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original contributions

Delirium as a Risk Factor for Mortality in Critically Ill Patients With Cancer

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QUESTION ASKED: What impact does delirium have on outcomes in critically ill patients with cancer?

SUMMARY ANSWER: Critically ill patients with cancer who developed delirium were over 10 times more likely to die in the intensive care unit (ICU) and almost six times more likely to die in the hospital than those without delirium. Critically ill patients with cancer who develop delirium also had an ICU length of stay (LOS) that was almost twice as long as those without delirium.

WHAT WE DID: We performed a retrospective analysis of 915 patients with cancer admitted to a mixed medical-surgical ICU at a national cancer institute–designated center between January and December 2018. Delirium was diagnosed using the Confusion Assessment Method for the ICU. Patients with < 24-hour stay in the ICU, terminal disease, and lack of active cancer diagnosis were excluded from analysis. We collected a series of variables related to delirium development and outcomes in critical illness including age, cancer type, pre-ICU LOS, recent chemotherapeutics, metastatic disease, CNS involvement, severity of illness, and use of mechanical ventilation. We then performed both univariable and multivariable analyses to identify risk factors for delirium development and determine delirium's impact on ICU and hospital mortality and LOS.

WHAT WE FOUND: Delirium occurred in 40.5% (n = 317) of patients with cancer admitted to the ICU. We found delirium to be an independent risk factor for increased ICU mortality (OR, 10.75; 95% CI, 5.91 to 19.55; $P < .001$), hospital mortality (OR, 5.84; 95% CI, 4.03 to 8.46; $P < .001$), and ICU LOS (estimate, 1.67; 95% CI, 1.54 to 1.81; $P < .001$) after adjusting for cofounding factors such as severity of illness and metastatic disease. We also found age, pre-ICU LOS, cancer involvement of the CNS, severity of illness, mechanical ventilation, and sepsis to be independently associated with delirium development. However, there was no difference in risk of delirium between hematologic and solid cancers or recent administration of chemotherapeutics.

BIAS, CONFOUNDING FACTORS, DRAWBACKS: Despite the significant results, the study was limited by its retrospective and single-center design predisposing it to selection bias and confounders. The study also lacks data on frailty and chronic cognitive dysfunction as screening for these diagnoses is limited to only select groups of patients at our institution.

REAL-LIFE IMPLICATIONS: Clinicians caring for critically ill patients with cancer should be aware that delirium is frequent in this patient population and associated with high ICU and hospital mortality and LOS. As such, systematic delirium screening should be integrated into the care of critically ill patients with cancer.

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ASSOCIATED CONTENT
Appendix
Data Supplement

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Delirium as a Risk Factor for Mortality in Critically Ill Patients With Cancer

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abstract

PURPOSE Although delirium is known to negatively affect critically ill patients, little data exist on delirium in critically ill patients with cancer.

METHODS We analyzed 915 critically ill patients with cancer between January and December 2018. Delirium screening was performed using the Confusion Assessment Method for the intensive care unit (ICU), performed twice daily. Confusion Assessment Method-ICU incorporates four features of delirium: acute fluctuations in mental status, inattention, disorganized thinking, and altered levels of consciousness. Multivariable analysis controlling for admitting service, pre-ICU hospital length of stay (LOS), metastatic disease, CNS involvement, Mortality Probability Model II score on ICU admission, mechanical ventilation, and others was performed to determine precipitating factors for delirium, ICU, and hospital mortality and LOS.

RESULTS Delirium occurred in 40.5% (n = 317) of patients; 43.8% (n = 401) were female; the median age was 64.9 (interquartile range, 54.6-73.2) years; 70.8% (n = 647) were White, 9.3% (n = 85) were Black, and 8.9% (n = 81) were Asian. The most common cancer types were hematologic (25.7%, n = 244) and gastrointestinal (20.9%, n = 191). Delirium was independently associated with age (OR, 1.01; 95% CI, 1.00 to 1.02; $P = .038$), longer pre-ICU hospital LOS (OR, 1.04; 95% CI, 1.02 to 1.06; $P < .001$), not resuscitating on admission (OR, 2.18; 95% CI, 1.07 to 4.44; $P = .032$), CNS involvement (OR, 2.25; 95% CI, 1.20 to 4.20; $P = .011$), higher Mortality Probability Model II score (OR, 1.02; 95% CI, 1.01 to 1.02; $P < .001$), mechanical ventilation (OR, 2.67; 95% CI, 1.84 to 3.87; $P < .001$), and sepsis diagnosis (OR, 0.65; 95% CI, 0.43 to 0.99; $P = .046$). Delirium was also independently associated with higher ICU mortality (OR, 10.75; 95% CI, 5.91 to 19.55; $P < .001$), hospital mortality (OR, 5.84; 95% CI, 4.03 to 8.46; $P < .001$), and ICU LOS (estimate, 1.67; 95% CI, 1.54 to 1.81; $P < .001$).

