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RESEARCH ARTICLE

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Factors Associated with Mortality in Patients with a Solid Malignancy Admitted to the Intensive Care Unit - A Prospective Observational Study

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Abstract

Purpose: Several studies show conflicting results regarding the prognosis and predictors of the outcome of critically ill patients with a solid malignancy. This study aims to determine the outcome of critically ill patients, admitted to a hospital, with a solid malignancy and the factors associated with the outcomes.

Methods and Materials: All patients with a solid malignancy admitted to an intensive care unit (ICU) at a tertiary academic medical center were enrolled. Clinical data upon admission and during ICU stay were collected. Hospital, ICU, and six months outcomes were documented.

Results: There were 252 patients with a solid malignancy during the study period. Urogenital malignancies were the most common (26.3%) followed by lung cancer (23.5%). Acute respiratory failure was the most common ICU diagnosis (51.6%) followed by sepsis in 46%. ICU mortality and hospital mortality were 21.8% and 34.3%. Six months mortality was 38.4%. Using multivariate analysis, acute kidney injury, OR 2.82, 95% CI 1.50-5.32 and P=0.001, use of mechanical ventilation, OR 2.67 95% CI 1.37 – 5.19 and P=0.004 and performance status of ≥2 with OR of 3.05, 95% CI of 1.5- 6.2 and P= 0.002 were associated with hospital mortality. There were no differences in outcome between African American patients (53% of all patients) and other races.

Conclusion: This study reports encouraging survival rates in patients with a solid malignancy who are admitted to ICU. Patients with a poor baseline performance status require mechanical ventilation or develop acute renal failure have worse outcomes.

Keywords: Solid malignancy, critical care, outcome

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Introduction

Cancer remains one of the leading causes of death in the United States of America (USA). Currently, intensive care units (ICU) play a significant role in the management of cancer patients. Recent studies reveal that patients with cancer account for 15% of total admissions to an ICU [1]. However, patients with malignancies are responsible for almost half of the total ICU bed-days [2]. Despite significant advances in the treatment of cancer, patients admitted to an ICU with malignancies still have a higher mortality rate than patients without malignancies. Knowledge of the factors that influence outcomes in these patients is pivotal in their management, as it will help significantly in making appropriate triage decisions. While several studies have been published on the outcome predictors in patients with cancer in general or those with hematologic malignancies, there are only a few in those with solid malignancies and controversies remain regarding outcome-predictors in these patients (3). Besides, there are limited data from the USA and a lack of data on racial differences on these predictors. The primary aim was to identify the general characteristics and outcomes of patients with solid malignancies who are admitted to the intensive care unit (ICU) of a tertiary medical

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center in the United States. The usefulness of different critical care scoring systems as prognostic tools as well as the and identification of factors associated with poor outcomes were also evaluated.

Methods

This was a prospective cohort study in which patients were sequentially recruited over a two year period in an ICU of a tertiary medical center with a comprehensive cancer center, in Detroit, Michigan, USA. The Institutional Review Board (IRB) of Wayne State University in Detroit, Michigan approved the study. The principal investigator and his research associates screened all new admissions to the ICU on a daily basis. Patients were deemed eligible for enrollment in the study if they met the following inclusion criteria: they were 18 years of age or older, had an established diagnosis of malignancy that was under treatment or surveillance, and had a need for admission to the ICU due to life-threatening conditions during the study period. The exclusion criteria were: patients admitted under the surgical intensive care unit service, patients who were admitted to the ICU only for monitoring of chemotherapy, patients who were admitted for less than 24 hours and readmitted to the ICU within the study period.

Once eligible patients were identified, baseline data including demographics, a detailed description of malignancy, the reason for admission to the ICU and several clinical and laboratory parameters at the time of ICU admission. Also included at the time of ICU admission were baseline performance status using ECOG (Eastern Cooperative Oncology Group) score. Additionally, the Charlson baseline comorbidity index was calculated. Data regarding the patient's stage and type of malignancy were collected from patient notes. It was considered a "New Diagnosis" if the diagnosis was made within four weeks of admission to the ICU. The absence of evidence of an active primary malignancy was considered a case "in remission". Patients with relapsing malignancy were considered as "relapsed". The patients were then followed throughout their ICU stay to get updates on their ICU course until they were discharged from the ICU. Various scoring systems were used including the Acute Physiologic and Chronic Health Evaluation II (APACHE II), the APACHE III, the Simplified Acute Physiologic Score I, (SAPSI) SAPS II, Sepsis-related Organ Failure Assessment (SOFA), the Cancer Mortality Model (CMM), the Mortality Probability Model MPM) and the Logistic Organ Dysfunction Score (LODS). The patients were followed afterwards only to determine the total duration of their hospitalization, condition at the time of discharge and any readmission to the ICU. Six months after their ICU admission, the patient's final outcome was determined. By reviewing the medical record, all other information was collected. No diagnostic interventions, including laboratory, work up, imaging studies and diagnostic procedure, were ordered for the sole purpose of the study. All diagnostic interventions were decided upon and ordered by the primary ICU team responsible for the patient, based on what they deemed clinically appropriate.

