Critical illness in patients with metastatic cancer: a population-based cohort study of epidemiology and outcomes

Lavi Oud

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Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Texas Tech University Health Sciences Center at the Permian Basin, Odessa, Texas, USA

Correspondence to
Dr Lavi Oud, Odessa, Texas, USA; lavi.oud@ttuhsc.edu

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ABSTRACT
The appropriateness of intensive care unit (ICU) admission of patients with metastatic cancer remains debated. We aimed to examine the short-term outcomes and their temporal pattern in critically ill patients with metastatic disease. We used state-wide data to identify hospitalizations aged ≥18 years with metastatic cancer admitted to ICU in Texas during 2010–2014. Multivariable logistic regression modeling was used to examine the factors associated with short-term mortality and its temporal trends among all ICU admissions and those undergoing mechanical ventilation. Among 136,644 ICU admissions with metastatic cancer, 50.8% were aged ≥65 years, with one or more organ failures present in 53.3% and mechanical ventilation was used in 11.1%. The crude short-term mortality among all ICU admissions and those mechanically ventilated was 28.1% and 62.0%, respectively. Discharge to home occurred in 57.1% of all ICU admissions. On adjusted analyses, short-term mortality increased with rising number of organ failures (adjusted OR (aOR) 1.399, 95% CI 1.374 to 1.425), while being lower with chemotherapy (aOR 0.467, 95% CI 0.432 to 0.506) and radiation therapy (aOR 0.832, 95% CI 0.749 to 0.924), and decreased over time (aOR 0.934 per year, 95% CI 0.924 to 0.945). Predictors of short-term mortality were largely similar among those undergoing mechanical ventilation. Most ICU admissions with metastatic cancer survived hospitalization, although short-term mortality was very high among those undergoing mechanical ventilation. Short-term mortality decreased over time and was lower among those receiving chemotherapy and radiation therapy. These findings support consideration of critical care in patients with metastatic cancer, but underscore the need to address patient-centered goals of care ahead of ICU admission.

Significance of this study

What is already known about this subject?
- ► Critically ill patients with metastatic cancer are reported to have high short-term mortality, mostly in single-center studies, and the appropriateness of their admission to intensive care unit (ICU) remains debated.
- ► Short-term mortality of critically ill patients with metastatic disease was reported to decrease over time in a single-center study.

What are the new findings?
- ► Overall short-term mortality is high among critically ill patients with metastatic cancer, but outcomes in identifiable subgroups are comparable with those of critical illness in the general population.
- ► Chemotherapy and radiation therapy are associated with improved outcomes.
- ► This study demonstrates at a population level a decreasing short-term mortality over time in critically ill patients with metastatic disease.

How might these results change the focus of research or clinical practice?
- ► The findings of this study support consideration of critical care in critically ill patients with metastatic cancer.
- ► Readily accessible clinical data can inform discussions of patient-centered goals of care ahead of and during ICU admission.

INTRODUCTION
Cancer remains a major public health problem worldwide. However, while cancer incidence continues to rise,[1] cancer survival has been improving over the past decades.[2] The latter improvement reflects marked progress in cancer diagnosis and management,[3] resulting in increasing number of patients living with cancer,[4 5] and thus increasing the number of those at risk of acute health crises and critical illness.

Although historically physicians often considered patients with cancer as unlikely to benefit from intensive care unit (ICU) admission due to poor outcomes,[3 6] some[7–9] but not all[10] recent analyses suggest decreasing short-term mortality among critically ill patients with cancer, hypothesized to reflect substantial progress in cancer therapy and improvement in critical care.[7]

It is unclear, however, whether the reported improvements in short-term outcomes of critically ill patients with cancer extend to those with metastatic disease. While physicians may have become more receptive to considering ICU

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admission of patients with cancer in general, it has been suggested that admission to ICU may be inappropriate for most patients with metastatic disease.[11 12]

However, the evidence base on critical illness among patients with metastatic cancer is scarce. The studies focusing specifically on critically ill patients with metastatic cancer were generally single-centered, with small cohorts,[13–17] focused on a single cancer type,[18] or reported only on specific life-sustaining interventions,[18 19] thus constraining modeling of prognostic factors and limiting the generalizability of reported findings. The reported short-term mortality of ICU patients with metastatic cancer varied widely, ranging from 23.1%[17] to 71%,[13] but temporal outcome trends were not addressed.[13–19] The only report, to our knowledge, on the longitudinal trends in short-term outcomes of ICU patients with metastatic cancer showed decreasing odds of 28-day mortality by 7.5% per year.[9] However, the latter study reported a single-center cohort of critically ill patients with cancer of all stages and did not provide data on the characteristics, mortality rates, or predictors of death in the subgroup with metastatic disease. It is thus unclear whether the latter favorable outcomes trends are generalizable at the population level.