CONCLUSION Delirium significantly worsens outcome in critically ill patients with cancer. Delirium screening and management should be integrated into the care of this patient subgroup.

INTRODUCTION

Delirium is defined as a state of fluctuating mental status and confusion attributed to reduced cholinergic activity, increased dopaminergic activity, and heightened systemic and neuroinflammation.[1-5] As a result of sepsis, shock, and polypharmacy, delirium is especially common in critical illness and may occur in more than half of all patients admitted to the intensive care unit (ICU).[6-9] Once delirium ensues, it is associated with longer ICU and hospital LOS, higher ICU and in-hospital mortality, increased cost of care, and long-term cognitive dysfunction.[10-14]

Up to 57% of hospitalized and 85% of terminally ill patients with cancer experience delirium.[15-17] Cancer, its associated treatment regimen, and related functional decline pose a set of unique risk factors, which may increase delirium incidence and worsen its outcome. However, only a few studies have examined delirium in this patient population, are decades old, focus on those with advanced or terminal disease, suffer from low sample size, and use different delirium screening tools.[15,18,19] Evidence in the critically ill, but not terminally ill, patients with cancer is even more scarce.[20] To date, there have been only four studies conducted on delirium in ICU patients with cancer who

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are not at the end of life.[21-24] These analyses also suffer from small sample size, have widely varying results, and lack in-depth outcomes analysis.

The purpose of this retrospective study is to provide a comprehensive examination of delirium in patients with cancer who require ICU care. The primary objective is to better assess the impact of delirium on ICU and hospital mortality and LOS. Our secondary objective is to assess the effects of demographic and clinical factors on delirium development.

METHODS

Study Design and Setting

We conducted a retrospective review of patients admitted between January and December 2018 to the 20-bed mixed medical-surgical adult ICU at the Memorial Sloan Kettering Cancer Center, a comprehensive cancer center in New York City. The Institutional Review Board approved the study and waived informed consent.

Participants

Patients were included if they were are $\geq$ 18 years, had active cancer, and were admitted to the ICU for $\geq$ 24 hours. Patients were excluded if they were age $<$ 18 years, did not have cancer or evidence of active disease, were admitted to the ICU for $<$ 24 hours or for noncritical illness, did not have a documented Confusion Assessment Method for the ICU (CAM-ICU), or had terminal disease. We defined terminal disease as a disease state that is progressive and irreversible, not amenable to further therapy, and with limited life expectancy.[17] Patients were also excluded if they required multiple episodes of mechanical ventilation during a single ICU stay because of difficulty in determining whether delirium was a cause or effect of mechanical ventilation as specific dates of positive CAM-ICU were not collected. All patients included in this study are unique individuals.

Data Collection

Using electronic medical records and ICU database, we collected demographic and clinical data, including age; sex; race and ethnicity; admission service (medical or surgical); cancer diagnosis; presence of distant metastases; cancer involvement of the CNS as defined by the presence of primary cancer or metastasis on magnetic resonance imaging or computed tomography of the brain within 6 months of ICU admission; reason for or diagnosis on ICU admission; Mortality Probability Model II (MPM_0-II) score on ICU admission; dates of intubation; use of mechanical ventilation; use of anticholinergics or high-dose steroids defined as prednisone $\geq$ 60 mg per day or its equivalent; chemotherapeutic agents (including both chemotherapy and immunotherapy and only agents known to penetrate CNS) within 2 weeks of ICU admission; use of continuous and noncontinuous benzodiazepine, opioids, and other sedatives (eg, propofol, dexmedetomidine, and ketamine)—except for end of life care; do not resuscitate (DNR) status on ICU admission; hospital admission and discharge dates; ICU admission and discharge dates; hospital discharge status (alive *v* dead); date of last clinical contact; and date of death.

