been treated in intensive care unite for sepsis and multi organ dysfunction as a result of the delayed malaria diagnosis. In addition to the presence of thrombocytopenia, anemia, metabolic acidosis, acute respiratory distress syndrome, hepatosplenomegaly and acute renal failure, aspergillus fumigatus emerged as a secondary opportunistic infection. Consent was obtained from the patient's family to publish and all patient specific information has been identified, as a case report and negligible risk to the patient; formal ethics approval was not required because it posed negligible risk to the patient.

Results: He was treated with therapeutic plasma exchange seven times, prone position for 36 hours, continued renal replacement therapy for 72 hours, three cycles of artesunate, artemether lumefantrine for three days, with clindamycin and doxycycline. Additionally, meropenem for empirical antibiotherapy, and voriconazole and amphotericin b for Aspergillus were used.

Conclusion: This case report showed that malaria should be suspected in patients with febrile illness and that travel history to a malaria-endemic region and when fever recurs during the treatment process, secondary opportunistic infections should be considered in addition to malaria. Pulmonary aspergillosis can be seen in people with supressed immune systems and should also be considered in patients with plasmodium falciparum. Since it has been shown that complications may continue even after the parasite load is eliminated, the addition of extracorporeal treatments to antimalarial therapy may be effective in reducing mortality.

Keywords: invasive aspergillus, malaria, plasmodium falciparum, therapeutic plasma exchange

Introduction

Malaria is an important health problem that threatens public health and is endemic in tropical regions around the world. Early diagnosis and treatment of malaria reduces disease and prevents deaths. WHO recommends that all suspected cases of malaria be confirmed using parasite based diagnostic testing. Multiple medicines are used to treat malaria when a malaria parasite is resistant to a medicine (1). Invasive aspergillosis is usually detected in severely immunocompromised patients, but it has also been reported in patients with severe malaria due to transient immunosuppression by plasmodium falciparum (2,3). It has been reported that cases of association of Aspergillus and Plasmodium falciparum generally result in death (4,5).

Since Plasmodium falciparum affects erythrocytes of all ages, its parasitemia is high and typical fever

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attacks occur every 24-48 hours. Anemia secondary to the destruction of erythrocytes, jaundice and hepatosplenomegaly are observed during the seizure. It is possible to make a diagnosis with thin and thick blood films. In the treatment combination treatments of chloroquine, artesunate, artemether 20 mg and lumefantrine 120 mg are available. Doxycycline is also used in cases of chloroquine resistance. In cases of severe malaria, adjunctive therapies are employed alongside antimalarial treatment to manage life-threatening complications such as severe anemia, metabolic acidosis, hypoglycemia, and organ dysfunction. These supportive interventions include blood transfusions, fluid and electrolyte management, anticonvulsants, renal replacement therapy, and mechanical ventilation, tailored to the patient's clinical condition.

In this case, the diagnosis and treatment process of opportunistic invasive aspergillosis secondary to Plasmodium falciparum malaria which was transmitted as a result of a trip to Tanzania, and treatment process of ARDS and multiple organ failure during intensive care follow up explained. We aim to prevent mortality and morbidity through early diagnosis and treatment in cases of Plasmodium falciparum malaria, which is rare in our country with this case study presentation.

Case Study

The patient, who was admitted to different hospitals for a week with symptoms of nausea, vomiting, weakness and persistent fever after returning from a trip to Tanzania, was admitted to our hospital due to increased respiratory distress. At the time of admission, he had tachypnea, thrombocytopenia, anemia, acute renal failure, metabolic acidosis, hepatosplenomegaly, confusion, severe fever (39.5 degrees C) and his Acute Physiology and Chronic Health Evaluation Score (APACHEII) was 11, Sequential Organ Failure Assessment (SOFA) Score was 10. The results of laboratory tests at admission and in next days are presented Table 1.

Table 1. Laboratory parameters of patient.

Parameters	**25.07**	**29.7**	**1.8**	**5.8**	**9.8**	**11.8**
C-reactive protein (0-5 mg/L)	125.9	48.4	160.7	55,5	16.4	8.7
Procalcitonin (<0.5 ng/mL)	41.7	95.93	14.74	3.72	0.44	0.21
Wbc (3.7-10.1 10e3/uL)	7.43	3.39	9,02	2,79	3.86	4.33
Platelet (155-366 10e3/uL)	9	32	130	198	180	196
Hemoglobin (12.9-15.9 g/dl)	12.6	8,7	8.2	7.4	7.8	7.7
Rbc (4.06-5.58 10e6/uL)	4.3	2,94	2.77	2.56	2.73	2.65
Creatinine (0.7-1.2 mg/dl)	1.61	2,04	2	2.34	2.17	1.40
Total bilirubin (<1.2 mg/dl)	2.12	1,01	0.85	0.79	0.84	0.68
Direct bilirubin (0-0.3 mg/dl)	0.95	0,9	0.5	0.6	0.4	0.3
Urea (17-43 mg/dl)	88.4	73,6	92.9	95.6	116.2	76.8
ALT (0-41 IU/L)	44.8	61,7	17.8	23.2	21.9	14.7
AST (0-37 U/L)	23.7	102,5	20.6	30.6	13.3	23.1
LDH (135-225 U/L)	281	195	231	174	362	325
pH (7.35-7.45)	7.37	7.38	7.49	7.4	7.5	7.5
PaO2 (75-100)	28	148	54	150	89	132
PaCO2 (35-45)	31	48	35	46	33	34
Be mmol/L	-6.6	2.9	3.6	3.4	2.9	2.9
Lactate mmol/L(0.5-2)	5.9	1.4	1	0.7	1	0.8

This table reviews clinical laboratory values fort he index patient; Abbreviation: Wbc: White blood cell, rbc: red blood cells, alt: alanine aminotransferase, ast: aspartate aminotransferase, ldh: lactate dehydrogenase.

Taking under consideration his history of mosquito bite during the trip to Tanzania suggested malaria, the thick and thin blood films were performed and Plasmodium falciparum infection detected at the emergency service. Since there was multiple organ failure, he was taken to the intensive care unit for the treatment process. On admission to the intensive care unit he was tachypneic, oliguric, he required continuous catecholamine infusion and his Glasgow Coma Scale was 12. CT scan of the abdomen showed enlarged spleen and liver. Serological test Plasmodium falciparum antigen was positive.

Treatment was initiated with 2.4 mg/kg artesunate and oxygen support, hydration for metabolic acidosis provided. On the second day he exhibited significant clinical deterioration, due to fever attacks, respiratory distress, increasing severity of renal failure and development septic shock (norepinephrine 1 mcg/kg/min and epinephrine 0.3 mcg/kg/min). He was intubated for severe acute respiratory distress syndrome (ARDS) Figure 1. Clindamycin 3x900 mg and meropenem 3x2gr were added as empirical antibiotics to his treatment. Continuous veno venous hemodiafiltration using an oxiris filter was applied in the treatment of septic shock-related acute kidney injury and external cooling therapy was applied for persistent fever. Since multi-organ failure developed with sepsis, therapeutic plasma exchange as immune adsorption treatment was started on the second day of intensive care admission (Table 2). Replaced plasma volume (1 plasma volume), fresh frozen plasma volume without anticoagulation was used for replacement fluid. As hemolysis continued and anemia developed, erythrocyte blood product transfusion was performed.

