Original Article

Outcome of Cancer Patients with an Unplanned Intensive Care Unit Admission: Predictors of Mortality and Long-term Survival

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Abstract

Background: Understanding the characteristics and outcomes of cancer patients with unplanned ICU admission is imperative for therapeutic decisions and prognostication purposes.

Objective: To describe the clinical characteristics of patients with hematological and non-hematological malignancies (NHM) who require unplanned ICU admission and to determine the predictors of mortality and long-term survival.

Methods: This retrospective study included all patients with cancer who had an unplanned ICU admission between 2011 and 2016 at a tertiary hospital in Saudi Arabia. The following variables were collected: age, gender, ICU length of stay (LOS), APACHE II score, type of malignancy, febrile neutropenia, source and time of admission, and need for mechanical ventilation (MV), renal replacement therapy (RRT), and treatment with vasopressors (VP). Predictors of mortality and survival rates at 28 days and 3, 6, and 12 months were calculated.

Results: The study included 410 cancer patients with 466 unplanned ICU admissions. Of these, 52% had NHM. The average LOS in the ICU was 9.6 days and the mean APACHE score was 21.9. MV was needed in 73% of the patients, RRT in 15%, and VP in 24%, while febrile neutropenia was present in 24%. There were statistically significant differences between survivors and non-survivors in the APACHE II score (17.7 ± 8.0 vs. 25.6 ± 9.2), MV use (52% vs. 92%), need for RRT (6% vs. 23%), VP use (42% vs. 85%), and presence of febrile neutropenia (18% vs. 30%). The predictors of mortality were need for MV (OR = 4.97), VP (OR = 3.43), RRT (OR = 3.31), and APACHE II score (OR = 1.10). Survival rates at 28 days, 3, 6, and 12 months were 52%, 28%, 22%, and 15%, respectively.

Conclusion: The survival rate of cancer patients with an unplanned admission to the ICU remains low. Predictors of mortality include need for MV, RRT, and VP and presence of febrile neutropenia. About 85% of cancer patients died within 1 year after ICU admission.

Keywords: APACHE II score, cancer, critical care, hematologic malignancies, intensive care unit, nonhematologic malignancies, mortality, survival rate

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INTRODUCTION

The incidence of cancer has been steadily increasing in Saudi Arabia in the past few years.[1] The majority of the cancer cases are due to solid tumors as opposed to hematological malignancies (HM), with 20,741 (85%) and 3744 (15%) cases annually, respectively.[2] It is estimated that in 2025, there will be >150,000 new cases of cancer in Saudi Arabia, with >30,000 deaths.[3] During the care process of patients with cancer, there is an increase in the probability of life-threatening events requiring admission to an intensive care unit (ICU).[4]

The ICU mortality rate of patients with cancer ranges between 30% and 77%.[5-7] This wide range is due to several factors such as the type of malignancy, the reason for admission, presence of metastasis, number of organ failures, and therapies received before ICU admission.[8] ICU has undoubtedly contributed significantly to the increase in survivability of acute illness in patients with cancer. In a study of 622 patients with solid cancer who were admitted to ICU, survivorship was 77.8%; of these, 58.7% survived 1 year.[9] The triage and prioritization of critically ill cancer patients for ICU admission depends on many factors with low agreement among intensivists.[10] The type and stage of cancer, short- and long-term prognosis, quality of life, age, treatment options, palliative care, patient's wishes, availability of resources, and cost are to be considered when a decision is made to admit cancer patients to ICU.[11]

There is limited data in Saudi Arabia that examines the characteristics and outcomes of cancer patients in the ICU. Anecdotal reports on a small cohort of cancer patients admitted to ICU showed an overall mortality rate of 57%,[12] 60% in patients with lung cancer,[13] and 73% with HM.[14] Another study found that the in-hospital mortality in 121 patients with HM who were admitted to ICU and required invasive ventilation was 71%.[15] However, there are no previous studies about the long-term mortality of oncology patients following unplanned ICU admissions in Saudi Arabia. Accordingly, updated and local data may enhance the understanding of outcomes of cancer patients in ICU, and allow intensivists to deliver more realistic expectations to patients and their families. Therefore, this study was conducted with the objective of describing the clinical characteristics of patients with HM and non-hematological malignancies (NHM) who required unplanned ICU admission at a tertiary hospital in Saudi Arabia and to determine the predictors of mortality and long-term survival.