A better understanding of the outcomes of critically ill patients with metastatic cancer can inform health policy, critical care resource allocation, clinicians' decision-making, and patients' and surrogates' considerations of goals of care ahead of and during critical illness. Here, we report a population-based study of patients with metastatic cancer admitted to ICU, aimed to (1) estimate the short-term outcomes following critical illness, (2) examine the factors associated with short-term mortality of ICU admissions, and (3) estimate the changes in short-term mortality over time.

MATERIALS AND METHODS

This was a retrospective, population-based cohort study. The reporting of the study finding followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines on reporting observational studies in epidemiology (online supplemental file 1).[20]

Data sources and study population

We used the Texas Inpatient Public Use Data File (TIPUDF) to identify the target population. Briefly, the TIPUDF is an administrative data set maintained by the Texas Department of State Health Services[21] and includes inpatient discharge data from state-licensed, non-federal hospitals, and estimated to capture approximately 97% of all hospital discharges in the state.

We identified hospitalizations of patients aged ≥18 years between the years 2010 and 2014 with a diagnosis of metastatic solid cancer (termed metastatic cancer hereafter) who were admitted to ICU. We identified metastatic cancer based on the presence of *International Classification of Diseases*, *Ninth Revision*, *Clinical Modification* (ICD-9-CM) codes in the Clinical Classification Software group 42[22] in the principal or secondary diagnosis fields. Hospitalizations with hematological malignancies were excluded because staging is complex and outcomes are different compared with metastatic solid cancer. ICU admissions were identified based on unit-specific revenue codes for an ICU or a coronary care unit.

Outcomes

The primary outcome was a combination of in-hospital mortality or discharge to hospice among ICU admissions, termed short-term mortality hereafter. We chose this combined outcome due to a progressive rise in the rate of discharge to hospice among hospitalized patients with metastatic cancer[23] and in other populations,[24] often with concomitant decrease of in-hospital mortality,[23 24] which can bias temporal trends and overall mortality estimates[24] when data are not available on time-based mortality (eg, 28-day mortality).

The secondary outcome was short-term mortality among ICU admissions with mechanical ventilation. In order to facilitate comparisons with prior studies we also examined hospital mortality among ICU admissions.

Data collection and definitions

Study variables were selected a priori based on clinical plausibility and prior reports.[15 19 25 26] We abstracted data on patients' age, sex, race/ethnicity, health insurance, major comorbidities (based on the Deyo modification of the Charlson Comorbidity Index[27 28]), type of cancer (based on the classification by Loh *et al*[19]), type of admission (emergent or non-emergent; medical or surgical, based on diagnosis related groups; admission during weekend or weekdays), organ failures as defined by Martin and colleagues,[29] All Patient Refined Diagnosis Related Group (APR-DRG) illness severity, APR-DRG risk of death,[30] sepsis, palliative care (ICD-9-CM code V66.7), hospitals' teaching status, hospital length of stay, hospital charges, hospital disposition, and year of hospitalization. Procedure use was identified using ICD-9-CM procedure codes for mechanical ventilation (96.7x), hemodialysis (39.95), blood transfusion (99.0x), chemotherapy (99.25, 99.28, 00.10), and radiation therapy (92.2x).

Because the TIPUDF data set does not include clinical data used to derive physiology-based severity of illness scores, we used the APR-DRG illness severity and risk of death, determined by the 3M APR-DRG Grouper System developed by the 3M Health Information Systems (Saint Paul, Minnesota).[31] The performance of APR-DRG as predictor of death among ICU patients is reported to be comparable with that of the Acute Physiology and Chronic Health Evaluation II (APACHE II) severity of illness score.[30] Sepsis was identified by the presence of either (1) a combination of ICD-9-CM codes for infection and one or more organ failures, as described by Angus *et al*[32]; or (2) 'explicit' codes for severe sepsis (995.92) or septic shock (785.52). This approach has been used in contemporary studies of sepsis in administrative data to align ICD-based algorithms with the framework of Sepsis-3.[24 33] Although detailed examination of palliative care utilization among ICU admissions with metastatic cancer was not an objective of the present study, we collected these data to provide further context for the effect size estimates of potential predictors of short-term mortality (see details under the Data analysis section).

Total hospital charges were adjusted for inflation using the consumer price index and reported in 2014 US dollars.[34]

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The TIPUDF and the state of Texas do not provide tools for conversion hospital charges to costs.

Data analysis

We summarized categorical variables as numbers and percentages, while continuous variables were reported as mean (SD) or median (IQR).

The TIPUDF data set provides discharge-level, rather than patient-level, information, precluding accounting for repeated admissions. Thus, we report the number of hospitalizations and ICU admissions as units of analysis, rather than number of patients.

