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AIMS AND SCOPE

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Journal of Critical and Intensive Care (J Crit Intensive Care) is the scientific and official publication of the Society of Turkish Intensivists (STI) (www.tuyud.org.tr). The Journal is an international open access journal, published 3 times a year (April, August, December). All processing is conducted through the online submission system on the web site: www.jcritintensivecare.org. Manuscripts are accepted for publication through an independent unbiased and double-blinded peer review process. Only manuscripts written in English are accepted and only unpublished manuscripts that are not under review for publication elsewhere can be submitted. Journal of Critical and Intensive Care does not accept multiple submissions even though the previous one was published in a different language.

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The journal is an open access journal, published 3 times a year and all of its contents are freely available with no cost and there is no fee for submission. It accepts manuscripts written only in English and evaluates submissions through its online submission system on the web site www.jcritintensivecare.org. It publishes original clinical, basic and translational research articles, case reports and letters to the editor related to intensive/critical care medicine and acute medicine. Editorials and review articles are only accepted upon invitation of the editor.

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Case Series and Report	1500	150	15	2
Editorial	500	-	10	
Letter to the Editor	500	No abstract	5	1

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Journal of Critical and Intensive Care

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The Journal publishes the reviewer list every year in the last issue to express the appreciation for the reviewers.

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Review

ORIGINAL INVESTIGATION

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Preparing High-Risk Patients with Hematologic Malignancies for Critical Care: A Pilot Study (PREP-ICU)

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Abstract

Aim: This study aimed to evaluate the feasibility, effectiveness, and acceptability of an intensive care unit (ICU) orientation intervention to improve advance care planning among patients with hematologic malignancies.

Study Design: This prospective observational cohort study enrolled high-risk hospitalized patients with hematologic malignancies who had a directive for full resuscitative measures. The intervention consisted of (1): a video outlining ICU interventions and outcomes; (2) a values and preferences workbook; and (3) a follow-up meeting to discuss goals of care. Feasibility outcomes included recruitment and completion rates for each study component. Effectiveness was assessed using pre- and post-video surveys measuring knowledge of ICU interventions and outcomes. Acceptability was evaluated using an emotional impact survey and the proportion of participants who chose to terminate the video prematurely.

Results: Fifteen participants were recruited. Regarding feasibility, 11 of 15 participants (73%) completed all study components. All participants (15/15) completed the video, and 13 of 15 (87%) completed the follow-up meeting. Regarding effectiveness, the proportion of participants achieving a score of 90% or higher increased from 8% (1/12) on the pre-video survey to 58% (7/12) on the post-video survey. Regarding acceptability, no participants terminated the video prematurely. Most participants reported being glad to have had the opportunity to discuss ICU-level care (11/12, 92%) and stated that they would recommend the video to others (10/12, 83%).

Conclusions: This pilot study provides important data to inform the development of a larger evaluation of an ICU orientation initiative aimed at promoting goal-concordant care in the event of critical illness.

Keywords: Advance care planning; critical care; hematologic malignancy; intensive care; palliative care, pilot projects.

*This work was partially presented as an abstract at the Critical Care Canada Forum held in Toronto, Canada in December 2025.

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Introduction

Critical illness is common among patients with hematologic malignancies (HM). For example, 20% of patients with acute leukemia are admitted to an intensive care unit (ICU) within 12 months of diagnosis [1]. Critical illness may result from either treatment- or disease-related complications, with acute hypoxemic respiratory failure and sepsis being the most common reasons for ICU admission [2,3]. Although outcomes for patients with HM admitted to the ICU have improved over time, ICU mortality remains between 30% and 50%, and 12-month mortality approaches 60% [4].

Critical illness often occurs suddenly and unexpectedly, leaving many patients too ill to communicate their wishes and preferences regarding care. Previous studies have shown that conversations about advance care planning (ACP) and life-sustaining therapies do not occur routinely [5]. Ideally, decisions regarding escalation to ICU-level care in the setting of critical illness should be initiated before clinical deterioration occurs and should be informed by: (1) an understanding of what ICU care entails and (2) the likelihood of survival and return to treatment. Patients should also have sufficient time to consider this information in light of their values and preferences to ensure that the care they receive is goal-concordant [6,7]. Unfortunately, once critical illness develops, patients often lack the time or decision-making capacity necessary to make informed choices [8].

When patients lack decision-making capacity, a substitute decision-maker (SDM) must guide treatment decisions based on the best available understanding of the patient's wishes. However, discussions between patients and their SDMs regarding treatment preferences are often absent before the onset of acute illness [9,10]. SDMs frequently experience stress, anxiety, and post-traumatic stress disorder (PTSD) related to decisions that may affect end-of-life (EOL) care [11]. Additionally, SDMs often choose more aggressive treatment approaches that may not align with the patient's preferences [12,13].

Advance care planning conversations with patients who have HMs often occur late in the disease trajectory or not at all [5,13-15]. Even among high-risk patients with HMs, ACP documentation is present in fewer than 50% of cases [15-17], and the conversations that do occur are rarely perceived as effective [5]. Patients with hematologic malignancies face several barriers to engaging in effective discussions about care planning in the setting of critical illness. Prognosis may be difficult to determine, treatment- and disease-related complications can result in life-threatening critical illness, and clinicians often struggle to identify when a patient is approaching the terminal phase of illness, particularly when substantial time and resources have been invested in treating the malignancy [18-20]. Consequently, patients with HMs are more likely than those with solid tumors to die in hospital or the ICU, receive more aggressive interventions, and have less involvement from palliative care services [21-24]. Furthermore, surrogate decision-makers for patients with HMs are more likely to experience elevated levels of PTSD [25,26]. Routinely exploring patients' values and preferences through meaningful ACP conversations may help mitigate some of the treatment-related burdens associated with HMs, facilitate the timely integration of palliative care, and maximize the likelihood that patients receive goal-concordant care.

Given the high incidence of critical illness in this population and the well-recognized challenges associated with timely and effective ACP discussions, innovative approaches are needed. The aim of this pilot study was to evaluate the feasibility, acceptability, and effectiveness of a video-based ICU orientation initiative designed to promote informed decision-making among hospitalized patients with HM who were actively receiving treatment with curative intent and were at high risk of developing critical illness. We hypothesized that a video-based ICU orientation tool would be feasible and acceptable and would be associated with improved ICU-related knowledge in this exploratory pilot study.

Materials and Methods

Study Design and Setting

We conducted a prospective observational pilot study in the acute leukemia and allogeneic hematopoietic stem cell transplant (HSCT) inpatient units at University Health Network in Toronto, Canada. The study was approved by the University Health Network Research Ethics Committee (Approval Number: 18-5317, Date: 03.05.2021). Informed consent was obtained from all participants prior to enrollment. All procedures were conducted in accordance with the ethical standards of the 1975 Declaration of Helsinki.

Participants

Patients were eligible for inclusion if they had a resusci-

tation status of "full cardiopulmonary resuscitation with no limitations," were receiving active treatment, and met one of the following criteria: (1) acute leukemia with relapsed, refractory, or secondary disease; (2) HSCT within the previous two years, age greater than 60 years, and two or more comorbid conditions (Appendix 1); or (3) HSCT within the previous two years with a confirmed or suspected infection (i.e., bacteremia, pneumonia, invasive fungal infection, or febrile neutropenia). These criteria were selected because of their association with clinical deterioration and poor outcomes. To standardize delivery of the video and workbook components in this pilot study, enrollment was limited to English-speaking patients. Patients were excluded if they had previously been admitted to the ICU; had a pre-existing "Do Not Resuscitate," "Do Not Intubate," or "Do Not Transfer to ICU" order; were receiving palliative treatment or treatment with palliative intent; or had an estimated life expectancy of less than seven days.

Study recruitment and data collection were undertaken by a trained research coordinator. The principal investigator, a critical care physician, communicated with each patient's most responsible physician to confirm eligibility and obtain approval before approaching patients regarding participation.

Intervention

An overview of the study framework is presented in Figure 1. The ICU orientation intervention consisted of three components delivered at the bedside within routine inpatient workflows. Part 1 consisted of a 14-minute educational video that described: (1) common ICU interventions (including intubation, invasive mechanical ventilation, central catheters, dialysis, and cardiopulmonary resuscitation); (2) short- and long-term ICU outcomes; and (3) factors relevant to decision-making regarding ICU care, with an emphasis on the importance of exploring personal values and preferences (Fig. 2). The video was viewed on a tablet at the patient's bedside with an ICU physician (attending physician or fellow) present. Patients were encouraged to pause the video as needed and could watch it in multiple shorter segments to accommodate symptoms, fatigue, or interruptions related to clinical care. Part 2 consisted of a workbook designed to encourage reflection on personal values and care preferences. Part 3 was a follow-up meeting conducted 24–48 hours later with the same ICU physician. The purpose of this meeting was to discuss the patient's values and preferences, answer questions regarding ICU-level care, and revisit goals of care (GOC). The outcomes of these discussions were documented and communicated to the patient's most responsible physician (MRP).

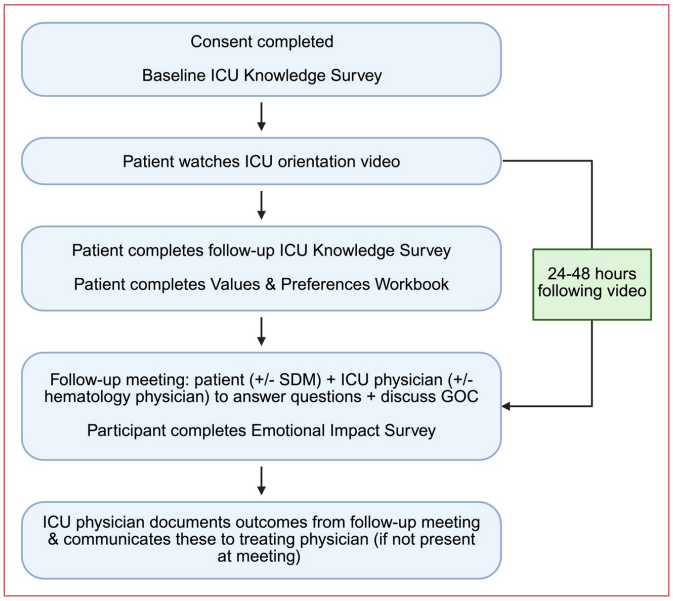

Figure 1. Overview of the study framework.

GOC: Goals of Care; ICU: Intensive Care Unit; SDM: Substitute Decision-Maker. Created with BioRender (Weir T., 2025, https://BioRender.com/y7qcd1w).

The ICU orientation video was developed using: (1) themes identified by a local working group consisting of intensivists, malignant hematologists, palliative care nurse practitioners, and palliative care physicians; (2) a review of the literature describing ACP interventions; and (3) presentations and discussions with relevant clinical stakeholder groups to identify content most applicable to their patient populations (e.g., leukemia physi-

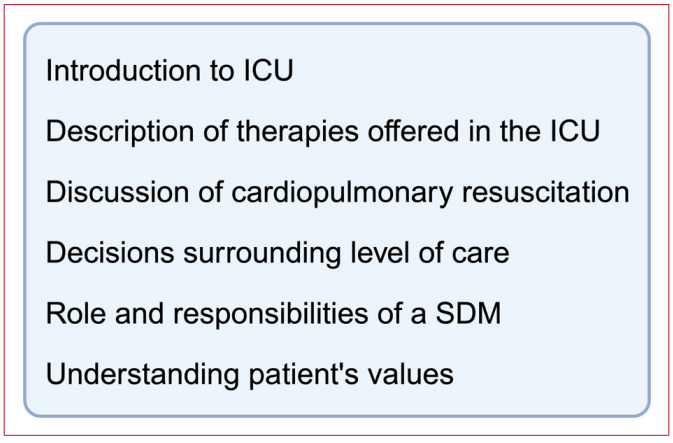

Figure 2. Key themes addressed in the orientation video.

ICU: Intensive Care Unit; SDM: Substitute Decision-Maker. Created with BioRender (Weir T., 2025, https://BioRender.com/8qyqx5n).

cians, allogeneic HSCT physicians, and ICU physicians). The video was subsequently presented at a meeting of the Critical Care Oncologic Investigative Network, a multidisciplinary, multicenter collaboration of oncology and critical care professionals, for additional feedback. A link to the video is provided in Appendix 2. A video-based ICU orientation intervention was selected for several reasons. First, it ensured that standardized information was delivered to all participants. Second, it provided patients with an opportunity to process the information and discuss it with loved ones before a formal goals-of-care conversation. Third, multiple studies have demonstrated benefits associated with video-assisted decision-support interventions without evidence of harm [27-29].

The workbook incorporated the Short Graphic Values History Tool together with questions regarding resuscitation preferences, designation of a substitute decision-maker, and decisional conflict. The Short Graphic Values History Tool is intended to reinforce patient-centered decision-making in the context of serious illness [30,31]. Participants were asked to complete the workbook before the follow-up GOC discussion.

Within 48 hours of viewing the video, each participant met with the same ICU physician to discuss GOC and document treatment preferences. This meeting also provided structured time to clarify understanding and address questions arising from the video, workbook, or subsequent reflection. Whenever possible, the discussion was scheduled during regular business hours (Monday to Friday, 09:00–17:00 h) and included the hematology MRP (or delegate) and the participant's SDM. Key themes emerging from the workbook and GOC discussion were documented in the medical record. When the hematology MRP or an appropriate delegate was unable to attend, the discussion summary was communicated via secure email.

Measures

The primary objectives of this pilot study were to assess: (1) effectiveness, (2) feasibility, and (3) acceptability. Effectiveness was evaluated by measuring changes in ICU-related knowledge using an ICU orientation knowledge questionnaire. The questionnaire was administered at enrollment (pre-intervention) and again within 24 hours after viewing the educational video (post-intervention). At the time the study was initiated, no validated ICU orientation knowledge instrument existed for this patient population. Accordingly, questionnaire items were adapted from previously published decision-aid instruments [27,28] and focused on ICU interventions, anticipated outcomes, and decision-making considerations. Draft items underwent expert review by intensivists, malignant hematologists, and palliative care clinicians to establish content validity and face validity before being refined for clarity and readability. The final questionnaire consisted of 10 multiple-choice questions, each with four response options. Participants selected the answer they believed to be correct. Correct responses received one point, while incorrect responses received zero points. Total scores ranged from 0 to 10, with higher scores indicating greater knowledge. Feasibility was assessed by examining recruitment rates, time to completion of the first and second study encounters, and completion rates for study components and outcome measures. Acceptability was assessed by recording the number of participants who requested to stop the video and the number of interruptions requested. Participants also completed an emotional impact survey to determine whether the intervention caused significant distress.

As an exploratory measure of potential impact, we also recorded any changes in goals of care following the intervention. Resuscitation preferences were categorized as: (1) all indicated life-prolonging treatments; (2) ICU admission with limitations on selected treatments; (3) ward-based medical management without resuscitation or ICU transfer; or (4) comfort-focused care. Participants could also indicate that they were undecided or open to ongoing discussion. Decisional confidence regarding ICU-related decisions was assessed using a 10-item version of the Decisional Conflict Scale [32,33].

Although we did not prospectively measure the time required by the research coordinator or ICU physicians to develop and deliver the intervention, all patient-facing activities occurred during regular working hours. The only additional resources required for the intervention were a tablet device for video playback and printed workbook materials.

Data Collection

Study recruitment and data collection were conducted by a trained research coordinator. The ICU orientation provider communicated with patients' MRPs to confirm eligibility, obtain approval before approaching patients, and communicate the outcomes of goals-of-care discussions. Baseline data collected for all participants

included age, sex, residence prior to hospital admission, pre-admission functional status, and comorbidities. Information regarding the hematologic malignancy, including diagnosis, disease status, treatment history, and disease- or treatment-related complications, was also recorded. Hospital outcomes collected included length of stay, rapid response team consultation, ICU admission, palliative care consultation, and discharge status (alive or deceased).

Data Analysis and Sample Size

Continuous variables were summarized using means and standard deviations, while categorical variables were summarized using frequencies and percentages. Pre- and post-intervention ICU knowledge survey scores were compared using a paired Student's t-test. Statistical significance was defined as a p value <0.05, corresponding to a 95% confidence level. The planned sample size for this pilot study was 15 patients. This sample size was selected to balance feasibility considerations with the need to generate sufficient information to refine and optimize the intervention before conducting a larger-scale study.

Results

Of the 49 patients who met the inclusion criteria and were screened for participation, 15 consented and were enrolled between March 2025 and May 2025, yielding a recruitment rate of 31%. Participant demographic and clinical characteristics are presented in Table 1.

Feasibility Outcomes

All 15 patients (100%) completed the baseline ICU orientation knowledge questionnaire and viewed the ICU orientation video. Thirteen participants (87%) participated in a GOC discussion with a critical care physician 24–48 hours after viewing the video. One participant and their substitute decision-maker declined further contact with the study team after watching the video, while another participant was discharged home unexpectedly before follow-up could occur. Completion rates for the post-intervention questionnaire, workbook, and emotional impact survey are summarized in Table 2.

Effectiveness Outcomes

Twelve participants (80%) completed both the pre- and post-intervention ICU orientation knowledge questionnaires. The mean knowledge score increased significantly following the intervention, from 6.2/10 (standard deviation [SD] 1.7) before the intervention to 8.3/10 (SD 1.9) after the intervention (p=0.0003). Detailed results of the ICU knowledge questionnaire are presented in Table 3. In particular, the proportion of participants correctly answering questions related to ICU therapies, the role of the SDM, the likelihood of hospital discharge following cardiac arrest, and the role of comfort-focused care increased after the intervention.

Table 1. Baseline characteristics of study participants

Age (mean±SD)	65±5
Sex	
Male, n (%)	8 (53%)
Female, n (%)	7 (47%)
Other, n (%)	0 (0%)
Primary hematologic diagnosis	
Acute myeloid leukemia (non-promyelocytic), n (%)	9 (60%)
Acute lymphocytic leukemia, n (%)	1 (6.7%)
Myelodysplastic syndrome, n (%)	4 (26%)
Other, n (%)	1 (6.7%)
HSCT, n (%)	9 (60%)
Charlson Comorbidity Index (median, IQR)	5 (4–6)
Reason for hospital admission	
Planned admission for chemotherapy or HSCT, n (%)	12 (80%)
Disease relapse, n (%)	1 (6.7%)
Suspected infection or febrile neutropenia, n (%)	1 (6.7%)
Other, n (%)	1 (6.7%)
Goals-of-care characteristics	
Previously documented GOC discussion, n (%)	15 (100%)
Full resuscitative measures documented at enrollment, n (%)	15 (100%)

GOC: Goals of Care; HSCT: Hematopoietic Stem Cell Transplant; IQR: Interquartile Range; SD: Standard Deviation.

Table 2. Completion of study components

Study component	Participants completing component, n (%)
Baseline knowledge questionnaire	15 (100%)
Viewed orientation video in its entirety	15 (100%)
Post-intervention knowledge questionnaire	12 (80%)
Values and preferences workbook	11 (73%)
Emotional impact survey	12 (80%)
Follow-up discussion	13 (87%)

Table 3. ICU knowledge questionnaire results

Question category	Correct responses pre-intervention, n (%)	Correct responses post-intervention, n (%)
Components of advance care planning	11/12 (92%)	11/12 (92%)
ICU-level therapies	5/12 (42%)	11/12 (92%)
Ability to change decisions regarding LST	9/12 (75%)	8/12 (67%)
How a SDM is appointed	7/12 (58%)	9/12 (75%)
Role of the SDM	8/12 (67%)	12/12 (100%)
Likelihood of hospital discharge following cardiac arrest	2/12 (17%)	8/12 (67%)
Components of comfort-focused care	3/12 (25%)	9/12 (75%)
Components of CPR	8/12 (67%)	10/12 (83%)
Utility of LST	9/12 (75%)	10/12 (83%)
Default treatment approach when no GOCs are established	12/12 (100%)	11/12 (92%)

CPR: Cardiopulmonary Resuscitation; GOC: Goals of Care; ICU: Intensive Care Unit; LST: Life-Sustaining Therapies; SDM: Substitute Decision-Maker.

Following the intervention, four participants (27%) changed their GOC from "full code" to "admit to ICU but do not perform cardiopulmonary resuscitation. All four survived to hospital discharge. An additional two participants died in hospital without escalation to ICU-level care. Four participants (27%) were admitted to the ICU after receiving the ICU orientation intervention. All received treatments consistent with their previously documented goals of care, and all survived to ICU discharge. All participants who completed the workbook indicated that they would be willing to accept intubation as a potentially life-sustaining intervention.

Acceptability Outcomes

All 15 participants completed the video without stopping it prematurely. Twelve participants (80%) completed the emotional impact survey following the intervention. Results of the emotional impact survey are presented in Table 4. Fewer than one-third of participants who completed the survey agreed or strongly agreed that hearing about or discussing critical illness, ICU care, and death made them feel sad or anxious. In contrast, most participants agreed or strongly agreed that they were glad to have had the opportunity to learn about and discuss ICU care, found the information presented in the video helpful, and would recommend both the video and this type of conversation to other patients.