He was reentubated when Aspergillus- associated ARDS and then successfully extubated at the end

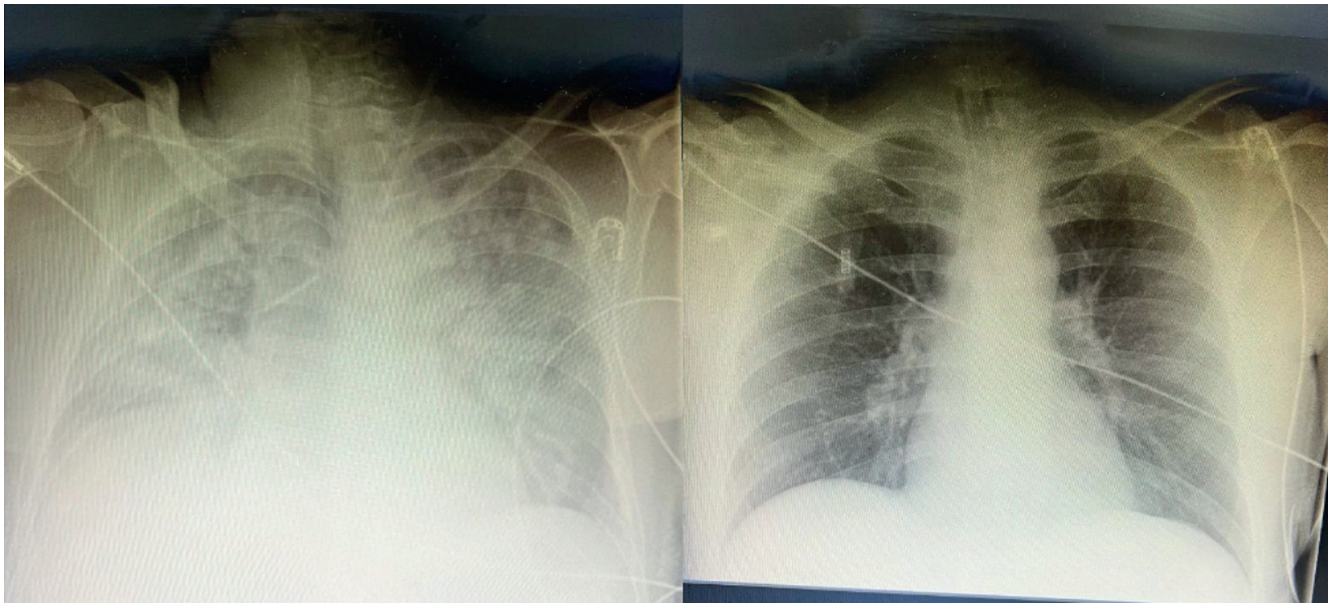

Figure 1. Chest x-ray before and after prone position

Table 2. Therapeutic plasma exchange.

Device	Version	Manufacturer	Anticoagulant	Plasma volume treated	Replacement fluid	Number of frequency of procedures
Prismaflex TPE 2000	3.3	Baxter Healthcare/ Gambro Lundia AB, Swedish	None	1	Fresh frozen plasma	7 procedures, daily

of the 10th day after seven times therapeutic plasma exchange, 36 hours of prone position treatment for ARDS and 72 hours of CRRT. The renal function gradually improved. Clindamycin treatment (3x900 mg) was changed to doxycycline (200 mg /day) due to clinical worsening elevated LDH and an increase in febrile seizures under artesunate and chloroquine treatment. Artesunate treatment was extended to 9 days as 3 cures and at the end artemether 20 mg was combined with lumefantrine 120 mg treatment for 3 days in the form 2x4 tablets. After the treatment the control blood films were examined and the parasite load and antigen were studied and it was documented that the parasite load has ended. (Table 3). Upon the recurrence of fever after external cooling treatment, which was applied and terminated twice for 4 days, galactomannan was tested and resulted positive in the broncoalveolar lavage sampling performed considering the suspicion of secondary opportunistic infection to malaria aggravation and aspergillus fumigatus infection was detected in the tracheal aspirate that was taken. Flexible bronchoscopy was performed by thin mucus plugs with an intensively hemorrhagic appearance, bronchoalveolar lavage samples were obtained for microbiological and serological diagnosis (Figure 2). Treatment was continued with voriconazole 2x6 mg/kg loading dose followed by 2x4 mg/kg maintenance dose. On the fourth day of voriconazole treatment, voriconazole treatment was discontinued due to skin reaction and treatment with amphotericin b 3mg/kg was adjusted (Figure 3). As a result of the 18th day treatment, the patient was cured without secondary organ damage and transferred to the infection service and was later discharged home

Discussion

The rate of complicated malaria is high in P. Falciparum cases encountered in non endemic regions. Since the frequency of falciparum malaria resistance to antimalarial drugs is high, alternative extracorporeal treatments are used in intensive care units in complicated forms (6,7). Since it has been shown that complications may continue even after the parasite load is eliminated, the addition of