METHODS

The STROBE guidelines for reporting observational studies has been followed in this study.[16]

Study design, setting, and patients

This is a retrospective study of patients with cancer who were admitted to the ICU at King Fahad Medical City (KFMC), Riyadh, between January 01, 2011, and December 31, 2016. Patients with planned ICU admissions, such as elective post-oncological surgical care, were excluded from the study. The study was approved by the local Institutional Review Board at KFMC.

Outcomes and Variables

The primary outcomes were predictors of mortality and survival rates at 28 days and 3, 6, and 12 months. The following characteristics were collected from the medical records: age, gender, ICU length of stay (LOS), APACHE II score, type of malignancy, source of admission (i.e., emergency department [ED] or hospital ward), time of admission (i.e., during the regular working hours or at night), need for invasive mechanical ventilation (MV), duration of MV, need for renal replacement therapy (RRT), need for treatment with vasopressors (VPs), and presence of febrile neutropenia. The 28-day survival rate was calculated by following up the medical records until discharge or death, while the 3-, 6-, and 12-month survival was determined by checking the hospital electronic records for admissions, clinic visits, emergency room visits, and/or death notes.

Data analysis

All collected data were reviewed by the primary investigator (G.A.S.), and when necessary, data were cleaned and verified. The statistical analysis was carried out using the R program (version 1.4.1103). Descriptive statistics for quantitative variables were carried out by calculating the mean, standard deviation, median, quartiles, minimum and maximum. The analysis of qualitative variables was determined by calculating the number and percentage of occurrences of each value. The comparison of values of qualitative variables in groups was done using Pearson's Chi-squared test with Yates' continuity correction. The quantitative variables comparison of the values in two groups was performed using Welch's two-sample *t*-test. A significance level of 0.05 was assumed in the analysis.

Logistic regression models were computed to determine the association between mortality and the following covariates: age, gender, ICU LOS, APACHE II score, type of malignancy, source of admission, time of admission,

need for MV, need for RRT, need for VP, and presence of febrile neutropenia. The logistic regression models were assessed for the goodness of fit using residual deviance, McFadden Pseudo-R^2, Hosmer and Lemeshow test, and Akaike's information criteria. The diagnostic tests performed on the models to test the assumptions were residual plots, marginal plots, Durbin-Watson test for autocorrelation, multicollinearity, and mean of residuals. Four different logistic regressions were done and the odds ratios were generated on the associations to predict mortality on all cancer patients admitted to ICU, those with HM and NHM, and patients who required MV.

The Cox proportional hazards model was computed to assess the hazard ratio (HR) of selected covariates. Aalen's additive regression model for censored data was computed to assess the effect of the independent variables over time. Kaplan–Meier curves for the ICU LOS were presented with the following variables: cancer type, gender, need for MV, need for RRT, VP use, and presence of neutropenia. ICU survival curves were analyzed at 28-days and at 3, 6, and 12 months.

RESULTS

Characteristics of the patients

Over the study period, 466 of 7491 (6%) admissions to the medical/surgical ICU were of 410 patients with cancer. Forty-eight patients (12%) had multiple admissions to the ICU: 40 (10%) had two admissions and 8 (2%) had three admissions. General data analysis is performed on the 466 admissions; however, survival analysis was performed on the 410 patients. In terms of malignancies, 240 (52%) admissions were NHM, while 226 (48%) were HM. Table 1 summarizes the characteristics of the patients in both groups. Patients with NHM were slightly older than those with HM (53.5 ± 16.3 years vs. 48.7 ± 19.9 years); however, the HM and NHM groups had comparable APACHE II scores (22.3 ± 9.6 vs. 21.5 ± 9.4) and ICU LOS (8.7 ± 11.5 days vs. 10.4 ± 15.4 days).

About three-fourth of the patients (73%) required invasive MV, while 4.5% received non-invasive ventilation and 22.5% did not require ventilatory support. The overall need for VP to attain stability in hemodynamics was 67%. More patients with HM presented with febrile neutropenia than patients with NHM (35% vs. 14%). The overall mortality rate was 52% of all patients with malignancies admitted to ICU [Table 2]. There were statistically significant differences between survivors and non-survivors in APACHE II score (17.7 ± 8.0 vs. 25.6 ± 9.2), MV use (52% vs. 92%), need for RRT (6% vs. 23%), VP use (42% vs. 85%), and presence of febrile neutropenia (18% vs. 30%). Figure 1 presents the Kaplan–Meier curve of ICU LOS for cancer patients admitted to ICU as a factor of the following covariates: gender, type of malignancy (HM vs. NHM), MV use, VP use, need for RRT, and presence of febrile neutropenia. The source of admission and time of admission had no impact on mortality.