Table 4. Acceptability outcomes based on the emotional impact survey

Survey statement	Participants responding "agree" or "strongly agree"
"I felt sad or anxious hearing about or discussing critical illness, ICU care, and death."	3/12 (25%)
"I was glad to have the opportunity to learn about and discuss ICU care."	11/12 (92%)
"I found the information presented in the video helpful."	11/12 (92%)
"I would recommend the video to other patients."	10/12 (83%)
"I would recommend this type of conversation to other patients."	10/12 (83%)

ICU: Intensive Care Unit.

Discussion

In this exploratory single-arm pilot study of hospitalized patients with HM at high risk of clinical deterioration, a brief video-based ICU orientation intervention combined with a facilitated GOC discussion was feasible, acceptable, and associated with improved ICU-related knowledge. Despite known challenges in implementing timely ICU-oriented ACP in this population, the intervention achieved high levels of engagement, generated positive patient feedback, and was associated with minimal emotional distress. To our knowledge, this is the first study to evaluate a structured, video-based ICU orientation intervention designed specifically to support decision-making regarding ICU care among patients with HMs.

Although patients with HMs face a substantial risk of sudden clinical deterioration, discussions regarding ICU care are often delayed or absent altogether [5]. In our study, 27% of participants were admitted to the ICU during their hospitalization, and all received care that was consistent with their documented preferences. While the single-arm design precludes causal inference, these findings are descriptively consistent with the delivery of goal-concordant care and highlight the potential value of proactively exploring patient preferences before decision-making capacity is compromised.

Although concerns about emotional distress are frequently cited as barriers to discussions regarding ICU care in patients with HMs, most participants reported being glad they had the opportunity to engage in these conversations. Only a minority reported increased feelings of sadness or anxiety, findings that are consistent with previous studies demonstrating that discussions about ICU interventions do not increase psychological distress among patients with serious illness [34-36].

Several findings warrant further consideration. First, four participants chose to modify their resuscitation preferences after completing the intervention, suggesting that structured discussions regarding ICU care may facilitate more deliberate and value-concordant decision-making. Second, although most participants expressed a willingness to undergo intubation, the nuanced nature of their preferences, including interest in time-limited trials of life-sustaining therapies, underscores the importance of individualized discussions that extend beyond binary treatment decisions. These findings support the value of the ICU orientation workbook and facilitated discussions in exploring the complexity of patient values and preferences regarding critical care.

Despite these encouraging findings, important barriers remain. Only one-third of eligible patients agreed to participate, suggesting that readiness to engage in discussions about critical illness and ICU care may be a significant limiting factor. We did not collect demographic information on eligible patients who declined participation. Previous studies have identified clinician hesitancy, prognostic uncertainty, and a culture emphasizing curative treatment as important barriers to early ICU-related discussions in patients with HMs [18,20]. Future interventions may benefit from integrating ICU orientation earlier in the disease trajectory as a routine component of care, thereby normalizing these conversations. Although the incremental material resources required for this pilot study were minimal, relying primarily on existing clinical workflows, printed workbooks, and a single tablet device, we did not prospectively measure the time commitment required of the research coordinator and ICU physicians involved in delivering the intervention. Future studies should evaluate these resource and staffing requirements to better inform scalability and implementation.

Our study has several limitations. First, as a single-center, non-randomized pilot study, it is susceptible to selection bias. Participants who agreed to enroll (or their surrogates) may have been more willing to engage in discussions about serious illness and end-of-life care than those who declined participation. Second, although informed by prior literature, the ICU orientation knowledge questionnaire was developed specifically for this intervention and has not undergone formal validation. Consequently, improvements in questionnaire scores should be interpreted cautiously. Third, restricting participation to English-speaking patients limits both inclusivity and the generalizability of our findings. Future work should focus on translating and culturally adapting study materials and incorporating professional interpretation services to support linguistically diverse patients and families. Finally, the short follow-up period precluded assessment of longer-term outcomes, including patient satisfaction, surrogate perceptions of end-of-life care quality, or substitute decision-maker burden. These outcomes should be examined in future studies. Future research should focus on integrating ICU orientation interventions earlier in the disease trajectory, refining educational content to address common misconceptions about critical care, and developing tailored strategies for patients with language barriers or limited readiness to engage in advance care planning discussions.

This pilot study provides important proof-of-concept evidence supporting the feasibility and acceptability of a video-based ICU orientation intervention among patients with HMs who are at high risk of developing critical illness. Facilitating meaningful discussions about ICU care with patients and their surrogates represents an important step toward improving goal-concordant care and supporting informed decision-making during episodes of critical illness.

Conclusion

A video-based ICU orientation intervention represents a promising strategy for standardizing the delivery of information about critical care, enhancing patient and surrogate understanding, and facilitating timely GOC discussions among hospitalized patients with hematologic malignancies. These findings support further evaluation of this approach in a larger multicenter study to better determine its impact on patient-centered outcomes and surrogate decision-making.

Ethics Committee Approval: Ethics committee approval was obtained from University Health Network Research Ethics Committee (Approval Number: 18-5317, Date: 03.05.2021).

Informed Consent: Written informed consent was obtained from all participants.

Conflict of Interest: The authors have no conflicts of interest to declare.

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ORIGINAL INVESTIGATION

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Longitudinal Changes in Cerebrospinal Fluid Lactate Predict Clinical Outcomes in Critically Ill Adults with Bacterial Meningitis: A Prospective Cohort Study

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Abstract

Aim: Despite advances in intensive care, bacterial meningitis remains associated with high mortality among critically ill adults. Although cerebrospinal fluid (CSF) lactate is well established as a diagnostic biomarker, its longitudinal prognostic value remains uncertain.

Study Design: This prospective, single-center cohort study enrolled 45 adults with confirmed bacterial meningitis admitted to a tertiary ICU between June and December 2024. CSF lactate was measured at admission and again on day 14. The primary outcome was in-hospital mortality. Prognostic performance was evaluated using receiver operating characteristic (ROC) analysis with bootstrap-derived 95% confidence intervals (CIs) and Kaplan–Meier survival analysis.

Results: Ten patients (22.2%) died during hospitalization. Compared with survivors, non-survivors were older and had lower Glasgow Coma Scale (GCS) scores and higher Acute Physiology and Chronic Health Evaluation II (APACHE II) scores. Among survivors, CSF lactate declined significantly from admission to day 14 (median Δ, −1.4 mmol/L, $p<0.001$), whereas non-survivors demonstrated a significant increase (median Δ, +1.3 mmol/L, $p<0.001$). Day-14 CSF lactate strongly predicted mortality (optimism-adjusted area under the curve=0.93, 95% CI: 0.84–0.99; $p<0.001$). Patients with a CSF lactate >4.3 mmol/L had significantly lower survival than those with lower levels (log-rank $p<0.001$).

Conclusions: Persistent elevation of CSF lactate after two weeks of treatment identifies critically ill adults with bacterial meningitis who are at high risk of death, likely reflecting ongoing cerebral metabolic dysfunction. Serial CSF lactate monitoring may serve as a simple, inexpensive adjunct for prognostic assessment in ICU patients.

Keywords: Bacterial meningitis; cerebrospinal fluid; critically ill adults; lactate; prognosis.

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Introduction

Acute bacterial meningitis remains a devastating disease associated with substantial mortality and long-term neurological sequelae despite advances in antimicrobial therapy and critical care [1]. Mortality among adults admitted to intensive care units (ICUs) may reach 20%–30%, and many survivors experience persistent cognitive impairment or neurological deficits [2]. Early identification of patients at greatest risk of poor outcomes is therefore essential, as it may guide the intensity of therapeutic interventions, monitoring strategies, and prognostic counseling for patients and their families.

Traditional prognostic assessment relies primarily on neurological status at presentation, particularly the Glasgow Coma Scale (GCS), and systemic severity scores such as the Acute Physiology and Chronic Health Evaluation II (APACHE II). Although these tools are clinically useful, they are nonspecific and may be influenced by sedation, systemic illness, or underlying comorbidities [3,4]. Conventional cerebrospinal fluid (CSF) parameters, including pleocytosis, protein concentration, and glucose level, remain the cornerstone of diagnosis, however, their ability to predict clinical outcomes is inconsistent [5]. Consequently, there remains a need for objective, reliable, and readily available biomarkers that complement clinical assessment in patients with bacterial meningitis.

Cerebrospinal fluid lactate, a byproduct of anaerobic glycolysis, increases in response to cerebral hypoxia, inflammation, and impaired oxidative metabolism [6]. Its diagnostic utility in differentiating bacterial from viral meningitis is well established, and it is widely used as a rapid, inexpensive biomarker, particularly in resource-limited settings [7]. However, its prognostic value remains uncertain. Most available evidence originates from neurosurgical or post-traumatic populations [8,9], while studies in bacterial meningitis have generally evaluated only admission lactate concentrations and have reported conflicting findings [10].

We hypothesized that serial measurement of CSF lactate, rather than a single admission value, would provide more robust prognostic information independent of initial disease severity in critically ill adults with bacterial meningitis. Persistent elevation of CSF lactate may reflect ongoing cerebral metabolic dysfunction despite appropriate treatment, whereas declining concentrations may indicate recovery. To our knowledge, few prospective studies have evaluated the prognostic significance of serial CSF lactate measurements in ICU patients with bacterial meningitis, particularly in low- and middle-income countries where diagnostic resources are limited.

Accordingly, this prospective cohort study was designed to evaluate the temporal kinetics of CSF lactate as a prognostic marker in adult ICU patients with bacterial meningitis and to compare its predictive performance with that of conventional CSF indices, systemic inflammatory biomarkers, and established clinical severity scores. By emphasizing serial rather than single admission measurements, this study addresses an important gap in the literature and represents one of the first prospective evaluations of serial CSF lactate kinetics in adults with bacterial meningitis admitted to a medical ICU. Furthermore, because serial CSF lactate measurement is simple, inexpensive, and widely available, it may represent a practical prognostic tool in resource-limited ICUs where advanced neuroimaging and specialized biomarker assays are not routinely accessible.

Materials and Methods

Study Design and Setting

This prospective, observational cohort study was conducted in the ICU of a tertiary referral fever hospital in Egypt between June and December 2024. The study protocol was approved by the institutional Research Ethics Committee (Approval No. 10/2024ANET39). Written informed consent was obtained from all participants or their legally authorized representatives before enrollment. The study was conducted in accordance with the Declaration of Helsinki and is reported in compliance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for observational studies.

Participants

Eligible participants were adults aged ≥18 years with a confirmed diagnosis of bacterial meningitis. Diagnosis required a compatible clinical presentation (including fever, headache, neck stiffness, or altered mental status) together with CSF pleocytosis, defined as a white blood cell count >5/μL. In addition, at least one of the following criteria was required: a positive CSF culture, a positive CSF Gram stain, or a positive blood culture yielding a recognized meningeal pathogen. For patients with negative cultures, the diagnosis was established based on compatible clinical features together with CSF findings

consistent with bacterial meningitis, specifically pleocytosis combined with either a CSF protein concentration >100 mg/dL or a CSF-to-serum glucose ratio <0.4. These diagnostic criteria were consistent with the Infectious Diseases Society of America guidelines [11]. Patients were excluded if they were pregnant, had a known coagulopathy, active malignancy, immunosuppression, recent traumatic brain injury, advanced liver disease, or known metabolic disorders that could affect lactate metabolism. Patients were also excluded if informed consent could not be obtained.

Data Collection

All patients underwent a comprehensive clinical assessment on admission, including neurological evaluation using the GCS and systemic severity assessment using the APACHE II score. In intubated or sedated patients, the verbal component of the GCS was assigned a score of 1 (intubated), and the total GCS score was calculated using the eye and motor components, consistent with standard practice in critically ill patients. Empirical intravenous antibiotic therapy was initiated immediately and consisted of ceftriaxone (2 g every 12 hours) plus vancomycin (15–20 mg/kg every 8–12 hours). Antibiotic therapy was subsequently adjusted according to culture results and sensitivity results, antimicrobial susceptibility testing, and local resistance patterns. Adjunctive dexamethasone (0.15 mg/kg every six hours for 2–4 days) was administered before or with the first dose of antibiotics. All patients received supportive care according to international ICU guidelines, including fluid resuscitation, vasopressor support for septic shock, and mechanical ventilation when indicated.

Cerebrospinal fluid was obtained by lumbar puncture under aseptic conditions within two hours of ICU admission. Samples were analyzed for cell count and differential, glucose, protein, microbiological culture, and lactate concentration. CSF lactate was measured by amperometry using the ABL800 FLEX analyzer (Radiometer Medical, Denmark). Repeat CSF sampling was performed on day 14 in all 45 enrolled patients because each met the institutional clinical criteria for follow-up lumbar puncture owing to persistent neurological impairment and/or ongoing systemic febrile manifestations. Daily laboratory investigations included complete blood count, renal and liver function tests, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), ferritin, procalcitonin (PCT), coagulation profile, and serum lactate. Although ESR was measured routinely, it was not included in the primary analyses because of its limited specificity and relatively slow response in acute bacterial meningitis.

Neurological status was assessed using the GCS, and systemic disease severity was evaluated using the APACHE II score by ICU physicians who were blinded to the study analysis. Laboratory personnel measuring CSF and serum biomarkers were blinded to clinical outcomes. CSF lactate results were not disclosed to the treating clinicians during the study period, and patient management was based exclusively on standard clinical and laboratory findings.

Outcome Definition

The primary outcome was all-cause in-hospital mortality. Secondary outcomes included associations between CSF lactate concentrations and other CSF indices, neurological status as assessed by the GCS, and disease severity as measured by the APACHE II score.

Statistical Analysis

Sample size was determined prospectively based on the primary objective of evaluating the prognostic performance of CSF lactate for predicting in-hospital mortality. A sample size of 45 patients was estimated to provide 80% power to detect an area under the receiver operating characteristic curve (AUC) of at least 0.75 for predicting in-hospital mortality at a significance level of α=0.05, assuming an event rate of approximately 22%. Given the single-center design and modest sample size, AUC estimates are presented with bootstrap-derived 95% confidence intervals (CIs) to better reflect statistical uncertainty.

Statistical analyses were performed using IBM SPSS version 27.0. (Armonk, NY, USA: IBM Corp., released 2020). Normality was assessed using the Shapiro–Wilk test. Continuous variables are presented as mean ± standard deviation (SD) or median (interquartile range [IQR]), and were compared using the t test or the Mann–Whitney U test. Categorical variables were compared using the χ^2 test or Fisher's exact test. Receiver operating characteristic (ROC) curve analysis was used to assess discriminatory performance, with AUCs reported together with 95% CIs. Optimism correction of the AUC was performed using 2,000 bootstrap resamples. Correlations were assessed using Spearman's rank correlation coefficient (ρ), with adjustment for multiple comparisons using the Benjamini–Hochberg false discovery rate procedure. Changes in paired CSF lactate concentrations between admission and day 14 were evaluated using the Wilcox-

on signed-rank test. Because only 10 deaths occurred, multivariable logistic regression was considered exploratory. A sample size of 45 patients provided 80% power to detect an AUC of at least 0.75 at a significance level of α=0.05. All analyses were verified using R version 4.3.

Results

Forty-five adults with confirmed bacterial meningitis were enrolled, of whom 35 (77.8%) survived and 10 (22.2%) died during hospitalization (Fig. 1). All deaths occurred after day 14 (mean survival, 26.5 days), allowing complete day-14 follow-up for all participants. The remaining in-hospital deaths occurred after day 14. Non-survivors were significantly older (59.7±5.9 vs. 39.0±19.5 years, p=0.006) and presented later after symptom onset (p=0.014). Sex distribution and comorbidities did not differ between groups. Classical meningeal signs were less frequent among non-survivors, with neck stiffness present in 60% compared with 100% of survivors (p=0.001), suggesting a more atypical presentation in severe disease (Table 1).

At admission, non-survivors had significantly lower GCS scores (8.70±0.67 vs. 11.86±1.52, p<0.001) and higher APACHE II scores (median, 22.0 [19.0–24.0] vs. 13.0 [9.0–18.0], p<0.001), indicating greater systemic illness severity. They also had significantly higher respiratory and heart rates than survivors (p<0.01) (Table 1).

By day 14, non-survivors demonstrated persistent systemic inflammation and multiorgan dysfunction. Compared with survivors, they had markedly higher CRP (145.5 [139–146] vs. 12 [12–26.5] mg/L), procalcitonin (68.03 [68.01–76.02] vs. 0.4 [0.12–0.72] ng/mL), ferritin (614 [544–776] vs. 310 [276–384] µg/L), and International Normalized Ratio (INR) (1.21 [1.2–1.58] vs. 1.02 [1.01–1.1]) (all p<0.001). Non-survivors also exhibited anemia, thrombocytopenia, and renal dysfunction, with serum creatinine levels of 3.9 [3.83–5.78] vs. 0.6 [0.5–0.7] mg/dL (p<0.001). Serum lactate followed a similar trajectory: although admission concentrations were only modestly higher in non-survivors (3.3 [3.1–3.4] vs. 3.0 [2.4–3.2] mmol/L; p=0.014), by day 14 they had increased markedly (4.4 [4.3–5.1] mmol/L), whereas survivors had declined to near-normal levels (1.9 [1.6–2.1] mmol/L; p<0.001). Collectively, these findings indicate persistent inflammation, progressive multiorgan dysfunction, and sustained metabolic derangement consistent with severe sepsis (Tables 2 and 3).

Admission CSF lactate concentrations did not differ significantly between survivors and non-survivors (median, 3.56 vs. 3.5 mmol/L, p=0.381). By day 14, however, survivors showed a decline in CSF lactate (median, 1.8 mmol/L), whereas non-survivors exhibited a substantial increase (median, 6.8 mmol/L; p<0.001). Longitudinal analysis demonstrated a significant reduction in CSF lactate among survivors (median change, −1.41 mmol/L; p<0.001) and an increase among non-survivors (median change, +1.33 mmol/L; p<0.001). The between-group difference in lactate change was substantial (median Δ difference, −2.74 mmol/L; p<0.001), indicating that persistent elevation, rather than baseline concentration, was associated with mortality. Consistent with these findings, admission CSF lactate showed poor prognostic performance (AUC=0.41, 95% CI: 0.25–0.57; p=0.32). In contrast, day-14 CSF lactate strongly predicted mo-

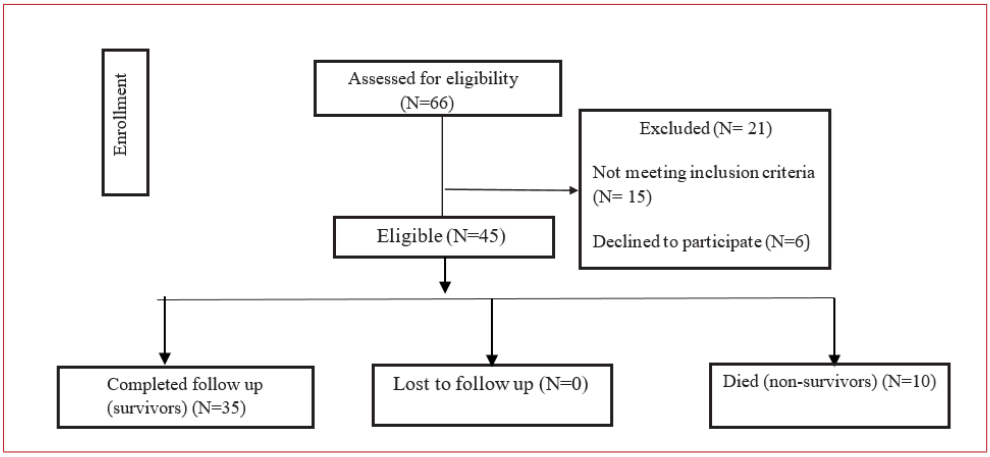

Figure 1. Study flow diagram.