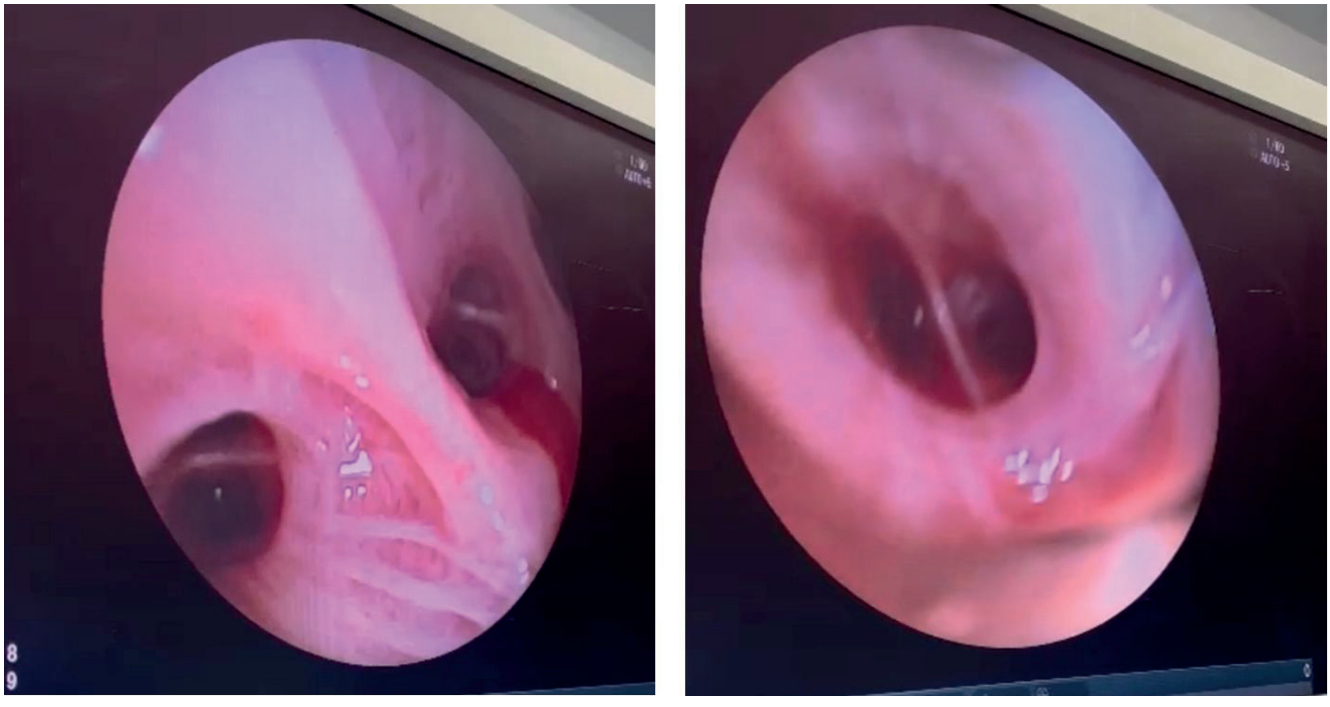

Figure 2. Bronchoscopic image showing intense hemorrhagic appearance

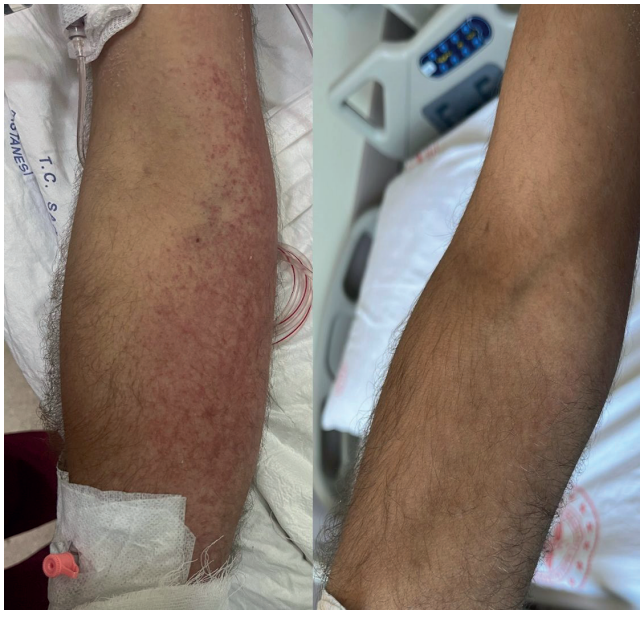

Figure 3. Voriconazole associated skin lesions and after drug discontinuation

extracorporeal treatments to antimalarial therapy may be effective in reducing mortality. In a review of 48 cases of complicated falciparum malaria, it was shown that mortality was reduced with the use of adjuvant plasmapheresis in addition to antimalarial treatment (8).

Aspergillosis is usually seen in immunocompromised patients, and it has a poor prognosis. Opportunistic fungal infections such as invasive aspergillosis, candidiasis and cryptococcal meningitis have been reported to be observed during falciparum malaria. Falciparum malaria can lead to suppression of both humoral and cellular immunity and also contributes to the deterioration of macrophage function. The reason for causing invasive fungal infections is due to the fact that macrophage monocytes and leukocytes are loaded with hemozoin and lose their phagocytosis ability (9). This macrophage suppression due to malaria occurs at the end of acute phase of the disease, and since it remains in the macrophages affected by hemozoin for several months, it can be observed in prolonged periods after recovery. This patient did not have a different comorbidity or neutropenia that supressed the immune system. The observation of aspergillosis at the stage when the parasite load decreases suggests that the supression of the immune system in the late phase secondary to malaria provides an environment for aspergillosis. Although the coexistence of malaria and aspergillus is rarely reported in the literature, malaria is more common in countries with limited resources, may be due to under reporting. Unlike the others, voriconazole and caspofungin were used together for aspergillosis in a case that did not result in death (3). In this case, voriconazole -related skin lesions were observed and amphotericin b was used instead.

Since this case was complicated and there was additional organ damage, both continuous veno venous hemodiafiltration therapy with oxiris filter and therapeutic plasma exchange were used, and mechanical ventilation support was used due to the due to the development of ARDS. Although the parasite load ended, the patient developed a secondary opportunistic infection, Aspergillus and its associated ARDS, as a result of the supression of the immune system. This mortal process was prevented with additional extracorporeal treatments.

Conclusion

We present a rare case of invasive Aspergillus in a patient with a previous Plasmodium Falciparum infection. In complicated Plasmodium Falciparum cases treated in intensive care units, the use of extracorporeal treatments should be considered in addition to antimalarial treatment to reduce parasite load and toxemia. Severe cases of P.falciparum malaria can be fatal even in individuals whose immune system is not supressed; in case of clinical worsening or recurrent fever, opportunistic fungal infections should be considered. Early diagnosis and rapid initiation of treatment are important for mortality and morbidity.

Ethical approval

Written informed consent was obtained from the patient legal represantatives.

Author contribution

Study conception and design: DB, data collection: DB, TK, analysis and interpretation of results: DB, ZÇ, HG, GOH, draft manuscript preparation: DB, TK, ZÇ, HG, GOH. The author(s) reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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CASE REPORT

A case of invasive pulmonary aspergillosis seen in a earthquake victim impacted by the disaster in Türkiye

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ABSTRACT

Objective: Invasive pulmonary aspergillosis (IPA) is a life-threatening fungal infection that predominantly affects immunocompromised individuals. Environmental exposure to large amounts of construction dust following natural disasters may also increase the risk of invasive fungal infections. We aimed to present a fatal case of IPA that developed in an earthquake survivor rescued from prolonged entrapment under collapsed buildings.

Methods: A female earthquake victim with no known chronic disease or history of immunosuppressive therapy was admitted to the intensive care unit (ICU) after prolonged entrapment under rubble, cardiac arrest, and severe crush-related complications. Clinical findings, microbiological results, imaging studies, treatment course, and outcome were retrospectively reviewed.

Results: The patient developed septic shock, acute kidney injury requiring renal replacement therapy, and persistent respiratory failure. Despite broad-spectrum antimicrobial therapy, fever and hypoxemia persisted. Thoracic computed tomography revealed multiple pulmonary nodular lesions and consolidations suggestive of invasive fungal infection. Aspergillus fumigatus was isolated from endotracheal aspirate cultures on the 17th day of ICU admission. Voriconazole therapy was initiated; however, the patient died on the 35th day of ICU hospitalization.

Conclusion: IPA should be considered in critically ill survivors of natural disasters, even in the absence of classical host-related risk factors. Early recognition of invasive fungal infections in patients exposed to substantial environmental dust and debris may facilitate timely antifungal treatment and potentially improve outcomes.

Keywords: c

Introduction

Invasive pulmonary aspergillosis (IPA) caused by a hyaline mold fungus Aspergillus is an important cause of mortality and morbidity in immunosuppressed patients. The prevalence of Aspergillus spp, is reported to be increasing in intensive care units (ICU) around the world (1). The incidence of IPA in ICU patients was determined to be 1-6.9%. IPA affects approximately 300,000 patients a year, and more than 30 million patients are thought to be at risk. The mortality rate of invasive aspergillosis can reach 80-90%, especially in immunocompromised patient groups. If diagnosis is delayed and severe neutropenia persists, death may occur in almost all cases. Aspergillus fumigatus and Aspergillus flavus are common agents in invasive infections, while Aspergillus niger is a rarely reported agent (2). Aspergillus species are common in nature and are found in soil, plants and flowers, household dust, building materials and on decomposing organic compounds. Its small spores can easily hang in the air and spread to the environment. Aspergillus infections are usually transmitted through the transmission of these spores into the respiratory tract. Spores grow in tissue and transform into hyphae, causing tissue invasion and widespread infection (3). The main clinical

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findings of IPA are dry cough, dyspnea, pleural chest pain, fever unresponsive to broad-spectrum antibiotic therapy, and pulmonary infiltrates. Less common clinical findings are hemoptysis, pleural effusion and pneumothorax (4). Invasive fungal infections have been increasingly detected as an infectious agent in ICU patients who are not immunosuppressed in recent years (5). Although Aspergillus species are rare, they are increasingly detected as an infectious agent. In this case, we aimed to discuss the presentation of a case of IPA who did not have a chronic disease and have been pulled alive from the rubble after the earthquake.