Standard descriptive statistics were used to describe the study population. Continuous variables were reported using the mean and standard deviation. Categorical variables were reported using counts and percentages. Univariate and multivariate logistic regression models, adjusting for the different confounding factors, were used to determine factors that could be associated with poor outcome. Receiver operator curves were produced for various scoring systems and the area under the curves were determined.

Results

Of the 252 patients with solid malignancy enrolled in the study, 142 (56.4%) with a mean age of 61.6 {SD±12.4} years were female. One hundred and thirty-three (53%) of the patients were African Americans. Urogenital cancers were the most frequently reported solid malignancies (66 patients;26.3%) followed by lung cancer (59;23.5%)while head and neck cancers were the least reported (26;10.4%). The cancer stage was I in 5% of patient, stage II in 6%, stage III in 10% and stage IV in 59% of patients. In 20% of cases, the cancer stage was unknown at the time of admission to the ICU. Eighty-five patients (34.4%) presented with a baseline performance status of 2. Most of the patients (147;58.3%) were in remission during their initial visit to the ICU. A significant majority of the patients (169; 67%) were smokers, on average most patients spent 2.3 days in the hospital before ICU admission. A lactic acid level of more than 2 was reported in 141(60%) of the patients. Major reasons for ICU admission included sepsis in 116(46%) of patients and respiratory failure in 130; 51.6% of the patients. Other minor reasons are shown in Table 1. Major ICU interventions included the use of mechanical ventilation 127(50.4%) and administration of antibiotics 189 (75%).

Table 1. Baseline Characteristics on Intensive Care Unit Admission

Variable	Mean±SD, n(%)
Age (years)	61.6 ±12.4
Sex	
Male	110 (43.6)
Female	142 (56.4)
Race	
White	102(40.6)
African American	134(53)
Other	16(6.4)
Underlying malignancy	
Lung	59(23.5)
Breast	32(12.7)
Urogenital	66(26.3)
Head and Neck	26(10.4)
GI	37(14.7)
Other	32(12.7)
Baseline Performance Status	
0	20(8.1)
1	56(22.3)
2	87(34.4)
3	74(29.5)
4	15(5.7)
Disease status at admission	
Remission	147(58.3)
New diagnosis	47(18.7)
Relapse	58(23)
Smoking History	
Yes	169(67)
No	73(29)
Unknown	10(4)
Days in a hospital before ICU admission	2.3±3.7
Absolute neutrophil count < 1000	22(8.7)
Lactic acid level >2	141(60)
Main reasons for ICU admission (patient may have more than one diagnosis)	
Sepsis	116(46)
Respiratory failure	130(51.6)
Pneumonia	76(30.2)
Liver failure	10(3.97)
Acute renal failure	45(17.9)
Narcotic overdose	8(3.17)
Following CPR	2(0.8)
Cardiogenic pulmonary edema	16(6.35)

In Receiver Operator Characteristic (ROC) analysis, an Area Under the Curve (AUC) greater than 0.7 was considered as a reasonable cutoff for predicting outcomes of the severity of illness. The SAPS III, Cancer Mortality Model, Mortality Probability Model II, APACHE II and APACHEIII were scores that met this cutoff, with the APACHE III being the highest, with an AUC of 0.72. The SOFA score had an AUC of 0.64 when 5.2 was used as the cutoff, as shown in Table 2.

The mean ICU length of stay was 5.5 days. There were 55 deaths reported in the ICU with an estimated ICU mortality of 21.8%. Hospital mortality was 34.3%, and the 6-month mortality was 38.4% (Table 3). One hundred and one patients (40%) were specified as "Do-Not-Resuscitate". Of these, 52 were discharged alive from the ICU, and 29 were discharged alive from hospital. Fifty-one patients (20%) were withdrawn from aggressive care being provided with comfort measures only while in the ICU. Four of these patients were discharged alive from hospital.