Table 1. Demographic and clinical characteristics according to in-hospital outcome

Characteristic	Total (n=45)	Survivors (n=35)	Non-survivors (n=10)	p
Sex				
Male	21 (46.7%)	18 (51.4%)	3 (30.0%)	0.296
Female	24 (53.3%)	17 (48.6%)	7 (70.0%)	
Age (years)	43.58±9.42	38.97±19.51	59.70±5.93	0.006
Comorbidities				
DM	10 (22.2%)	6 (17.1%)	4 (40.0%)	0.194
HT	12 (26.7%)	7 (20.0%)	5 (50.0%)	0.101
Asthma	6 (13.3%)	5 (14.3%)	1 (10.0%)	1.000
IHD	4 (8.9%)	3 (8.6%)	1 (10.0%)	1.000
Time from symptom onset to admission				
<1 day	25 (55.6%)	23 (65.7%)	2 (20.0%)	0.014
≥2 days	20 (44.4%)	12 (34.3%)	8 (80.0%)	
Antibiotic therapy before admission				
No	38 (84.4%)	29 (82.9%)	9 (90.0%)	1.000
Yes	7 (15.6%)	6 (17.1%)	1 (10.0%)	
Clinical presentation				
Headache	39 (86.7%)	29 (82.9%)	10 (100.0%)	0.312
Fever	37 (82.2%)	27 (77.1%)	10 (100.0%)	0.168
Vomiting	29 (64.4%)	21 (60.0%)	8 (80.0%)	0.292
Blurred vision	24 (53.3%)	20 (57.1%)	4 (40.0%)	0.476
Kernig's sign	21 (46.7%)	17 (48.6%)	4 (40.0%)	0.729
Brudzinski's sign	11 (24.4%)	7 (20.0%)	4 (40.0%)	0.228
Neck stiffness	41 (91.1%)	35 (100.0%)	6 (60.0%)	0.001
APACHE II score at admission				
Min–Max	6.0–28.0	6.0–25.0	10.0–28.0	<0.001
Median (IQR)	15.0 (10.0–21.0)	13.0 (9.0–18.0)	22.0 (19.0–24.0)	

DM: Diabetes mellitus; HT: Hypertension; IHD: Ischemic heart disease; APACHE II: Acute Physiology and Chronic Health Evaluation II.

Table 2. Neurological status and vital signs

Characteristic	Total (n=45)	Survivors (n=35) Mean±SD	Non-survivors (n=10) Mean±SD	p
Neurological status				
GCS at admission	11.16±1.91	11.86±1.52	8.70±0.67	<0.001
GCS score on day 14	12.0±4.32	14.26±0.70	4.10±0.57	<0.001
Vital signs				
Temperature (°C)	39.40±0.62	39.33±0.66	39.62±0.41	0.202
Respiratory rate (breaths/min)	22.51±2.85	21.51±2.12	26.0±2.31	<0.001
Heart rate (beats/min)	108.8±13.66	105.7±11.53	119.5±15.62	0.004
Systolic blood pressure (mmHg)	117.6±25.60	114.6±21.47	128.0±36.15	0.287
Diastolic blood pressure (mmHg)	74.0±12.68	72.86±11.78	78.0±15.49	0.350

GCS: Glasgow Coma Scale.

Table 3. Laboratory findings at admission and day 14

Variable	Total (n=45)	Survivors (n=35)	Non-survivors (n=10)	p
Hematological parameters, median (IQR)				
Hb (g/dL), admission	12.6 (11.5-12.9)	12.6 (11.6-13.2)	11.85 (10.83-12.9)	0.250
Hb (g/dL), day 14	11.5 (10.5-12.4)	11.8 (11.3-12.85)	7 (6.93-7.08)	<0.001
TLC (×10³/μL), admission	17 (15.7-23)	17 (15.85-24)	15.85 (15.7-22.7)	0.366
TLC (×10³/μL), day 14	13 (8.3-18.6)	11.1 (8-14)	27 (26.25-32.75)	<0.001
PLT (×10³/μL), admission	287 (256-345)	310 (273-357)	260.5 (256-277)	0.007
PLT (×10³/μL), day 14	306 (191-365)	316 (268.5-378)	75 (48.5-82.5)	<0.001
Inflammatory markers, median (IQR)				
CRP (mg/L), admission	103 (86-126)	118 (96-127.5)	62 (61-94)	<0.001
CRP (mg/L), day 14	24 (12-49)	12 (12-26.5)	145.5 (139-146)	<0.001
PCT, admission	6.8 (2.9-9.2)	5.8 (2.85-9)	6.9 (6.8-9.2)	0.396
PCT, day 14	0.7 (0.2-1.6)	0.4 (0.12-0.72)	68.03 (68.01-76.02)	<0.001
Coagulation, median (IQR)				
INR, admission	1.2 (1.05-1.49)	1.1 (1.04-1.27)	1.77 (1.74-2.04)	<0.001
INR, day 14	1.04 (1.01-1.12)	1.02 (1.01-1.1)	1.21 (1.2-1.58)	<0.001
Iron studies, median (IQR)				
Ferritin, admission	794 (569-873)	690 (559.5-860.5)	1319 (863.75-1324.25)	<0.001
Ferritin, day 14	325 (298-417)	310 (276-384)	614 (544-776)	<0.001
Renal function, median (IQR)				
Creatinine (mg/dL), admission	0.9 (0.7-1.2)	0.8 (0.7-1.1)	1.05 (1-1.2)	0.083
Creatinine, day 14	0.6 (0.5-1.35)	0.6 (0.5-0.7)	3.9 (3.83-5.78)	<0.001
Urea (mg/dL), admission	38 (34-60)	37 (32-59.5)	45.5 (45-60)	0.208
Urea, day 14	28 (25-136)	27 (23-31)	180 (178.5-224.5)	<0.001
Metabolic markers, median (IQR)				
RBG (mg/dL), admission	146 (116-176)	136 (108.5-149)	177 (176-266)	<0.001
RBG (mg/dL), day 14	116 (100-124)	110 (94-122.5)	132.5 (124-180.75)	<0.001
Serum lactate (mmol/L), admission	3.1 (2.5-3.4)	3.0 (2.4-3.2)	3.3 (3.1-3.4)	0.014
Serum lactate (mmol/L), day 14	2.1 (1.7-2.4)	1.9 (1.6-2.1)	4.4 (4.3-5.1)	<0.001
Microbiology, n (%)				
No growth	15 (33.3%)	11 (31.4%)	4 (40.0%)	1.000
Staphylococcus aureus	2 (4.4%)	2 (5.7%)	0 (0.0%)	–
Streptococcus pneumoniae	27 (60.0%)	21 (60.0%)	6 (60.0%)	–
Neisseria meningitidis	1 (2.2%)	1 (2.9%)	0 (0.0%)	–

Hb: Hemoglobin; TLC: Total leukocyte count; PLT: Platelet count; CRP: C-reactive protein; PCT: Procalcitonin; INR: International Normalized Ratio; RBG: Random blood glucose.

rality (optimism-adjusted AUC=0.93, 95% CI: 0.84–0.99; p<0.001). A threshold of >4.3 mmol/L yielded 92% sensitivity, 91% specificity, a positive predictive value of 79%, and a negative predictive value of 96% (Table 4).

A strong positive correlation was observed between day-14 CSF lactate and concurrent serum lactate concentrations (Spearman's ϱ=+0.78, p<0.001), suggesting a close association between cerebral and systemic metabolic dysfunction during the second week of illness. Higher day-14 CSF lactate was associated with lower GCS scores at admission (ϱ=−0.65, p<0.001) and day 14 (ϱ=−0.57, p<0.001), higher APACHE II scores (ϱ=+0.57, p<0.001), higher CSF protein concentrations (ϱ=+0.53, p<0.001), and lower CSF

Table 4. Comparison of cerebrospinal fluid biochemical and cytological parameters between survivors and non-survivors

Marker	Time point	Total (n=45)	Survivors (n=35)	Non-survivors (n=10)	p
Lactate (mmol/L)	Admission	3.50 (3.37-3.80)	3.56 (3.14-3.90)	3.5 (3.4-3.5)	0.381
	Day 14	2.1 (1.7-2.3)	1.8 (1.5-2.1)	6.8 (5.7-7.1)	<0.001
Neutrophils (×10⁶/L)	Admission	16.37 (14.92-22.61)	16.66 (14.97-21.73)	15.533 (14.95-22.7)	0.883
	Day 14	0.28 (0-6.12)	0.147 (0-0.38)	15.93 (11.81-17.59)	<0.001
Lymphocytes (×10⁶/L)	Admission	0.56 (0.31-0.91)	0.785 (0.36-1.26)	0.195 (0-0.32)	<0.001
	Day 14	9.6 (7.3-13.72)	8.4 (7.02-13.51)	11.07 (9.23-15.1)	0.338
Protein (mg/dL)	Admission	177 (100-200)	180 (98-197.5)	176.5 (160.25-207.25)	0.545
	Day 14	37 (32-52)	35 (29.5-37)	112.5 (94.25-127.5)	<0.001
Glucose (mg/dL)	Admission	20 (14-25)	23 (12.5-25)	18 (15.5-19.75)	0.840
	Day 14	59 (45-65)	63 (56.5-65)	33 (30.25-34.75)	0.006

All values are presented as median (interquartile range [IQR]).

glucose concentrations (ϱ=−0.30, p=0.047). These associations remained significant after adjustment for age and APACHE II score using partial correlation analysis.

Kaplan–Meier analysis demonstrated a mean survival time of 26.5 days, with 77.8% of patients surviving to hospital discharge. Patients with day-14 CSF lactate concentrations >4.3 mmol/L had significantly lower survival than those with lower concentrations (log-rank p<0.001) (Fig. 2).

In an exploratory logistic regression model including age, APACHE II score, and day-14 CSF lactate concentration, only lactate remained associated with mortality (odds ratio=3.81 per 1 mmol/L increase; 95% CI: 1.5–9.4; p=0.004). These findings should be interpreted cautiously because of the limited number of deaths (n=10) (Table 5).

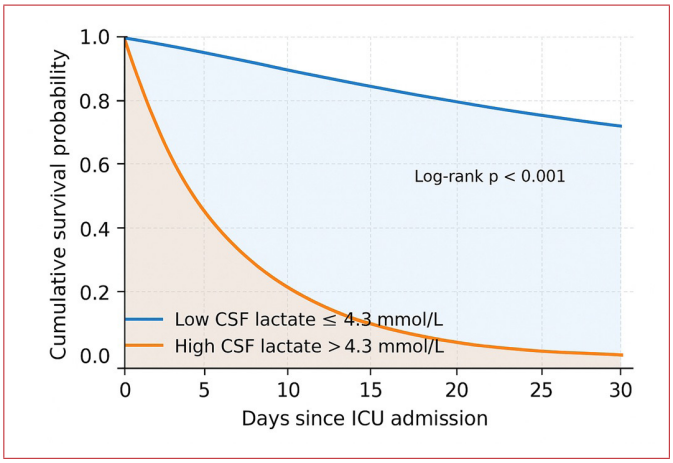

Figure 2. Kaplan–Meier survival curves stratified according to day-14 cerebrospinal fluid (CSF) lactate concentration.

Table 5. Exploratory multivariable logistic regression analysis of predictors of in-hospital mortality

Variable	Odds ratio (95% CI)	p
Age (per 1-year increase)	1.08 (0.98-1.20)	0.112
APACHE II score at admission (per 1-point increase)	1.13 (0.93-1.38)	0.228
Day-14 CSF lactate (per 1 mmol/L increase)	3.81 (1.55-9.38)	0.004

Discussion

The principal finding of this study is that the temporal kinetics of CSF lactate, rather than its admission concentration, provide meaningful prognostic information in critically ill adults with bacterial meningitis. Although admission CSF lactate levels were comparable between survivors and non-survivors, longitudinal analysis demonstrated a significant decline from admission to day 14 among survivors and a significant increase among non-survivors. The difference in these trajectories was substantial (median Δ difference, −2.74 mmol/L; p<0.001). This pattern suggests that although patients may initially present with comparable cerebral metabolic disturbances, recovery of cerebral metabolism, as reflected by declining CSF lactate concentrations, is closely associated with survival.

Normalization of CSF lactate in survivors likely reflects effective antimicrobial therapy, resolution of inflammation, and recovery of aerobic cerebral metabolism. In contrast, persistently elevated CSF lactate probably indicates

ongoing cerebral hypoxia, microcirculatory dysfunction, or mitochondrial impairment despite microbiological control of infection. Consequently, a follow-up CSF lactate measurement obtained two weeks after admission appears to provide a more informative assessment of cerebral metabolic recovery than admission values alone, which may be influenced by delays in presentation or prehospital treatment.

Previous studies have highlighted the prognostic value of CSF biochemical markers in different forms of meningitis. Abassi et al. [12] reported that elevated CSF lactate in cryptococcal meningitis was associated with altered consciousness, seizures, and elevated intracranial pressure, whereas Tubiana et al. [1] identified low leukocyte count, hypoglycorrhachia, and elevated protein concentration as independent predictors of adverse outcomes in bacterial meningitis. Our findings are consistent with these observations, suggesting that persistently elevated CSF lactate concentrations, rather than admission values, are associated with unresolved cerebral metabolic dysfunction. Similarly, De Almeida et al. [5] demonstrated that persistent lactate elevation predicted mortality, while Liu et al. [13] found that elevated CSF lactate within 48 hours predicted poor outcomes in tuberculous meningitis. Abbasi et al. [12] similarly reported higher CSF lactate concentrations in bacterial and cryptococcal meningitis, demonstrating good diagnostic performance.

Not all studies have reached similar conclusions. Makowiecki et al. [10] reported no difference in lactate between survivors and non-survivors with community-acquired bacterial meningitis, suggesting that prognostic performance may depend on patient population and sampling time. Our findings help reconcile these discrepancies by showing that serial measurements capture metabolic recovery, whereas a single admission measurement does not. This finding may help explain the inconsistent results reported in previous studies. To our knowledge, this is among the first prospective studies in an adult medical ICU population to evaluate the prognostic significance of CSF lactate kinetics. Our findings may help reconcile these conflicting reports by demonstrating that serial assessment of CSF lactate, rather than reliance on a single admission measurement, more accurately reflects recovery of cerebral metabolism. By evaluating longitudinal changes in CSF lactate within individual patients and comparing trajectories between survivors and non-survivors, our study provides a longitudinal perspective that has been lacking in many previous cross-sectional studies. This approach may help explain why admission CSF lactate concentrations alone have shown inconsistent prognostic value, whereas serial measurements reveal a clearer association with mortality.

By day 14, non-survivors also demonstrated higher CSF protein concentrations and lower CSF glucose levels, findings consistent with persistent blood–brain barrier disruption and impaired substrate transport, similar to those reported by Makowiecki et al. [10]. Neurological status also remained an important prognostic indicator, as non-survivors had significantly lower GCS scores both at admission and during follow-up, consistent with previous reports by Park et al. [3], Martín-Cerezuela et al. [4], and others. Additionally, delayed hospital presentation was associated with poorer outcomes, in agreement with the findings of Tubiana et al. [1].

Beyond its prognostic performance, CSF lactate demonstrated clinically meaningful associations with several markers of disease severity. Both admission and day-14 CSF lactate concentrations were negatively correlated with GCS scores and CSF glucose concentrations and positively correlated with CSF protein concentrations, APACHE II scores, and systemic inflammatory markers, including CRP, ESR, PCT, and ferritin. The lower admission CRP concentrations observed in non-survivors may reflect variability in the timing or magnitude of the acute-phase response, whereas the marked increase by day 14 is consistent with progressive systemic inflammation and organ dysfunction. A notable finding was the significantly lower admission CRP concentrations in non-survivors. Although admission CRP concentrations were lower in non-survivors, they increased markedly by day 14, indicating progressive systemic inflammation and organ dysfunction rather than immune exhaustion. The initially lower CRP concentration may reflect differences in the timing of presentation or individual variability in the acute-phase response; however, the subsequent marked elevation is consistent with progressive systemic inflammation and organ dysfunction. In this context, a low admission CRP concentration could represent an ominous indicator of an inadequate inflammatory response rather than less severe disease (4). Significant positive correlations were also observed between CSF lactate and renal function indices (urea and creatinine), as well as serum lactate. The strong correlation between day-14 serum and CSF lactate concentrations (ρ=+0.78) suggests that persistent cerebral metabolic dysfunction parallels systemic metabolic failure and shock. This find-

ing is consistent with the presence of multiorgan dysfunction in non-survivors and reinforces the concept that elevated CSF lactate serves as an integrative marker of both cerebral and systemic disease severity. The inverse correlation between CSF lactate and GCS scores suggests that increasing CSF lactate concentrations parallel worsening neurological status, whereas its positive associations with inflammatory markers and renal function indices further support its role as an integrative marker of overall illness severity. This multidimensional pattern of correlations strengthens the biological plausibility and clinical relevance of CSF lactate as a dynamic biomarker of disease severity rather than merely an isolated metabolic byproduct. [1,5,7,10].

Clinical presentation also differed between outcome groups. Although fever and headache were common in both survivors and non-survivors, neck stiffness was observed in all survivors but in only 60% of patients who died. This lower frequency among non-survivors likely reflects a more severe disease course, in which profound impairment of consciousness, as evidenced by significantly lower GCS scores, may obscure or reduce the elicitation of classical meningeal signs. In these patients, the clinical presentation is often dominated by the systemic manifestations of sepsis and multiorgan dysfunction rather than by focal neurological signs. Our findings are consistent with previous reports showing that the classic triad of bacterial meningitis is frequently incomplete, particularly in critically ill adults and those with fatal disease, potentially contributing to delays in diagnosis and treatment initiation [14,15]. Accordingly, the absence of neck stiffness in a patient with suspected central nervous system (CNS) infection should not reduce clinical suspicion for bacterial meningitis; rather, it may indicate more severe disease requiring prompt, aggressive management. These findings underscore the importance of integrating clinical assessment with laboratory and biomarker data, rather than relying on any single clinical sign, for early risk stratification in the ICU.

Several systemic abnormalities were also associated with mortality in our cohort. Non-survivors exhibited tachycardia, tachypnea, anemia, thrombocytopenia, and marked leukocytosis, consistent with previous reports by Yang et al. [16], Wall et al. [17], and Matulyte et al. [18]. Inflammatory and coagulation markers, including procalcitonin, C-reactive protein, ferritin, and INR, were also significantly elevated, in agreement with previous studies [4,7,10,19,20]. Renal dysfunction was strongly associated with mortality, consistent with the findings of Makowiecki et al. [10] and Iwata et al. [21] Collectively, these findings suggest that persistent elevation of CSF lactate reflects both cerebral and systemic organ dysfunction, supporting its potential role as an integrated marker of disease severity.

This study has several strengths. Blinded measurement of CSF lactate and blinded outcome assessment minimized observer bias. Serial CSF sampling enabled assessment of metabolic trajectories rather than isolated measurements, complemented by comprehensive clinical and laboratory evaluation. Finally, the focus on critically ill adults treated in a resource-limited ICU enhances the clinical applicability of serial CSF lactate monitoring in similar healthcare settings.

This study also has several limitations. First, the relatively small sample size limited statistical power and restricted adjustment for potential confounders. Because only 10 deaths occurred, we were unable to determine whether serial CSF lactate independently predicted mortality beyond established risk factors such as age and illness severity. Although the observed association was strong, confirmation in larger studies is required.

Second, we excluded patients with immunocompromising conditions, recent trauma, liver disease, or septic shock to reduce potential confounding. Although these exclusion criteria improved cohort homogeneity, they may limit the generalizability of our findings. Furthermore, the prognostic performance of CSF lactate may be overestimated compared with that observed in broader, more heterogeneous ICU populations. To minimize overfitting, bootstrap-adjusted estimates and conservative statistical methods were used throughout the analyses.

Third, the limited sample size precluded analyses stratified by the causative bacterial pathogen. Fourth, although elevated CSF protein concentrations and reduced CSF glucose concentrations at day 14 suggested ongoing blood–brain barrier dysfunction, we were unable to determine whether these abnormalities reflected persistent inflammation or residual infection. Although follow-up cultures were negative, more sensitive molecular diagnostic techniques, such as polymerase chain reaction (PCR), were not performed and therefore residual bacterial DNA could not be assessed. Consequently, the underlying mechanism responsible for the persistent CSF abnormalities observed in non-survivors remains uncertain.

Furthermore, because all patients in our medical ICU cohort met the institutional criteria for follow-up lumbar puncture on day 14 owing to persistent neurological impairment and/or ongoing systemic manifestations, complete serial CSF data were obtained without selection bias. However, this also indicates that our cohort represents the more severe end of the bacterial meningitis spectrum, and the findings may not be generalizable to patients with milder disease who do not require repeat lumbar puncture.

These limitations highlight the need for larger, multicenter studies to validate our findings and further characterize CSF lactate kinetics. Future studies should also evaluate earlier serial measurements, such as on days 3–5, to determine whether changes in CSF lactate can identify high-risk patients sufficiently early to guide clinical management. Incorporation of molecular microbiological testing into serial CSF assessment may also help distinguish persistent inflammation from residual infection in patients with poor clinical recovery.

Overall, this study provides preliminary prospective evidence supporting the prognostic value of serial CSF lactate monitoring in adults with bacterial meningitis and establishes a foundation for larger studies.

Conclusion

In this prospective ICU cohort of adults with bacterial meningitis, serial CSF lactate measurements provided robust prognostic information. Admission CSF lactate concentrations did not distinguish survivors from non-survivors, whereas persistently elevated concentrations after two weeks were strongly associated with mortality, likely reflecting sustained cerebral metabolic dysfunction. Given its simplicity, low cost, and wide availability, serial CSF lactate monitoring may represent a practical adjunct for risk stratification. Larger multicenter studies are warranted to confirm these findings and to determine the optimal integration of CSF lactate kinetics into prognostic models alongside established clinical and laboratory predictors .