Case presentation

A female patient, who does not have any known chronic diseases and a history of drug use, was left under the rubble after the collapse of the building in which it is located during the earthquake on February 6, 2023. As a result of the search and rescue activities, the patient was pulled alive from the rubble (time to stay by collapsed building?) and was quickly transported to the nearest hospital by the 112 emergency service team. As a result of the development of cardiac arrest of unknown etiology in the hospital where she was taken, cardiopulmonary resuscitation was performed for 30 minutes. After the return of spontaneous circulation (ROSC) was obtained, invasive mechanical ventilator support was provided to the patient. Bilateral below-knee amputation was performed in the patient who developed necrosis due to compression of the lower extremities. Due to the patient's need for advanced level ICU, she was transferred to the third level general ICU of our hospital. In the cranial, spinal, thoracic, abdominal and pelvic computed tomography (CT) scans of the patient done due to trauma, no fracture was observed in the bone structures. In the examination performed at the admission of the patient to the ICU, she was intubated and although she did not take sedative-hypnotic drug, she was unconscious and there was no cooperation and orientation. The pupil diameteres were normal size and bilateral pupils showed normal constriction when light was shown in the eyes. Bilateral lower extremities were amputated above the knee level and the wound site was clean, no purulent drainage and no necrotic tissue area. In other areas the skin integrity was intact, conjunctiva and oral mucosa were pallor, pulses were not felt sufficiently, heart sounds were normal, abdominal examination was normal and crepitan rales were heard in the lower zones of both lungs. Arterial blood pressure value 80/50 mmHg (under noradrenaline support at a dose of 0.5 mcg/kg/min), body temperature: 37.6 °C, breath: 20 times/min and heart rate: 110 beats / min and bedside ECG: sinus tachycardia. Laboratory values at first admission to the ICU: leukocytes: 10.200 /ul, hemoglobin: 7.5 mg/dl, neutrophils: 9170/ul, lymphocytes: 750/ul, platelets: 45.000/ul, CRP: 178 mg/dl, procalcitonin: 10 ng/ml, pH: 7.32, pCO2: 30 mmHg, HCO3: 15 mmol/L, pO2: 55 mmHg, sO2: 88%, urea: 95 mg/dL, creatinine: 3.4 mg/dL, sodium: 135 mEq/L, potassium: 5.27, phosphate: 5.2 mg/dL, mEq/L, AST: 602 U/L, ALT: 212 U/L, LDH: 1635 U/L, CK: 21267 U/L, and lactate: 1.39 mmol/L. The patient was anuric (24/h urine output was <100 ml). Due to increased renal function values, metabolic acidosis and hyperkalemia, the patient underwent intermittent hemodialysis and continuous veno-venous hemodialysis / hemodiafiltration as needed and according to her condition. In the diffusion-weighted MRI performed in the patient for hypoxic ischemic enfecephalopathy: At the centrum semiovale level, an appearance consistent with an acute infarct was observed which was hyperintense on diffusion-weighted imaging and hypointense on ADC maps. Follow-up, endotracheal aspirate, urine, central venous catheter and blood cultures were performed. Acinetobacter baumannii grew in endotracheal aspirate and methicillin-resistant Staphylococcus aureus was grown in the central venous catheter. Despite receiving broad-spectrum antibiotic treatment for gram-negative and gram-positive agents for a long time due to septic shock, a chest CT was performed due to persistent fever and low oxygen saturation values. In the CT report summary: patchy consolidation areas with air bronchogram and ground-glass opacity are

observed in the right lung upper lobe posterior and middle lobe areas. In addition, there are widespread multiple nodular lesions, mostly in the right lung. When the findings were evaluated together, the CT result was interpreted in favor of pulmonary aspergillosis (Figure 1). On day 17 of ICU admission, endotracheal aspirate showed Aspergillus fumigatus. The patient received voriconazole treatment for 13 days due to IPA diagnosis, died on the 35th day of ICU while receiving voriconazole treatment.

Discussion

IPA is an opportunistic infection and occurs in some hosts where risk factors are present. In IPA cases, apart from malignant diseases and immunosuppressive cytostatic treatments, organ transplant recipients, underlying diseases such as diabetes, malnutrition, steroid use, uremia, haemodialysis patients, liver cirrhosis and chronic obstructive pulmonary disease have also been shown to pose a risk. Invasive aspergillosis is difficult to diagnose definitively (6). However, ICU patients who do not have known classical risk factors and for whom European Organisation for Research and Treatment of Cancer and the Mycosis Study Group Education and Research Consortium (EORTC/MSGERC) diagnostic criteria cannot be used are also at risk for IPA. In these patients, EORTC/MSGERC diagnostic criteria are not useful and in this study, AspICU criteria proposed by Blot et al were used in the diagnosis of IPA (7). According to AspICU criteria, growth of Aspergillus spp. in the lower respiratory tract sample is the entry criterion and patients with clinical and radiological findings worsening with classical host factors (neutropenia, hematological malignancy, bone marrow transplantation, corticosteroid use, etc.) are evaluated as having IPA (8). If the classical host factor is not present, pure Aspergillus spp. growth should be obtained from the bronchoalveolar lavage (BAL) sample (7). The importance of BAL sample is emphasized in many diagnostic algorithms or guidelines. This sample can be used not only for culture purposes but also for the detection of biomarkers such as galactomannan (GM), β-D-glucan and Aspergillus specific DNA (9-11). The sensitivity of these biomarkers in BAL sample is higher than in culture (12). Although valuable in diagnosis, BAL is not a frequently used sample. In serum/plasma samples, GM antigen test, Aspergillus PCR or β-D glucan test (BDG) tests can be performed. Positivities in these samples indicate invasive infection more strongly. Aspergillus PCR is not a test that can be performed in every center. Due to limited resources in our hospital, we diagnosed our patient with IPA based on aspergillus growth in endotracheal aspiration and suspicion of aspergillus pneumonia in thorax CT. Our patient had no history of any past medication use, including steroids, or chronic disease. There was no event or situation that would predispose the patient to the growth of aspergillus species, such as an aspergillosis outbreak in the hospital, a pandemic process, construction activities such as renovation, demolition, maintenance, excavation in and around the hospital, or fire. Cardiopulmonary arrest was observed in our patient. Pneumonia may occur in patients after cardiac arrest, but pneumonia due to

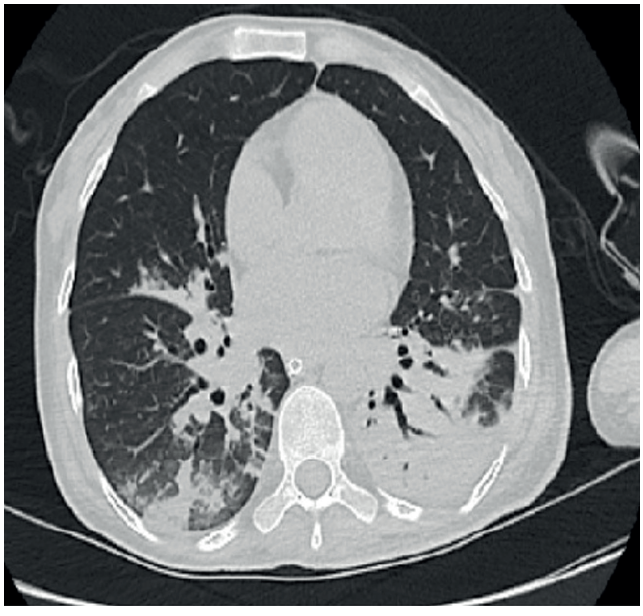

Figure 1. Axial CT scan demonstrates a consolidation with air bronchogram in the left lower lung lobe and and increased atelectatic density with air bronchogram in the right lung lower lobe causing volume loss

aspergillosis has not yet been reported as a major complication (13). The first reported fungal outbreak associated with natural disasters began in 1985 with soft tissue infections caused by Rhizopus arrhizus in eight people following a volcanic eruption, and the frequency of these infections has increased steadily since then (14). A 68-year-old female patient who was followed up with the diagnosis of Tsunami Lung after the Great East Japan Earthquake in 2011, grew Aspergillus fumigatus on the 13th day of her stay in the ICU and the patient died on the 18th day (15). In 2005, aspergillus meningitis was observed in 5 pregnant women in Sri Lanka after cesarean section with spinal anesthesia due to the tsunami effect. The average incubation period was 11.2 days. Three patients died. Fungal cultures of four patients were positive for Aspergillus fumigatus.