Following univariate analysis of possible variables associated with hospital mortality, ten factors were statistically significant. These factors included Lactic acid >2 mg/dL, use of mechanical ventilation, acute kidney injury, use of vasopressors, liver failure, sepsis, ICU length of stay ≥5 days, ACLS in the ICU, respiratory failure and performance status ≥2. All the scoring

Table 2. Severity of illness scores on admission to the ICU

Severity of illness Score	Score Mean±SD	ROC AUC value to predict Mortality
SAPS II	42.7±13.8	0.69
SAPS III	70.2±16	0.71
SOFA	5.2±4	0.64
Cancer Mortality Model	0.5±0.25	0.72
Mortality Probability Model III	0.50±0.3	0.70
APACHE II	21.4±7.5	0.70
APACHE III	74.3±28.1	0.72
LODS	0.2±0.2	0.65
Charlson Comorbidity Index>7	7.8±2.8	0.59

Table 3. ICU interventions and outcomes

ICU interventions	Number (%)
Vasopressors	53(21)
Antibiotics	189(75)
Non-invasive ventilation	38(15)
Mechanical Ventilation	127(50.4)
Chemotherapy	6(2.4)
Renal replacement therapy	16(6.6)
Outcome data	
Length of stay in ICU, d	5.5±7.4
ICU mortality	55(21.8)
Hospital mortality	86(34.3)
6 Month Mortality	97(38.4)

systems used were statistically significant except for the Charlson comorbidity index when a cutoff of >7 was used (Table 4). During multivariable analysis, the severity of illness scores were not used in the model to avoid collinearity. Factors that were significantly associated with hospital mortality included acute kidney injury, OR 2.97, 95% CI 1.48-5.96 and P=0.002, use of mechanical ventilation, OR 3.13 95% CI 1.40 – 7.02 and P=0.006 and performance status of ≥2 with OR of 3.54, 95% CI of 1.64- 7.65 and P= 0.001 as seen in Table 5. The receiver operator curves for the above factors were determined. The area under the curve (AUC) for acute kidney injury was 0.65. For the use of mechanical ventilation the AUC was 0.63, and for performance status, it was 0.59.

Outcome measures were compared between African Americans and non-African Americans. ICU, hospital and six months mortality for African Americans were 21%, 34% and 40%, respectively compared to 24%, 33% and 37%, respectively in non-African Americans. There were no differences in factors associated with mortality between the two groups (Table 6).

Discussion

In this prospective study to determine outcomes of patients with solid malignancy admitted to the ICU an ICU mortality of 21.8% and hospital mortality of 34.4% was reported. Similar results were reported in recent studies from Europe and South America [3]. In a prospective study in Brazil, Soares et al. (2010) reported an ICU mortality of 21% and hospital mortality of 30%, while in France, Mokart et al. (2012) reported an ICU mortality of 32% and hospital mortality of 41%[4,5]. In the latter study, a significant number of patients had a hematologic malignancy, and this was an essential difference between the two studies. Most of the patients in Mokart's study (2012) died as a result of secondary viral infections. In the study by Soares (2010), a significant number of patients had a solid malignancy with only a small fraction having a hematologic malignancy, making the results more suitable to be compared with the current study. In a recent systematic review of the literature, Puxty et al. (2014) reported the survival in solid cancer patients following ICU admission indication that ICU mortality ranged from 4.5% to 85% with

Table 4. Univariate analysis of possible predictors of hospital mortality

Variable	Patient Cases	Mortality	OR	95% CI	P- Value
Neutrophil count <1000	22	12	1.68	0.69 – 4.05	0.25
Lactic acid>2	131	53	1.80	1.05 – 3.08	0.031
Mechanical Ventilation	126	58	3.00	1.72 – 5.21	0.001
Non-invasive ventilation	38	16	1.49	0.73 – 3.00	0.27
Acute kidney injury	52	31	3.79	2.15 – 6.70	0.001
Vasopressors	52	25	2.10	1.12 – 3.91	0.02
Liver failure	13	10	4.17	1.40 – 12.4	0.01
Sepsis	113	48	1.96	1.15 – 3.32	0.01
Pneumonia	75	28	1.21	0.68 – 2.13	0.50
APACHE II ≥ 20	148	65	3.13	1.74 – 5.64	<0.0001
APACHE III ≥ 75	115	57	3.69	2.12-6.41	<0.0001
SAPS II ≥ 40	150	65	2.98	1.65-5.37	<0.0001
SAPS III ≥ 70	127	62	4.06	2.29 – 7.20	<0.0001
SOFA score≥5	85	54	2.20	1.28 – 3.77	0.004
Cancer Mortality Model ≥0.5	125	64	3.24	1.86 – 5.63	<0.0001
Mortality Probability Model III ≥0.5	115	56	3.40	1.96 – 5.90	<0.0001
ICU LOS ≥ 5 days	80	36	1.99	1.14 – 3.45	0.015
Charlson Comorbidity	175	68	2.09	1.12-3.9	0.02
Performance Status ≥2	173	70	2.72	1.43-5.16	0.002
Renal Replacement Therapy	16	7	1.48	0.53-4.14	0.45
Disease Status					
Remission	144	47	----		
New diagnosis	47	15	0.97	0.48-1.95	0.93
Relapse	57	23	1.40	0.74-2.63	0.30