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ORIGINAL INVESTIGATION

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Evaluation of Sedation Practices and Associated Clinical Outcomes in a Medical Intensive Care Unit: A Retrospective Observational Study

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Abstract

Aim: Sedative and analgesic medications are among the most commonly used agents in the intensive care unit (ICU). This study aimed to evaluate sedation practices and examine associated clinical characteristics among critically ill patients admitted to a medical ICU.

Study Design: This single-center retrospective study was conducted in the medical intensive care unit of a tertiary education and research hospital in Istanbul, Türkiye. Adult patients admitted between March and August 2025 who received continuous sedative–analgesic infusions for at least 24 hours were included. Data were extracted from medical records. Sedation depth was assessed using the Richmond Agitation–Sedation Scale (RASS), and potential drug–drug interactions were evaluated.

Results: Forty-five patients (mean age, 60.0±17.4 years; 51.1% male) were included. Sedation was most commonly initiated to facilitate mechanical ventilation (68.9%). Dexmedetomidine and remifentanil were the most frequently used agents. The mean RASS score (-2.17±1.20) indicated a tendency toward moderate sedation. The median number of potential drug–drug interactions (Lexicomp category D or X) per patient was 2 (interquartile range, 0–4). Antipsychotic use (17.8%) was associated with a higher number of potential drug–drug interactions. ICU length of stay was positively correlated with the duration of mechanical ventilation (ρ=0.889, p<0.001), dexmedetomidine infusion (ρ=0.647, p<0.001), and remifentanil infusion (ρ=0.550, p=0.001).

Conclusions: Although sedative selection was largely consistent with current guideline recommendations, the findings indicate a tendency toward moderate sedation and polypharmacy. Continuous monitoring, structured assessment, and individualized dose titration are essential to optimize sedation quality and improve clinical outcomes in critically ill patients.

Keywords: Analgosedation; Clinical pharmacy; Dexmedetomidine; Drug–drug interactions; Intensive care unit; Remifentanil.

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Introduction

Agitation is common among patients admitted to intensive care units (ICUs) and may result from endotracheal intubation, invasive mechanical ventilation, positioning, pain, fear, anxiety, dyspnea, or delirium. Agitation can lead to adverse outcomes, including self-removal of endotracheal tubes or intravascular catheters, patient–ventilator dyssynchrony, and increased sympathetic activity.[1] Sedative and analgesic agents are among the most frequently used medications in the ICU and play a central role in preventing these complications while improving patient comfort and tolerance of treatment.[2]

Deep sedation has been associated with prolonged mechanical ventilation, longer ICU stays, and increased mortality in multicenter prospective cohort studies.[3,4] Therefore, except in specific clinical situations such as intracranial hypertension, refractory status epilepticus, or prevention of awareness during neuromuscular blockade, unnecessary deep sedation should be avoided in critically ill patients.[1,5] Sedation depth should be assessed regularly using validated instruments such as the Richmond Agitation–Sedation Scale (RASS) or the Sedation–Agitation Scale (SAS) to optimize sedation therapy.[6] No single sedative or analgesic agent has demonstrated clear superiority over others. Instead, drug selection should be individualized according to pharmacokinetic properties, potential drug–drug interactions, organ function, drug availability, and cost.[2] Because benzodiazepines are associated with delirium and other adverse effects, their routine use is discouraged except when clearly indicated, such as for status epilepticus or alcohol withdrawal.[7]

Pain is another major contributor to agitation in critically ill patients. Approximately 71% of patients discharged from the ICU report experiencing moderate to severe pain during their ICU stay.[1] Untreated pain may lead to increased energy expenditure, oxygen consumption, hypercoagulability, and immune dysfunction in the short term, while post-traumatic stress disorder may develop in the long term.[2] Therefore, routine pain assessment and adequate analgesia are fundamental components of intensive care. Because pain is subjective experience, patient self-report remains the gold standard for pain assessment. However, pain assessment is particularly challenging in critically ill patients who are unable to communicate. The 2018 PADIS (Pain, Agitation/Sedation, Delirium, Immobility, and Sleep) guidelines recommend the Numerical Rating Scale (NRS) or Visual Analog Scale (VAS) for communicative patients and behavioral assessment tools, such as the Behavioral Pain Scale (BPS) or the Critical-Care Pain Observation Tool (CPOT), for patients unable to communicate.[6]

Because pain is highly prevalent in the ICU, initiating sedative therapy without first assessing pain may mask the underlying cause of agitation and is generally considered inappropriate. Conversely, administering high doses of analgesics solely to achieve sedation may increase the risk of dose-dependent adverse effects. Accordingly, an analgesia-first (analgosedation) approach, in which analgesia is prioritized before or alongside sedation, is recommended to maximize patient comfort while minimizing medication-related adverse effects.[8] To reduce opioid-related adverse effects, multimodal analgesia incorporating adjunctive agents such as acetaminophen, ketamine, or dexmedetomidine is recommended, as opioids are often the first-line agents for pain management.[9]

In routine ICU practice, achieved sedation depth often differs from guideline-recommended targets, and the distribution of Richmond Agitation–Sedation Scale scores may have important implications for clinical outcomes.[1,2] Additionally, critically ill patients receiving continuous sedative and analgesic infusions are particularly susceptible to potential drug–drug interactions because of polypharmacy, altered pharmacokinetics, and the frequent use of multimodal therapeutic regimens.[2] Although comprehensive guidelines are available, real-world data describing sedation and analgosedation practices—particularly regarding achieved sedation depth and the burden of potential drug–drug interactions—remain limited. A better understanding of these practices from a clinical pharmacy perspective may help optimize sedation management and improve patient-centered care. Therefore, this study aimed to evaluate sedation practices and examine associated clinical characteristics in patients receiving continuous sedative therapy in a medical ICU.

Materials and Methods

Study Design and Participants

This single-center retrospective study was conducted in the medical intensive care unit of a tertiary education and research hospital in Istanbul, Türkiye. At the time of the study, no formal written sedoanalgesia protocol had been

implemented in the unit. Sedative and analgesic management was individualized and guided by daily clinical assessment. Drug selection and dose titration were based on the underlying indication (mechanical ventilation or agitation), patient response, and target RASS scores, in accordance with current guideline recommendations. The medical and electronic health records of adult patients (≥18 years) admitted to the ICU between March 1 and August 31, 2025, were retrospectively reviewed.

Patients who did not require continuous deep sedation and who received at least one sedative–analgesic agent by continuous infusion for at least 24 hours were eligible for inclusion. Patients with indications for continuous deep sedation (e.g., intracranial hypertension, refractory status epilepticus, or treatment with neuromuscular blocking agents), those with incomplete or missing medication records, and those with an ICU stay of less than 24 hours were excluded.

Data Collection

Data were collected retrospectively from the hospital information management system and patients' medical records. Demographic variables included age, sex, body mass index (BMI), presence and number of chronic diseases, Charlson Comorbidity Index (CCI), and Clinical Frailty Scale (CFS). Clinical variables included the primary reason for ICU admission, ICU length of stay, discharge status, duration of mechanical ventilation, duration of continuous renal replacement therapy (CRRT), presence of acute kidney injury (AKI), Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Sequential Organ Failure Assessment (SOFA) score, and Glasgow Coma Scale (GCS) score. APACHE II scores were calculated using the worst recorded values within the first 24 hours after ICU admission, whereas SOFA and GCS scores were recorded at the time of ICU admission.

Sedative and analgesic treatment data included the agents administered, indications for treatment initiation, use of combination regimens, infusion duration, and cumulative and unit doses of each medication. The primary sedative and analgesic agents were defined according to the predominant continuous infusion administered during the ICU stay. Sedation and pain assessments included Richmond Agitation–Sedation Scale, Full Outline of UnResponsiveness (FOUR) score, Behavioral Pain Scale (BPS), and Visual Analog Scale, where applicable. For each patient, all recorded assessment scores during the ICU stay were reviewed retrospectively, and the mean values during the sedation period were used for analysis. RASS scores between −2 and −3 were considered indicative of moderate sedation, whereas scores ≤−4 were classified as deep sedation.

Drug-related variables included the total number of medications prescribed within the first 24 hours after ICU admission, antipsychotic use, and potential drug–drug interactions. Potential drug–drug interactions were evaluated using the Lexicomp® database.[10] and classified as category D (therapy modification recommended) or category X (combination should be avoided). Additional clinical data included the occurrence of constipation, defined as the absence of defecation for at least three consecutive days.

Study Outcomes

Primary Outcome

The primary outcome was the evaluation of sedation practices, including the initial indication for sedation (mechanical ventilation or agitation), selection of specific pharmacological regimens (e.g., dexmedetomidine monotherapy or multimodal combinations), and the depth of sedation achieved, as measured by the mean RASS and FOUR scores.

Secondary Outcomes

The secondary outcomes were the number of potential drug–drug interactions per patient and factors associated with ICU length of stay, including its relationship with the duration of mechanical ventilation and continuous sedative infusions.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics (version 27.0; IBM Corp., Armonk, NY, USA). The normality of continuous variables was assessed using the Shapiro–Wilk test. Data are presented as mean ± standard deviation for normally distributed variables, median (interquartile range) for non-normally distributed variables, and frequency (percentage) for categorical variables.

Comparisons between groups were performed using the independent-samples t test for normally distributed variables and the Mann–Whitney U test for non-normally distributed variables. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Correlations between continuous variables were assessed using Spearman's rank correlation coefficient (ϱ). A two-tailed p value <0.05 was considered sta-

tistically significant.

Ethical Considerations

The study protocol was reviewed and approved by Marmara University Faculty of Medicine Non-Drug and Medical Device Research Ethics Committee (Approval Number: 09.2025-25-0836, Date: 26.09.2025). The study was conducted in accordance with the principles of the Declaration of Helsinki. Because of the retrospective study design, the requirement for informed consent was waived by the Ethics Committee.

Results

After screening all patients admitted between March 1 and August 31, 2025, who met the eligibility criteria, 45 patients were included in the final analysis (Fig. 1). The mean age of the study population was 60.0±17.4 years, and 51.1% were male. Demographic and clinical characteristics are summarized in Table 1.

The most common indication for initiating sedation was mechanical ventilation (68.9%). Dexmedetomidine was the most frequently used agent as monotherapy. Medication-related data and assessment scores are presented in Table 2.

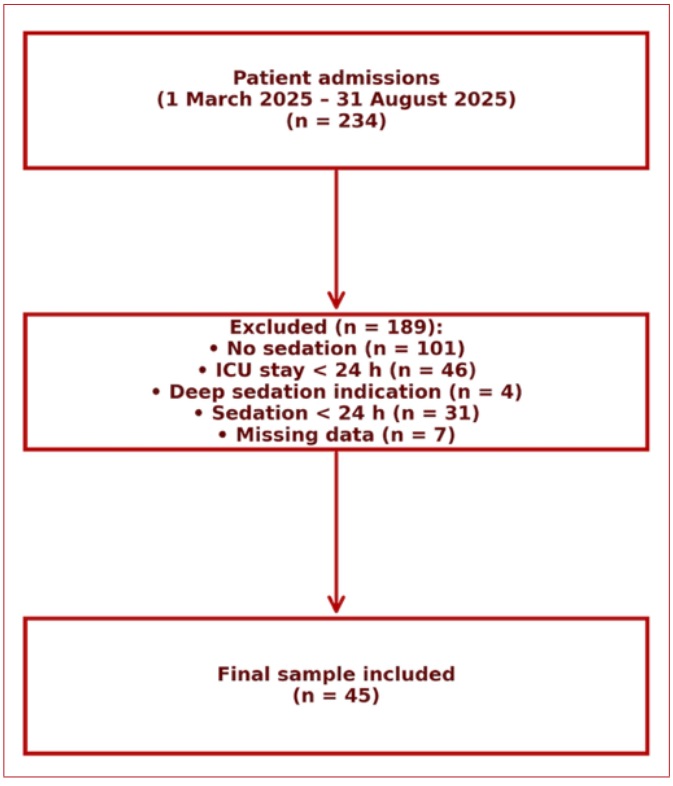

Figure 1. Flowchart of patient selection.

Table 1. Demographic and clinical characteristics of the study population (n=45)

Variable	
Age (years), mean±SD	60.0±17.4
Sex (male), n (%)	23 (51.1%)
BMI (kg/m²), median (IQR)	23.6 (21.4–26.8)
Number of comorbidities, mean±SD	2.9±1.9
Charlson Comorbidity Index, mean±SD	4.5±3.2
Total number of medications at ICU admission, mean±SD*	12.0±3.4
Clinical Frailty Scale, mean±SD	5.7±2.1
APACHE II score, mean±SD	24.4±7.1
SOFA score, mean±SD	8.9±3.7
GCS score, mean±SD	9.2±4.6
Acute kidney injury, n (%)	30 (66.7%)
CRRT use, n (%)	19 (42.2%)
Duration of CRRT (days), mean±SD	10.8±7.6
Mechanical ventilation use, n (%)	34 (75.6%)
Duration of mechanical ventilation (days), mean±SD	12.0±9.8
ICU length of stay (days), median (IQR)	11.0 (5.0–16.0)
ICU mortality, n (%)	26 (57.8%)

Data are presented as mean±standard deviation (SD), median (IQR) or number (%). *The total number of medications at ICU admission was defined as all medications prescribed within the first 24 hours after ICU admission. BMI: Body mass index; CRRT: Continuous renal replacement therapy; GCS: Glasgow Coma Scale; ICU: Intensive care unit; SOFA: Sequential Organ Failure Assessment.

A total of 112 potential drug–drug interactions were identified during the study period. Of these, 18 were classified as category X (combination should be avoided), and the remaining 94 were classified as category D (therapy modification recommended), according to the Lexicomp® database. The median number of potential drug–drug interactions per patient was 2 (interquartile range [IQR], 0–4), with category D interactions occurring most frequently. Representative examples of potential drug–drug interactions and their observed frequencies are summarized in Table 3.

Constipation lasting ≥3 days occurred in 35.6% of patients during remifentanil infusion. Compared with patients who did not develop constipation, those who developed constipation had a significantly longer total duration of remifentanil treatment [161.5 (115.3–289.3) vs. 29.0 (19.0–59.0) hours; p<0.001] and a higher cumulative remifentanil dose [3133.0 (1431.0–5428.6) vs. 270.0 (188.3–744.8) mcg/kg; p<0.001]

Patients who received sedation for mechanical ven-

Table 2. Sedation practices, regimens, and medication exposure

Parameter	
Indication for sedation – mechanical ventilation, n (%)	31 (68.9%)
Indication for sedation – agitation, n (%)	14 (31.1%)
Predominant sedative agent – dexmedetomidine, n (%)	21 (46.7%)
Predominant analgesic agent – remifentanil, n (%)	5 (11.1%)
Two-drug regimen, n (%)	16 (35.6%)
Three-drug regimen, n (%)	2 (4.4%)
Dexmedetomidine infusion duration (hours), median (IQR)	87.0 (40.5–178.0)
Remifentanil infusion duration (hours), median (IQR)	109.0 (29–198)
Ketamine infusion duration (hours), median (IQR)	38.5 (22.3–137.3)
Propofol infusion duration (hours), median (IQR)	74.0 (69.3–116.8)
Remifentanil infusion rate (mcg/kg/min), median (IQR)	0.200 (0.100–0.300)
Dexmedetomidine infusion rate (mcg/kg/h), median (IQR)	0.200 (0.200–0.525)
Ketamine infusion rate (mg/h), median (IQR)	62.5 (33.7–119.6)
Propofol infusion rate (mg/h), median (IQR)	100.4 (72.8–114.6)
Mean RASS score, mean±SD	–2.17±1.20
Mean FOUR score, mean±SD	10.6±4.1
Mean BPS score, mean±SD	2.90±0.59
Mean VAS score, mean±SD	0.15±0.37
Antipsychotic use, n (%)	8 (17.8%)

BPS: Behavioral Pain Scale; CRRT: Continuous renal replacement therapy; FOUR: Full Outline of UnResponsiveness; MV: Mechanical ventilation; RASS: Richmond Agitation–Sedation Scale; VAS: Visual Analog Scale. **Note:** Remifentanil was classified as an analgesic agent rather than a sedative. Predominant sedative and analgesic agents refer to the primary continuously infused agents used as the backbone of the sedation regimen during ICU follow-up, whereas additional agents could be added as part of a multimodal sedation strategy. Accordingly, the predominant analgesic category includes only patients in whom remifentanil served as the primary analgesic infusion, although it was more commonly administered as a component of multimodal analgosedation. Two- and three-drug regimens refer to the concurrent use of two or three continuously infused sedative and/or analgesic agents during ICU follow-up.

tilation had higher disease severity scores, including APACHE II and SOFA scores, deeper levels of sedation, and lower consciousness scores than patients who received sedation for agitation. Antipsychotic use was associated with a greater comorbidity burden, longer dexmedetomidine infusion duration, and a higher number of potential drug–drug interactions. Comparisons between the main clinical subgroups are summarized in Table 4.

Intensive care unit length of stay was positively correlated with the durations of mechanical ventilation, remifentanil infusion, and dexmedetomidine infusion. Correlation analyses are presented in Table 5.

Discussion

This study evaluated sedation practices, potential drug–drug interactions, and associated clinical characteristics in ICU patients. Mechanical ventilation was the most common indication for sedative–analgesic therapy. Dexmedetomidine and remifentanil were commonly used, often as part of multimodal regimens. A tendency toward moderate sedation and a higher number of potential drug–drug interactions among patients receiving antipsychotics were also observed.

The most common indication for initiating sedative–analgesic therapy was mechanical ventilation. This finding is consistent with previous reports indicating that intravenous sedatives are initiated in up to 85% of ICU patients receiving mechanical ventilation.[11, 12] The high proportion of patients who required mechanical ventilation in the present study likely explains the frequent use of sedative–analgesic medications to alleviate pain, anxiety, and agitation associated with mechanical ventilation and to facilitate treatment. The frequent use of remifentanil and dexmedetomidine in sedation regimens, likely reflecting their analgesic efficacy,[1] suggests the adoption of an analgesia-first approach in the ICU. Remifentanil was the most frequently used opioid for continuous analgesia in this study. However, it was more often administered as part of multimodal analgosedation than as the sole predominant agent. It therefore served as the primary analgesic infusion in only five patients (11.1%) (Table 2), whereas dexmedetomidine, which also has analgesic properties, was more often the predominant continuously infused agent. Remifentanil's metabolism by plasma esterases, lack of requirement for dose adjustment in organ failure, rapid onset, short duration of action, and ease of titration make it well suited for use in ICU practice.[13-15] The median remifentanil infusion rate in this study was consistent with the dose range recommended in the PADIS guidelines (0.008–0.250 μg/kg/min).[2,6] The low behavioral and visual pain scores suggest that pain was generally well controlled during ICU follow-up. Constipation occurred in 35.6% of patients during the study period. Compared with patients without constipation, those who developed constipation had a significantly longer remifentanil infusion duration

Table 3. Representative examples and frequencies of potential drug–drug interactions identified in the study

Interacting drug pair	Category	Mechanism	n (%)
Amiodarone + olanzapine	D	Additive QTc prolongation	2 (4.4)
Bisoprolol + dexmedetomidine	D	Additive risk of bradycardia and AV block	6 (13.3)
Quetiapine + metoclopramide	X	Additive antidopaminergic effects	2 (4.4)
Domperidone + propofol	X	Additive QTc prolongation	2 (4.4)
Remifentanil + tramadol	D	Additive CNS depression	5 (11.1)
Patient-level prevalence of pDDIs			
Patients with ≥1 interaction	D	-	32 (71.1)
Patients with ≥2 interactions	D	-	26 (57.8)
Patients with ≥3 interactions	D	-	17 (37.8)
Patients with ≥1 interaction	X	-	10 (22.2)
Patients with ≥2 interactions	X	-	5 (11.1)
Patients with ≥3 interactions	X	-	3 (6.7)

Note: The interactions shown are representative examples and do not necessarily represent the most frequent interactions identified in the cohort. Frequencies indicate the number and percentage of patients in whom each interaction was identified (N=45). Values in the patient-level prevalence section represent unique patients meeting each threshold rather than the total number of interaction pairs.
AV: Atrioventricular; CNS: Central nervous system; pDDI: Potential drug–drug interaction; Category D: Therapy modification recommended; Category X: Combination should be avoided.

Table 4. Comparisons between major clinical subgroups

Variable	Comparative groups		p
Sedation indication	Mechanical ventilation (n=31)	Agitation (n=14)	
APACHE II score, mean±SD	26.5±7.0	19.9±6.2	0.003
SOFA score, mean±SD	9.8±3.4	6.7±3.1	0.007
GCS score, mean±SD	8.1±3.9	11.9±4.2	0.009
RASS score, mean±SD	–2.68±0.90	–0.90±1.00	<0.001
Antipsychotic use	Users (n=8)	Non-users (n=37)	
Dexmedetomidine infusion duration (h), median (IQR)	164.7 (113.2–239.5)	69.4 (43.1–111.9)	0.004
Number of potential drug–drug interactions, mean±SD	4.6±2.8	2.0±1.9	0.002
Number of comorbidities, mean±SD	4.4±1.5	2.6±1.8	0.013

APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment; GCS: Glasgow Coma Scale; RASS: Richmond Agitation–Sedation Scale.