Predictors of mortality

The logistic regression analysis to predict mortality in all patients with malignancies admitted to ICU is presented in Table 3. For cancer patients admitted to the ICU, the predictors for mortality in order of importance included the need for MV (OR = 4.97, CI: 2.48–9.98), need for VP (OR = 3.43, CI: 1.87–6.27), need of RRT (OR = 3.31, CI: 1.41–7.78), and APACHE II score (OR = 1.10, CI: 1.06–1.14) [Table 3]. For HM patients admitted to the ICU, the predictors for mortality in order of importance included the need for MV (OR = 19.67, CI: 4.53–85.46), need for VP (OR = 4.58, CI: 1.48–14.16), and APACHE II score (OR = 1.07, CI: 1.01–1.14) [Table 4]. The same predictors hold for mortality in NHM: need for

Table 1: Characteristics of the cancer patients admitted to the intensive care unit by type of cancer

Characteristics	All (*n*=466)	Type of cancer		
		Hematologic malignancies (*n*=226; 48%)	Nonhematologic malignancies (*n*=240; 52%)	*P*
Age (years)	51.2±18.3	48.7±19.9	53.5±16.3	0.005*
Male, *n* (%)	224 (48)	114 (50)	110 (46)	0.367
APACHE II score	21.9±9.5	22.3±9.6	21.5±9.4	0.351
ED admission, *n* (%)	133 (28)	51 (23)	82 (34)	0.008*
Regular hours admission, *n* (%)	193 (41)	108 (48)	85 (35)	0.009*
ICU LOS (days)	9.6±13.7	8.7±11.5	10.4±15.4	0.186
MV use, *n* (%)	340 (73)	173 (76)	167 (69)	0.112
Days on MV	7.4±9.6	7.0±8.8	7.8±10.4	0.475
Need for RRT, *n* (%)	70 (15)	43 (19)	27 (11)	0.027*
VP use, *n* (%)	264 (67)	137 (70)	127 (64)	0.301
Febrile neutropenia, *n* (%)	114 (24)	80 (35)	34 (14)	<0.001*

*Statistically significance. ED – Emergency department; MV – Mechanical ventilation; RRT – Renal replacement therapy; VP – Vasopressors; ICU – Intensive care unit; LOS – Length of stay; APACHE II – Acute Physiology and Chronic Health Evaluation II

Table 2: Outcomes of the cancer patients admitted to the intensive care unit

Characteristics	All (*n*=466)	Outcome		
		Survivors (*n*=222; 48%)	Nonsurvivors (*n*=244; 52%)	*P*
Age (years)	51.2±18.3	50.5±18.7	51.8±17.9	0.442
Male, *n* (%)	224 (48)	103 (46)	121 (50)	0.551
APACHE II	21.9±9.5	17.7±8.0	25.6±9.2	<0.001*
ED admission, *n* (%)	133 (28)	66 (30)	67 (27)	0.660
Regular hours admit, *n* (%)	193 (41)	84 (37)	109 (45)	0.161
ICU LOS	9.6±13.7	9.5±13.5	9.7±13.8	0.886
MV use, *n* (%)	340 (73)	115 (52)	225 (92)	<0.001*
Days on MV	7.4±9.6	7.7±9.8	7.3±9.6	0.753
Need for RRT, *n* (%)	70 (15)	14 (6)	56 (23)	<0.001*
VP use, *n* (%)	264 (67)	72 (42)	192 (85)	<0.001*
Febrile neutropenia, *n* (%)	114 (24)	41 (18)	73 (30)	<0.006*

*Statistically significance. ED – Emergency department; MV – Mechanical ventilation; RRT – Renal replacement therapy, VP – Vasopressors; ICU – Intensive care unit; LOS – Length of stay; APACHE II – Acute Physiology and Chronic Health Evaluation II