Because triage criteria for ICU admission may change over time, the resultant changes in patient mix can confound interpretation of temporal trends in short-term mortality, even following adjusted analyses (eg, increasingly relaxed ICU admission criteria would result in reduced illness acuity and thus decreased patient mortality over time). In order to provide further anchoring context to the temporal trajectories of short-term mortality, we used weighted least-squares regression to examine the corresponding temporal trends of the burden of chronic illness and severity of illness, using the Deyo Comorbidity Index and the number of organ failures as proxy measures. Because APR-DRG illness severity and APR-DRG risk of death did not meet linearity criteria, they were not used for trend analysis (online supplemental figure 1).

We used multivariable logistic regression modeling to examine the association of potential independent predictors with short-term mortality as dependent variable among ICU admissions, following examination for multicollinearity using the variance inflation factor. Sex was not included in the multivariable model due to inclusion of sex-specific cancer types. The multivariable logistic model included the following covariates: age, race/ethnicity, health insurance, Deyo Comorbidity Index (adjusted after excluding the point score for cancer), congestive heart failure, chronic lung disease, renal disease, diabetes mellitus, liver disease, type of cancer, emergent versus non-emergent admission, medical versus surgical admission, admission during the weekend versus weekday, number of organ failures, APR-DRG illness severity, APR-DRG risk of death, sepsis, mechanical ventilation, hemodialysis, blood transfusion, chemotherapy, radiation therapy, palliative care, teaching status of the hospital, and year of admission. We reported model findings as adjusted OR (aOR) and 95% CI. In order to better illustrate the outcomes of ICU admissions with metastatic cancer, we calculated their adjusted short-term mortality, using empirical Bayesian posterior estimates from the multivariable logistic regression model. We used similar approach and covariates (after excluding respiratory failure from the number of organ failures and mechanical ventilation as candidate predictors) to specify another multivariable model to identify independent predictors of short-term mortality among ICU admissions who have undergone mechanical ventilation and to derive the adjusted short-term mortality in this group.

Because the mortality of critically ill patients is determined in part by treatment limitations, that is, whether life support interventions were withheld or withdrawn, lack of consideration of the later practices can confound the effect estimates of 'traditional' predictors of mortality (eg, organ failure).[35] Although data on withholding or withdrawing of life support measures are not available in administrative data sets, including palliative care in predictive models may be a useful proxy.[36 37] This is because palliative care among hospitalized patients in the USA is provided selectively, being used preferentially in patients considered by clinicians as very likely to die or when death is seen as imminent, and thus palliative care is much more common among patients who die in the hospital.[36–38] Patients receiving palliative care may have life support interventions withheld or withdrawn in accordance with patients' goals of care. Thus, although we could not determine the timing of palliative care in relation to withholding or withdrawing of life support from our data set, inclusion of palliative care in our models, as employed in prior epidemiological studies using administrative data,[37] can address in part the confounding effect of these practices on the effect size of other modeled covariates and could improve the accuracy of the observed estimates.

Data management was performed using Excel and Access (Microsoft, Redmond, Washington) and statistical analyses were performed with MedCalc V.19.4.1 (MedCalc Software, Ostend, Belgium). A two-sided p value <0.05 was considered statistically significant.

RESULTS

Characteristics of ICU admissions

There were 136,644 ICU admissions with metastatic cancer in 386 hospitals during the study period. The characteristics of hospitalizations with metastatic cancer admitted to ICU are detailed in table 1. ICU admissions were aged ≥65 years in 50.8% and 41.2% were racial/ethnic minority. Lung cancer (21.9%) was the most common specific cancer type. Chemotherapy and radiation therapy were provided in 6.5% and 2.2%, respectively. One or more organ failures were present in about half (53.3%) of ICU admissions, involving most commonly the renal (27.4%) and respiratory (22.2%) systems. Mechanical ventilation and hemodialysis were used in 11.1% and 3.2%, respectively. Among ICU admissions, palliative care was used in 35.0% of those who died in the hospital (and in 34.6% of those who died in the hospital or were discharged to hospice) and in 8.9% of those who did not (and in 3.4% of who did not die in the hospital and were not discharged to hospice). The mean (SD) hospital length of stay and total hospital charges were 8.5 (8.6) days and $88,348 ($98,398), respectively.

Outcomes of ICU admissions

The Deyo Comorbidity Index, number of organ failures, APR-DRG illness severity, and APR-DRG risk of death have all increased during the study period (online supplemental table 1).

