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ORIGINAL RESEARCH

Characteristics and outcomes of patients with solid tumors admitted to the intensive care unit in Saudi Arabia

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Abstract

Background: Critically ill cancer patients present complex challenges due to the combined effects of malignancy and acute critical illness. This retrospective cohort study evaluated the clinical characteristics and mortality outcomes of adult patients with solid tumors admitted to intensive care units (ICUs) in Saudi Arabia. **Methods**: We conducted a single-center, retrospective analysis of all adult ICU patients with solid tumors between January 2018 and October 2021. The primary endpoint of the study was to describe their clinical characteristics and outcomes, while the secondary endpoint was to identify risk factors for ICU and in-hospital mortality. Data collected included demographics, tumor types, recent treatments, severity scores such as Acute Physiology and Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA), functional impairments, complications, and outcomes. Determinants of mortality were identified using multivariable Cox proportional hazards regression. **Results**: Of 3224 screened patients, 273 were included. Patients were 58 $\pm$ 14.4 years old, with 52.4% males. Lower gastrointestinal tract cancer was the most common (51.2%) diagnosis. Recent chemotherapy and radiotherapy rates were 65.2% and 12.1%, with mean APACHE II and SOFA scores of 14.8 $\pm$ 6.8 and 3.3 $\pm$ 3.2, respectively. ICU and in-hospital mortality rates were 26.4% and 37% respectively. Recent chemotherapy and higher severity scores were independently associated with increased mortality risk. **Conclusions**: This study highlights key characteristics, mortality patterns, and predictors in critically ill patients with solid tumors. The association of recent chemotherapy and severity scores with mortality underscores the utility of these variables for disease severity assessment and risk stratification.

Keywords

Intensive care units; Mortality; Critical illness; Neoplasms; Risk factors

1. Introduction

The intersection between critical illness and cancer presents a complex and evolving challenge in modern healthcare. Cancer patients often face a wide range of medical complications that may necessitate admission to the intensive care unit (ICU) [1]. These admissions can be triggered by various factors, including the progression of the underlying malignancy and drug-related toxicities, post-surgical complications or unrelated acute medical conditions [2, 3]. The need to address this intricate interplay is underscored by the growing population of individuals living with cancer—a result of an aging population, improvements in diagnostic methods, and a decline in cancer-related mortality [4, 5]. In 2020, the World Health Organization (WHO) reported 19.2 million new cancer cases, 9.9 million cancer-related deaths, and an estimated 50 million individuals living with cancer worldwide [6].

In this context, Saudi Arabia emerges as a significant focal point grappling with an impending surge in the number of cancer cases. Projections indicate a dramatic rise in the annual cancer incidence, from 16,859 cases in 2016 to approximately 40,000 by 2030, with an estimated 19,000 cancer-related deaths [6, 7]. Despite these challenges, the landscape of critically ill cancer patients in Saudi Arabia remains poorly characterized with limited systematic data and an absence of a comprehensive national registry for this patient population [7].

The intricacies of cancer-related ICU admissions further complicate the critical care landscape. Existing literature from Saudi Arabia highlights the formidable task of managing critically ill cancer patients. For example, Al-Dorzi *et al.* [8] reported a notably high in-hospital mortality rate of 70.5% among patients with hematological malignancies requiring intensive care and mechanical ventilation (MV), with septic shock and male gender identified as significant predictors of poor outcomes. Overall, there is a scarcity in studies assessing factors that influence ICU outcomes in cancer patients. Moreover, the available research is often limited by short follow-up durations and heterogeneous patient populations [9, 10]. These limitations typically stem from the inclusion of both hematological and non-hematological malignancies, small sample sizes, and insufficient follow-up periods.

To address these critical gaps in knowledge, this study aimed to evaluate the clinical characteristics and mortality outcomes of critically ill patients with solid tumors admitted to intensive care units (ICUs) in Saudi Arabia. By examining patterns in patient demographics, clinical features, treatment courses, and outcomes, the study seeks to provide meaningful insights into the critical care prognosis of oncology patients in the region.