Delirium Data

Delirium is diagnosed at our institution using CAM-ICU, a widely used and validated tool for delirium screening.[9,25] CAM-ICU incorporates four features of delirium: acute changes or fluctuations in mental status, inattention, disorganized thinking, and altered levels of consciousness. Mental status is assessed using the Richmond Agitation and Sedation Scale. Inattention is assessed using the Attention Screening Examination and includes both visual and auditory components. Disorganized thinking is assessed through standardized questions to determine if the patient is having rambling conversations or illogical flow of ideas. Finally, altered levels of consciousness are assessed by rating the patient as vigilant, lethargic, stuporous, or comatose. Patients screen positive for delirium when there are acute fluctuations in mental status, inattention, and either disorganized thinking or altered levels of consciousness.[9] Nurses trained in the use of CAM-ICU performed delirium screening at least once a shift. Assessments were not performed if the Richmond Agitation and Sedation Scale was –4 or –5 given the deep level of sedation or coma. Patients were considered to have delirium if at least one positive CAM-ICU was documented during their ICU stay. Similarly, patients with negative CAM-ICU throughout their ICU stay were deemed not to have delirium. Date of the first positive CAM-ICU was recorded for each patient.

Outcome Variables

This study establishes the incidence of delirium in patients with cancer who require ICU care. The primary outcome is to assess the effects of delirium on ICU and hospital mortality and LOS in critically ill patients with cancer. The secondary objective is to determine the effects of clinical and demographic factors such as age, sex, race and ethnicity, cancer type, CNS involvement, metastatic disease, DNR status on ICU admission, ICU admission diagnosis, mechanical ventilation, and relevant medications on delirium development.

Statistical Analysis

Categorical variables are presented as absolute numbers and percentages and compared between the two groups using Fisher's exact test. Continuous variables are summarized using median and interquartile range (IQR) and compared between the two groups using the Wilcoxon rank-sum test. Univariable logistic regression and multivariable logistic regression were used to analyze hospital and ICU mortality. ICU LOS was natural log transformed to normalize the distribution and was analyzed using univariable and multivariable linear regression models. Estimates of the LOS models were exponentiated for ease of interpretation. Because of expected high correlation between ICU and hospital LOS, we

constructed the multivariable model for ICU LOS because this end point is of direct interest in this study. Multivariable models were constructed using a backward selection process starting with variables with $P < .1$ in univariable analyses.[26,27] For patient outcomes, delirium was forced into the final models to assess if there is an independent effect on each outcome while controlling for other significant factors. An exploratory subgroup analysis assessing medication and delirium versus no delirium was performed. Patients who were diagnosed with delirium on the day of ICU admission were removed from this analysis because their medication status was unknown before ICU admission. SAS version 9.4 SAS institute Inc, Cary, NC was used for all analyses. All tests were two-sided, and $P < .05$ was considered significant.

RESULTS

Demographics and Clinical Characteristics

Between January and December 2018, 1,009 patients were admitted to the ICU at our institution. After excluding patients with missing data, ICU stay < 24 hours, lack of active cancer, and multiple courses of mechanical ventilation, 915 unique patients were included in the final analysis. Of these, 43.8% (n = 401) were female and the median age was 64.9 (IQR, 54.6-73.2) years; 71.5% (n = 654) of patients were admitted from a medical service with a median LOS in the hospital before ICU admission of 1 (IQR, 0.0-6.0) day. In our cohort, 78.0% (n = 714) had metastatic disease and 6.0% (n = 55) had CNS involvement. The median MPM_0II score was 29.4 (IQR, 15.5-54.0) with 4.2% (n = 38) of patients carrying a DNR order. The most common reason for ICU admission was respiratory failure (27.2%, n = 249) followed by sepsis (25.1%, n = 230); 27.7% (n = 253) of patients required mechanical ventilation during their ICU stay. Additional demographic and clinical data are summarized in Table 1.

Furthermore, 170 had incomplete data on the use of continuous sedatives, anticholinergics, and high-dose steroids, which precluded multivariable analysis (Data Supplement, online only). We found delirium development to only be associated with the use of continuous sedatives.