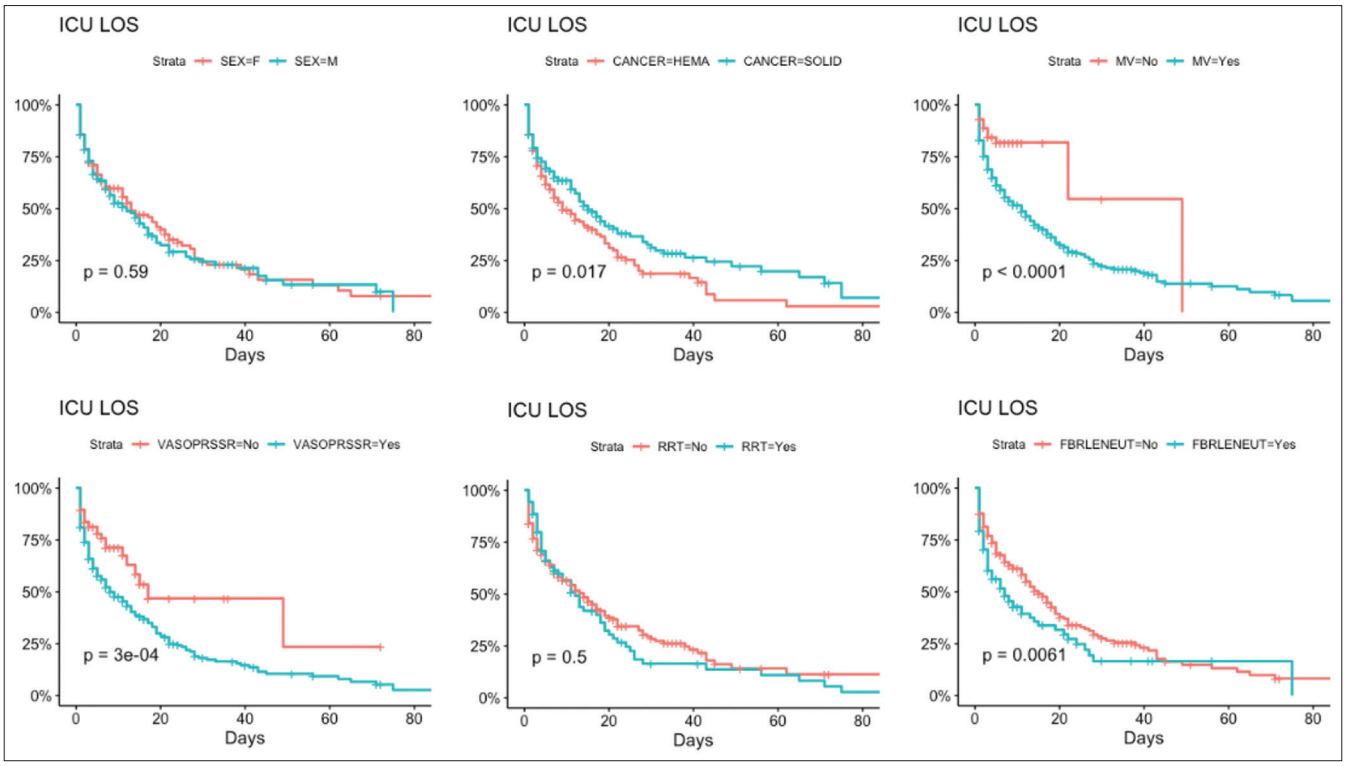

Figure 1: Kaplan–Meier curve of intensive care unit (ICU) length of stay for cancer patients admitted to the ICU based on covariates. ICU – Intensive care unit; LOS – Length of stay; MV – Mechanical ventilation; RRT – Renal replacement therapy

MV (OR = 4.85, CI: 1.97–11.97), need for VP (OR = 3.87, CI: 1.70–8.81), and APACHE II score (OR = 1.09, CI: 1.03–1.14) [Table 5]. For cancer patients who were admitted to ICU and required MV, the predictors of mortality were the need for VP (OR = 5.21, CI: 2.23–12.16), need for RRT (OR = 3.54, CI: 1.13–11.08), HM (OR = 2.33, CI: 1.10–4.91) and APACHE II score (OR = 1.10, CI: 1.04–1.15) [Table 6].