2. Material and methods

2.1 Study design

This retrospective, descriptive cohort study included critically ill adult patients with solid tumors who were admitted to a tertiary hospital between 01 January 2018, and 31 October 2021. Solid tumors were identified and recorded using the International Statistical Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-AM) codes, or based on information extracted from patient medical records. Patients were followed-up throughout their hospital stay from the date of ICU admission until either hospital discharge or death. The study adhered to the ethical guidelines, including the World Medical Association Declaration of Helsinki and local institutional regulations. The study protocol was approved by the institutional review board of the respective center (No. E-21-5793). The requirement for informed consent was waived due to the retrospective nature of the study.

2.2 Study setting

This study was conducted at King Saud University Medical City, a distinguished 1200-bed tertiary academic medical center in Riyadh, Kingdom of Saudi Arabia.

2.3 Study participants

All adult patients aged 18 years or older admitted to ICUs with solid tumors during the study period were screened for eligibility. Patients were excluded if they had hematological malignancies, an ICU length of stay (LOS) $\leq$24 h, or died within the first 24 h of ICU admission.

2.4 Data collection

Data on patient demographics, baseline characteristics (age, gender, comorbidities, the type of malignancy, presence of metastasis, and cancer treatments regimen), admission diagnoses, data pertaining severity of illness scores (Karnofsky, Charlson comorbidity index, Simplified Acute Physiology Score (SAPS II), and Acute Physiology and Chronic Health Evaluation II (APACHE II) score) during the first 24 hours after ICU admission, and the Sequential Organ Failure Assessment (SOFA) score within the first 24 hours after ICU admission, prognostic factors, necessity for MV, ICU LOS, and patients outcomes. All data were obtained from two primary sources: an institutional ICU database and electronic patient chart reviews. These sources provided a comprehensive set of prospectively collected and regularly updated patient data.

2.5 Endpoints

The primary endpoint of this study was to comprehensively describe the clinical characteristics and outcomes of critically ill patients with solid cancer tumors admitted to the ICUs. Secondary endpoints included the impact of specific factors on ICU and in-hospital mortality rates. Furthermore, this study examined the occurrence of complications during ICU stay, LOS, and ICU readmission rates.

2.6 Statistical analysis

Categorical variables (gender, comorbidities, type of tumor, presence of metastasis, location before ICU admission, reason for ICU admission, chemotherapy and radiation before ICU admission, *etc.*) are presented as frequencies and percentages. Continuous variables (age and severity of illness scores) are expressed as means with standard deviation (SD) or medians with interquartile ranges (IQRs). Comparisons of categorical variables were performed using the Chi-square test or Fisher's exact test, as appropriate. Independent continuous variables with normal distribution were compared using *t*-tests, while non-normally distributed variables were analyzed using the Mann-Whitney U test. Factors associated with mortality were identified through multivariable Cox proportional hazards regression analysis. Covariate selection was guided by clinical relevance as established in previous studies [8–10]. Cox regression was preferred over logistic regression as it accounts for the timing of events, offering a more accurate model of ICU or hospital mortality. Patients were censored if they were discharged alive, or if death did not occur at the end of the study period. Hazard ratios (HRs) with 95% confidence intervals (CIs) are reported. Statistical significance was defined as $p < 0.05$. All statistical analyses were performed using the STATA 17 software (StataCorp LP, College Station, TX, USA).

3. Results

3.1 Patient characteristics

During the study period, medical records of 3224 patients were reviewed, of which 273 patients met the inclusion criteria (Fig. 1). Their characteristics are summarized in Table 1. The mean age of the cohort was 57.8 ± 14.4 years, with a balanced gender distribution, encompassing 52.4% male and 47.6% female patients. The majority of ICU admissions (61.2%) originated from the operating room. Among the primary tumor types, lower gastrointestinal tract cancer was the most prevalent (51.2%), followed by breast cancer (11.8%) and upper gastrointestinal tract cancer (10.3%). A substantial proportion of patients (65.2%) underwent chemotherapy within 4 weeks prior to ICU admission, while 12.1% had undergone radiotherapy in the same timeframe. Metastatic cancer was noted in 28.8% of the patients. The clinical severity of the cases was represented by a mean APACHE II score of 14.8 (SD 6.8) and a mean SOFA score of 3.3 (SD 3.2). Additionally, 50.9% of patients required blood transfusions during their ICU stay (Table 1).