The crude short-term mortality among ICU admissions with metastatic cancer was 28.1%, of which 12.8% were in-hospital deaths and 15.3% discharges to hospice. The crude short-term mortality among ICU admissions with and without palliative care was 79.8% and 20.9%, respectively. Among ICU admissions who were mechanically ventilated, the crude short-term mortality was 62.0%. The adjusted short-term mortality among all ICU admissions and those

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Table 1 Characteristics of ICU admissions with metastatic cancer

Variables	ICU admissions* (n=136,444)
Age (years)	
18–44	10,920 (8.0)
45–64	56,375 (41.3)
≥65	69,349 (50.8)
Sex†	
Female	64,244 (49.3)
Race/ethnicity‡	
White	80,386 (58.8)
Hispanic	26,168 (19.2)
Black	18,899 (13.8)
Other	10,826 (7.9)
Health insurance§	
Private	54,923 (40.2)
Medicare	59,847 (43.8)
Medicaid	10,045 (7.3)
Uninsured	10,021 (7.3)
Other	1425 (1.0)
Deyo Comorbidity Index, mean (SD)	8.20 (2.17)
Selected comorbidities	
Congestive heart failure	18,227 (13.3)
Chronic lung disease	34,319 (25.1)
Renal disease	18,301 (13.4)
Diabetes	33,063 (24.20
Liver disease	10,847 (7.9)
Cancer subtype	
Lung	29,908 (21.9)
Breast	9431 (6.9)
Genitourinary	13,205 (9.7)
Colon	15,066 (11.0)
Other cancer or >1 cancer subtype	67,536 (49.4)
No identified subtype	1298 (1.0)
Type of admission	
Emergent	83,029 (60.8)
Weekend	25,551 (18.7)
Medical	88,923 (65.1)
Any organ failure	72,886 (53.3)
≥3 organ failures	14,062 (10.3)
Type of organ failure	
Respiratory	30,347 (22.2)
Cardiovascular	13,937 (10.2)
Renal	37,393 (27.4)
Hematological	17,068 (12.5)
Hepatic	3442 (2.5)
Neurological	12,638 (9.2)
Sepsis	37,937 (27.8)
APR-DRG disease severity	
Minor	4151 (3.0)
Moderate	28,353 (20.7)
Major	63,353 (46.4)
Extreme	40,587 (29.7)
APR-DRG risk of mortality	
Minor	3916 (2.9)

Continued

Table 1 Continued

Variables	ICU admissions* (n=136,444)
Moderate	36,238 (26.5)
Major	61,625 (45.1)
Extreme	34,665 (25.4)
Chemotherapy	8882 (6.5)
Radiation therapy	2956 (2.2)
Mechanical ventilation	15,133 (11.1)
Hemodialysis	4321 (3.2)
Blood transfusion	34,439 (25.2)
Palliative care	16,653 (12.2)
Teaching hospital	53,439 (39.1)
Hospital length of stay	
Mean (SD)	8.5 (8.6)
Median (IQR)	6 (3–11)
Total hospital charges	
Mean (SD)	88,348 (98,398)
Median (IQR)	60,245 (35,014–106,718)
Hospital disposition	
Death or discharge to hospice	38,352 (28.1)
Death	17,448 (12.8)
Hospice	20,904 (15.3)
Home	78,002 (57.1)
Home routine	62,400 (45.7)
Home with home health	15,602 (11.4)
Acute care hospital	2353 (1.7)
Postacute care facility	17,490 (12.8)
Leave against medical advice	247 (0.2)

*The parenthesized figures represent per cents, except for Deyo Comorbidity Index, hospital length of stay, and hospital charges; percentage figures may not add to 100 due to rounding.
†Gender was reported for 130,331 ICU admissions; the per cent figures for gender refer to the available gender data as denominator.
‡Race/ethnicity data were missing for 165 (0.12%) ICU admissions.
§Health insurance data were missing for 183 (0.13%) ICU admissions.
APR-DRG, All Patient Refined Diagnosis Related Group; ICU, intensive care unit.

who were mechanically ventilated was 27.9% (95% CI 27.8 to 28.0) and 62.5% (95% CI 62.1 to 62.8), respectively. When stratified by cancer type, adjusted short-term mortality among all ICU admissions ranged from 25.5% to 31.9% (online supplemental table 2). The corresponding adjusted short-term mortality among those who were mechanically ventilated ranged from 61.6% to 65.6% (online supplemental table 3).

Among all ICU admissions 57.1% were discharged to home, corresponding to 79.4% of those without in-hospital death or discharge to hospice. Discharge to home occurred in 18.9% of those undergoing mechanical ventilation, corresponding to 49.7% of those without in-hospital death or discharge to hospice. Among ICU admissions undergoing mechanical ventilation who had isolated respiratory failure, 31.8% were discharged to home.