Of the 915 patients, 15.2% (n = 139) were transitioned to comfort care during their ICU stay and 7% (n = 66) died in the ICU. 687 patients survived to hospital discharge; of these, 12 were lost to follow up. Further analysis of the remaining 675 patients demonstrated the median survival of 15.0 months (95% CI, 11.05 to 17.70) for the whole cohort, 8.7 months (95% CI, 5.76 to 14.77) for patients with delirium, and 16.7 months (95% CI, 13.29 to 20.63) for patients without delirium ($P = .073$; Data Supplement).

Risk Factors for Delirium Development

Delirium occurred in 40.5% (n = 371) of patients. Patients with delirium were older (65.8 *v* 63.9 year-old; $P = .004$); admitted in greater proportion from medical rather than surgical services (77.6% *v* 67.3%; $P < .001$); had longer pre-ICU hospital LOS (median 3 *v* 1 day; $P < .001$); were more likely to have metastatic disease (82.5% *v* 75.0%; $P = .007$) and CNS involvement (9.2% *v* 3.9%; $P = .002$); had higher MPM_0II scores (38.9 *v* 26.0; $P < .001$); and required mechanical ventilation in greater numbers (28.3% *v* 14.7%; $P < .001$) (Table 1). Patients with delirium had similar rates of cancer type and recent chemotherapy and immunotherapy administration as patients without delirium.

Multivariable analysis found age (OR, 1.01; 95% CI, 1.00 to 1.02; $P = .038$), pre-ICU hospital LOS (OR, 1.04; 95% CI, 1.02 to 1.06; $P < .001$), DNR on admission (OR, 2.18; 95% CI, 1.07 to 4.44; $P = .032$), MPM_0II score (OR, 1.02; 95% CI, 1.01 to 1.02; $P < .001$), neurologic diagnosis (OR, 2.84; 95% CI, 1.69 to 4.79; $P < .001$), mechanical ventilation (OR, 2.67; 95% CI, 1.84 to 3.87; $P < .001$), and CNS involvement (OR, 2.25; 95% CI, 1.20 to 4.20; $P = .011$) to be independently associated with delirium development. Conversely, admission from a surgical service (OR, 0.62; 95% CI, 0.44 to 0.87; $P = .008$) or sepsis diagnosis (OR, 0.65; 95% CI, 0.43 to 0.99; $P = .046$) was associated with lower odds of delirium (Table 2). Recent chemotherapeutics (OR, 0.91; 95% CI, 0.63 to 1.29; $P = .584$), diagnoses of shock (OR, 1.10; 95% CI, 0.78 to 1.55; $P = .601$), and cancer type defined as hematologic or solid cancer (OR, 1.35; 95% CI, 1.00 to 1.81; $P = .050$) did not correlate with delirium development in univariable analysis (Data Supplement).

Outcomes Associated With Delirium Development

Patients with delirium had higher ICU (24.0% *v* 2.6%; $P < .001$) and hospital (45.3% *v* 11.0%; $P < .001$) mortality compared with those without delirium (Appendix Figure A1, online only; Data Supplement). After controlling for metastatic disease, MPM_0II score, and ICU admission diagnosis, delirium was found to be an independent risk factor for increased ICU mortality (OR, 10.75; 95% CI, 5.91 to 19.55; $P < .001$). Similarly, delirium was independently associated with increased hospital mortality (OR, 5.84; 95% CI, 4.03 to 8.46; $P < .001$) after controlling for admission service, pre-ICU hospital LOS, DNR status on ICU admission, MPM_0II score, ICU admission diagnosis, and metastatic disease (Table 3).

Patients with delirium also experienced significantly longer ICU (median 6.0 *v* 3.0 days; $P < .001$) and hospital (median 20.0 *v* 12.0 days; $P < .001$) LOS (Appendix Figure A1). While adjusting for admission service, pre-ICU hospital LOS, ICU admission diagnosis, and mechanical ventilation before delirium development, patients with delirium had ICU LOS 1.67 (estimate, 1.67; 95% CI, 1.54 to 1.81; $P < .001$) times longer than patients without delirium (Table 3).