3.2 Complications, length of stay, and readmission

The intricacies of critical care for cancer patients were further highlighted by the increased prevalence of ICU-acquired infections, which affected 43.2% of patients. Within this group, 30% of the patients developed sepsis or septic shock. Among the study population, 30% required invasive mechanical ventilation (MV), while 5.5% underwent renal replacement therapy (RRT). Vasopressor or inotrope support was administered to 32% of patients. Additionally, two patients who received blood transfusions experienced myocardial infarction and cerebral ischemia (Table 2).

The median ICU LOS was 4 days, whereas the median hospital LOS was 17 days. Beyond the confines of the ICU, the post-critical care landscape revealed 8.4% ICU readmission rate at 60 days, and 9.9% readmission rate at 90 days, and 13.6% readmission rate at 1 year, highlighting the complexity of long-term patient management.

3.3 Mortality outcomes

The ICU and in-hospital mortality rates were 26.4% and 37%, respectively, with a one-year mortality of 44% (Table 2). Cox proportional hazards regression revealed several factors intricately linked to mortality outcomes. Recent chemotherapy within 4 weeks before ICU admission was a strong predictor of both ICU (HR = 2.2; 95% CI: 1.198–4.189) and in-hospital mortality (HR = 2.1; 95% CI: 1.208–3.579). In addition, higher severity of illness scores, as measured by APACHE II and SOFA scores, were significantly correlated with increased risk of ICU and in-hospital mortality (Table 3).