The Cox proportional hazards model for mortality of cancer patients admitted to ICU is presented in Figure 2. The most significant covariates were the need for MV (HR = 4.45, CI: 2.65–7.48, $P < 0.001$), need for VP (HR = 2.19, CI: 1.47–3.27, $P < 0.001$), and presence of febrile neutropenia (HR = 1.43, CI: 1.05–1.94, $P = 0.023$). Aalen's additive regression model for censored data demonstrated the effects of the covariates over time. There was a steep slope and then abrupt change in the need for MV, VP use, and to a lesser extent with febrile neutropenia [Figure 3].

Survival curves

The overall ICU survival rate for cancer patients admitted to ICU was 48% (HM: 42%; NHM: 53%). The 28-day ICU survival was 52%. The survival rate decreased progressively at 3, 6, and 12 months to 28%, 22%, and 15%, respectively [Figure 4].

Table 3: Logistic regression to predict mortality in cancer patients admitted to the intensive care unit

Variables	Mortality	
	Logit	OR (2.5%–97.5%)
Age	0.004	1.00 (0.99–1.02)
Male	0.278	1.32 (0.76–2.29)
APACHE II score	0.095***	1.10 (1.06–1.14)
HM	0.045	1.05 (0.59–1.84)
MV use	1.604***	4.97 (2.48–9.98)
RRT need	1.197**	3.31 (1.41–7.78)
VP use	1.231***	3.43 (1.87–6.27)
Febrile neutropenia	0.445	1.57 (0.80–3.08)

**$P<0.05$; ***$P<0.01$. HM – Hematologic malignancy; MV – Mechanical ventilation; RRT – Renal replacement therapy; VP – Vasopressors; OR – Odds ratio; ICU – Intensive care unit; LOS – Length of stay; APACHE II – Acute Physiology and Chronic Health Evaluation II

Table 4: Logistic regression to predict mortality in patients with hematological malignancies admitted to the intensive care unit

Variables	Mortality	
	Logit	OR (2.5%–97.5%)
Age	−0.008	1.00 (0.97–1.02)
Male	−0.082	1.24 (0.37–2.29)
APACHE II score	0.067*	1.07 (1.01–1.14)
Regular hours admit	−0.177	0.84 (0.32–2.18)
ED admit	−0.714	0.49 (0.16–1.48)
ICU LOS	−0.033	0.97 (0.94–1.00)
MV use	2.979***	19.67 (4.53–85.46)
RRT need	1.263	3.53 (0.95–13.12)
VP use	1.522**	4.58 (1.48–14.16)
Febrile neutropenia	−0.240	0.79 (0.29–2.16)

*$P<0.1$; **$P<0.05$; ***$P<0.01$. ED – Emergency department; MV – Mechanical ventilation; RRT – Renal replacement therapy; VP – Vasopressors; OR – Odds ratio; ICU – Intensive care unit; LOS – Length of stay; APACHE II – Acute Physiology and Chronic Health Evaluation II

Table 5: Logistic regression to predict mortality in patients with nonhematological malignancies admitted to the intensive care unit

Variables	Mortality	
	Logit	OR (2.5%–97.5%)
Age	0.014	1.00 (0.99–1.02)
Male	0.261	1.30 (0.61–2.75)
APACHE II score	0.082**	1.09 (1.03–1.14)
Regular hours admit	−0.336	0.71 (0.32–2.18)
ED admit	−0.527	0.59 (0.27–1.30)
ICU LOS	−0.023	0.98 (0.95–1.01)
MV use	1.579***	4.85 (1.97–11.97)
VP use	1.354**	3.87 (1.70–8.81)
Febrile neutropenia	0.849	2.34 (0.79–6.89)

**$P<0.05$; ***$P<0.01$. ED – Emergency department; LOS – Length of stay; MV – Mechanical ventilation; VP – Vasopressors; OR – Odds ratio; ICU – Intensive care unit; APACHE II – Acute Physiology and Chronic Health Evaluation II

Table 6: Logistic regression to predict mortality in cancer patients requiring mechanical ventilation admitted to the intensive care unit

Variables	Mortality	
	Logit	OR (2.5%–97.5%)
Age	0.014	1.01 (0.99–1.04)
Male	−0.077	0.93 (0.45–1.93)
APACHE II score	0.093***	1.10 (1.04–1.15)
ICU LOS	−0.065**	0.94 (0.89–0.98)
MV duration (days)	0.056	1.06 (0.99–1.13)
HM	0.845*	2.33 (1.10–4.91)
VP use	1.650***	5.21 (2.23–12.16)
RRT need	1.263*	3.54 (1.13–11.08)