DISCUSSION

To our knowledge, in this largest to date cohort of patients with cancer admitted to the ICU, the incidence of delirium was 40%. This frequency is similar to previous reports on critically ill, but not terminally ill, patients with cancer requiring ICU care, which ranges from 22.9% to 39.3%.[22-24]

TABLE 1. Demographic and Clinical Characteristics

Characteristic	Delirium (n = 371)	No Delirium (n = 544)	Total (n = 915)	*P*
Sex, No. (%)				.249
Male	217 (58.5)	297 (54.6)	514 (56.2)	
Female	154 (41.5)	247 (45.4)	401 (43.8)	
Age, years, median (IQR)	65.8 (57.5-73.7)	63.9 (53.2-72.8)	64.9 (54.6-73.2)	.004
Race/ethnicity, No. (%)				.518
Asian	28 (7.6)	53 (9.7)	81 (8.9)	
Black	34 (9.2)	51 (9.4)	85 (9.3)	
Hispanic/Latino	23 (6.2)	37 (6.8)	60 (6.6)	
Others	21 (5.7)	20 (3.7)	41 (4.5)	
White	264 (71.4)	383 (70.4)	647 (70.8)	
Cancer type, No. (%)				
Breast	24 (6.5)	37 (6.8)	61 (6.7)	
Gastrointestinal	59 (15.9)	132 (24.3)	191 (20.9)	
Genitourinary	39 (10.5)	49 (9.0)	88 (9.62)	
Gynecologic	15 (4.0)	33 (6.1)	48 (5.3)	
Head and neck	21 (5.7)	32 (5.9)	53 (5.8)	
Hematologic	112 (30.2)	132 (24.3)	244 (26.7)	
Neurologic	10 (2.7)	6 (1.1)	16 (1.8)	
Other—miscellaneous solid	33 (8.9)	55 (10.1)	88 (9.6)	
Thoracic	58 (15.6)	68 (12.5)	126 (13.8)	
Admitting service, No. (%)				< .001
Medicine	288 (77.6)	366 (67.3)	654 (71.5)	
Surgery	83 (22.4)	178 (32.7)	261 (28.5)	
Pre-ICU hospital LOS, days, median (IQR)	3.0 (0.0-9.0)	1.0 (0.0-40)	1.0 (0.0-6.0)	< .001
Chemotherapeutics, No. (%)				
Chemotherapy				.617
Yes	51 (13.8)	68 (12.5)	119 (13.0)	
No	320 (86.3)	476 (87.5)	796 (87.0)	
Immunotherapy				.425
Yes	22 (5.9)	41 (7.5)	63 (6.9)	
No	349 (94.1)	503 (92.5)	852 (93.1)	
Chemotherapy and immunotherapy				> .95
Yes	10 (2.7)	15 (2.8)	25 (2.7)	
No	361 (97.3)	529 (97.2)	890 (97.3)	
Metastatic disease, No. (%)				.007
Yes	306 (82.5)	408 (75.0)	714 (78.0)	
No	65 (17.5)	136 (25.0)	201 (22.0)	
CNS involvement, No. (%)				.002
Yes	34 (9.2)	21 (3.9)	55 (6.0)	
No	337 (90.8)	523 (96.1)	860 (94.0)	
MPM_0-II score on ICU admission, median (IQR)	38.9 (20.2-62.6)	26.0 (13.4-46.2)	29.4 (15.5-54.0)	< .001
DNR on ICU admission, No. (%)				.017
Yes	23 (6.2)	15 (2.8)	38 (4.1)	
No	348 (93.8)	529 (97.2)	877 (95.9)	

(continued on following page)

TABLE 1. Demographic and Clinical Characteristics (continued)

Characteristic	Delirium (n = 371)	No Delirium (n = 544)	Total (n = 915)	*P*
ICU admitting diagnosis, No. (%)				< .001
Bleeding	23 (6.2)	52 (9.6)	75 (8.2)	
Cardiovascular	31 (8.4)	68 (12.5)	99 (10.8)	
Neurologic	64 (17.3)	36 (6.6)	100 (10.9)	
Others	39 (10.5)	70 (12.9)	109 (11.9)	
Renal/metabolic	25 (6.7)	28 (5.2)	53 (5.8)	
Respiratory	107 (28.8)	142 (26.1)	249 (27.2)	
Sepsis	82 (22.1)	148 (27.2)	230 (25.1)	
Shock, No. (%)				.656
Yes	67 (18.1)	91 (16.7)	158 (17.3)	
No	304 (81.9)	453 (83.3)	757 (82.7)	
Mechanical ventilation, No. (%)				< .001
Yes	105 (28.3)	80 (14.7)	185 (20.2)	
No	266 (71.7)	464 (85.3)	730 (79.8)	

Abbreviations: DNR, do not resuscitate; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; MPM_0-II, Mortality Probability Model II.