Predictors of short-term mortality among ICU admissions

The predictors of short-term mortality among all ICU admissions with metastatic cancer and those undergoing

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Table 2 Multivariable logistic regression analysis of predictors of short-term mortality among ICU admissions with metastatic cancer

Variables	Adjusted OR (95% CI)	P value
Age (years)		
18–44	Reference	
45–64	1.168 (1.093 to 1.248)	<0.001
≥65	1.324 (1.232 to 1.421)	<0.001
Race/ethnicity		
White	Reference	
Hispanic	1.139 (1.094 to 1.186)	<0.001
Black	1.051 (1.005 to 1.100)	0.0292
Other	0.985 (0.930 to 1.043)	0.6140
Health insurance		
Private	Reference	
Medicare	0.965 (0.928 to 1.004)	0.0808
Medicaid	1.189 (1.116 to 1.266)	<0.001
Uninsured	1.152 (1.080 to 1.227)	<0.001
Other	1.068 (0.926 to 1.233)	0.3644
Deyo Comorbidity Index	1.017 (1.008 to 1.026)	0.0002
Selected comorbidities		
Congestive heart failure	1.403 (1.371 to 1.447)	<0.001
Chronic lung disease	1.021 (0.972 to 1.089)	0.4185
Renal disease	1.353 (1.322 to 1.351)	<0.001
Diabetes	0.907 (0.883 to 1.025)	0.2709
Liver disease	1.858 (1.690 to 2.043)	<0.001
Cancer subtype		
Lung	Reference	
Breast	0.719 (0.672 to 0.760)	<0.001
Genitourinary	0.642 (0.606 to 0.681)	<0.001
Colon	0.551 (0.520 to 0.584)	<0.001
Other cancer or >1 cancer subtype	0.745 (0.716 to 0.774)	<0.001
No identified subtype	0.824 (0.707 to 0.961)	0.0138
Type of admission		
Emergent	1.531 (1.481 to 1.584)	<0.001
Weekend	1.135 (1.094 to 1.178)	<0.001
Medical	0.975 (0.938 to 1.023)	0.5088
Number of organ failures	1.399 (1.374 to 1.425)	<0.001
Sepsis	1.187 (1.145 to 1.231)	<0.001
APR-DRG disease severity	1.464 (1.416 to 1.513)	<0.001
APR-DRG risk of mortality	1.715 (1.660 to 1.772)	<0.001
Chemotherapy	0.467 (0.432 to 0.506)	<0.001
Radiation therapy	0.832 (0.749 to 0.924)	0.0006
Mechanical ventilation	1.678 (1.601 to 1.760)	<0.001
Hemodialysis	1.196 (1.103 to 1.297)	<0.001
Blood transfusion	1.206 (1.174 to 1.281)	<0.001
Palliative care	14.223 (13.576 to 14.901)	<0.001
Teaching hospital	0.739 (0.715 to 0.764)	<0.001
Year of admission	0.934 (0.924 to 0.945)	<0.001

APR-DRG, All Patient Refined Diagnosis Related Group; ICU, intensive care unit.

Table 3 Multivariable logistic regression analysis of predictors of short-term mortality among mechanically ventilated ICU admissions with metastatic cancer

Variables	Adjusted OR (95% CI)	P value
Age (years)		
18–44	Reference	
45–64	0.976 (0.832 to 1.145)	0.7715
≥65	1.012 (0.851 to 1.203)	0.8879
Race/ethnicity		
White	Reference	
Hispanic	1.121 (1.013 to 1.242)	0.0268
Black	1.099 (0.989 to 1.222)	0.0787
Other	0.994 (0.870 to 1.135)	0.9290
Health insurance		
Private	Reference	
Medicare	0.944 (0.857 to 1.039)	0.2406
Medicaid	1.235 (1.070 to 1.426)	0.0038
Uninsured	1.231 (1.055 to 1.436)	0.008
Other	0.829 (0.594 to 1.158)	0.2719
Deyo Comorbidity Index	1.012 (1.005 to 1.035)	0.0005
Selected comorbidities		
Congestive heart failure	0.872 (0.741 to 1.152)	0.6293
Chronic lung disease	1.140 (0.826 to 1.227)	0.2901
Renal disease	1.115 (1.092 to 1.188)	<0.001
Diabetes	0.951 (0.817 to 1.142)	0.3915
Liver disease	1.632 (1.315 to 2.026)	<0.001
Cancer subtype		
Lung	Reference	
Breast	0.671 (0.569 to 0.790)	<0.001
Genitourinary	0.585 (0.503 to 0.682)	<0.001
Colon	0.414 (0.358 to 0.478)	<0.001
Other cancer or >1 cancer subtype	0.596 (0.540 to 0.657)	<0.001
No identified subtype	0.538 (0.399 to 0.726)	<0.001
Type of admission		
Emergent	1.607 (1.484 to 1.740)	<0.001
Weekend	1.081 (0.986 to 1.186)	0.0969
Medical	0.997 (0.919 to 1.080)	0.9426
Number of organ failures	1.372 (1.322 to 1.424)	<0.001
Sepsis	1.317 (1.213 to 1.431)	<0.0001
APR-DRG disease severity	1.381 (1.340 to 1.417)	<0.001
APR-DRG risk of mortality	1.806 (1.648 to 1.979)	<0.001
Chemotherapy	0.846 (0.705 to 1.014)	0.0705
Radiation therapy	0.510 (0.382 to 0.681)	<0.001
Hemodialysis	1.44 (1.241 to 1.684)	<0.001
Blood transfusion	1.053 (0.967 to 1.127)	0.8135
Palliative care	10.280 (8.931 to 11.834)	<0.001
Teaching hospital	0.687 (0.633 to 0.745)	<0.001
Year of admission	0.927 (0.902 to 0.953)	<0.001