In conclusion, after a chaotic environment such as an earthquake, where there may be many casualties and building demolitions, the prognosis for survivors in the hospital and intensive care unit may be poor due to the difficulty in obtaining appropriate diagnostic tools and the scarcity of trained professionals in mycology, little awareness, low research funding and lack of information. IPA is a disease with a high mortality rate in all conditions. Especially keeping in mind that fungal infections may also be a factor in pneumonia cases that may develop after natural disasters and studying appropriate methods to make the diagnosis within hospital possibilities can help increase the success of patient management and reduce mortality.

Ethical approval

Written consent could not be obtained because the patient's relatives could not be reached by any via after she was hospitalized.

Author contribution

Study conception and design: BSK, AD; Data collection: BSK, SY, AD; Analysis and interpretation of results: AD, AIS; Draft manuscript preparation: BSK, AD; Critical revision of the manuscript: SY, AIS. The author(s) reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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CASE REPORT

Methanol poisoning: Case series and treatment approaches in intensive care unit

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ABSTRACT

Objective: This case series aims to present the clinical characteristics, diagnostic processes, treatment strategies, and outcomes of patients with methanol intoxication treated in the intensive care unit (ICU).

Methods: Eight male patients, aged between 31 and 75 years, who were treated in the ICU for methanol intoxication within three weeks, were included. Their medical histories, clinical findings, laboratory results, treatments, and prognoses were described.

Results: The patients presented with a variety of symptoms such as visual loss, nausea, vomiting, abdominal pain, altered mental status, and respiratory distress. All patients had a history of consuming homemade alcohol, although in some cases the exact source and amount of alcohol were unknown. Arterial blood gas analyses revealed metabolic acidosis with elevated lactate levels. Negative blood ethanol levels, along with increased anion and osmolar gaps, supported the diagnosis of methanol intoxication. Patients received intravenous ethanol infusion, hemodialysis, and appropriate ICU supportive treatments. Three patients died (37.5%), while five survived.

Conclusion: This case series emphasizes the importance of prompt intervention in emergencies such as methanol intoxication. Early diagnosis and administering antidotes like ethanol and hemodialysis improve survival rates. Preventing the production of counterfeit alcohol and raising public awareness of its dangers should be key priorities.

Keywords: methanol intoxication, metabolic acidosis, anion gap

Introduction

Toxic alcohols are compounds that can induce severe systemic toxicity when ingested and are predominantly employed in industrial settings. Among them, methanol, isopropyl alcohol (isopropanol), and ethylene glycol represent the most frequent causes of poisoning. Methanol intoxication arises from the accidental or intentional ingestion of adulterated or illegally produced alcohol. Within the body, methanol is metabolized by alcohol dehydrogenase to formic acid (1). The formic acid concentration correlates directly with morbidity and mortality (2). Clinical manifestations of methanol poisoning may include nausea, vomiting, abdominal pain, confusion, visual impairment, acute renal failure, and coma (3,4). Diagnostic confirmation relies on a high index of suspicion in conjunction with laboratory and imaging findings, such as elevated osmolarity, severe high-anion gap metabolic acidosis, methanol levels, and cranial imaging (4,5). The therapeutic approach typically encompasses ethanol or fomepizole administration, hemodialysis, bicarbonate replacement, and folate supplementation (4-6). This case series aims to evaluate the clinical features, diagnostic modalities, therapeutic interventions, and outcomes of patients with methanol intoxication managed in our intensive care unit (ICU). The admission arterial blood gas parameters of all patients are summarized in Table 1.

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Table 1. Arterial blood gas analyses of the patients

Parameters	CASE 1	CASE 2	CASE 3	CASE 4	CASE 5	CASE 6	CASE 7	CASE 8
pH	6,9	6,6	6,8	7,3	7,1	6,7	6,6	7,0
$PaCO_2$	25	35	50	37	22	62	36	27
PaO_2	48	219	115	58	48	58	358	55
HCO_3	5.5	4.4	7	18	9.9	6	3,8	9
BE	-24	-28	-22	-7	-20	-24	-28	-24
Lactate	12	9	13	6,9	6,8	12,5	13	6,5
Anion Gap	24	26	31	28	25	27	25	14

Case 1

A 75-year-old male patient was admitted to the emergency department with confusion. His history indicated the ingestion of 200 ml of homemade alcohol. He had no notable past medical history. On examination, his overall condition was moderate, and he was conscious with a Glasgow Coma Scale (GCS) score of 14, although orientation and cooperation were impaired. Tachypnea and dyspnea were evident. Vital signs were as follows: heart rate 95 bpm, blood pressure (BP) 170/86 mmHg, SpO_2 92% (room air). The initial arterial blood gas analysis demonstrated: pH 6.9, pCO_2 25 mmHg, pO_2 48 mmHg, base excess −24 mmol/L, lactate 12 mmol/L Anion gap was 24 mEq/L. The serum ethanol concentration was 18 mg/dl, and the urine ethyl glucuronide level exceeded 2000 ng/dl. Methanol intoxication was strongly suspected based on the increased anion and osmolar gaps, and intravenous ethanol therapy (10 cc/kg loading dose followed by 2 cc/kg/h maintenance infusion) was initiated. The patient was subsequently admitted to the ICU, where continuous venovenous hemodiafiltration (CVVHDF) was initiated. He was transferred to the internal medicine department on the third day of hospitalization.

Case 2

A 34-year-old male patient was admitted with an altered mental status. He had a history of alcohol consumption, although the source and quantity were unknown. His past medical history was unremarkable. On examination, his overall condition was poor, and he was unconscious, lacking orientation and cooperation. The pupils were mid-dilated. The GCS score was 3, and during cranial Computed Tomography (CT) imaging, cardiopulmonary resuscitation (CPR) was required for 5 minutes. The patient was subsequently transferred to the ICU. Initial arterial blood gas analysis demonstrated: pH 6.6, pCO_2 35 mmHg, pO_2 219 mmHg, base excess −28 mmol/L, lactate 9 mmol/L, with an anion gap of 26 mEq/L. Serum ethanol concentration was <10 mg/dl, and urine ethyl glucuronide exceeded 2000 ng/dl. Methanol intoxication was strongly suspected, and intravenous ethanol therapy (10 cc/kg loading dose, followed by 2 cc/kg/h maintenance infusion) was initiated. Due to hemodynamic instability requiring vasopressor support, CVVHDF was commenced. By the 7th hour of continuous renal replacement therapy (CRRT), the patient developed refractory metabolic acidosis, severe hyperlactatemia, and cardiac arrest. CPR was performed for 42 minutes. Following resuscitation, the patient was diagnosed with ischemic, hypoxic, and metabolic encephalopathy. Brain death was confirmed on the 7th day of hospitalization after a positive apnea test. The patient died on the 10th day of hospitalization.