[161.5 (115.3–289.3) vs. 29.0 (19.0–59.0) hours] and a higher cumulative remifentanil dose [3133.0 (1431.0–5428.6) vs. 270.0 (188.3–744.8) mcg/kg] (both $p<0.001$). These findings suggest that prolonged opioid exposure may increase the risk of gastrointestinal dysmotility, even when opioids are administered within recommended dose ranges. The dose- and duration-related adverse effects of opioids support the use of multimodal analgesic strategies that incorporate agents such as acetaminophen, dexmedetomidine, or low-dose ketamine as part of multimodal analgesia.[16, 17]

Dexmedetomidine was another agent frequently used as monotherapy. Compared with benzodiazepines, dexmedetomidine has advantages in delirium management and is associated with lighter, more arousable sedation, which has supported its increasing use in the ICU, particularly for agitation management.[1, 18, 19] In our cohort, antipsychotic use was more frequent among patients receiving dexmedetomidine. Although some studies have reported that dexmedetomidine reduces the need for antipsychotic therapy, our finding may reflect the complexity of real-world ICU practice. In clinical settings, dex-

Table 5. Correlation analyses

Variables	Spearman's ρ	p
ICU length of stay ↔ MV duration	0.889	<0.001
ICU length of stay ↔ remifentanil infusion duration	0.550	0.001
ICU length of stay ↔ dexmedetomidine infusion duration	0.647	<0.001
ICU length of stay ↔ cumulative remifentanil dose	0.443	0.011
ICU length of stay ↔ cumulative dexmedetomidine dose	0.473	0.003
RASS score ↔ FOUR score	0.727	<0.001

FOUR: Full Outline of UnResponsiveness; ICU: Intensive care unit; MV: Mechanical ventilation; RASS: Richmond Agitation–Sedation Scale.

medetomidine is often used in patients with persistent agitation or delirium, who may already be more likely to require additional antipsychotic treatment. Therefore, this association may reflect greater patient complexity rather than reduced dexmedetomidine efficacy. The association between longer dexmedetomidine infusion duration and antipsychotic use further suggests that dexmedetomidine was commonly used for agitation management. The reported prevalence of antipsychotic use in ICU patients is 11.8%,[20] compared with 17.8% in the present study. Although antipsychotics are not routinely recommended in the ICU, they may be used in selected patients with severe agitation or delirium when nonpharmacological measures and optimized analgesia–sedation strategies are insufficient.[6] Antipsychotics may also increase the risk of drug–drug interactions.[21, 22] In the present study, antipsychotic use was associated with a higher number of potential drug–drug interactions. This may be related to additive central nervous system depression and QT-interval prolongation when antipsychotics are combined with other medications. Despite the high frequency of potential drug–drug interactions, not all interactions are clinically significant. Furthermore, the concurrent use of sedative–analgesic agents as part of a multimodal approach may also result in additive central nervous system depressant effects. These findings highlight the importance of evaluating the clinical relevance of drug combinations in ICU practice and the potential contribution of clinical pharmacists to multidisciplinary care.[23] The association between antipsychotic use and a greater comorbidity burden (p=0.013) is also consistent with previous reports linking multimorbidity to delirium and agitation.[24, 25]

Beyond patient-level factors such as antipsychotic exposure, the overall burden of potential drug–drug interactions in our cohort merits comparison with previously published ICU studies. Potential drug–drug interactions are common in critically ill patients admitted to intensive care units because of the frequent use of multiple medications.[23] For example, previous studies have reported a high prevalence of potential drug–drug interactions in ICU patients, largely attributable to polypharmacy. A retrospective study from Brazil found a prevalence of potential drug–drug interactions (pDDI) of approximately 70%, and the number of potential drug–drug interactions was positively correlated with the number of medications prescribed.[26] Another study conducted in Türkiye found that at least one pDDI was present in 81.9% of ICU patients, with moderate and severe interactions occurring particularly frequently.[27] In the present study, 112 potential drug–drug interactions were identified among 45 critically ill patients, with a median of 2 interactions per patient (IQR, 0–4), including Lexicomp category D and X interactions. The concomitant use of remifentanil and tramadol, both opioid analgesics, may represent a potentially inappropriate or controversial prescribing practice. Although this combination is not considered a standard or recommended analgesic approach, it may occur in real-world ICU settings. Its presence in our cohort highlights potential drug-related problems and underscores the importance of identifying inappropriate or suboptimal pharmacological practices. This finding further emphasizes the need for careful medication review and optimization in critically ill patients.

Patients who received sedation for mechanical ventilation had significantly higher APACHE II scores, suggesting that greater disease severity was associated with the need for deeper sedation. This finding is consistent with previous reports indicating that mechanically ventilated patients may require deeper sedation to facilitate ventilator synchrony and prevent agitation-related complications.[28] However, prolonged or excessive sedation has been associated with longer mechanical ventilation duration and prolonged intensive care unit stay.[1, 29] Therefore, although deeper sedation may be clinically justified in some mechanically ventilated patients, structured sedation assessment, daily sedation interruption when appropriate, and target-directed dose titration are needed to avoid unnecessary oversedation. In contrast, lower patients who received sedation for agitation had lighter sedation levels, with a mean RASS score of -0.90. This is

more consistent with current recommendations favoring light, arousable sedation.[30] Taken together, these findings support individualized sedation strategies guided by validated assessment scales.

Correlation analyses showed that longer ICU stays were strongly associated with prolonged mechanical ventilation and longer exposure to sedative–analgesic infusions. These relationships are consistent with previous studies reporting associations between prolonged sedation exposure and clinical outcomes in critically ill patients. Previous evidence has also shown that the depth and duration of sedation are important determinants of these outcomes.[31] These correlations may reflect the greater clinical complexity and prolonged treatment requirements of critically ill patients and underscore the importance of careful sedation assessment and monitoring.[32]

This study has certain limitations. First, its single-center and retrospective design limits the generalizability of the findings. Second, the relatively small sample size precluded the evaluation of mortality and other clinical outcomes and did not permit causal inferences. Third, delirium was not formally assessed. Finally, potential drug–drug interactions were identified using a database and were not classified according to their observed clinical significance. Despite these limitations, the study has several key strengths. It provides real-world data on sedation practices and potential drug–drug interactions in critically ill patients. The analysis included multiple sedative agents, dosing patterns, and their associations with ICU outcomes. Additionally, the study incorporated objective sedation and pain assessment measures and highlighted the potential contribution of clinical pharmacists to sedation management.

Conclusion

Taken together, our findings provide a real-world overview of sedation management in critically ill patients. Sedation practice in this tertiary ICU was characterized by a tendency toward moderate sedation and prolonged exposure to sedative agents. Longer durations of mechanical ventilation and sedative infusion were correlated with longer ICU stays. The predominant use of dexmedetomidine and remifentanil was broadly consistent with current guideline-recommended approaches, whereas the use of propofol, ketamine, and antipsychotics reflected individualized multimodal management. The findings also demonstrated a substantial burden of potential drug–drug interactions, particularly among patients receiving antipsychotics. Prospective multicenter studies are needed to confirm these observations and determine whether structured sedation protocols incorporating clinical pharmacist involvement can improve the safety and quality of sedation management.

Ethics Committee Approval: Ethics committee approval was obtained from Marmara University Faculty of Medicine Non-Drug and Medical Device Research Ethics Committee (Approval Number: 09.2025-25-0836, Date: 26.09.2025).

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ORIGINAL INVESTIGATION

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Impact of Small-for-Gestational-Age Severity on Mortality and Morbidity in Very Preterm Infants

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Abstract

Aim: The aim of this study was to investigate the impact of the severity of small-for-gestational-age status on mortality and prematurity-related morbidities in very preterm infants.

Study Design: Data from all inborn very preterm infants (<32 weeks' gestation) were evaluated. Infants with congenital anomalies or those who were large-for-gestational-age were excluded.

Results: Of the 461 infants included, 74 (16%) were classified as small for gestational age (SGA). The rates of culture-proven late-onset sepsis and mortality were higher in the SGA group than in the non-SGA group (p<0.05). However, no significant differences were observed in other prematurity-related morbidities between the groups (p>0.05). The Z-score cut-off value for predicting mortality was –1.68, with a sensitivity of 71.4% and a specificity of 66.7% (area under the curve: 0.696; 95% confidence interval: 0.574–0.819; p=0.005).

Conclusions: SGA infants had higher rates of sepsis and mortality than non-SGA infants. Furthermore, among SGA preterm infants, a lower birth weight Z-score was associated with increased mortality. Careful perinatal follow-up is essential for preterm infants born SGA.

Keywords: Intrauterine growth restriction; Preterm; Small for gestational age; Z-score.

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Introduction

Intrauterine growth restriction (IUGR) is associated with a significantly increased risk of perinatal morbidity and mortality, as well as adverse long-term health outcomes in infants.[1] Fetal growth is influenced by a variety of factors, including uteroplacental function, maternal health, cardiovascular disease, altitude, maternal nutrition, tobacco and substance use, and pathological conditions such as infections and certain genetic abnormalities.[2] In an otherwise healthy fetus, uteroplacental insufficiency is the most common cause of impaired fetal growth.[2] A fetus is classified as small for gestational age (SGA) when its size, determined by biometric assessment, falls below a specific threshold for its gestational age (GA). An estimated fetal weight (EFW) or abdominal circumference (AC) below the 10th percentile is the most commonly used criterion for SGA. Other proposed thresholds include

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the 3rd or 5th percentile or a Z-score below –2.[2] The risks of stillbirth and perinatal death increase in fetuses with birth weights below the 10th percentile, with the highest risk observed among those with birth weights below the 3rd percentile.[3, 4]

Intrauterine growth restriction is a major cause of preterm birth.[5] Both fetal growth restriction and preterm delivery are associated with an increased risk of neonatal mortality and morbidity. Additionally, SGA infants are at greater risk of morbidity and mortality during the first year of life compared with appropriately grown infants, particularly when born preterm.[6]

This study aimed to evaluate the association between SGA and prematurity-related mortality and morbidities in infants born before 32 weeks of gestation.

Materials and Methods

This retrospective study analyzed preterm infants born between January 2014 and July 2022 with GAs ranging from $23^{0/7}$ to $31^{6/7}$ weeks. GA was determined using the first day of the last menstrual period and confirmed by first-trimester ultrasonography. Infants with congenital anomalies, those born outside our center, or those classified as large for gestational age were excluded (Fig. 1). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Owing to the retrospective study design, the requirement for informed consent was waived by the Ethics Committee.

Neonatal data included GA, birth weight, sex, mode of delivery, antenatal corticosteroid exposure, conception by assisted reproductive technology, abnormal Doppler findings, multiple pregnancy, and 1- and 5-minute Apgar scores. Neonatal outcomes, including respiratory distress syndrome (RDS),[7] intraventricular hemorrhage (IVH),[8] patent ductus arteriosus (PDA),[9] necrotizing enterocolitis (NEC),[10] retinopathy of prematurity (ROP),[11] bronchopulmonary dysplasia (BPD),[12] duration of hospitalization, and mortality, were extracted from hospital medical records. An available-case analysis was per-

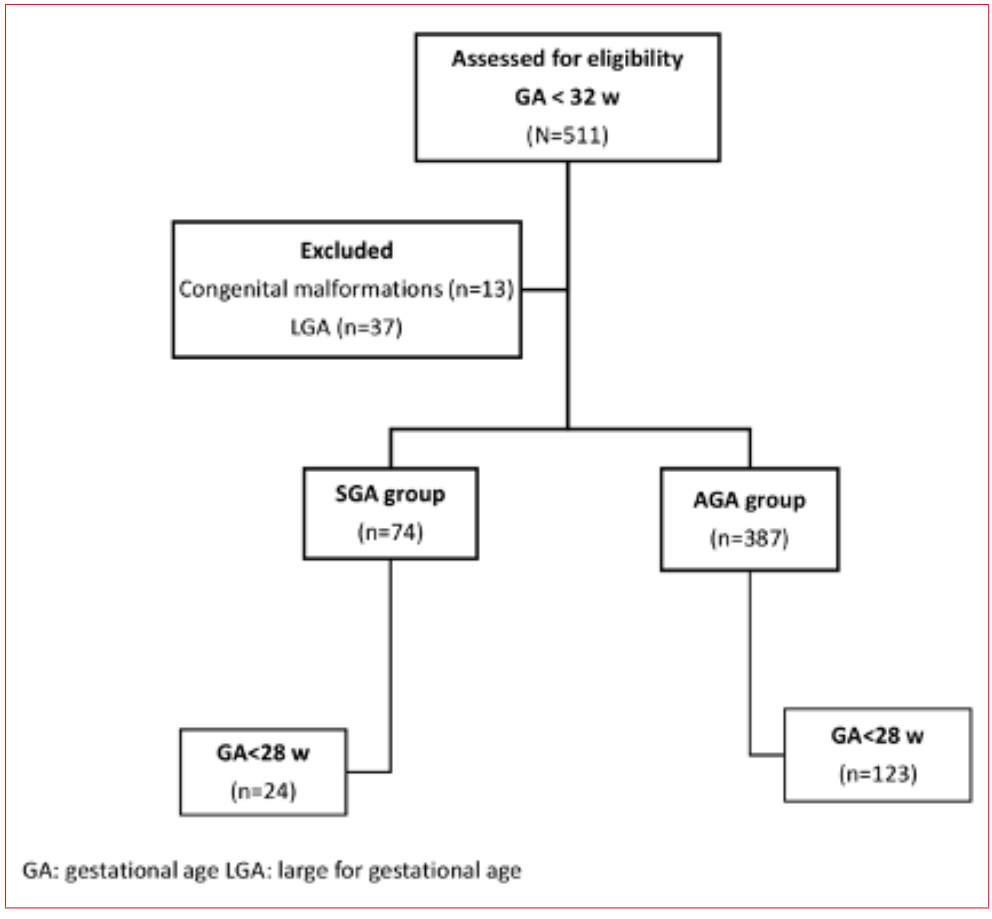


Figure 1. Flowchart of participant selection.

formed for morbidity outcomes. Infants who died before undergoing the relevant diagnostic evaluation (e.g., cranial ultrasonography, echocardiography, or ophthalmologic examination) were excluded from the denominator for that specific outcome. IVH and hemodynamically significant patent ductus arteriosus (hsPDA) analyses included only infants who underwent at least one cranial ultrasound and echocardiographic examination, respectively. ROP analyses included only infants who received at least one ophthalmologic examination. BPD analyses included infants who survived to 36 weeks' postmenstrual age and were evaluated for BPD at that time.

Small for gestational age was defined as a birth weight below the 10th percentile for GA and sex according to the Fenton growth charts.[13] The infants were divided into two groups according to birth weight for gestational age. The primary outcome was mortality before discharge from the neonatal intensive care unit (NICU). Secondary outcomes included prematurity-related morbidities.

Categorical variables are presented as frequencies and percentages (n, %). Associations between categorical variables were assessed using Pearson's chi-square test when its assumptions were met; otherwise, Fisher's exact test was used. Continuous variables that did not meet the assumptions for parametric analysis were compared using the Mann–Whitney U test. The distribution of numerical data was assessed using the Kolmogorov–Smirnov test, and homogeneity of variances was assessed using Levene's test. Descriptive statistics for continuous variables are presented as mean ± standard deviation. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA).

Results

A total of 511 infants who met the eligibility criteria were born at our center between January 2014 and July 2022. After applying the exclusion criteria, 461 infants were included in the study cohort. Of these, 74 (16%) were classified as SGA according to the Fenton growth charts. Table 1 summarizes the neonatal anthropometric, prenatal, and perinatal characteristics according to SGA status. As expected, the SGA group had significantly lower mean birth weight and birth weight Z-scores than the appropriate-for-gestational-age (AGA) group (p<0.001). Sex distribution, gestational age at delivery, and the proportion of infants born before 28 weeks' gestation were comparable between the groups. Antenatal steroid exposure was also similar (p=0.255). However, abnormal antenatal Doppler findings and indicated emergency delivery were more common in the SGA group (both p<0.001). Additionally, median 1- and 5-minute Apgar scores were lower in the SGA group (p=0.010 and p=0.036, respectively).

Table 1. Neonatal anthropometric, prenatal, and perinatal characteristics of the study population*

	SGA (n=74)	AGA (n=387)	p
Neonatal anthropometrics			
Birth weight (g)	741 (±212)	1202 (±336)	**<0.001**
Birth weight percentile	5.02 (±2.73)	48.86 (±23.03)	**<0.001**
Birth weight Z-score	-1.71 (±0.31)	-0.01 (±0.74)	**<0.001**
Prenatal and perinatal characteristics			
Gestational age (weeks)	28.64 (±2.08)	28.78 (±2.14)	0.543
Gestational age <28 weeks	24 (32.9)	123 (31.7)	0.843
Male sex	29 (39.7)	173 (44.6)	0.442
Antenatal steroid exposure	54 (74)	310 (79.9)	0.255
Conception by assisted reproductive technology	8 (11.0)	93 (24.0)	**0.014**
Abnormal antenatal Doppler findings	33 (45.2)	24 (6.2)	**<0.001**
Indicated delivery	62 (84.9)	119 (30.7)	**<0.001**
Cesarean delivery	67 (91.8)	320 (82.5)	**0.047**
1-minute Apgar score	5 (1–8)	6 (0–9)	**0.010**
5-minute Apgar score	7 (3–10)	8 (1–10)	**0.036**
Multiple pregnancy	17 (23.3)	165 (42.5)	**0.002**

*Mann–Whitney U and Pearson's chi-square tests were used.

Table 2 presents prematurity-related morbidities and mortality according to SGA status. The frequencies of RDS, hsPDA, NEC, BPD, moderate-to-severe BPD, and ROP did not differ significantly between the SGA and AGA groups, including the subgroup of infants born before 28 weeks' gestation. Similarly, the frequencies of IVH of any grade and severe IVH (grade ≥3) were comparable between the groups. However, among infants born before 28 weeks' gestation, both IVH of any grade and severe IVH occurred more frequently in the AGA group. Culture-proven late-onset sepsis (LOS) was more common in SGA infants (p=0.016), whereas LOS rates were similar between groups among infants born before 28 weeks' gestation. Logistic regression analysis showed that SGA was associated with an increased risk of cul-

Table 2. Prematurity-related morbidities and mortality*

	SGA (n=74)	AGA (n=387)	p
RDS	36 (49.3)	170 (43.8)	0.386
GA <28 weeks	20 (83.3)	86 (69.9)	0.180
IVH (any grade)[a]	14 (21.5)	92 (24.9)	0.565
GA <28 weeks	3 (16.7)	50 (46.7)	**0.017**
IVH (grade ≥3)[a]	3 (4.6)	31 (8.4)	0.297
GA <28 weeks	0 (0.0)	21 (19.6)	**0.039**
hsPDA[b]	11 (18.3)	87 (23.6)	0.370
GA <28 weeks	6 (42.9)	50 (47.2)	0.761
NEC (any stage)	13 (17.8)	67 (17.3)	0.911
GA <28 weeks	5 (20.8)	35 (28.5)	0.443
BPD (any grade)[c]	12 (26.7)	87 (26.4)	0.975
GA <28 weeks	4 (66.7)	57 (70.4)	0.584
Moderate-to-severe BPD[c]	11 (24.4)	45 (13.7)	**0.058**
GA <28 weeks	4 (66.7)	28 (34.6)	0.129
Culture-proven late-onset sepsis	26 (35.6)	87 (22.4)	**0.016**
GA <28 weeks	8 (33.8)	41 (33.8)	>0.99
ROP (any stage)[d]	4 (8.5)	39 (11.6)	0.529
GA <28 weeks	3 (42.9)	26 (30.6)	0.386
ROP requiring treatment[d]	4 (8.5)	12 (3.6)	0.113
GA <28 weeks	3 (42.9)	10 (11.8)	**0.056**
Duration of hospitalization	37.68 (±34.66)	37.27 (±25.62)	0.55
GA <28 weeks	31.29 (±49.26)	50.24 (±35.60)	**0.005**
Mortality	28 (38.4)	59 (15.2)	**<0.001**
GA <28 weeks	18 (75.0)	40 (32.5)	**<0.001**

*Mann–Whitney U and Pearson's chi-square tests were used. [a]Analyzed in infants who underwent at least one cranial ultrasonographic examination. [b]Analyzed in infants who underwent at least one echocardiographic examination. [c]Analyzed for infants who reached 36 weeks' postmenstrual age or were discharged from the NICU. [d]Analyzed in infants who underwent at least one ophthalmologic examination for ROP. BPD: Bronchopulmonary dysplasia; GA: Gestational age; hsPDA: Hemodynamically significant patent ductus arteriosus; IVH: Intraventricular hemorrhage; NEC: Necrotizing enterocolitis; RDS: Respiratory distress syndrome; ROP: Retinopathy of prematurity.

ture-proven LOS (odds ratio [OR]: 1.914; 95% confidence interval [CI]: 1.121–3.268; p=0.017) (Table 3). After adjustment for GA, sex, and antenatal steroid exposure, the OR was 1.985 (95% CI: 1.142–3.449; p=0.015) (Table 3). The duration of hospitalization was similar between groups. Although the incidence of moderate-to-severe BPD was twice as high in SGA infants, the difference was not statistically significant. After adjustment for gestational age, sex, and antenatal steroid exposure, SGA was associated with a 3.8-fold increased risk of moderate-to-severe BPD (OR: 3.841; 95% CI: 1.602–9.206; p=0.003). Mortality was higher in the SGA group (Table 2), with an OR of 3.470 (95% CI: 2.008–5.997; p<0.001) and an adjusted OR of 4.664 (95% CI: 2.431–8.948; p<0.001) (Table 3).