Table 5. Multivariable analysis of predictors of hospital mortality

Covariate	OR	95% CI	P- Value
Acute Kidney Injury	2.82	1.50 – 5.32	0.001
Mechanical Ventilation	2.67	1.37 – 5.19	0.004
ICU Length of Stay ≥5 days	1.11	0.56 – 2.20	0.76
Vasopressor use	0.89	0.40– 1.20	0.79
Liver failure	2.95	0.91 – 9.58	0.07
Sepsis	1.49	0.76 – 2.93	0.245
Performance status≥ 2	3.05	1.50– 6.20	0.002

an average mortality of 31.2% [6]. The present study provides results from prospectively collected data exclusively from critically ill patients with a solid malignancy.

The improved outcome of critically ill patients with a solid malignancy is reasonably well established. , however, the primary challenge is identifying the factors that predict an outcome. Such factors may provide valuable information for patients, their families and physicians to avoid futile care and better management of resources. The current study showed that patients with performance status ≥2, requiring mechanical ventilation with acute renal failure had a worse prognosis. Taccone et al. (2009) in their study carried out in 198 participating European ICUs, showed that patients with more than three organ dysfunctions resulted in high mortality (58%) [1]. In another study, Soares et al. (2010) looked at the characteristics and outcome of cancer patients in Brazilian ICUs. They found that there is increased mortality in patients admitted for medical complications compared to patients admitted postoperatively. The presence of an active underlying malignancy in recurrence or progression, higher SOFA scores, poor performance status, the need for mechanical ventilation and the number of hospital days before ICU admission, were all predictors of a poor outcome. However, it is important to note that the majority of the patients in the study had solid tumors and were admitted to the ICU postoperatively [4]. Mendoza et al. (2008) reported that the presence of metastatic disease and use of vasopressor agents were predictors of a poor outcome [7]. Puxtry et al. (2014) reported that poor functional status, invasive mechanical ventilation in addition to poor physiological scores, were associated with a poor prognosis [6].

The present study also addresses the value of the severity of illness and organ failure scores in predicting patient outcome. None of these scores (Table 2) accurately predicted the outcome of critically ill patients with a solid malignancy. Multiple studies evaluated one or more of these scores with variable results [8-12]. The current study is in accord with the overall impression that no one score system is better in predicting an outcome. Based on this conclusion, patients should not be denied admission to an ICU based on the severity of illness scores or severity of organ failure scores. Such patients should be given aggressive ICU care and then re-assessed. A better indicator of outcome, reported in some studies [3, 13], was the organ function status after an "ICU trial" for 3-5 days, whereas in the study by Lecuyer et al. (2007) the persistence or worsening of organ failure was stated to be a better outcome predictor [13].

In general, the outcome of cancer is worse in an African American population [14], however, the effect of race on the outcome of a critically ill patient remains controversial, with some studies suggesting worse outcomes in African Americans [15-17].

An important finding of the present study is that the short-term mortality of critically ill patients with a solid malignancy was not different between African Americans and other races.

The study has many strengths, being prospective with a relatively large number of enrolled diverse racial patients, reporting on only solid malignancies with

Table 6. Predictors of Hospital Mortality associated with Ethnicity

Covariate	OR for African Americans	95% CI	P- Value	OR for Non-African Americans	95% CI	P- Value
Acute Kidney Injury	1.21	0.70- 1.99	0.90	0.52	0.14- 1.99	0.35
Mechanical Ventilation	0.88	0.52- 1.48	0.61	0.69	0.24 – 1.69	0.50
ICU Length of Stay ≥5 days	0.70	0.40- 1.21	0.20	0.76	0.24 – 2.37	0.64
Vasopressor use	0.83	0.44- 1.58	0.58	1.14	0.33– 3.89	0.83
Liver failure	0.76	0.24- 2.42	0.64	1.07	0.12 – 0.14	0.95
Sepsis	0.71	0.42- 1.20	0.20	0.42	0.13 – 1.29	0.13
Performance status≥ 2	1.30	0.74- 2.27	0.36	1.50	0.45- 5.00	0.51

purely medical indications for ICU admission. However, there are a few limitations including being a single center experience and the lack of comparison of outcomes in cancer-patients with non-cancer patients. It would be helpful to study changes in severity of illness scores after patients' admission to the ICU and determine whether these can provide better outcome-predictions. Also, the study does not provide predictors of long-term outcomes in these patients. Further prospective multicenter studies are still needed to validate the current data.

Conclusions

The current study shows encouraging ICU, hospital and six months survival rates in patients with solid malignancies who are admitted to an ICU. There were no differences in outcome between races. The need for mechanical ventilation, acute renal failure and poor performance status were associated with worse outcomes.

Conflict of interest

None to declare

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