Case 3

A 45-year-old male patient was admitted to the emergency department with acute vision loss, nausea, and respiratory distress. His history indicated alcohol ingestion from an unidentified source. He had no significant past medical history. On examination, his overall condition was poor, and he was unconscious,

without orientation or cooperation. The pupils were isocoric. The GCS score was 8, and he subsequently developed worsening acidosis. The patient was intubated in the emergency department, and CPR was performed for 4 minutes. He was transferred to the ICU, where CVVHDF was initiated. Arterial blood gas analysis demonstrated: pH 6.85, pCO_2 50 mmHg, pO_2 115 mmHg, base excess −22 mmol/L, lactate 13 mmol/L. The anion gap was 31 mEq/L. Serum ethanol concentration was <10 mg/dl, and urine ethyl glucuronide exceeded 2000 ng/dl. Methanol intoxication was strongly suspected based on the elevated anion and osmolar gaps in conjunction with vision loss. Brain Magnetic Resonance Imaging (MRI) revealed hemorrhage in the right basal ganglion (Figure 1). On the 10th day of hospitalization, the patient underwent tracheostomy and was transferred to a secondary care ICU.

Case 4

A 58-year-old male patient was admitted with head trauma and a history of alcohol consumption. According to his history, he had been assaulted after alcohol intake. He had no significant past medical history. On examination, his overall condition was poor, and he was confused, with impaired orientation and cooperation. The pupils were isocoric. The GCS score was 8. Following vomiting and aspiration, the patient was intubated in the emergency department. He was subsequently transferred to the ICU. Arterial blood gas analysis demonstrated: pH 7.31, pCO_2 37 mmHg, pO_2 58 mmHg, base excess −7 mmol/L, lactate 6.9 mmol/L. The anion gap was 28 mEq/L. Serum ethanol concentration was <10 mg/dl, and urine ethyl glucuronide exceeded 2000 ng/dl. Neurosurgical consultation was obtained, and acute neuropathology was not suspected on CT imaging. Methanol intoxication was considered based on the elevated anion and osmolar gaps together with altered mental status. CVVHDF was initiated in the ICU. Further imaging demonstrated diffusion restriction in the corpus callosum and bilateral basal ganglia (Figure 2). The patient subsequently underwent tracheostomy and was transferred to a secondary care ICU with a GCS score of 5.

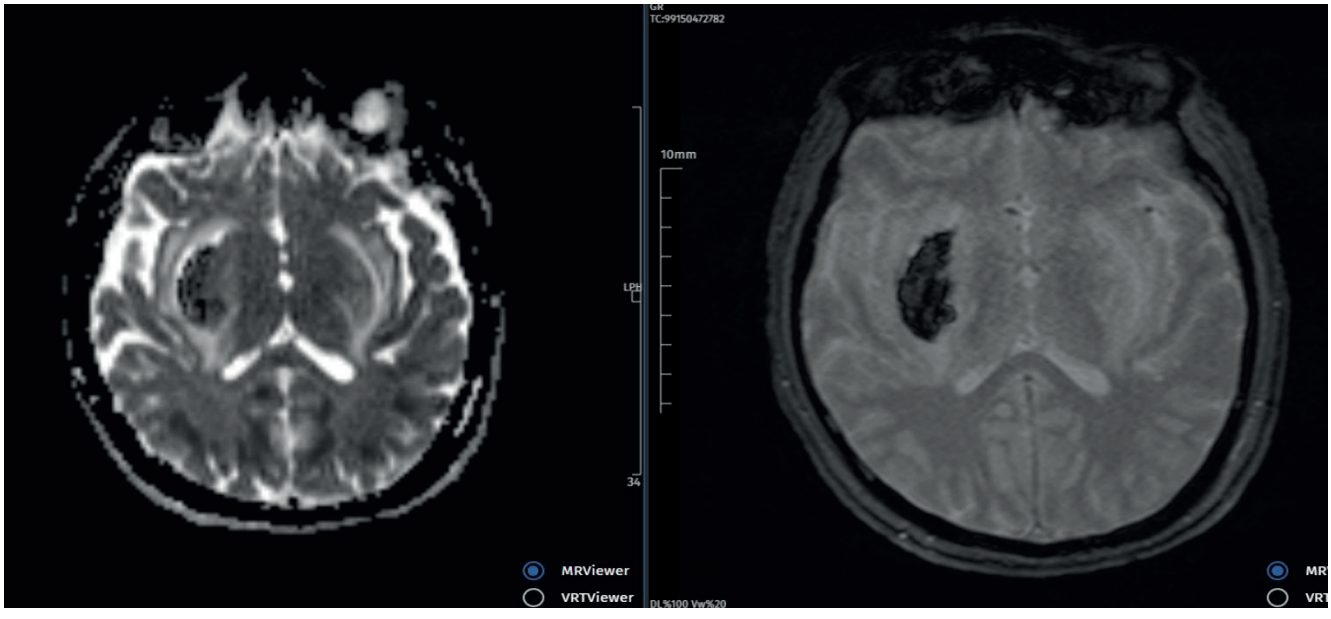

Figure 1. MRI image a hemorrhage in the right basal ganglion

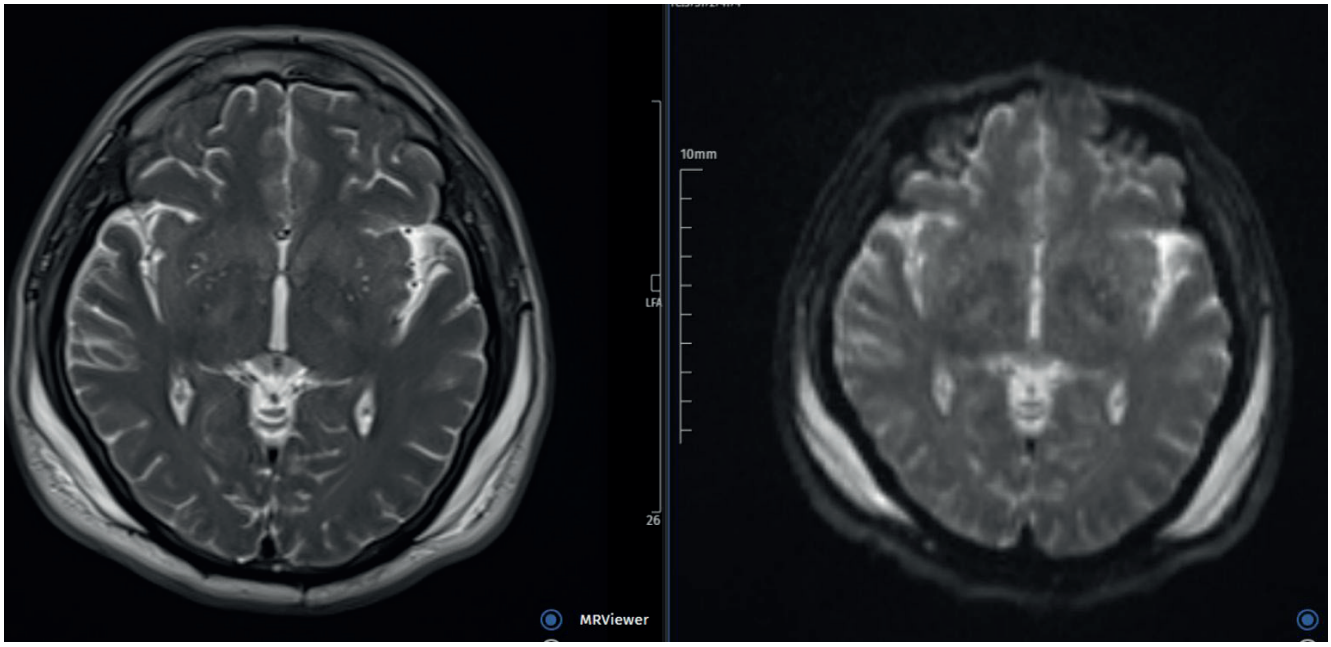

Figure 2. MRI image diffusion restriction in the corpus callosum and bilateral basal ganglia