*$P<0.1$; **$P<0.05$; ***$P<0.01$. LOS – Length of stay; MV – Mechanical ventilation; HM – Hematologic malignancy; VP – Vasopressors; RRT – Renal replacement therapy; OR – Odds ratio; ICU – Intensive care unit; APACHE II – Acute Physiology and Chronic Health Evaluation II

DISCUSSION

Admissions to ICU by oncology patients vary significantly among hospitals. In our study, around 6% of ICU admissions over the 6-year study period were related to cancer, which is similar to the rates reported previously.[17,18] The disease severity requires patients to stay for a longer duration in ICU and may require multiple ICU admissions during their disease course. The mortality rate for cancer patients who are admitted to the ICU remains high despite the medical and pharmacological advances.[19]

There are many factors contributing to poor prognosis and increased mortality that are beyond the scope of ICU, such as advanced disease state, and care rendered at home, emergency room, and general wards. Our study showed a mortality rate of 52% in patients with cancer who had an unplanned admission to the ICU, with non-significant differences between HM and NHM patients. The crude mortality rates in similar studies have been reported to vary from 16% to 47%.[20-22]

Efforts to reduce the 28-day mortality in cancer patients with an ICU admission need to encompass the entire journey of such patients. However, factors that are independently associated with higher mortality in cancer patients admitted to ICU include emergency department admission, sepsis, invasive MV, and chemotherapy-induced adverse events.[18] Moreover, the use of VP and CPR before ICU admission are predictors of mortality.[22] Unexpected readmission of cancer patients to ICU has been shown to increase the risk of hospital mortality. The ICU readmission rates in cancer patients vary from 20% to 34%;[23] in our population, the rate of ICU readmission was 12%. The APACHE II score remains a reliable indicator for disease severity in cancer patients admitted to the ICU.[24] There was no significant difference in APACHE II scores between patients with HM or NHM. Notably, the patients in the current study had a high disease severity, as evidenced by the high APACHE II scores with significant

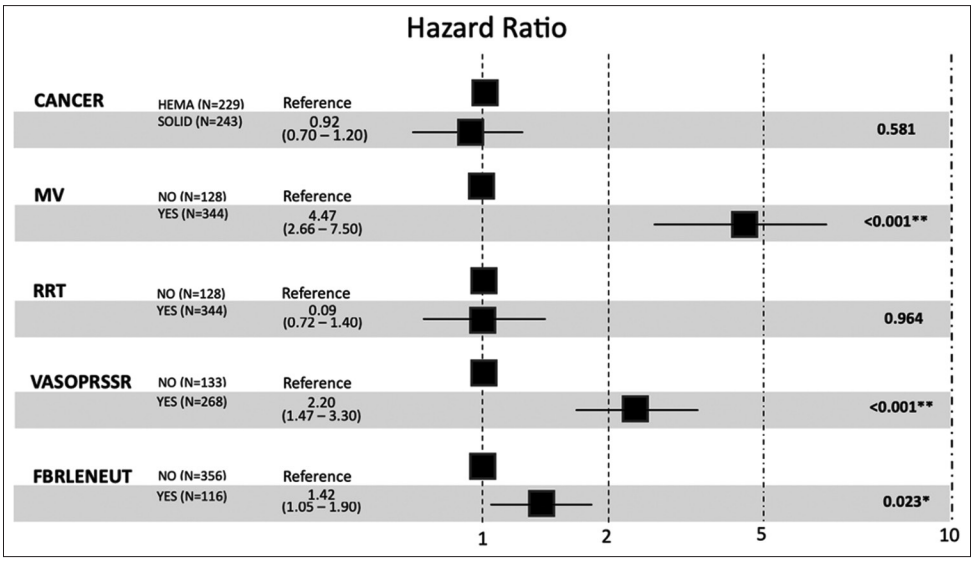

Figure 2: Cox proportional hazards model for mortality of cancer patients admitted to intensive care unit. MV – Mechanical ventilation; RRT – Renal replacement therapy. **P* < 0.1; ***P* < 0.05; ****P* < 0.01