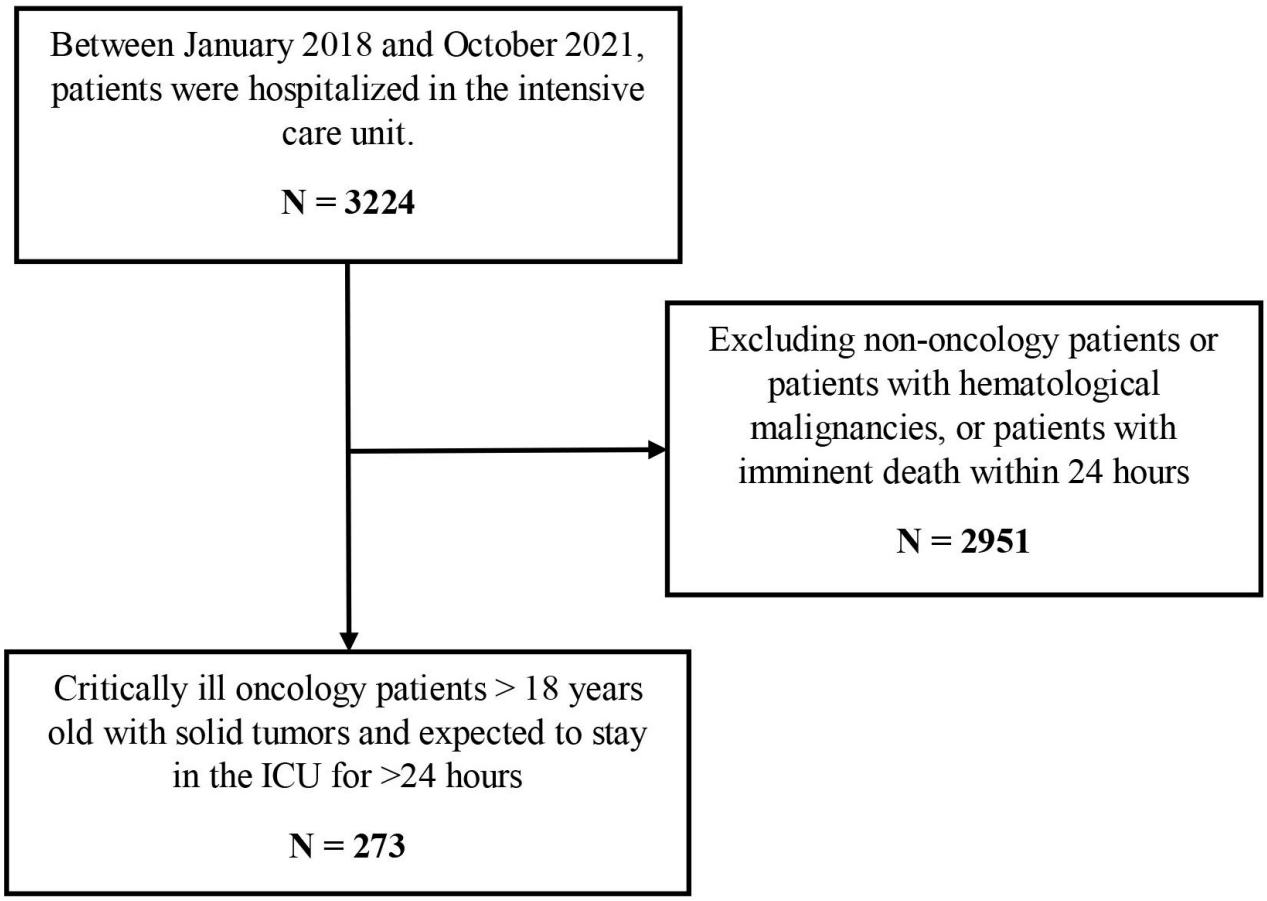

FIGURE 1. Flow diagram of subject enrolment. ICU, intensive care unit.

TABLE 1. Demographics and clinical characteristics of the study patients.

Variable	N = 273
Age (yr), mean (SD)	57.8 ± (14.4)
Male, n (%)	143 (52.4)
Body mass index (kg/m^2), mean (SD)	26.8 ± (13.4)
Comorbidities, n (%)	
Cardiovascular	142 (52.0)
Endocrine	139 (50.9)
Hematological	47 (17.2)
Gastrointestinal	26 (9.5)
Renal	26 (9.5)
Neurological	16 (5.9)
Respiratory	10 (3.7)
Severity of illness, mean ± (SD)	
Karnofsky scale	53.1 ± (20.0)
Charlson comorbidity index	5.4 ± (2.5)
SAPS II score	29.3 ± (14.7)
APACHE II score	14.8 ± (6.8)
SOFA score	3.3 ± (3.2)
Type of Tumor, n (%)	
Lower gastrointestinal tract cancer	140 (51.2)
Breast cancer	32 (11.8)
Upper gastrointestinal Tract cancer	28 (10.3)
Genitourinary tract cancer	18 (6.6)
Gynecologic cancer	16 (5.9)
Central nervous system	10 (3.7)
Sarcomas	10 (3.7)
Lung cancer	9 (3.3)
Head and neck cancer	8 (2.9)
Germ cell cancer	5 (1.8)
Skin cancer	5 (1.8)
Presence of metastasis, n (%)	79 (28.8)
Location before ICU admission, n (%)	
Operating room	167 (61.2)
General wards	54 (19.8)
Emergency department	47 (17.2)
Out of the hospital	5 (1.8)
Reason for ICU admission, n (%)	
Post-op complications	168 (61.5)
Hemodynamic instability	41(15.0)
Sepsis/septic shock	27 (9.9)
Respiratory failure	12 (4.4)
Cardiac arrest	1 (0.4)
COVID-19 complication	1 (0.4)
Others^	23 (8.4)
Chemotherapy and radiation within 4 weeks of ICU admission, n (%)	
Chemotherapy 4 weeks before	178 (65.2)
Radiotherapy 4 weeks before	33 (12.1)

TABLE 1. Continued.

Variable	N = 273
Organ dysfunction in ICU, n (%)	
Respiratory	133 (48.7)
Cardiovascular	100 (36.7)
Central nervous system	86 (31.5)
Gastrointestinal	74 (27.1)
Hematology	62 (22.7)
Renal	52 (19.1)
Site of infections, n (%)	
Lung	49 (18)
Urine	29 (10.6)
Blood	22 (8.1)
Abdomen	20 (7.3)
Wound	12 (4.4)
Soft tissue	5 (1.8)
Central nervous system	2 (0.7)
Unknown	33 (12.1)
Microorganisms, n (%)	
Gram-negative isolates	53 (19.5)
Gram-positive isolates	24 (8.8)
Fungi	2 (0.7)
No isolated pathogen	217 (79.5)
Received blood transfusion	139 (50.9)

APACHE II, Acute Physiology and Chronic Health Evaluation II; ICU, Intensive care unit; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment; SD, Standard Deviation.
^Diabetic ketoacidosis, hypotension, loss of consciousness, hypovolemic shock, anaphylactic shock, undifferentiated shock, desaturation, or upper gastrointestinal bleeding.