Case 5

A 65-year-old male patient was admitted with vision loss. He reported ingestion of approximately 300 ml of alcohol from an unidentified source. He had no notable past medical history. On examination, his overall condition was moderate, and he was conscious, oriented, and cooperative. Vital signs were BP 170/110 mmHg, heart rate 85 bpm, SpO_2 96%. Arterial blood gas analysis revealed: pH 7.14, pCO_2 22 mmHg, pO_2 48 mmHg, base excess −20 mmol/L, lactate 6.8 mmol/L. Following hemodialysis, the patient was transferred to the ICU. The anion gap was calculated as 25 mEq/L. Serum ethanol concentration was <10 mg/dl, while urine ethyl glucuronide exceeded 2000 ng/dl. Cranial imaging demonstrated no abnormalities. Based on the elevated anion and osmolar gaps together with vision loss, methanol intoxication was strongly suspected. The patient was observed in the ICU for 24 hours and subsequently discharged.

Case 6

A 64-year-old male patient was admitted with vision loss. His history revealed alcohol consumption from an unidentified source. He had a medical history of hypertension and coronary artery disease. During observation in the emergency department, he developed hypoventilation and required endotracheal intubation. On examination, his overall condition was poor, and his consciousness was sedated. Vital signs were as follows: blood pressure 135/52 mmHg (while receiving noradrenaline infusion at 1 mcg/kg/min), heart rate 79 bpm, SpO_2 95%. Arterial blood gas analysis showed: pH 6.7, pCO_2 62 mmHg, pO_2 58 mmHg, base excess −24 mmol/L, lactate 6 mmol/L. He was transferred to the ICU, where CVVHDF was commenced. Despite ongoing vasopressor therapy, his blood pressure remained unstable, and he died following discontinuation of CVVHDF.

Case 7

A 47-year-old male patient was admitted to the emergency department with abdominal pain. His history indicated alcohol ingestion from an unidentified source. He had no notable past medical history. The patient was hemodynamically unstable and experienced a cardiac arrest following rapid

deterioration. CPR was performed for 8 minutes, after which sinus rhythm was restored. He was subsequently transferred to the ICU. Arterial blood gas analysis demonstrated: pH 6.64, pCO2 36 mmHg, pO_2 358 mmHg, base excess −28 mmol/L, lactate 13 mmol/L. Intravenous ethanol therapy was administered, and CVVHDF was initiated. Despite these interventions, the patient remained profoundly hypotensive and died 6 hours after ICU admission.

Case 8

A 31-year-old male patient was admitted to the emergency department with confusion. His history indicated consumption of homemade alcohol. He had no notable past medical history. On examination, his overall condition was moderate, and he was conscious, oriented, and cooperative. Vital signs were SpO2 92%, heart rate 92 bpm, and blood pressure 127/69 mmHg. The pupils were isocoric with a positive light reflex. Arterial blood gas analysis revealed: pH 7.0, pCO_2 27 mmHg, pO_2 55 mmHg, base excess −24 mmol/L, lactate 6.5 mmol/L. The anion gap was 14 mEq/L. Serum ethanol concentration was 18 mg/dl, and urine ethyl glucuronide exceeded 2000 ng/dl. Given the elevated anion and osmolar gap, methanol intoxication was strongly suspected, and the patient was admitted to the ICU. He received intravenous hydration and bicarbonate therapy. There was no indication for CVVHDF. He was transferred to the internal medicine department on the second day of hospitalization.

Discussion

This case series comprised eight patients who presented to the emergency department over 3 weeks with diverse clinical manifestations. The diagnoses were established based on strong clinical suspicion, elevated anion and osmolar gaps on arterial blood gas analysis, and negative serum ethanol concentrations. However, a definitive diagnosis of methanol poisoning necessitates advanced and costly techniques such as gas or liquid chromatography (7). Despite its diagnostic significance, methanol levels could not be measured in our hospital, and therefore, methanol toxicity could not be biochemically confirmed in blood samples.

All patients in our series were male, consistent with findings from previous studies (8). This phenomenon is considered to be attributable to the higher prevalence of illicit alcohol consumption among men in society. Rising alcohol prices and the increasing availability of illegally produced alcohol may have contributed to the consumption of counterfeit products.

In a retrospective study conducted in Turkey between 2002 and 2010, which included 383 fatalities due to methanol poisoning, it was reported that 64.7% (n=248) of the deaths occurred at home, 7.5% (n=29) in open areas, 9.9% (n=38) in other locations, and only 12.8% (n=49) in hospitals (9). In our case series, three of the eight patients died in the ICU, and two were palliative care patients with a diagnosis of metabolic encephalopathy. Our cohort's observed mortality rate of 37% was comparable to the mortality rates reported in other outbreaks (28-48%) (10,11).

Ethanol was administered as an antidote in three of our patients. Owing to the high cost and limited availability of fomepizole, it was not utilized in the emergency department. Five of the eight patients underwent CVVHDF in the ICU, and one patient received hemodialysis in the emergency department. Considering the delay before ICU admission, early initiation of hemodialysis in the emergency department—without awaiting ICU transfer—may improve survival outcomes. A study conducted by Alhusain et al. reported a substantially lower mortality rate (17%), attributed to the initiation of fomepizole within the first 3 hours of hospital admission, followed by hemodialysis (12). In all cases, urine ethyl glucuronide levels exceeded 2000 ng/dl, whereas blood ethanol levels were negative. Only one patient demonstrated a serum ethanol concentration of 18 mg/dl. In this case, there was no indication of CVVHDF. Previous studies have shown that concurrent ingestion of ethanol

and methanol attenuates clinical manifestations and prolongs the half-life of methanol (13,14).

In a retrospective cross-sectional study including 306 patients conducted in Iran during the COVID-19 pandemic, the most prominent neuroimaging findings associated with poor prognosis were hypodensity in the cerebellar nuclei, diffuse cerebral edema, and intracranial hemorrhage (15). In the neuroimaging of two patients diagnosed with metabolic encephalopathy and low GCS scores, intracranial hemorrhage and diffusion restriction in the basal ganglia were identified. However, basal ganglia lesions observed on imaging may not necessarily correlate with clinical outcomes, and putaminal lesions that resolve within one month following toxicity may not result in permanent functional impairment (16).

Based on this case series, we propose that a multidisciplinary approach to the diagnosis and management of methanol poisoning—emphasizing rapid identification and early initiation of hemodialysis—can substantially reduce morbidity and mortality. National diagnostic and therapeutic strategies warrant reevaluation, and new evidence-based guidelines should be developed. Furthermore, regulatory inspections must be strengthened, and public awareness regarding the dangers of counterfeit alcohol should be enhanced.

Ethical approval

Written informed consent was obtained from the patients' legal representatives.

Author contribution

Study conception and design: FÖ, DB, ZÇ; data collection: FÖ, DB; analysis and interpretation of results: FÖ, DB, ZÇ; draft manuscript preparation: FÖ, DB. The authors reviewed the results and approved the final version of the article.