It is also comparable with rates of delirium in ICU patients without cancer, which range from 20% to 80%.[9,28] In addition, we also found that patients with delirium had significantly higher ICU and hospital mortality compared with patients without delirium.

Delirium's negative impact on mortality outcome has been well demonstrated in ICU patients without cancer.[8,10,29,30]

TABLE 2. Multivariable Regression Analysis on Variables Associated With Delirium Development

Variable	OR	95% CI	*P*
Age	1.01	1.00 to 1.02	.038
Admitting service			
Surgery *v* medicine	0.62	0.44 to 0.87	.006
Pre-ICU hospital LOS	1.04	1.02 to 1.06	< .001
CNS involvement	2.25	1.20 to 4.20	.011
MPM_0-II score on ICU admission	1.02	1.01 to 1.02	< .001
DNR on admission			
Yes *v* no	2.18	1.07 to 4.44	.032
ICU admission diagnosis			
Bleeding *v* respiratory	0.61	0.33 to 1.11	.104
Cardiovascular *v* respiratory	0.64	0.37 to 1.11	.113
Neurologic *v* respiratory	2.84	1.69 to 4.79	< .001
Others *v* respiratory	0.92	0.55 to 1.53	.750
Renal/metabolic *v* respiratory	1.44	0.76 to 2.73	.263
Sepsis *v* respiratory	0.65	0.43 to 0.99	.046
Mechanical ventilation	2.67	1.84 to 3.87	< .001

Abbreviations: DNR, do not resuscitate; ICU, intensive care unit; LOS, length of stay; MPM_0-II, Mortality Probability Model II; OR, odds ratio.

However, this association is yet to be fully appreciated in patients with cancer admitted to the ICU. Sieber et al[24] found delirium in this patient subgroup to increase hospital mortality by almost 6-fold in univariable analysis, but results failed to maintain significance after controlling for severity of illness, sepsis, and shock. On the other hand, Sanchez-Hurtado et al[22] noted a lower ICU mortality in patients with cancer diagnosed with delirium (12%) than in those with no delirium (15%). Causes for these conflicting results are likely due to skewed patient demographics and low sample size.

Our study, which examined a large cohort of well mixed medical-surgical patients, found delirium to be a significant risk factor for both ICU and hospital mortality in univariable and multivariable analyses. Remarkably, patients with cancer who developed delirium were over 10 times more likely to die in the ICU and almost six times more likely to die in the hospital than those without delirium. This increase comes even after adjusting for other contributing factors of mortality such as severity of illness and the presence of metastatic disease. To our knowledge, this is the first analysis to establish an independent and highly significant association between delirium and mortality in critically ill, but not terminally ill, patients with cancer. More interestingly, delirium's effects on mortality in this study of oncologic patients appear to be double that of nononcologic patients, where mortality is reported to increase by a modest 2.5- to 3.2-fold.[10]

Although not statistically significant, delirium appears to affect long-term survival in patients with cancer. Among patients who survived to hospital discharge, median survival time was half as long in those with delirium compared with those without. This is consistent with findings in patients