APR-DRG, All Patient Refined Diagnosis Related Group; ICU, intensive care unit.

mechanical ventilation are outlined in tables 2 and 3, respectively. Among all ICU admissions, the odds of short-term mortality increased markedly with age (aOR 1.324 among those aged ≥65 years vs those aged 18–44 years, 95% CI 1.232 to 1.421), among black patients (aOR 1.051, 95% CI 1.005 to 1.100) and Hispanics (aOR 1.139, 95% CI 1.094 to 1.186), both of the latter compared with white patients, in those with Medicaid insurance (aOR 1.189, 95% CI 1.116 to 1.266) and the uninsured (aOR 1.152, 95% CI 1.080 to 1.227), both of the latter compared with private insurance, as well as in those receiving mechanical ventilation (aOR 1.678, 95% CI 1.601 to 1.760) and hemodialysis (aOR 1.196, 95% CI 1.103 to 1.297). When compared

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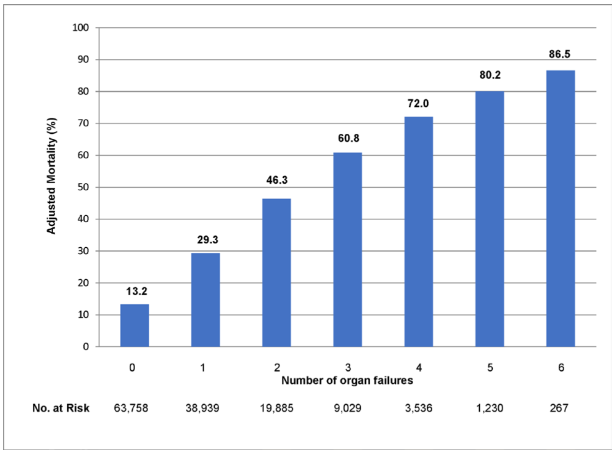

Figure 1 Adjusted short-term mortality of ICU admissions with metastatic cancer during 2010–2014, stratified by number of organ failures. Short-term mortality is defined as that of ICU admissions with in-hospital death or discharge to hospice. Short-term mortality estimates were adjusted, using multivariable logistic regression, for age, race/ethnicity, health insurance, Deyo Comorbidity Index (adjusted after excluding the point score for cancer), congestive heart failure, chronic lung disease, renal disease, diabetes mellitus, liver disease, type of cancer, emergent versus non-emergent admission, medical versus surgical admission, admission during the weekend versus weekday, number of organ failures, APR-DRG illness severity, APR-DRG risk of death, sepsis, mechanical ventilation, hemodialysis, blood transfusion, chemotherapy, radiation therapy, palliative care, teaching status of the hospital, and year of admission. APR-DRG, All Patient Refined Diagnosis Related Group; ICU, intensive care unit.

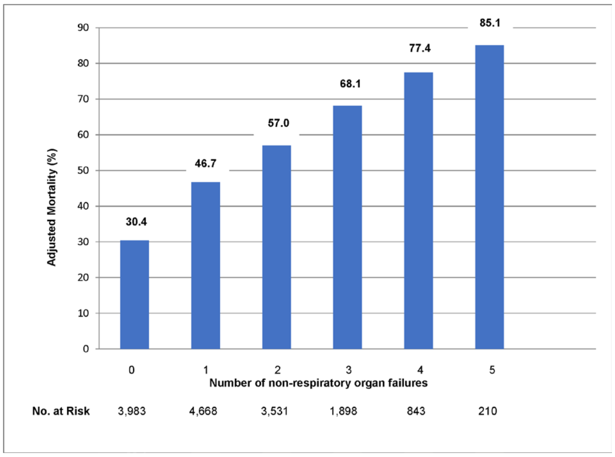

Figure 2 Adjusted short-term mortality of ICU admissions with metastatic cancer undergoing mechanical ventilation during 2010–2014, stratified by number of non-respiratory organ failures. Short-term mortality is defined as that of ICU admissions with in-hospital death or discharge to hospice. Short-term mortality estimates were adjusted, using multivariable logistic regression, for age, race/ethnicity, health insurance, Deyo Comorbidity Index (adjusted after excluding the point score for cancer), congestive heart failure, chronic lung disease, renal disease, diabetes mellitus, liver disease, type of cancer, emergent versus non-emergent admission, medical versus surgical admission, admission during the weekend versus weekday, number of organ failures, APR-DRG illness severity, APR-DRG risk of death, sepsis, hemodialysis, blood transfusion, chemotherapy, radiation therapy, palliative care, teaching status of the hospital, and year of admission. APR-DRG, All Patient Refined Diagnosis Related Group; ICU, intensive care unit.

with lung cancer, the odds of short-term mortality among all ICU admissions were lower across all the remaining examined cancer types.