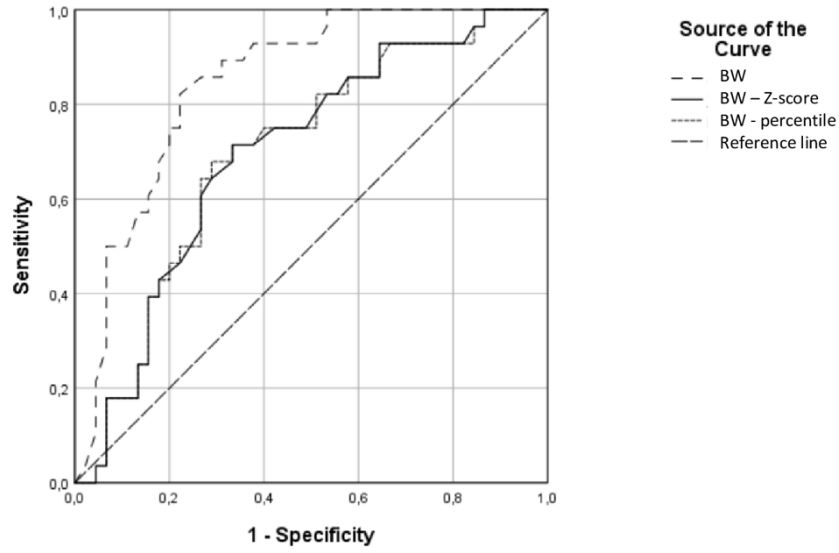
Among SGA infants, receiver operating characteristic (ROC) curve analysis demonstrated that both birth weight Z-score and birth weight percentile significantly predicted mortality (Fig. 2). The Z-score cut-off was –1.68 (area under the curve [AUC]: 0.696; 95% CI: 0.574–0.819; p=0.005), with a sensitivity of 71.4% and a specificity of 66.7%. The corresponding birth weight percentile cut-off was 4.54 (AUC: 0.697; 95% CI: 0.574–0.819; p=0.005), with the same sensitivity and specificity. A birth weight cut-off of 692 g provided the best predictive performance for mortality, with a sensitivity of 82.1%, a specificity of 77.8%, and an AUC of 0.847 (95% CI: 0.759–0.936; p<0.001).

Table 4 presents mortality and morbidity among SGA infants stratified by birth weight percentile (<4.5 vs. 4.5–10). Infants with birth weight percentiles below 4.5 had a 3.2-fold higher risk of RDS (OR: 3.286; 95% CI: 1.258–8.581; p=0.015) and a fivefold higher risk of mortality (OR: 5.00; 95% CI: 1.789–13.975; p=0.002). The frequencies of culture-proven LOS, IVH, and BPD were similar between the two subgroups.

Table 3. Association between SGA status and neonatal morbidities and mortality

	Crude OR	95% CI	p	Adjusted OR*	95% CI	p
Culture-proven LOS	**1.914**	**1.121–3.268**	**0.017**	**1.985**	**1.142–3.449**	**0.015**
IVH (any grade)	0.829	0.439–1.568	0.565	0.808	0.415–1.575	0.531
IVH (grade ≥3)	0.529	0.157–1.784	0.305	0.492	0.139–1.750	0.274
BPD (any grade)	1.011	0.500–2.046	0.975	1.647	0.693–3.916	0.259
Moderate-to-severe BPD	2.042	0.965–4.319	0.062	**3.841**	**1.602–9.206**	**0.003**
Mortality	**3.470**	**2.008–5.997**	**<0.001**	**4.664**	**2.431–8.948**	**<0.001**

BPD: Bronchopulmonary dysplasia; CI: Confidence interval; LOS: Late-onset sepsis; IVH: Intraventricular hemorrhage; OR: Odds ratio. *ORs were adjusted for gestational age, sex, and antenatal corticosteroid exposure.



	Cut-off	p value	Sensitivity	Specificity	AUC (95 % CI)
BW	692	<0.001	%82.1	%77.8	0.847 (0.759-0.936)
BW – Z-score	-1.68	0.005	%71.4	%66.7	0.696 (0.574-0.819)
BW - percentile	4.54	0.005	%71.4	%66.7	0.697 (0.574-0.819)

AUC: area under curve, BW: birth weight, CI: confidence interval

Figure 2. Receiver operating characteristic (ROC) curves for birth weight, birth weight Z-score, and birth weight percentile for predicting mortality in small-for-gestational-age (SGA) preterm infants.

Discussion

This study demonstrated that preterm infants with SGA had higher risks of mortality and LOS than AGA infants. Most prematurity-related morbidities were comparable between the two groups. However, among infants born before 28 weeks' gestation, AGA infants had higher rates of IVH than SGA infants. Additionally, moderate-to-severe BPD was more frequent in the SGA group. Mortality occurred predominantly among infants with birth weight percentiles below 4.5 and birth weight Z-scores below –1.68. It should be noted that the ROC-derived

Table 4. Mortality and prematurity-related morbidities according to birth weight percentile among SGA infants

		n	%	Crude OR	95% CI	p
RDS	<4.5th percentile	23	65.7	**3.286**	1.258–8.581	**0.015**
	4.5th–10th percentile	14	36.8			
Culture-proven LOS	<4.5th percentile	14	40.0	1.444	0.552–3.779	0.454
	4.5th–10th percentile	12	31.6			
IVH (any grade)	<4.5th percentile	8	26.7	1.758	0.532–5.805	0.355
	4.5th–10th percentile	6	17.1			
BPD (any grade)	<4.5th percentile	6	40	2.667	0.680–10.458	0.159
	4.5th–10th percentile	6	20			
Moderate-to-severe BPD	<4.5th percentile	6	40	3.333	0.814–13.658	0.094
	4.5th–10th percentile	5	16.7			
Mortality	<4.5th percentile	20	**57.1**	**5.000**	**1.789–13.975**	**0.002**
	4.5th–10th percentile	8	21.1			

BPD: Bronchopulmonary dysplasia; CI: Confidence interval; LOS: Late-onset sepsis; IVH: Intraventricular hemorrhage; OR: Odds ratio; RDS: Respiratory distress syndrome.

cut-off values showed only moderate discriminative ability (AUC: 0.69). These thresholds lack external validation and should be considered exploratory findings rather than validated clinical predictors.

Survival rates among preterm SGA infants vary across centers. Chalubinski et al.[14] reported an 87.9% survival rate in neonates with IUGR, while Brodszki et al.[15] reported a survival rate of 89%. In our study, the survival rate among SGA infants was 61.6%, which is comparable to the 69% reported by Baschat et al. [16] Chalubinski et al.[14] also demonstrated that neonatal mortality increased when the Z-score was below –1.96 in growth-restricted infants. Most published studies have similarly reported an association between SGA status and increased mortality.[17, 18] In contrast, one prospective cohort study found no significant difference in mortality,[19] although the infants included in that study had a higher gestational age than those in our cohort. Nevertheless, similar mortality rates have been reported among infants born at earlier gestational ages. Brodszki et al.[15] reported similar mortality and neonatal morbidity rates in infants with IUGR and non-IUGR controls born before 30 weeks' gestation.

Prematurity-related morbidities may also vary according to gestational age. Engineer et al.[18] reported increased risks of RDS, neonatal sepsis, and NEC in infants with IUGR, with higher mortality primarily attributed to sepsis and respiratory failure. Silva et al.[20] found higher rates of nosocomial sepsis, ROP, and BPD in IUGR infants, whereas IVH, PDA, and NEC occurred at similar rates in IUGR and non-IUGR infants. Likewise, a retrospective case-control study demonstrated a higher prevalence of LOS among SGA and IUGR neonates.[20] Consistent with these findings, SGA infants in our cohort had higher rates of LOS than AGA infants. This increased risk may be related to delayed enteral feeding, prolonged central venous catheter use, extended dependence on total parenteral nutrition. Furthermore, reduced transplacental transfer of maternal immunoglobulins and bone marrow suppression may also increase the risk of sepsis. However, our study did not find a statistically significant difference in LOS rates among infants born before 28 weeks' gestation. This finding may be explained by the inherently high incidence of sepsis in extremely preterm neonates, regardless of whether they are appropriate for gestational age or small for gestational age.

Zeitlin et al.[17] demonstrated a strong association between lower birth weight percentiles and increased risks of mortality and BPD. Similarly, Brodszki et al.[15] reported a greater need for supplemental oxygen at 36 weeks' postmenstrual age among infants with IUGR. This finding was observed in fetuses with IUGR and abnormal fetal blood flow and was associated with the subsequent development of chronic lung disease. In our study, the overall incidence of BPD was similar between SGA and AGA infants. However, moderate-to-severe BPD was more common in the SGA group. After adjustment for GA, sex, and antenatal steroid exposure, SGA was associated with a 3.8-fold increased risk of moderate-to-severe BPD.

Neither Zeitlin et al.[17] nor the present study identified an association between birth weight percentile and IVH risk in preterm infants. Interestingly, among infants born before 28 weeks' gestation, AGA infants had higher rates of both any-grade IVH and severe IVH than SGA infants.

The findings of this study are generally consistent with those reported in the literature. However, the major limitation of this study was its retrospective design, which limited the availability of important clinical data, including antenatal Doppler findings. Another limitation of our regression model is the lack of adjustment for certain baseline characteristics, such as multiple pregnancy and conception by assisted reproductive technology, which requires cautious interpretation of the reported odds ratios. However, adjustment for intermediate clinical variables, such as abnormal Doppler findings and indicated delivery, was intentionally avoided to prevent overadjustment bias because these variables are intrinsically linked to the pathophysiology of severe SGA status. Another limitation is the small sample size in certain subgroup analyses (e.g., SGA infants born before 28 weeks' gestation and birth weight percentile subgroups), which limits statistical power and requires cautious interpretation of these findings.

The definition of SGA in this study was based solely on birth weight percentiles in accordance with current clinical practice. Additionally, BPD was evaluated only in infants who survived to 36 weeks' postmenstrual age, introducing the potential for survival bias because mortality was higher among SGA infants. Consequently, severe respiratory morbidity may have been underestimated in this group. Furthermore, because the study period extended over nearly a decade, gradual changes in NICU practices, including respiratory management and nutritional strategies, may have influenced the incidence of some neonatal morbidities, representing anoth-

er limitation of this retrospective cohort. Despite these limitations, the study has several strengths, including its conduct at a tertiary referral neonatal intensive care center and the inclusion of a relatively large cohort of 461 inborn very preterm infants. Moreover, unlike many previous studies that included infants born up to 36 weeks' gestation, our cohort was limited to infants born before 32 weeks' gestation.

There is currently no universally accepted definition of SGA status in relation to clinical outcomes in preterm infants. Severe SGA is generally defined as a birth weight below the 3rd percentile; however, the thresholds associated with neonatal morbidity and mortality vary among studies and NICUs. Although international frameworks traditionally define severe growth restriction using the 3rd percentile or a Z-score below -2, our ROC analysis identified a statistical cut-off of 4.54. Because this threshold is specific to our study population, it should be interpreted cautiously as an exploratory finding rather than a replacement for established clinical definitions. Close collaboration between obstetricians and neonatologists is essential to optimize clinical management and improve neonatal outcomes.

Conclusion

Early identification, careful monitoring, and timely delivery of SGA infants are essential for improving both short- and long-term neonatal outcomes. Appropriate postnatal follow-up of infants with SGA may reduce prematurity-related morbidities.

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REVIEW

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Intensive Care Management of Chimeric Antigen Receptor (CAR) T-Cell Therapy-Associated Toxicities

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Abstract

Aim: Chimeric antigen receptor (CAR) T-cell therapy has revolutionized the treatment of relapsed or refractory hematologic malignancies, offering durable responses in selected patients while introducing unique immune-mediated toxicities that can rapidly become life-threatening and require intensive care management. This narrative review provides an evidence-based, practical overview of CAR T-cell therapy, focusing on the recognition and management of its major complications in clinical and critical care settings. Current evidence on CAR T-cell biology, clinical indications, toxicity grading, diagnostic evaluation, and intensive care management is synthesized, with particular emphasis on cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), and immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome (IEC-HS). Effective management depends on early recognition, standardized grading, close multidisciplinary collaboration, prompt initiation of immunomodulatory therapy, and timely organ support when indicated. Although the use of CAR T-cell therapy is expanding globally, published clinical experience from Türkiye remains limited, highlighting the need for specialized treatment centers, standardized national protocols, multidisciplinary expertise, and prospective outcome registries. This review provides a practical framework for intensivists caring for patients receiving CAR T-cell therapy, particularly in newly established programs and resource-limited settings, and emphasizes strategies to optimize clinical outcomes through early diagnosis and timely intervention.

Keywords: Chimeric antigen receptor T-cell therapy; cytokine release syndrome; immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome; immune effector cell-associated neurotoxicity syndrome; intensive care unit; management; toxicities.

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Introduction

Chimeric antigen receptor (CAR) T-cell therapy has emerged as one of the most significant advances in cancer immunotherapy, transforming the treatment landscape for hematologic malignancies. By genetically engineering a patient's T cells to recognize and eliminate malignant cells, CAR T-cell therapy provides targeted, immune-mediated cytotoxic activity that differs substantially from conventional chemotherapy and radiotherapy. Since the approval of cluster of differentiation 19 (CD19)-directed CAR T-cell products, this treatment modality has achieved remission rates of approximately 60%–90%, depending on the dis-

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ease type, CAR T-cell product, and patient population. Its use has rapidly expanded across various B-cell malignancies, including acute lymphoblastic leukemia, diffuse large B-cell lymphoma, and multiple myeloma.[1,2] In addition, ongoing studies are evaluating its potential role in solid tumors, although important challenges related to the tumor microenvironment and antigenic heterogeneity remain.[3] Beyond hematologic and solid malignancies, CD19-directed CAR T-cell therapy has also shown promise in refractory autoimmune diseases through the depletion of autoreactive B cells and plasmablasts. Early evidence in systemic lupus erythematosus, idiopathic inflammatory myositis, and systemic sclerosis suggests the potential for sustained, drug-free remission with an acceptable safety profile.[4]

As indications broaden and access to treatment increases worldwide, the number of patients receiving CAR T-cell therapy continues to grow. This treatment has recently been introduced in Türkiye and is expected to become more widely available in the coming years.[5] Despite its clinical success, CAR T-cell therapy is associated with a distinct spectrum of toxicities that differs markedly from those observed with traditional chemotherapy or hematopoietic stem cell transplantation. These adverse effects are primarily driven by excessive immune activation and dysregulated cytokine release, which can lead to severe systemic inflammation and multiorgan dysfunction. Among these toxicities, cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) are the most common and potentially life-threatening complications.[6,7]

From an intensive care perspective, the management of CAR T-cell therapy–associated toxicities presents substantial clinical challenges. Patients may deteriorate rapidly and require advanced hemodynamic monitoring, vasopressor support, invasive or noninvasive mechanical ventilation, renal replacement therapy, and complex immunomodulatory interventions. Furthermore, the dynamic interplay among malignancy, immune dysregulation, infection risk, and critical illness necessitates close multidisciplinary collaboration among intensivists, hematologists, oncologists, neurologists, infectious disease specialists, and other healthcare professionals involved in patient care.[8,9]

As CAR T-cell therapy becomes increasingly integrated into routine clinical practice, intensivists are more frequently involved in the care of these patients. Nevertheless, clinical experience remains heterogeneous across institutions, particularly in countries and centers where CAR T-cell programs are newly established. This highlights the growing need for practical, intensive care unit (ICU)-oriented guidance that integrates current evidence with real-world clinical experience.

This review provides a clinically focused overview of CAR T-cell therapy and its associated toxicities, emphasizing their recognition and management in inpatient and intensive care settings. It examines the underlying mechanisms, clinical indications, major complications, diagnostic and grading approaches, and current treatment strategies, with particular attention to CRS, ICANS, and immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome (IEC-HS). The review aims to provide intensivists with a practical framework for managing critically ill patients receiving CAR T-cell therapy, with particular relevance to the Turkish context, where clinical experience is limited and institutional infrastructure is still developing. By synthesizing current evidence and real-world clinical experience, this review seeks to address important knowledge gaps in newly established CAR T-cell programs.

What Is Chimeric Antigen Receptor T-Cell Therapy?

CAR T-cell therapy is a form of adoptive cellular immunotherapy in which a patient's T lymphocytes are genetically modified to express synthetic receptors known as chimeric antigen receptors. These receptors are designed to recognize specific tumor-associated antigens. CARs typically consist of an extracellular antigen-recognition domain derived from the single-chain variable fragment (scFv) of a monoclonal antibody, a hinge region, a transmembrane domain, and intracellular signaling domains that mediate T-cell activation and costimulation. Unlike conventional T-cell receptors, CARs recognize surface antigens independently of the major histocompatibility complex (MHC), thereby circumventing an important mechanism of tumor immune evasion, such as MHC downregulation.[10,11]

The CAR T-cell manufacturing process generally involves leukapheresis for T-cell collection, ex vivo genetic modification, most commonly using lentiviral or retroviral vectors, followed by cellular expansion and reinfusion after lymphodepleting chemotherapy. The incorporation of costimulatory domains such as CD28 or

4-1BB represented a major advance in CAR design by improving in vivo persistence, proliferation, and antitumor efficacy. Subsequent generations of CAR constructs have incorporated additional modifications, including cytokine-producing transgenes and strategies designed to enhance tumor penetration and cell function within the immunosuppressive tumor microenvironment.[12,13]

CAR T-cell therapy has demonstrated remarkable efficacy in relapsed or refractory hematologic malignancies, particularly B-cell malignancies. Currently approved products for lymphoma and leukemia primarily target CD19, whereas therapies for multiple myeloma target B-cell maturation antigen (BCMA). U.S. Food and Drug Administration (FDA)-approved CD19-directed therapies include tisagenlecleucel (tisa-cel, Kymriah®), the first FDA-approved CAR T-cell therapy, initially approved for acute lymphoblastic leukemia (ALL) in 2017 and subsequently indicated for other B-cell malignancies, including diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL); axicabtagene ciloleucel (axicel, Yescarta®), the second FDA-approved CAR T-cell therapy, initially approved for DLBCL and subsequently indicated for other B-cell malignancies, including FL; lisocabtagene maraleucel (liso-cel, Breyanzi®), indicated for DLBCL; and brexucabtagene autoleucel (brexu-cel, Tecartus®), indicated for mantle cell lymphoma (MCL) and ALL. BCMA-targeted therapies approved for multiple myeloma include ciltacabtagene autoleucel (cilta-cel, Carvykti®) and idecabtagene vicleucel (ide-cel, Abecma®). Additional antigen targets under investigation include CD20, CD22, dual-target CAR T-cell strategies, and G protein-coupled receptor class C group 5 member D (GPRC5D) for multiple myeloma.[14,15]

Beyond hematologic malignancies, CAR T-cell therapy is being investigated for solid tumors, including melanoma and lung, colorectal, ovarian, hepatocellular, and bone cancers such as osteosarcoma. However, its efficacy in solid tumors remains limited by tumor heterogeneity, the scarcity of suitable tumor-specific antigens, T-cell exhaustion, and the immunosuppressive tumor microenvironment.[16,17]

Autoreactive B cells also play a central role in the pathogenesis of several autoimmune diseases, contributing to chronic inflammation, progressive organ damage, and increased mortality. Conventional B-cell–targeted therapies can deplete B cells or inhibit their activation; however, sustained drug-free remission remains difficult to achieve, and prolonged immunosuppression is often required. By targeting CD19, CAR T-cell therapy may induce more profound B-cell depletion and durable immune reprogramming. Emerging evidence from case reports and small clinical series supports the feasibility and early efficacy of this approach in severe autoimmune diseases, including lupus erythematosus and systemic sclerosis.[4]

As the applications of CAR T-cell therapy expand, novel approaches, including nanotechnology-based delivery systems, allogeneic "off-the-shelf" CAR T cells, natural killer (NK) cell-based therapies, and induced pluripotent stem cell-derived platforms, are being investigated to improve efficacy, accessibility, and safety.[18,19]

Despite its substantial clinical benefits, CAR T-cell therapy is associated with unique and potentially severe toxicities. The following sections address the major life-threatening complications of CAR T-cell therapy, particularly CRS, ICANS, and IEC-HS, which may necessitate intensive care management.