TABLE 3. Multivariable Regression Analysis on Delirium and Mortality and LOS

	ICU Mortality			Hospital Mortality			ICU LOS		
Variable	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***	**Estimate**	**95% CI**	***P***
Delirium	10.75	5.91 to 19.55	< .001	5.84	4.03 to 8.46	< .001	1.67	1.54 to 1.81	< .001
Cancer type									
Hematologic *v* solid	1.10	0.70 to 1.74	.677	0.79	0.52 to 1.21	.280	1.02	0.92 to 1.12	.748
Admitting service									
Surgery *v.* medicine	0.62	0.31 to 1.21	.161	0.42	0.25 to 0.71	.001	0.90	0.82 to 0.98	.015
Pre-ICU hospital LOS, days	1.01	0.99 to 1.02	.377	1.03	1.01 to 1.04	.001	1.004	1.00 to 1.01	.012
Metastatic disease	3.13	1.43 to 6.87	.004	2.52	1.40 to 4.54	.002	1.03	0.93 to 1.14	.598
MPM_0-II score on ICU admission	1.02	1.01 to 1.03	< .001	1.01	1.01 to 1.02	< .001	1.001	1.00 to 1.00	.349
DNR status on ICU admission									
Yes *v* no	NA[a]			2.38	1.11 to 5.08	.026		NA[a]	
ICU admission diagnosis									
Bleeding *v* respiratory	0.36	0.12 to 1.02	.056	0.36	0.15 to 0.83	.017	0.78	0.68 to 0.91	.001
Cardiovascular *v* respiratory	0.42	0.18 to 0.99	.048	0.80	0.42 to 1.52	.491	0.76	0.66 to 0.86	< .001
Neurologic *v* respiratory	0.11	0.04 to 0.33	< .001	0.33	0.18 to 0.62	< .001	0.75	0.65 to 0.86	< .001
Others *v* respiratory	0.64	0.28 to 1.46	.288	0.62	0.31 to 1.21	.157	0.74	0.65 to 0.85	< .001
Renal/metabolic *v* respiratory	0.71	0.29 to 1.75	.462	0.68	0.32 to 1.45	.313	0.95	0.80 to 1.12	.523
Sepsis *v* respiratory	0.43	0.23 to 0.80	.008	0.82	0.51 to 1.32	.413	0.91	0.82 to 1.01	.079
Mechanical ventilation	0.95	0.55 to 1.65	.865	NA			1.35	1.22 to 1.49	< .001

Abbreviations: DNR, do not resuscitate; ICU, intensive care unit; LOS, length of stay; MPM_0-II, Mortality Probability Model II; OR, odds ratio.
[a]NA, not available for multivariable regression analysis. See univariable analysis in the Data Supplement.

without cancer where delirium was found to be an independent risk factor for mortality at 6 months.[10,30]

We also determined delirium to be an independent risk factor for longer ICU stay, a finding consistent with existing data.[31-33] Sieber et al[24] demonstrated that delirium increased ICU LOS in critically ill patients with cancer by hours to days after controlling for shock, sepsis, and severity of illness. In patients without cancer who require ICU care, this increase is moderately higher with a 2- to 4-fold longer ICU LOS after delirium ensues.[10]

A longer hospital LOS before ICU admission also appears to significantly increase the risk of delirium development. Patients with delirium spent a median of 3 days in the hospital before ICU transfer compared with 1 day in patients without delirium. Even after adjusting for severity of illness, admission service, and use of mechanical ventilation, pre-ICU hospital LOS remained an independent risk factor for delirium, increasing its incidence by 4% with every day spent in the hospital before ICU admission. This rise in risk of delirium after such a short period of time may represent the rapidity with which delirium develops after hospital admission. It may further indicate a gradual but perhaps overlooked increase in severity of illness with each additional day of inpatient care. Such a finding raises questions regarding the benefits of an early ICU admission as a path to addressing potentially reversible medical conditions, thereby lowering delirium incidence.

Our study observed an association between CNS involvement by cancer and delirium development, a finding that is consistent with previous studies.[34] Interestingly, multivariable logistic regression analysis demonstrated no association between metastatic disease and delirium development. This could be explained by the fact that metastatic disease, although defined similarly for all cancers, possesses gradients of severity and thus has an influence on a patient's clinical course. Since ICU delirium can reflect both a disease state and severity of illness, differences in burden of metastases could have different effects on delirium development.

Univariable analysis found continuous sedatives to be a third factor associated with delirium development. Medications used to manage pain and anxiety in the ICU have been shown to increase risk of delirium by three folds in patients without cancer.[35,36] However, this has only been preliminarily examined in critically ill patients with cancer in two observational studies with small sample sizes.[22,23] Guidelines from the Society of Critical Care Medicine have recommended daily sedation interruption as an effective mitigating tool for delirium.[37] These guidelines were based on studies of mixed medical-surgical ICU patients without any particular emphasis on patients with cancer. Our study invites similar considerations in the judicious use of sedatives and daily sedation vacation in the prevention and shortening of delirium.