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Conflict of interest

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LETTER TO THE EDITOR

The procalcitonin kinetics paradox in hemoadsorption therapy for septic shock: Infection source, immunomodulation, and biomarker reliability

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Dear Editor,

We read with great interest the study by Gül et al., published in Turk J Intensive Care, which evaluated protocol-based HA330 hemoadsorption therapy (1). The authors demonstrated that early hemoadsorption in patients with refractory septic shock reduced 28-day mortality (30.8% vs. 49.3%; p=0.037) and improved SOFA scores on day 3, providing valuable real-world data in this controversial field. When considered alongside the retrospective analysis by Efe et al. and the Bayesian network meta-analysis by Meco et al., these findings support the potential benefit of hemoadsorption, particularly in the hyperinflammatory phenotype (2,3). This observation is also consistent with the biphasic immune trajectory of sepsis; hemoadsorption applied during the early hyperinflammatory phase may confer greater clinical benefit compared to the late phase, when the compensatory anti-inflammatory response predominates (4).

However, a clinically important paradox is noteworthy in this study: despite improvements in clinical status and organ function in the hemoadsorption group, procalcitonin (PCT) levels remained significantly higher compared to the control group on days 2 and 3 (day 2: 7.38 vs. 1.85 ng/mL; day 3: 6.40 vs. 2.0 ng/mL; p<0.001). This finding suggests a marked dissociation between clinical improvement and biomarker response, raising questions about the reliability of PCT as a marker of treatment response.

The most likely explanation for this paradoxical finding lies in differences in infection sources and pathogen distributions between groups. Bacteremia was significantly more frequent in the hemoadsorption group (26.9% vs. 8.0%; p=0.004), whereas pneumonia was predominant in the control group (58.7% vs. 23.1%; p<0.001). This is clinically relevant, as it is well established that PCT concentrations are substantially higher in bacteremic patients compared to those with pulmonary-source sepsis, regardless of pathogen type, while CRP levels remain similar (5). Furthermore, considering that the "other Gram-negative" organisms, which were significantly more frequent in the hemoadsorption group (34.6% vs. 9.3%; p<0.001), may include enteric-source pathogens carrying a high endotoxin burden, cytokine-independent stimulation of PCT production may have been further amplified. We therefore suggest that sharing the pathogen distribution within this category in a supplementary analysis would provide valuable insight; however, since this distribution was not detailed in the article, this interpretation remains speculative. The observation that CRP levels were similar between groups across all time points (p>0.05) strongly supports the notion that the elevated PCT levels may reflect patient profile

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rather than a selective biomarker shift. Additionally, the significantly higher and more prolonged use of continuous renal replacement therapy (CRRT) in the hemoadsorption group (71.2% vs. 26.7%; p<0.001; median duration 10 vs. 5 days; p=0.016) warrants consideration. In the setting of acute kidney injury, reduced renal PCT clearance may accelerate PCT accumulation; conversely, although CRRT can eliminate PCT, persistently elevated levels in this group further reflect a higher baseline burden of bacteremic infection. Taken together, these findings suggest that the elevated PCT levels in the hemoadsorption group more likely reflect a more severe baseline infection profile rather than a treatment-related alteration in biomarker kinetics.

The potential impact of immunomodulation on PCT kinetics should also not be overlooked. Despite the cytokine-lowering effect of hemoadsorption, cytokine-independent stimuli such as endotoxin burden and immune dysfunction may sustain PCT production (6). This may render biomarker interpretation particularly complex in immunomodulated septic shock. Prospective data incorporating cytokine levels and immune status markers (e.g., HLA-DR expression) are needed to validate this hypothesis (7).

These findings suggest that PCT may be insufficient for monitoring treatment response in patients undergoing hemoadsorption, and that alternative biomarkers less influenced by the site of infection may be required. Presepsin (sCD14-ST) emerges as a promising candidate in this context due to its specificity for bacterial infection and its relatively infection-driven kinetic profile; however, whether presepsin is adsorbed by the HA330 cartridge has not yet been systematically investigated, and its kinetic reliability in the hemoadsorption setting requires prospective validation (8). IL-6, while of interest for real-time monitoring of treatment efficacy, is directly adsorbed by the cartridge; therefore, measured levels may reflect adsorption capacity rather than infection burden, and its use as a standalone monitoring biomarker is not recommended (9).

In conclusion, despite growing evidence supporting the clinical benefit of hemoadsorption, the interpretability of biomarkers remains a key source of uncertainty. Future multicenter, prospective studies incorporating biomarker-based patient phenotyping, stratified analysis of PCT kinetics by infection source, and simultaneous immune marker measurements will enable more accurate and clinically meaningful assessment of both diagnosis and treatment response. In this context, it should be considered that PCT levels in patients with septic shock undergoing hemoadsorption may reflect underlying infection characteristics rather than treatment response. We therefore believe that interpreting biomarkers independently of clinical context may lead to misleading conclusions and should be approached with caution in patients undergoing hemoadsorption.

Yours sincerely,

Author contribution

Study conception and design: Hİ, Vİ; data collection: Hİ, Vİ; analysis and interpretation of results: Hİ, Vİ; draft manuscript preparation: Hİ, Vİ. The author(s) reviewed the results and approved the final version of the article.

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Conflict of interest

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LETTER TO THE EDITOR

Reconsidering the interplay between PEEP, optic nerve sheath diameter, and neurological assessment in critically ill patients

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Dear Editor,

The article entitled "The relationship between optic nerve sheath diameter, Glasgow Coma Scale, and the effect of PEEP in critically ill patients: a prospective observational study" was read with great interest (1). The evaluation of optic nerve sheath diameter (ONSD) as a noninvasive surrogate marker of intracranial pressure (ICP) in mechanically ventilated patients is highly relevant to contemporary intensive care practice. However, several aspects of the study merit further clarification.

First, the interpretation of the effect of positive end-expiratory pressure (PEEP) on ONSD would benefit from a more detailed discussion within the context of respiratory physiology. The interaction between PEEP and intracranial dynamics is complex and influenced by lung compliance, chest wall elastance, and venous return. It has been demonstrated that the transmission of intrathoracic pressure to the intracranial compartment varies significantly depending on respiratory mechanics, particularly in patients with low lung compliance, such as those with ARDS (2). In the absence of key ventilatory parameters such as plateau pressure, driving pressure, or compliance, it remains unclear whether the observed changes in ONSD can be directly attributed to PEEP or instead reflect broader cardiopulmonary interactions.

Second, although a correlation between ONSD and the Glasgow Coma Scale (GCS) was reported, the clinical validity of this relationship remains uncertain. In critically ill patients, the assessment of GCS is frequently confounded by sedation, neuromuscular blockade, and metabolic disturbances, all of which may compromise its reliability. Previous studies suggest that ONSD correlates more consistently with directly measured ICP than with clinical scoring systems (3). Furthermore, the relationship between ONSD and neurological severity scores appears to vary across different patient populations (4). Without adjustment for sedation depth or subgroup analyses, the reported correlation may not accurately reflect true neurological status.

Finally, although the study suggests that PEEP-induced changes in ONSD may reflect alterations in ICP, the lack of clinically relevant endpoints limits the applicability of the findings. While ONSD is a promising noninvasive marker, its role in predicting meaningful clinical outcomes remains uncertain. Current evidence indicates that ONSD should not be used as a standalone tool without correlation to invasive monitoring or patient-centered outcomes (3,5). Demonstrating whether changes in ONSD translate into neurological deterioration or adverse outcomes would substantially strengthen the study.

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In conclusion, a more comprehensive evaluation incorporating respiratory mechanics, adjustment for neurological confounders, and clinically relevant endpoints is needed to define the clinical significance of these findings better.

Author contribution

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