Cytokine Release Syndrome

Definition and Pathophysiology

Cytokine release syndrome is the most common acute toxicity associated with CAR T-cell therapy and results from a supraphysiologic systemic inflammatory response triggered by CAR T-cell activation and expansion. When CAR T cells engage target antigens on malignant cells, rapid proliferation and activation of immune effector cells occur, leading to the release of large amounts of proinflammatory cytokines and chemokines. Key mediators include interleukin-6 (IL-6), IL-1, IL-2, IL-8, IL-10, interferon-gamma (IFN-γ), monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1beta (MIP-1β), and tumor necrosis factor-alpha (TNF-α), which collectively drive systemic inflammation. The inflammatory cascade also induces endothelial activation, reflected by increased circulating levels of biomarkers such as von Willebrand factor and angiopoietin-2.

In addition to CAR T-cells, monocytes and macrophages play a central role in amplifying the cytokine cascade, particularly through IL-6 production. Serum IL-6 levels correlate strongly with CRS severity. Endothelial activation further contributes to nitric oxide production, increased vascular permeability and capillary leak, coagulopathy, and hemodynamic instability with hypotension. The resulting clinical picture resembles sepsis and is

characterized by fever, vasodilatory shock, and varying degrees of organ dysfunction.[20,21]

Prevalence and Risk Factors

Cytokine release syndrome of any grade has been reported in approximately 40%–95% of patients receiving CAR T-cell therapy, whereas severe CRS (grade ≥3) develops in approximately 10%–25% of cases, depending on the specific product and patient population. Several factors influence the incidence and severity of CRS, including high tumor burden, higher CAR T-cell dose, baseline inflammatory status, specific CAR constructs and costimulatory domains, rapid in vivo CAR T-cell expansion, and, in some studies, older age. Thus, patients with a high disease burden and aggressive hematologic malignancies are at particularly high risk for severe CRS and ICU admission. CAR T-cell products containing CD28 domains generally induce earlier and, in some settings, more severe CRS than those containing 4-1BB domains.[22,23]

Clinical Presentation

Cytokine release syndrome typically occurs within the first several days after CAR T-cell infusion, with a median onset of approximately three days. However, onset may range from a few hours to 10–15 days after infusion, depending on the CAR construct, disease burden, and product characteristics. Peak severity generally occurs within the first 1–2 weeks after infusion.

The clinical spectrum ranges from mild, self-limited symptoms to life-threatening shock requiring vasopressor support and invasive mechanical ventilation (IMV). Fever (≥38°C) is the hallmark initial manifestation and may be accompanied by influenza-like symptoms, including chills, malaise, fatigue, myalgias, arthralgias, and rash. As CRS progresses, systemic inflammation and endothelial dysfunction may result in capillary leak syndrome, pulmonary edema, acute respiratory distress syndrome (ARDS), shock, disseminated intravascular coagulation (DIC), hepatic dysfunction, acute kidney injury, cardiac dysfunction, and multiorgan failure.

Cardiovascular complications include arrhythmias, left ventricular dysfunction, vasodilatory shock, and, rarely, cardiogenic shock. Respiratory failure may rapidly progress from a mild supplemental oxygen requirement to severe ARDS requiring IMV.

Common laboratory abnormalities include elevated C-reactive protein (CRP), hyperferritinemia, cytopenias, coagulopathy, elevated liver enzymes, hyperlactatemia, and other markers of organ dysfunction. Although IL-6 levels often correlate with CRS severity, IL-6 is not routinely measured in clinical practice.

Because CRS frequently mimics infection or septic shock, concurrent evaluation for infection and prompt initiation of empiric antimicrobial therapy are essential.[24,25]

Grading

The severity of CRS is commonly graded according to the American Society for Transplantation and Cellular Therapy (ASTCT) consensus criteria, which are based primarily on three clinical parameters: fever, hypotension, and hypoxia. Severity ranges from mild (grade 1), characterized by fever alone, to severe (grade 3–4), characterized by significant hemodynamic compromise and/or respiratory failure requiring escalating levels of cardiovascular or respiratory support.

Accurate grading is essential because it directly guides therapeutic decision-making, escalation of care, and ICU referral (Table 1).[24-26]

Monitoring and Follow-up

Before CRS Development

Before CAR T-cell infusion, patients should undergo a comprehensive baseline evaluation, including cardiac and respiratory assessments, measurement of baseline inflammatory markers, complete blood count and coagulation profile, liver and renal function tests, infection screening, and neurologic assessment.

Patients with a high tumor burden or other established risk factors for CRS should undergo enhanced monitoring during the early post-infusion period.[27]

After CRS Development

Once CRS develops, monitoring should include continuous assessment of vital signs, serial neurologic examinations, close monitoring of fluid balance and urine output, and frequent laboratory evaluation, including complete blood count (CBC), CRP, ferritin, coagulation parameters, renal and liver function tests, lactate, other clinically indicated markers. Continuous cardiac telemetry should be considered in patients with grade ≥2 CRS.

Because CRS may progress rapidly within hours, frequent clinical reassessment and timely escalation of care are essential. Early involvement of the ICU team is recommended for patients with escalating oxygen or vasopressor requirements or rapidly progressive CRS.[27]

Table 1. Assessment and management of cytokine release syndrome (CRS)

Grade	Clinical definition	Recommended management
Grade 1	Fever ≥38°C without hypotension or hypoxia	• Supportive care, including antipyretics and intravenous fluid administration; initiate empiric antimicrobial therapy when infection is suspected • Granulocyte colony-stimulating factor (G-CSF) may be considered for prolonged neutropenia according to institutional practice • Close clinical monitoring • Consider tocilizumab 8 mg/kg IV (maximum 800 mg) for persistent fever (>48–72 hours), clinically significant symptoms, older adults (>65 years), or selected high-risk patients • In selected patients receiving B-cell maturation antigen (BCMA)-directed CAR T-cell therapy, particularly for multiple myeloma, some institutional protocols incorporate dexamethasone 10 mg IV every 24 hours
Grade 2	Fever ≥38°C with hypotension not requiring vasopressors and/or hypoxia requiring low-flow supplemental oxygen	• Tocilizumab 8 mg/kg IV; repeat every 8 hours as clinically indicated, for a maximum of four doses • Dexamethasone 10 mg IV every 12–24 hours if hypotension persists after tocilizumab or in selected recipients of BCMA-directed CAR T-cell therapy • Continue supportive care • Consider ICU consultation or early transfer if hemodynamic status worsens • If there is no clinical improvement within 24 hours, escalate therapy as clinically indicated and reassess for progression to grade 3 CRS
Grade 3	Fever ≥38°C with hypotension requiring one vasopressor, with or without vasopressin, and/or hypoxia requiring high-flow nasal cannula or facemask oxygen	• ICU admission or management in an ICU setting • Tocilizumab 8 mg/kg IV (maximum four doses) • Dexamethasone 10–20 mg IV every 6–12 hours • Intensive supportive care, including fluid administration, vasopressor support, supplemental oxygen, and empiric antimicrobial therapy • If there is no clinical response or further deterioration occurs, escalate therapy and reassess for progression to grade 4 CRS
Grade 4*	Life-threatening CRS characterized by hypotension requiring multiple vasopressors and/or hypoxia requiring positive-pressure ventilation, including continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP), or invasive mechanical ventilation, or severe organ dysfunction	• Immediate ICU management • Tocilizumab 8 mg/kg IV (maximum four doses) • Dexamethasone 10–20 mg IV every 6–12 hours • In refractory cases, consider methylprednisolone 0.5–1 g/day IV for three days, with further escalation individualized according to clinical response • Provide comprehensive organ support, including vasopressor therapy, mechanical ventilation, and renal replacement therapy when indicated • Administer broad-spectrum antimicrobial therapy and provide transfusion support as clinically indicated

*In refractory CRS, additional therapies may be considered, including anakinra (interleukin-1 [IL-1] receptor blockade; 100–200 mg IV or SC every 6–12 hours), siltuximab (an anti-IL-6 monoclonal antibody; 11 mg/kg IV administered over 1 hour as a single dose), and ruxolitinib (Janus kinase 1/2 inhibition; 5–10 mg orally twice daily).

ICU Admission Criteria

Intensive care unit admission should be strongly considered in patients with persistent hypotension, vasopressor requirement, escalating oxygen needs (particularly those requiring high-flow nasal oxygen or noninvasive mechanical ventilation), altered mental status, rapidly progressive organ dysfunction, severe metabolic abnormalities such as metabolic acidosis, hyperlactatemia, or clinically significant electrolyte disturbances, or cardiac complications such as arrhythmias or ventricular dysfunction. Most patients with severe CRS (grade ≥3) require ICU-level care. Early ICU admission may also be appropriate for older patients or those with limited physiologic reserve, high tumor burden, substantial comorbidity, rapidly progressive symptoms, concomitant neurologic manifestations, or an inadequate response to initial treatment. Early ICU transfer is preferable to delayed transfer after advanced organ failure has developed.[28]

ICU Management

In addition to supportive critical care, immunomodulatory therapies, particularly tocilizumab and corticosteroids, are central to the management of moderate-to-severe CRS and are discussed below. Early recognition and timely intervention are critical to preventing progression to irreversible organ dysfunction.

Hemodynamic instability should be managed according to standard critical care principles, including judi-

cious fluid resuscitation, avoidance of fluid overload given the risk of capillary leak, dynamic assessment of fluid responsiveness, and early initiation of vasopressor therapy, most commonly with norepinephrine. Bedside echocardiography and, when clinically indicated, invasive hemodynamic monitoring may assist in evaluating refractory shock or complex hemodynamic profiles.

Respiratory support may range from supplemental oxygen to noninvasive ventilation and, in severe cases, IMV. Supportive respiratory strategies include high-flow nasal oxygen, noninvasive ventilation, and lung-protective IMV in patients with ARDS, together with a conservative fluid management strategy in patients with pulmonary edema.[24-26]

Close monitoring for organ dysfunction, including renal and hepatic impairment and coagulation abnormalities, is also essential. Additional ICU management may include renal replacement therapy, management of coagulopathy, cardiac monitoring and support, nutritional support, and administration of broad-spectrum antimicrobials while infection is being evaluated. Because CRS and sepsis may coexist, initiation of empiric antimicrobial therapy is strongly recommended.[24-26]

Targeted and Immunomodulatory Therapies

Targeted immunomodulatory therapy is a cornerstone of the management of moderate-to-severe CRS (Table 1). Tocilizumab, an IL-6 receptor antagonist, is the principal targeted therapy for CRS and can rapidly reverse CRS-related manifestations, particularly fever, hypotension, capillary leak, and oxygen requirements. The standard adult dose is 8 mg/kg intravenously and may be repeated at intervals of at least 8 hours as clinically indicated, for a maximum of four doses. Importantly, tocilizumab does not appear to significantly compromise CAR T-cell antitumor efficacy. Early administration in patients with progressive CRS has been associated with improved symptom control without adversely affecting treatment outcomes.

Corticosteroids, most commonly dexamethasone, are recommended for severe CRS, CRS refractory to tocilizumab, concomitant ICANS, or rapidly progressive clinical deterioration. A commonly used regimen is dexamethasone 10 mg intravenously every 6–12 hours. Although corticosteroids are effective in controlling inflammation, their use should be balanced against their potential effects on CAR T-cell persistence.

Failure to improve after one or two doses of tocilizumab should prompt reassessment for alternative diagnoses, including infection, macrophage activation syndromes such as IEC-HS, and progressive CRS requiring escalation of immunomodulatory therapy. In refractory CRS, additional therapies may be considered, including anakinra (IL-1 receptor blockade), siltuximab (an anti-IL-6 monoclonal antibody), ruxolitinib (Janus kinase 1/2 inhibition), and therapies targeting granulocyte-macrophage colony-stimulating factor (GM-CSF). However, evidence supporting these approaches remains limited.[24-26]

Immune Effector Cell-Associated Neurotoxicity Syndrome

Definition and Pathophysiology

Immune effector cell-associated neurotoxicity syndrome is among the most frequent and potentially severe toxicities associated with CAR T-cell therapy. It encompasses a broad spectrum of neurologic manifestations resulting from immune-mediated dysfunction of the central nervous system (CNS). Neurotoxicity may occur concurrently with CRS, after CRS has resolved, or, less commonly, as an isolated complication.

The pathophysiology of ICANS remains incompletely understood and is considered multifactorial. Current evidence suggests that systemic inflammation, endothelial activation, and blood–brain barrier (BBB) disruption are central mechanisms. Elevated circulating cytokines, particularly IL-1, IL-6, IFN-γ, GM-CSF, and other inflammatory mediators, increase BBB permeability and promote cytokine trafficking into the CNS. Endothelial dysfunction and microvascular injury further contribute to cerebral edema and neuroinflammation. In addition, activation of resident CNS immune cells, including microglia, may amplify local inflammatory responses, ultimately leading to neuronal dysfunction and diffuse encephalopathy. CAR T cells and other immune cells have been detected within the CNS; however, their direct contribution to the pathogenesis of ICANS remains incompletely defined. As with CRS, the degree of endothelial activation appears to correlate with the severity of neurotoxicity.[29]

Prevalence and Risk Factors

ICANS develops in approximately 15%–65% of patients receiving CAR T-cell therapy, whereas grade ≥3 neurotoxicity occurs in approximately 10%–31% of cases, depending on the CAR T-cell product, disease indication, and grading criteria. Higher incidences have been reported in pediatric ALL cohorts and with certain CAR T-cell con-

structs, with neurologic complications occurring in up to 70%–80% of patients and severe neurotoxicity in 30%–40%. These variations likely reflect differences in patient populations, CAR products, and diagnostic criteria.

The timing of ICANS is also variable. Neurotoxicity typically develops 5–7 days after CAR T-cell infusion but may occur within hours of infusion or be delayed for up to 2–3 weeks, depending on the CAR T-cell product and clinical course.

Several factors have been associated with an increased risk of ICANS, including high tumor burden, severe or concurrent CRS, acute lymphoblastic leukemia, pediatric age, older age in some adult cohorts, substantial comorbidity, preexisting neurologic disease or CNS injury, elevated baseline inflammatory markers such as CRP, early post-infusion hyperferritinemia, thrombocytopenia, intensive lymphodepleting chemotherapy with fludarabine and cyclophosphamide in some studies, and rapid CAR T-cell expansion.

BCMA-directed CAR T-cell therapies have additionally been associated with delayed or persistent neurologic toxicities, including movement disorders and cranial or peripheral neuropathies.[30,31]

Clinical Presentation

ICANS typically begins with subtle neurocognitive abnormalities and may progress rapidly over hours to days. Early manifestations commonly include headache, impaired attention, mild confusion, word-finding difficulties, dysgraphia, tremor, and behavioral changes. Expressive aphasia is a particularly characteristic and sensitive early manifestation and may precede more severe neurologic deterioration. As neurotoxicity progresses, patients may develop delirium, global aphasia, agitation, psychosis, altered level of consciousness, focal neurologic deficits, motor weakness, ataxia, seizures, status epilepticus, and coma. Diffuse cerebral edema is a rare but devastating complication of severe ICANS and is associated with high mortality.[32,33]

Unlike CRS, fever is not required for the diagnosis of ICANS. Neuroimaging findings may remain normal despite severe clinical manifestations. Electroencephalography (EEG) frequently demonstrates diffuse slowing and may identify otherwise unrecognized nonconvulsive seizures or nonconvulsive status epilepticus. Cerebrospinal fluid (CSF) analysis may reveal elevated protein concentrations and lymphocytic pleocytosis.

Monitoring and Grading

Early detection of ICANS relies on systematic neurologic assessment. All patients receiving CAR T-cell therapy should undergo baseline neurologic evaluation before infusion and regular reassessment thereafter. The Immune Effector Cell-Associated Encephalopathy (ICE) score is widely used for bedside assessment and evaluates orientation, naming, ability to follow commands, writing, and attention. The ICE score comprises the following components: orientation (correctly identifying the year, month, city, and hospital; 1 point each, maximum 4 points), naming (correctly naming three objects, such as a clock, sink, and computer; 1 point each, maximum 3 points), following commands (correctly following a simple command; 1 point), writing (writing a complete sentence; 1 point), and attention (counting backward from 100 by 10; 1 point). The maximum score is 10, with lower scores indicating greater neurologic impairment. Serial assessment is essential for detecting subtle changes and facilitating timely intervention.

The ASTCT has developed a standardized grading system for ICANS incorporating the ICE score, level of consciousness, seizure activity, motor findings, and evidence of increased intracranial pressure or cerebral edema. Severity ranges from grade 1, representing mild neurologic impairment, to grade 4, representing life-threatening neurologic dysfunction (Table 2).

Serial neurologic assessments should be performed in hospitalized patients and daily in outpatient settings during the period of highest risk. The frequency of assessment should be individualized according to the patient's clinical status, severity of ICANS, and level of care, including outpatient, inpatient ward, intermediate care, or ICU settings. Accurate grading is critical because it guides both the need for ICU admission and the intensity of therapeutic interventions. Patients with high-grade ICANS frequently require ICU care because of the risks of seizures, impaired airway protection, and, rarely, malignant cerebral edema, which is associated with substantial mortality.[31-33]

ICU Management

Patients with high-grade ICANS (grades 3–4), rapidly progressive neurologic symptoms, seizures, depressed consciousness, suspected cerebral edema, or impending airway compromise should be transferred promptly to the ICU. ICU management requires a structured, multidisciplinary approach with close neurologic monitoring and rapid escalation of care when deterioration occurs. Serial

Table 2. Classification and management of immune effector cell-associated neurotoxicity syndrome (ICANS)

Grade	ICE score	Clinical definition	Recommended management*
Grade 1	7–9	Mild cognitive impairment without depressed level of consciousness, seizures, motor deficits, or evidence of cerebral edema	• Close neurologic monitoring with serial immune effector cell-associated encephalopathy (ICE) assessments • Brain computed tomography (CT) or magnetic resonance imaging (MRI) and electroencephalography (EEG) as clinically indicated • Supportive care • Consider dexamethasone 10 mg IV for persistent or progressive symptoms
Grade 2	3–6	Moderate cognitive impairment; patient awakens to voice, without seizures, motor deficits, or evidence of cerebral edema	• Frequent neurologic assessments • Brain CT or MRI and EEG as clinically indicated • Dexamethasone 10 mg IV; reassess after 6–12 hours and continue every 6–12 hours if symptoms persist • Consider ICU admission because of the risk of rapid neurologic deterioration
Grade 3	1–2	Severe encephalopathy; patient awakens only to tactile stimulation and/or has brief seizures responsive to treatment, nonconvulsive seizures detected on EEG, or focal cerebral edema	• ICU management • Continuous neurologic monitoring • Brain imaging and EEG monitoring • Prompt initiation of appropriate antiseizure therapy when indicated • Dexamethasone 10–20 mg IV every 6 hours or methylprednisolone 1-2 mg/kg IV daily
Grade 4	0	Life-threatening condition characterized by unresponsiveness or coma, prolonged or recurrent seizures, severe motor deficits, diffuse cerebral edema, or increased intracranial pressure	• Immediate ICU management, with airway protection and mechanical ventilation when indicated • Continuous EEG monitoring and neuroimaging • Aggressive management of seizures and cerebral edema • Pulse-dose corticosteroid therapy (methylprednisolone 500–1,000 mg IV daily for 3 days, followed by tapering according to clinical response) • In steroid-refractory cases, consider anakinra 100–200 mg IV or SC every 6–12 hours

*When ICANS occurs concurrently with CRS of any grade, consider adding tocilizumab (8 mg/kg IV, up to a maximum of four doses)

neurologic assessment should be performed at a frequency appropriate to the patient's clinical condition and level of care, preferably using standardized tools such as the ICE score. Continuous EEG monitoring should be considered in patients with persistent altered mental status or suspected seizures because nonconvulsive seizure activity may occur. Brain computed tomography (CT) or magnetic resonance imaging (MRI) should be performed when clinically indicated to evaluate for cerebral edema, structural abnormalities, and alternative causes of neurologic deterioration. If imaging demonstrates substantial cerebral edema or findings suggestive of increased intracranial pressure, early neurosurgical consultation should be considered.

Some centers use antiseizure prophylaxis with antiepileptic agents such as levetiracetam, particularly in patients with moderate-to-severe ICANS; however, practices vary across institutions. Clinical seizures should be treated promptly according to established critical care protocols. High-dose corticosteroids should be initiated promptly in patients with moderate-to-severe ICANS.

In cases of suspected or confirmed cerebral edema, neurocritical care principles should be applied, including head-of-bed elevation, osmotherapy (e.g., hypertonic saline or mannitol), and careful optimization of oxygenation and ventilation. Airway protection and mechanical ventilation may be required in patients with a decreased level of consciousness or refractory seizures.