TABLE 2. Mortality and clinical outcomes of the study patients.

Outcomes	N = 273
Mortality, n (%)	
ICU mortality	72 (26.4)
In-hospital mortality	101 (37.0)
1-year mortality	120 (44.0)
Complications, n (%)	
Infections	118 (43.2)
Sepsis/septic shock	82 (30.0)
Need for invasive mechanical ventilation	82 (30.0)
Need for renal replacement therapy	15 (5.5)
Need for vasopressors/inotropes support	87 (31.9)
Acute myocardial infarction	1 (0.4)
Cerebral ischemia	1 (0.4)
Length of Stay (d), median (IQR)	
ICU	4 (3–6)
Hospital	17 (10–28)
ICU readmission, n (%)	
Readmission 60 days	23 (8.4)
Readmission 90 days	27 (9.9)
Readmission 6 months	29 (10.6)
Readmission 1 year	37 (13.6)

ICU, Intensive Care Unit; IQR, Interquartile Range.

TABLE 3. Multivariable Cox proportional hazard regression for factors associated with ICU and in-hospital mortality in patients with solid tumors admitted to the ICU.

Variable	Hazard ratio (HR)	95% Confidence interval (CI)	*p* value
ICU mortality			
Age	1.006	0.987–1.025	0.55
Gender (male)	0.808	0.442–1.476	0.49
Chemotherapy 4 weeks before ICU admission	2.240	1.198–4.189	0.01
Radiotherapy 4 weeks before ICU admission	0.639	0.280–1.456	0.29
Received blood transfusion	0.712	0.393–1.289	0.26
Pre-Septic shock	1.959	0.753–5.097	0.17
Hemodynamic instability	2.036	0.903–4.592	0.09
APACHE II score	1.053	1.006–1.102	0.03
SOFA score	1.091	1.005–1.184	0.04
Respiratory comorbidity	0.258	0.077–0.866	0.03
Neurological comorbidity	0.427	0.170–1.072	0.07
Cardiovascular comorbidity	1.083	0.597–1.966	0.79
Renal comorbidity	1.386	0.494–3.888	0.54
Endocrine comorbidity	0.743	0.425–1.300	0.30
Hematological comorbidity	1.186	0.601–2.339	0.62
Presence of metastasis	0.749	0.418–1.343	0.33
Need for MV	1.501	0.777–2.901	0.23
Need for RRT	0.413	0.180–0.946	0.04
Hospital mortality			
Age	1.007	0.991–1.023	0.39
Gender (male)	0.808	0.442–1.476	0.49
Chemotherapy 4 weeks before ICU admission	2.100	1.208–3.579	0.01
Radiotherapy 4 weeks before ICU admission	0.905	0.466–1.756	0.77
Received blood transfusion	1.060	0.648–1.735	0.82
Pre-Septic shock	0.795	0.366–1.730	0.56
Hemodynamic instability	0.974	0.502–1.890	0.94
APACHE II score	1.041	1.003–1.081	0.05
SOFA score	1.099	1.024–1.179	0.01
Respiratory comorbidity	0.170	0.0613–0.470	0.01
Neurological comorbidity	0.501	0.239–1.049	0.07
Cardiovascular comorbidity	1.326	0.806–2.181	0.27
Renal comorbidity	2.528	1.031–6.195	0.04
Endocrine comorbidity	0.721	0.449–1.159	0.18
Hematological comorbidity	1.272	0.720–2.248	0.41
Presence of metastasis	0.769	0.480–1.232	0.23
Need for MV	1.562	0.915–2.670	0.10
Need for RRT	0.537	0.264–1.091	0.09

APACHE II, Acute Physiology and Chronic Health Evaluation II; ICU, Intensive Care Unit; MV, Mechanical Ventilation; RRT, Renal Replacement Therapy; SOFA, Sequential Organ Failure Assessment.