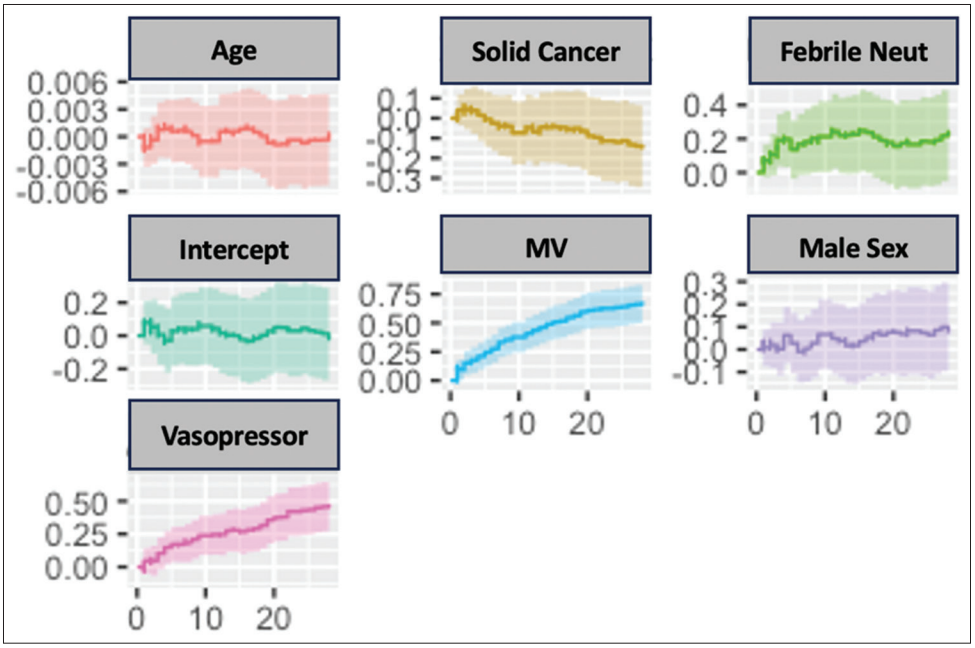

Figure 3: Aalen's additive regression model for censored data for mortality of cancer patients admitted to intensive care unit

differences in APACHE II scores between survivors and non-survivors.

Our study revealed that the need for MV in cancer patients in ICU is a strong predictor of mortality. In a systematic review of 22 studies, the ICU mortality rate and the long-term mortality were 68% and 90%, respectively, among the 3115 cancer patients requiring invasive MV.[25] A recent study that included lung cancer patients who needed MV found that the 28-day mortality was 52% among those with metastasis and 66% among those without metastasis, which was higher compared to other cancer patients needing MV: 44% and 62%, respectively.[26] The need for RRT of cancer patients in ICU has increased substantially over the past decades and varies from 10% to 34%.[27] The rate of acute kidney injury with subsequent RRT in ICU is higher in HMs.[28] In our study, the requirement of RRT in cancer patients in ICU was a strong predictor of mortality (OR = 3.31; 1.41–7.78), with more patients with HM compared with NHM. The use of VPs in cancer patients in ICU is associated with worse outcomes, especially if VPs are used in conjunction with other organ support such as MV and RRT.[29,30]