Close attention should also be paid to concurrent systemic toxicities, particularly CRS, because these conditions frequently overlap and may contribute to clinical deterioration.[31-33]

Targeted and Immunomodulatory Therapies

Unlike CRS, the management of ICANS primarily relies on corticosteroids as first-line therapy. Dexamethasone is commonly used for moderate ICANS, whereas high-dose methylprednisolone may be required for severe or rapidly progressive neurotoxicity. Tocilizumab, an IL-6 receptor antagonist, is generally ineffective for isolated ICANS because of its limited penetration across the BBB, and is therefore not recommended as monotherapy in this setting. When ICANS occurs concurrently with CRS,

tocilizumab should be administered to treat the CRS component, while corticosteroids remain the primary therapy for the neurologic manifestations.

Emerging evidence suggests a potential role for IL-1 blockade with anakinra and other immunomodulatory therapies in refractory ICANS. Among available adjunctive agents, anakinra, an IL-1 receptor antagonist, has accumulated the greatest clinical experience in refractory cases. Other agents, including siltuximab, an anti-IL-6 monoclonal antibody, have also been used in selected refractory cases. However, the available evidence remains limited, and these therapies are generally reserved for selected patients managed in specialized centers (Table 2).

The decision to initiate immunosuppressive therapy should balance the need for rapid control of neurotoxicity against the potential impact on CAR T-cell treatment efficacy. Nevertheless, available clinical data suggest that the appropriate use of corticosteroids for toxicity management does not substantially compromise treatment efficacy.[31-33]

Chronic and Delayed Neurotoxicity

Although ICANS is usually reversible, delayed neurologic complications have increasingly been recognized, particularly following BCMA-directed CAR T-cell therapy. Reported manifestations include parkinsonism, cognitive impairment, personality changes, cranial and peripheral neuropathies, persistent tremor, and gait abnormalities.

These syndromes may develop weeks to months after CAR T-cell infusion and are often poorly responsive to dopaminergic therapies, including levodopa. Management remains largely supportive and is not well established; however, corticosteroids and strategies aimed at eliminating persistent CAR T cells have been explored in severe or refractory cases.[30,31]

Immune Effector Cell-Associated Hemophagocytic Lymphohistiocytosis-Like Syndrome

Definition and Pathophysiology

Immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome is a rare but potentially life-threatening hyperinflammatory complication that may develop after immune effector cell therapies, particularly CD19- and BCMA-directed CAR T-cell therapy. Although IEC-HS resembles secondary hemophagocytic lymphohistiocytosis (HLH), growing evidence suggests that it represents a distinct clinicopathologic entity with unique biological mechanisms and temporal characteristics. It is characterized by uncontrolled immune activation, cytokine excess, macrophage and histiocyte proliferation, cytopenias, coagulopathy, hepatic dysfunction, and multiorgan failure.[34,35]

IEC-HS frequently overlaps with CRS and may also occur in patients with ICANS, making diagnosis particularly challenging in critically ill patients.

The pathophysiology of IEC-HS is incompletely understood but appears to involve profound dysregulation of both innate and adaptive immune responses following immune effector cell activation. After CAR T-cell infusion, rapid activation and expansion of CAR T cells results in the release of inflammatory cytokines, including IL-6, IL-1, IFN-γ, TNF-α, IL-18, and GM-CSF. Persistent immune activation may subsequently trigger excessive macrophage and histiocyte activation, resulting in a hyperinflammatory cascade resembling that observed in macrophage activation syndrome (MAS) and HLH.[34,35]

Key pathophysiologic features include excessive cytokine production (cytokine storm), hyperactivation of macrophages and monocytes, endothelial dysfunction with increased capillary leak, dysregulation of cytotoxic T-cell and natural killer (NK)-cell function, hemophagocytosis in the bone marrow, liver, spleen, and lymphoid tissues, and abnormalities of coagulation and fibrinolysis.

Although CRS and IEC-HS share several inflammatory pathways, IEC-HS generally develops later, may persist despite CRS-directed therapy, and is characterized by more pronounced hyperferritinemia, hypofibrinogenemia, cytopenias, and progressive organ dysfunction.

Epidemiology and Prevalence

IEC-HS is an uncommon but increasingly recognized complication of CAR T-cell therapy. Its reported incidence varies substantially because of differences in diagnostic criteria and grading systems. Published studies have reported an incidence of approximately 1%–6% among adult CAR T-cell recipients, although higher rates have been reported in pediatric patients with acute lymphoblastic leukemia.[34,35]

Mortality may be substantial in severe cases, particularly when recognition and initiation of immunomodulatory therapy are delayed. Earlier studies may have underesti-

mated the incidence of IEC-HS because some cases were classified as severe CRS before standardized diagnostic criteria for IEC-HS became available.

Risk Factors

Several factors have been associated with an increased risk of IEC-HS, including severe or prolonged CRS, high tumor burden, aggressive hematologic malignancy, baseline systemic inflammation, preexisting hepatic dysfunction, rapid CAR T-cell expansion, early elevations in cytokines, and prior allogeneic hematopoietic stem cell transplantation. Among these factors, severe CRS appears to be one of the strongest predictors of subsequent IEC-HS.

Several laboratory abnormalities may serve as early indicators of evolving IEC-HS or support its diagnosis, including rapidly rising ferritin levels, elevated CRP, cytopenias, hypertriglyceridemia (fasting triglycerides >265 mg/dL), elevated lactate dehydrogenase, transaminitis (>5 times the upper limit of normal), direct hyperbilirubinemia, and hypofibrinogenemia (<150 mg/dL or below the lower limit of normal).[34,35] These abnormalities should be interpreted in the context of the overall clinical presentation rather than in isolation.

Clinical Manifestations

IEC-HS typically develops several days to weeks after CAR T-cell infusion, most commonly as CRS is resolving or after its resolution.

Common manifestations include persistent or recurrent fever, cytopenias, new-onset hepatosplenomegaly, hypotension, capillary leak, respiratory failure, acute kidney injury, neurologic abnormalities, coagulopathy, and multiorgan failure.[34,35]

Bone marrow examination may demonstrate hemophagocytosis; however, this finding is neither sufficiently sensitive nor specific and is not required for the diagnosis of IEC-HS.

Diagnosis

The diagnosis of IEC-HS remains challenging because its clinical and laboratory features overlap with those of CRS, sepsis, DIC, disease progression, classical HLH, drug-induced liver injury, and thrombotic microangiopathy. In critically ill patients, a comprehensive evaluation for infection is essential, particularly before escalation of immunosuppressive therapy, because occult infection may coexist with IEC-HS and may worsen with further immunosuppression.

Diagnostic approaches to IEC-H vary across guidelines. The American Society of Clinical Oncology (ASCO) guidelines have described criteria that include marked hyperferritinemia (ferritin >10,000 ng/mL) together with evidence of organ toxicity, such as bone marrow or organ hemophagocytosis, significant hepatic or renal dysfunction, or pulmonary edema. An ASTCT expert panel has proposed defining IEC-HS as a pathologic and biochemical hyperinflammatory syndrome that is attributable to immune effector cell (IEC) therapy that is clinically distinct from CRS and ICANS. Characteristic features include new or progressive cytopenias, hyperferritinemia, coagulopathy with hypofibrinogenemia, transaminitis, and other manifestations consistent with MAS/HLH.[36,37]

Grading

The ASTCT has proposed a grading system that categorizes IEC-HS severity according to the degree of organ dysfunction and the intensity of interventions required (Table 3).

This framework helps guide clinical monitoring, escalation of immunomodulatory therapy, and decisions regarding ICU management. Early recognition of progression from mild disease to fulminant hyperinflammation is essential to facilitate timely escalation of immunosuppressive therapy and supportive care.

ICU Management

Management of IEC-HS requires rapid control of the hyperinflammatory response while preserving antitumor immune activity whenever possible.

ICU management includes hemodynamic support, supplemental oxygen or mechanical ventilation as needed, renal replacement therapy when indicated, blood product support, correction of coagulopathy, and empiric broad-spectrum antimicrobial therapy when infection is suspected or cannot be reliably excluded.

Outcomes in IEC-HS depend on early recognition, the severity of organ dysfunction, response to immunomodulatory therapy, the presence of concurrent infection, and the status of the underlying malignancy. Delayed diagnosis, severe coagulopathy, refractory shock, and multiorgan failure are associated with increased mortality.[34-36] Serial monitoring of ferritin, fibrinogen, complete blood counts, liver function tests, coagulation parameters, and markers of organ dysfunction is essential for assessing disease progression and response to therapy.

Table 3. Suggested grading and management of immune effector cell–associated hemophagocytic lymphohistiocytosis-like syndrome (IEC-HS)

Grade	Clinical definition	Recommended management
Grade 1	Mild or asymptomatic laboratory abnormalities with minimal or no organ dysfunction	• Close clinical and laboratory monitoring • Supportive care • Consider corticosteroid therapy in patients with progressive laboratory abnormalities: dexamethasone 10 mg IV every 6 hours or methylprednisolone 0.5–1 mg/kg/day IV)
Grade 2	Moderate clinical manifestations requiring medical intervention, with moderate cytopenias or coagulopathy and mild organ dysfunction	• Initiate corticosteroid therapy with dexamethasone 20 mg IV every 6 hours or methylprednisolone 1–2 mg/kg/day IV • Consider pulse-dose methylprednisolone 500–1,000 mg IV daily for 3 days in patients with rapidly progressive disease • Consider early initiation of anakinra 100–200 mg IV or SC every 6–12 hours • Consider ICU consultation for patients with clinical deterioration or evolving organ dysfunction
Grade 3	Severe organ dysfunction with significant hypoxemia and/or hypotension requiring ICU-level care	• ICU admission and management • Administer high-dose corticosteroids with dexamethasone 20 mg IV every 6 hours or methylprednisolone 1–2 mg/kg/day IV, alternatively, consider pulse-dose methylprednisolone 500–1,000 mg IV daily for 3 days • Administer anakinra 100–200 mg IV or SC every 6–12 hours • Provide comprehensive organ support as clinically indicated • In corticosteroid-refractory disease, consider second-line therapy with ruxolitinib (10 mg orally twice daily), emapalumab (1 mg/kg IV as an initial dose), or etoposide (50–100 mg/m² IV as an initial dose)
Grade 4	Life-threatening multiorgan failure requiring mechanical ventilation, vasopressor therapy, or other advanced organ support, with severe coagulopathy and/or encephalopathy	• Immediate ICU management with comprehensive organ support • Administer pulse-dose methylprednisolone 500–1,000 mg IV daily for 3 days • Administer anakinra 100–200 mg IV or SC every 6–12 hours • In refractory progressive disease, consider escalation to second-line immunomodulatory therapy with ruxolitinib (10 mg orally twice daily), emapalumab (1 mg/kg IV as an initial dose), or etoposide (50–100 mg/m² IV as an initial dose) • Ensure multidisciplinary management involving hematology, intensive care, and infectious diseases specialists

Targeted and Immunomodulatory Therapies

Corticosteroids are considered first-line therapy for IEC-HS, with dexamethasone or methylprednisolone commonly used according to disease severity. Pulse-dose corticosteroids may be required in fulminant cases. Tocilizumab may be considered when IEC-HS occurs concurrently with CRS; however, IL-6 receptor blockade alone is generally insufficient for isolated IEC-HS. Anakinra is increasingly used in moderate-to-severe IEC-HS because of its established role in MAS, favorable safety profile, and growing clinical experience.

Emapalumab, a monoclonal antibody targeting IFN-γ and approved for primary HLH, has been used in selected refractory cases, although clinical experience in IEC-HS remains limited.

Ruxolitinib has emerged as a potential therapeutic option for refractory hyperinflammatory syndromes because of its ability to inhibit multiple cytokine signaling pathways. Etoposide may also be considered in refractory or rapidly progressive disease, particularly when the clinical presentation resembles fulminant HLH despite initial immunomodulatory therapy (Table 3).

However, immunomodulatory therapies should be used cautiously because they may impair CAR T-cell persistence, cause significant myelosuppression, and increase the risk of infection.[34-36]

Other Complications

Cytopenias

Many patients develop leukopenia/neutropenia, anemia, and/or thrombocytopenia as adverse effects of lymphodepletion or CAR T-cell therapy itself. Some patients may remain cytopenic for weeks to months and, rarely, indefinitely. Persistent or unexplained cytopenias beyond approximately two months should prompt bone marrow evaluation to exclude disease relapse, myelo-

dysplasia, infection, or other bone marrow pathology.

Management of cytopenias should be individualized according to severity. Patients with Grade 1 cytopenias (hemoglobin >10 g/dL, absolute neutrophil count >1,500/mm³, or platelet count >75,000/mm³) generally require only close monitoring and supportive care. For Grade 2 cytopenias (hemoglobin 8–10 g/dL, absolute neutrophil count 1,000–1,500/mm³, or platelet count 50,000–75,000/mm³), careful clinical assessment and ongoing supportive management are recommended. Patients with Grade 3–4 cytopenias (hemoglobin <8 g/dL, absolute neutrophil count <1,000/mm³, or platelet count <50,000/mm³) typically require blood product support, including red blood cell and platelet transfusions, in accordance with institutional transfusion thresholds and clinical indications. Granulocyte colony-stimulating factor (G-CSF) may be considered for severe or prolonged neutropenia but is generally deferred until cytokine release syndrome has completely resolved because of concerns about the potential exacerbation of inflammatory toxicity, although practice patterns vary across institutions. In patients with persistent cytopenias following prior hematopoietic stem cell transplantation, infusion of previously cryopreserved autologous stem cells may be considered when available.[38,39]

B-Cell Aplasia/Hypogammaglobulinemia

B-cell aplasia following CD19-directed CAR T-cell therapy may result in prolonged hypogammaglobulinemia, sometimes persisting for up to two years, thereby increasing the risk of recurrent infections. Immunoglobulin (Ig) levels should be monitored regularly. In patients with IgG levels below 400–600 mg/dL who experience serious or recurrent infections, monthly intravenous immunoglobulin (IVIG) replacement therapy (up to 400–500 mg/kg) may be considered. IVIG therapy may be continued until IgG levels recover and infections resolve. Considerable variability exists in clinical practice regarding the use of IVIG replacement therapy.[40]

Disseminated Intravascular Coagulation

Disseminated intravascular coagulation is an uncommon but potentially life-threatening complication associated with CAR T-cell therapy, most frequently occurring in the context of severe CRS or IEC-HS. Management focuses on treating the underlying inflammatory syndrome and providing supportive critical care. Supportive measures include transfusion of blood products when indicated, correction of hypofibrinogenemia and other coagulation abnormalities, serial monitoring of coagulation parameters, and management of organ dysfunction. Immunomodulatory therapies, such as tocilizumab, corticosteroids, or anakinra should be considered based on the underlying CRS or IEC-HS rather than on the presence of DIC itself.[38-40]

Infection Risk

Infections remain a significant cause of morbidity and mortality following CAR T-cell therapy, affecting approximately 23%–60% of patients during the post-infusion period. Susceptibility to infection is multifactorial, reflecting the combined effects of the underlying hematologic malignancy, cumulative exposure to prior therapies, lymphodepleting chemotherapy, treatment-related immune dysfunction, and prolonged cytopenias. Additional risk factors include severe CRS requiring immunosuppressive therapy and a greater burden of prior treatment. The spectrum of pathogens evolves over time. Bacterial infections predominate during the first month after CAR T-cell infusion, whereas viral infections—particularly respiratory viral infections and those caused by varicella-zoster virus and herpes simplex virus—become more common between 30 days and one year. Invasive fungal infections, including *Aspergillus* spp., as well as *Pneumocystis jirovecii* pneumonia (PJP), are relatively uncommon but occur more frequently after BCMA-directed than after CD19-directed CAR T-cell therapy. In the late phase, persistent B-cell aplasia, plasma cell depletion, hypogammaglobulinemia, and delayed immune reconstitution become the principal determinants of infectious risk. Consequently, comprehensive infectious risk assessment before CAR T-cell therapy, close monitoring of immune recovery, regular evaluation of Ig levels, and individualized infection-prevention strategies are essential. Antiviral and PJP prophylaxis are routinely recommended, whereas antibacterial and mold-active antifungal prophylaxis should be reserved for selected high-risk patients. IVIG replacement therapy should be considered in patients with significant hypogammaglobulinemia accompanied by recurrent or severe infections.[41]

Secondary Malignancies

Secondary malignancies are an uncommon but recognized late complication of CAR T-cell therapy. Long-term follow-up studies have reported an overall incidence of approximately 4%–16%, although most cases are not considered directly attributable to the CAR T-cell product. Particular concern has been raised regarding the rare

occurrence of T-cell malignancies, including CAR-positive lymphomas, prompting the U.S. Food and Drug Administration to issue safety alerts and mandate boxed warnings for both CD19- and BCMA-directed CAR T-cell therapies. Nevertheless, current evidence indicates that these events are exceedingly rare, and the overall benefit–risk profile of CAR T-cell therapy remains favorable. Moreover, the incidence of secondary malignancies does not appear to exceed that expected in heavily pretreated patients, in whom cumulative exposure to chemotherapy and radiotherapy, together with the underlying disease biology, contributes substantially to the development of subsequent malignancies. Continued long-term surveillance remains essential to better define the true incidence, underlying mechanisms, and clinical significance of these rare events.[38-40]

CAR T-Cell Therapy in Türkiye and Intensive Care–Relevant Outcomes

Experience with CAR T-cell therapy in Türkiye remains limited. According to a report by the Turkish Society of Hematology Scientific Subcommittee on Cell and Gene Therapies (TSH-CGT SSC), approximately 507 patients are estimated to require CAR T-cell therapy annually in Türkiye; however, only 23 patients received this therapy between 2019 and March 2024.[42] Nine patients received treatment as part of an academic study conducted in Türkiye, whereas 14 received treatment abroad, primarily in Germany. Consequently, published national data consist mainly of early academic studies and small retrospective cohorts, providing limited information on clinical outcomes.

The first Turkish academic CAR T-cell study, ISIKOK-19, evaluated a locally developed CD19-directed CAR T-cell product in patients with relapsed/refractory B-cell acute lymphoblastic leukemia and non-Hodgkin lymphoma (NHL). Seven heavily pretreated patients received CAR T-cell infusions, with an overall response rate of 72%. Treatment-related toxicities included CRS, neurotoxicity, and pancytopenia. According to the published report, most adverse events were grade 1–2 and were managed with supportive care, tocilizumab, and corticosteroids as needed. Importantly, the study demonstrated the feasibility of academic CAR T-cell manufacturing and administration in Türkiye.[5]

Additional data from a retrospective cohort of 13 CAR T-cell recipients in Türkiye identified CRS and neurotoxicity as the predominant early complications. Grade 1 CRS occurred in 38.5% of patients, and neurological manifestations, including cognitive impairment, dysgraphia, and somnolence, were also observed. Notably, two patients required ICU admission because of combined CRS and neurotoxicity.[43]

Although the published Turkish experience remains limited, the reported toxicity profile is consistent with international data, with CRS, ICANS, prolonged cytopenias, and infection-related complications among the major adverse events. However, detailed national data on ICU admission rates, organ support requirements, mechanical ventilation, vasopressor use, renal replacement therapy, and ICU mortality are currently lacking. This represents a significant limitation of our review, as the scarcity of local data constrains our ability to tailor recommendations to the Turkish context and may limit the applicability of international guidelines, particularly in resource-limited settings.

The report of the TSH-CGT SSC initiative.[42] highlights considerable challenges in implementing CAR T-cell therapy in Türkiye. These challenges include high costs, inadequate infrastructure, a shortage of trained personnel, regulatory uncertainties, and insufficient reimbursement frameworks. The report also provides strategic recommendations, including the establishment of government funding and reimbursement mechanisms through the Social Security Institution (SGK); standardization of clinical protocols; creation of a centralized system for data collection and outcome monitoring; expansion of certification and training programs to develop a skilled workforce; adoption of Good Manufacturing Practice (GMP)-compliant quality management systems; and strengthening of international collaborations to harmonize standards and foster innovation. By formulating a comprehensive national strategic roadmap, this initiative seeks to facilitate the broader adoption of CAR T-cell therapy and improve access to this advanced treatment modality for patients across Türkiye.

Conclusion

In conclusion, CAR T-cell therapy has reshaped the treatment landscape for several malignant and non-malignant B-cell diseases, particularly relapsed and refractory hematologic malignancies. Although it offers substantial clinical benefits, CAR T-cell therapy is associated with a unique spectrum of potentially life-threatening toxici-

ties. Among these, CRS, ICANS, and IEC-HS are the most clinically significant complications and may require ICU admission and organ support.

As CAR T-cell therapy continues to expand globally and gains momentum in Türkiye, intensivists will play an increasingly pivotal role in the care of these patients. Early recognition, accurate grading, timely initiation of immunomodulatory therapies, and comprehensive organ support are essential to prevent progression to severe organ dysfunction and improve clinical outcomes. Successful management also depends on close multidisciplinary collaboration among intensivists, hematologists, oncologists, neurologists, infectious disease specialists, and other members of the CAR T-cell therapy team.

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