4. Discussion

This study examined the challenges faced by severely ill cancer patients hospitalized in ICUs, focusing on their clinical characteristics, mortality outcomes, and predictors of adverse outcomes. Our study analyzed 273 patients with solid tumors, majority of whom were admitted to the ICU due to postoperative complications. Nearly half of the patient cohort had lower gastrointestinal tract cancer, one-quarter presented with metastasis, and two-thirds received chemotherapy within four weeks before ICU admission. The ICU and hospital mortality rates were 26.4% and 37%, respectively. Recent administration of chemotherapy emerged as a significant risk factor for mortality, with APACHE II and SOFA scores also demonstrating associations with mortality outcomes.

We acknowledge the seminal work by Al-Dorzi *et al.* [8], who reported a notably high in-hospital mortality rate of 70.5% among patients with hematologic malignancies requiring mechanical ventilation. Septic shock and male gender were identified as significant predictors of mortality in this population. Additionally, a retrospective study by AlSaied *et al.* [9] included 410 cancer patients admitted to the ICU, with patients having hematologic malignancies constituting 48% and those with non-hematologic malignancies comprising approximately 52%. The overall ICU mortality rate for cancer patients with non-hematological malignancies was 47%. Significant predictors of mortality included need for MV, RRT, vasopressor use, and presence of febrile neutropenia. Furthermore, Lababidi *et al.* [10] examined the clinical characteristics linked to outcomes and determinants of ICU mortality in cancer patients. They included a total of 108 cancer patients admitted to the ICU. Their cohort consisted of 43% with hematologic malignancies and 57% with non-hematologic malignancies. The mortality rate for patients with non-hematological malignancies was 61%, whose key predictors included use of vasopressor, cardiopulmonary resuscitation before ICU admission, sepsis, and the need for invasive ventilatory support. In contrast to the abovementioned studies, our cohort, which exclusively examined patients with solid tumors admitted to the ICU, showed notably lower rates of ICU and hospital mortality. This discrepancy may be attributed to variability in patient population, baseline characteristics, illness severity risk profiles, and the nature of medical interventions. Moreover, the 1-year mortality rate observed in our study was 44%, offering a nuanced perspective on these challenging cases, given that the reported long-term in-hospital mortality rate ranges from 11% to 54% in patients with solid tumors after critical illness [11, 12]. In addition, the results of our study emphasize the role of recent chemotherapy as a distinct and significant prognostic indicator of mortality. Likewise, our findings underscore factors such as higher severity of illness scores as strong predictors of mortality, which is consistent with prior literature.

Colorectal and other gastrointestinal malignancies were heavily represented in this ICU cancer population. Notably, 28.8% of patients had metastatic disease, and 65.2% had received chemotherapy within four weeks prior to ICU admission, reflecting a cohort with substantial oncologic burden and recent exposure to immunosuppressive therapy (Table 1). High complication rates were also observed, with infections (43.2%), mechanical ventilation (30%), and vasopressor use (31.9%) being the most frequent. These indicators reflect the high acuity of illness in this population (Table 2).

Hospitalization among critically ill patients with solid tumors may be prolonged in those who have recently received chemotherapy. Shaz *et al.* [11] investigated 73 patients who received chemotherapy during ICU admission and reported significantly longer ICU LOS (median 7 days) and hospital LOS (median 15 days) compared to patients who did not receive chemotherapy. In contrast, our cohort population included 65% of the patients who had received chemotherapy within 4 weeks of ICU admission, with median ICU and hospital LOS of 4 and 17 days, respectively. ICU readmission rates increased progressively over time, reaching 13.6% at one year. This emphasizes the importance of post-discharge surveillance and continuity of care in cancer patients recovering from critical illness (Table 2).

Our research reinforces the pivotal role of organ failure as a key prognostic indicator in critically ill cancer patients admitted to the ICU, consistent with previous studies [13, 14]. The clinical trajectory of critically ill patients with solid tumors is primarily determined by the number and severity of organ dysfunctions. In the critical care setting, scoring systems are valuable tools to quantify the severity of illness, thus allowing patients at high risk of hospital mortality to be identified [15]. Our study supports that the need for aggressive interventions such as vasopressor support, renal replacement therapy, and other invasive procedures is significantly associated with increased mortality risk [16, 17]. Additionally, recent exposure to chemotherapy is linked to increased mortality rates among cancer patients admitted to ICU. Studies focusing on solid tumors show ICU mortality rates of between 27.6% and 48.9% when chemotherapy is administered urgently or within 30 days, compared to 23.4% to 25.5% in the control groups. Hospital mortality in these patients ranged from 55.3% to 77%, with one study observing a 90-day mortality rate of 65.8%, in contrast to 59.9% in control groups [18–20].