The adjusted short-term mortality for all ICU admissions with metastatic cancer increased progressively with the number of organ failures, ranging from 13.2% and 29.3% among those with no organ failure and one organ failure, respectively, to 86.5% among those with six organ failures (figure 1). Among the subgroup undergoing mechanical ventilation, the corresponding adjusted short-term mortality was 30.4% among those without non-respiratory organ failure (eg, those with only respiratory failure), 46.7% in those with one non-respiratory organ failure, and increased progressively to 85.1% among those with five non-respiratory organ failures (figure 2).

On the other hand, provision of radiation therapy and especially chemotherapy was strongly associated with reduced short-term mortality, with odds of death being lower by 17% and 53%, respectively. Finally, the odds of short-term mortality decreased annually by 6.6% during the study period (aOR 0.934 per year, 95% CI 0.924 to 0.945).

The predictors of short-term mortality among ICU admissions with metastatic cancer receiving mechanical ventilation were generally similar to those observed among all ICU admissions. However, age, black race, use of chemotherapy, as well as congestive heart failure, blood transfusion, and admission on weekend were no longer associated with short-term mortality among the former.

DISCUSSION

Key findings

In this population-based study, short-term mortality occurred in over one in four of all ICU admissions and 57.1% were discharged home. Increased number of organ failures was associated with a steep rise in short-term mortality, while chemotherapy and radiation therapy were associated with a lower risk of death among ICU admissions. The odds of short-term mortality decreased annually both among all ICU admissions and those who were mechanically ventilated.

Relationship to previous studies

The short-term mortality in our cohort, representing the first population-based study focused on ICU-managed patients with metastatic cancer in the USA, is slightly higher than that reported in a single-center study in Illinois (28.1% vs 23.1%,[17] respectively, with corresponding hospital mortality of 12.8% vs 18.9%, respectively). These hospital mortality estimates are markedly lower than those reported in non-US studies of critically ill patients with metastatic cancer, which ranged from 29.8%[15] to 71%.[13]

The lower short-term mortality among critically ill patients with metastatic cancer in the USA likely represents differences in case mix, practice patterns, in-ICU care,

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and importantly the markedly higher per capita ICU bed capacity and related lower threshold for ICU admission in the USA.[39] The latter two factors are considered key drivers of the markedly lower severity of illness among ICU admissions in the general population in the USA than in non-US ICUs,[40] with the vast majority of ICU admissions in the USA not requiring organ support, such as mechanical ventilation,[40 41] and with hospital mortality more than 50% lower than that reported in non-US critically ill patients.[40–42] Importantly, the finding that over 50% of short-term mortality in our cohort involved discharge to hospice underscores the limitations of in-hospital mortality as an outcome measure when time-based mortality data are not available.

Our finding of relatively closely clustered adjusted short-term mortality across the examined cancer types among all ICU admissions and those undergoing mechanical ventilation is consistent with prior studies showing that the characteristics of underlying malignancy are not a key determinant of short-term mortality among critically ill patients with cancer.[43–45] In addition, the comparable high short-term mortality among mechanically ventilated patients with metastatic cancer in our study and that reported among mechanically ventilated patients with cancer in general (62% vs 64%[46] to 67.6%,[47] respectively) suggests, similarly to prior studies in critically ill patients with cancer,[43 44] that cancer stage may not be a key determinant of short-term mortality among the mechanically ventilated. However, the latter proposition requires further direct comparisons.

Notably, although the short-term mortality among all ICU admissions in our study was markedly higher, as expected, than that among critically ill patients in the general population in the USA,[41] most were discharged home at rates similar to those in the general population (57.1% vs 58.9%,[41] respectively).

Our study provides population-level quantification of adjusted short-term mortality with increasing number of organ failures in critically ill patients with metastatic cancer, extending prior reports in patients with cancer of all stages.[48 49] Notably, 90% of our cohort had up to two organ failures, with an upper bound mortality in this group (46.3%) comparable with that reported among specific groups of critically ill patients in the general population routinely admitted to the ICU (eg, acute respiratory distress syndrome (ARDS),[50] septic shock[51]). Similarly, although the overall short-term mortality was very high in the subset of ICU admissions undergoing mechanical ventilation, it varied nearly threefold, being as low as 30.4% in the absence of non-respiratory organ failures. In particular, the outcome among mechanically ventilated patients in the presence of one non-respiratory organ failure was similar to that reported among patients with ARDS in the general population (46.7% vs 45%, respectively[50]). These estimates provide detailed patient-centered outcome data that can inform goals-of-care discussions and physicians' decision-making in critically ill patients with metastatic cancer. Although organ failures are often present at the time of hospital admission, diligence in providing early preventive measures may help limit the development of new ones.