Contrary to earlier studies, chemotherapeutics and a diagnosis of shock did not contribute to the development of delirium in our study.[38,39] We saw two potential reasons for these findings. First, although we only considered chemotherapeutic regimens with neurotoxic potential and administered shortly before ICU admission, a better baseline functional status of patients who are candidates for chemotherapy might have contributed to the lack of delirium association. Second, the relationship between circulatory shock and delirium is thought to be related to hypotension and poor oxygen delivery to the brain.[39] Our institution has a track record of prompt response to hypotensive episodes with fluids and vasopressors, thereby minimizing hypoperfusion. Such a tradition may explain the lack of association between shock and delirium in our study.

To our knowledge, to date, this is the largest study of delirium in critically ill patients with cancer. Our findings are strengthened by the size of the studied population, the patient mix, and both the breadth of variables we included and the comprehensive statistical analysis we performed. Yet, there are several limitations to this study. First, the retrospective, single-centered design of our analysis predisposes it to selection bias and confounders. Second, our study did not include data on frailty or chronic cognitive dysfunction as screening for these diagnoses is limited to select groups of patients at our institution. Finally, we included only chemotherapy and immunotherapy with the ability to penetrate the CNS for analysis. Chemotherapeutics that do not cross the blood brain barrier may cause electrolytes or blood count abnormalities, thereby indirectly causing delirium.

In conclusion, our analysis demonstrates that ICU delirium is very common in critically ill patients with cancer and is associated with increased ICU and hospital mortality and increased ICU and hospital LOS. Critical care specialists should perform systematic screening for delirium in patients with cancer admitted to the ICU and implement early mitigating interventions to prevent delirium and shorten its duration.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Delirium as a Risk Factor for Mortality in Critically Ill Patients With Cancer

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APPENDIX

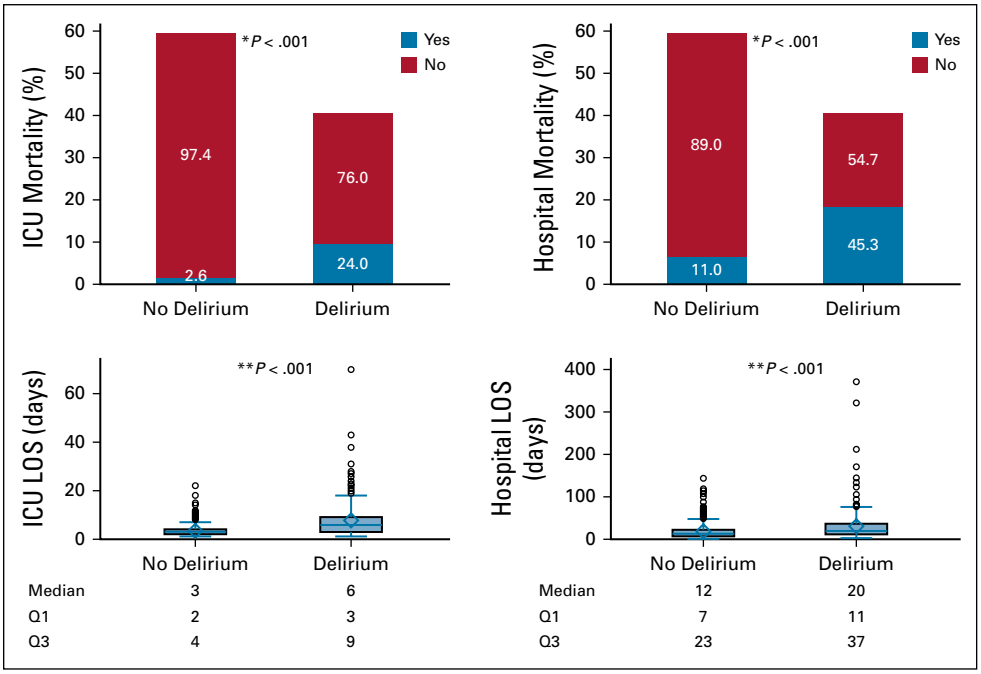

FIG A1. Association between delirium and mortality and LOS. ICU, intensive care unit; LOS, length of stay; Q1, Quartile 1; Q3, Quartile 3.