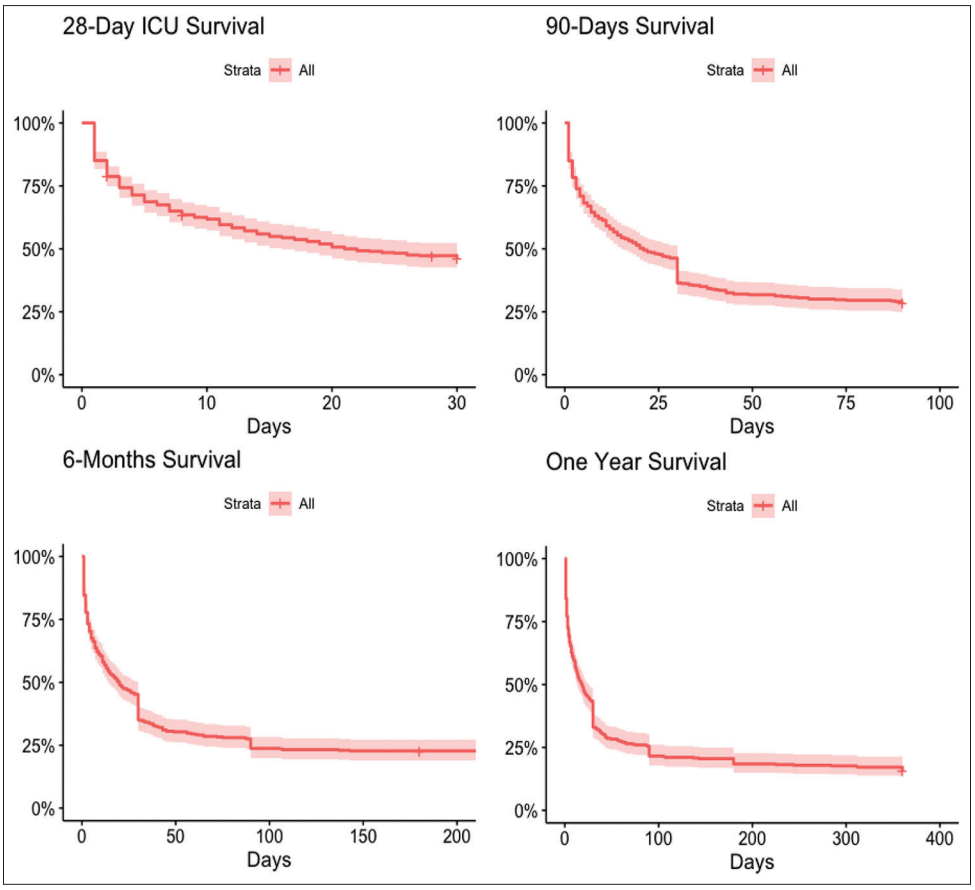

Figure 4: Kaplan–Meier survival curves for cancer patients admitted to intensive care unit. ICU – Intensive care unit

The presence of febrile neutropenia in cancer patients admitted to ICU is associated with increased morbidity and mortality,[31] especially if they require invasive ventilation.[32,33] Although there were more cases with febrile neutropenia in our study in the HM group (35%) compared with the NHM group (14%), febrile neutropenia was a predictor of mortality in NHM (OR = 2.34) but not in HM (OR = 0.79).

The long-term survival of cancer patients remains low and decreases progressively over a 12- month period following an ICU admission. The 3-, 6-, and 12-month survival rates of the current are consistent with those reported previously.[34] However, controversy remains whether the causes of the poor outcome are related to the underlying malignancy or non-cancer-related illnesses.[35]

Limitations

This study has several limitations. First, it is a retrospective and single-center study; however, KFMC is a tertiary referral center with more than 40% of the patients are from areas outside Riyadh. Second, data on the total number of cancer patients who were admitted to KFMC during this period was not available to quantitate the percentage of cancer patients who required ICU admission. Third, the study did not differentiate between medical and surgical unplanned ICU admissions. However, from the experience of the authors, the surgical unplanned ICU admissions are a minority (<10% of the total admissions). Fourth, the survival data did not include detailed patients' characteristics, and thus no multivariate analysis was conducted on follow-up visits or admissions.

CONCLUSION

The survival rate of cancer patients with an unplanned admission to the ICU remains low. Mortality predictors include the need for MV, RRT, and VP and the presence of febrile neutropenia. The long-term survival of cancer patients is low and decreases progressively over 12 months after an ICU admission.

Ethical considerations

The research was approved by the Institutional Review Board at KFMC, Riyadh, Saudi Arabia (IRB log number 16-073; IRB registration number with KACST, KSA: H-01-R-012; IRB registration number with OHRP/NIH, USA: IRB00008644; Approval number Federal Wide

Assurance NIH, USA: FWA0018774). The requirement for informed consent was waived owing to the study design. The study adhered to the principles of the Declaration of Helsinki, 2013.

Peer review

This article was peer-reviewed by two independent and anonymous reviewers.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author contributions

Conceptualization: G.S., A.A., and M.A.; Methodology: G.S., H.L., T.A., and S.A.; Data analysis: G.S., H.L., and M.A.; Writing–original draft preparation: G.S., T.A., S.A, and M.A.; Writing – review and editing: G.S and H.L.; Supervision: G.S. and M.A.

All authors have read and agreed to the published version of the manuscript.

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Conflicts of interest

There are no conflicts of interest.

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