Moreover, it is possible that patients with respiratory comorbidities were less likely to receive invasive mechanical ventilation, particularly considering that a significant portion of the cohort was undergoing chemotherapy. Existing literature regarding cancer patients advocates for the avoidance of invasive mechanical ventilation within this population, as it is correlated with improved outcomes [21–23]. Another plausible explanation is the presence of residual confounding related to differences in care delivery; patients with respiratory comorbidities might have received closer monitoring and more attentive management by healthcare staff, which could have contributed to the observed trend in mortality outcomes.

Our study has important clinical implications for the management of critically ill cancer patients. The independent association of SOFA and APACHE II scores with higher mortality highlights the value of validated scoring systems in quantifying disease severity and guiding risk stratification [24]. These tools enable clinicians to identify patients at elevated risk of poor outcomes, thereby supporting more targeted interventions and efficient resource allocation. Our study's findings

highlight the necessity of a multidisciplinary approach for treating critically ill cancer patients, involving oncologists, intensivists, clinical pharmacists, and other specialists to improve patient care.

This study has several important limitations to consider. It was a retrospective, single-center study conducted in Saudi Arabia, which may limit the generalizability of the findings to a broader national or international context. Additionally, there exists a potential selection bias inherent in the study design that could have impacted the significance of the results. Detailed information concerning the stage or grade of cancer was not available, complicating the evaluation due to variations in the illness's nature and the decision-making processes related to ICU admission, discharge, and treatment; thus, making inter-study mortality comparisons challenging. Additionally, the lack of long-term follow-up data limited our ability to assess post-discharge outcomes such as functional recovery and quality of life. Nevertheless, we were able to report hospital readmission and mortality outcomes within one year of discharge. A longitudinal study design could provide a more comprehensive understanding of dynamic changes in patient characteristics, interventions, and outcomes over time. The application of advanced analytical approaches such as machine learning algorithms for predicting ICU admission and mortality in cancer patients could offer enhanced precision and individualized care. Collaborative multicenter studies including diverse patient populations and healthcare settings are crucial to enhance the generalizability and robustness of our findings.

Nonetheless, our findings help bridge a critical gap in understanding the intensive care needs of cancer patients in the region. By identifying predictors of mortality, we contributed to the evolving landscape of oncologic critical care in Saudi Arabia, offering insights that may inform clinical practice, resource allocation, and future research.

5. Conclusions

This study explored the complex clinical landscape of critically ill cancer patients admitted to intensive care units, shedding light on their clinical characteristics, mortality outcomes, and predictors of mortality. This study not only adds to the body of knowledge in critical care for cancer patients, but also emphasizes the intricate balance between critical illness and cancer management. Understanding the association of recent chemotherapy and severity scores with mortality underscores the utility of these variables for assessing disease severity, guiding risk stratification, enhanced patient management, and tailored interventions. As we navigate the evolving healthcare landscape, this study offers valuable direction for enhancing the quality and outcomes of critical care delivered to cancer patients in Saudi Arabia.

AVAILABILITY OF DATA AND MATERIALS

The dataset supporting the conclusions of this study is available upon request from the corresponding authors.

AUTHOR CONTRIBUTIONS

AMA and SSA—conceptualized and designed the study. SSA, LTA, RHA and AZA—carried out the investigation and collected the data. MHA—provided the software and conducted the formal analyses. AMA, MHA, FSA and KAAS—checked the validity of the analysis, visualization of the results, and its interpretation. AMA, SSA, LTA and RHA—were major contributors to the writing of the initial draft of the manuscript. NAA, RMA, FSA, KAAS, RKA, MAA and MIA—critically reviewed the manuscript for important intellectual content. All of the authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study protocol was approved by the Institutional Review Board of King Saud University Medical City, Riyadh, Saudi Arabia (No. E-21-5793). The requirement for informed consent was waived by the Institutional Review Board of King Saud University Medical City, Riyadh, Saudi Arabia.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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