The findings of a strongly protective association of chemotherapy and radiation therapy with short-term mortality among critically ill patients with metastatic cancer were unexpected. This is because in order to positively impact short-term mortality, both interventions would be expected to be administered for a markedly longer duration than that of the hospitalizations in the present study. Thus, reception of chemotherapy and radiation therapy by critically ill patients with metastatic disease in this study could represent inpatient continuation of outpatient therapy and may be, additionally, a surrogate marker of more favorable prognostic patient traits that are not captured in administrative data, thus possibly introducing selection bias. However, the data set used in the present study does not include information on prehospital care. Our findings contrast the report by Kruser *et al*,[17] which showed worse hospital mortality among ICU admissions with metastatic cancer who have undergone palliative radiation therapy prior to hospitalization. The sources for these conflicting findings are unclear and the investigators of the latter study were uncertain about the causes of the adverse prognostic impact of radiation theory in their cohort.[17] There were no other reports, to our knowledge, on the prognostic impact of chemotherapy on short-term mortality among ICU admissions with metastatic cancer. Further studies are needed to elucidate the role of these interventions in critically ill patients with metastatic disease.

A key finding of this study is the decrease in the odds of short-term mortality by 6.6% per year during the study period among ICU admissions with metastatic cancer and by 7.3% per year in the subset undergoing mechanical ventilation. This improvement in short-term outcomes occurred despite the concomitant rise in the burden of chronic illness and in measures of illness severity during the study period and thus is not consistent with a reduced threshold for ICU admissions over time. Our findings extend to a population level the single-center observations by Sauer *et al*[9] and indicate that the short-term outcome gains among critically ill patients with cancer in general[7–9] may apply to the subset with metastatic disease.

Implications of the present study

The progressively improving short-term outcomes in critically ill patients with metastatic cancer in the present study support consideration of ICU admission in this population. Although our study reaffirms the average poorer prognosis of patients with cancer requiring mechanical ventilation, our findings also underscore the considerable heterogeneity of short-term outcomes in this group, as well as among critically ill patients with metastatic cancer in general, thus providing further guidance to inform patient-centered decision-making.

Together, given the lack of accurate predictive tools at the time of potential ICU admission of patients with cancer,[4] our findings support considering an 'ICU trial'[11 52] in patients with metastatic cancer. However, patients' goals of care would be best served when advance care planning precedes acute health crises and with palliative care introduced early following diagnosis of metastatic disease.

Strengths and limitations

The present study is the largest to date focusing specifically on patients with metastatic solid cancer managed in the ICU, capturing a cohort from a state with a large (over

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27 million), diverse population. The use of a state-wide, all-payer, high-quality data set of consecutive hospitalizations allowed transcending local variation in case mix and practice patterns, including limitations of generalizability involved in cohorts managed at dedicated cancer centers. Notably, the large number of hospitalizations allowed for more comprehensive examination of the spatial and temporal aspects of the outcomes of ICU admissions.

This study has, however, several limitations, related mostly to its retrospective design and use of administrative data. First, because patient groups were identified by ICD codes, there is a potential for misclassification. Second, data on the indications for ICU admission were not available in our data set, thus limiting comparisons with other studies. This limitation remains a common trade-off between gaining broader, more generalizable, perspectives on epidemiological questions from administrative data and use of more granular data gleaned for clinical records, generally on a smaller cohort scale. Our primary focus in the present study was an examination of the downstream phenomena driven by specific complications (eg, development of organ failure, need of organ support interventions) and resultant outcomes. Third, we did not have information on patients' performance status or processes of care, nor the timing of ICU admission, all of which may have affected our findings. Thus, residual confounding cannot be excluded. Last, the generalizability of our findings to other regions and countries is unknown.

CONCLUSIONS

The majority of ICU admissions with metastatic cancer survived hospitalization, but short-term mortality was very high among those undergoing mechanical ventilation. The number of organ failures was a major determinant of short-term mortality, while chemotherapy and radiation therapy were associated with more favorable outcomes. Although ICU admissions were increasingly ill, their odds of short-term mortality decreased over time. These findings support consideration of critical care in patients with metastatic cancer, while underscoring the need to address patient-centered goals of care ahead of ICU admission.

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ORCID iD

Lavi Oud http://orcid.org/0000-0002-9003-6845

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