



Characteristics and clinical subtypes of cancer patients in the intensive care unit: a retrospective observational study for two large databases

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Background: Previous studies have reported very different mortality rates among cancer patients in the intensive care unit (ICU), implying different clinical subtypes. We aimed to reveal the clinical subtypes and demonstrate the importance of segregating the patients in clinical research, and to report the ICD-level mortality of cancer patients in the ICU.

Methods: Two ICU databases (MIMIC-III and eICU) were utilized to identify cancer patients. Mortality based on ICD-level diagnoses were calculated, and K-means clustering was used to identify different clinical subtypes in the MIMIC database. Clinical characteristics and outcomes were compared among subtypes, and the calibration of SAPS II and APACHE IV among different subtypes was evaluated.

Results: In total, 6,505 (13.8%) cancer patients of the MIMIC database and 7,351 (4.9%) ones in eICU database, were enrolled in the study. Metastasis involving pleura, metastasis involving the liver, and acute myeloid leukemia were in the top 5 diagnoses with the highest mortality in both databases. Clinical subtypes identified by K-means clustering were closely associated with admission type (elective or emergency) and clinical service provider (surgical or medical). In a four-cluster pattern, nearly all patients in the first cluster were elective admissions (99.1%), whereas in the rest of the clusters, most were emergency admissions (93.7%). Most surgical patients were in the 1+2 clusters (92.0%) and most medical patients were in the 3+4 clusters (93.5%). Most characteristics and outcomes as well as the calibration of SAPS II and APACHE IV scoring systems were significantly different among clinical subtypes.

Conclusions: Different clinical subtypes can be well identified by admission type and clinical service provider among ICU patients with cancer. Caution should be exercised when considering these patients as a whole population both in clinical practice and research. Moreover, APACHE IV has better calibration than SAPS II for cancer patients at low risk of mortality in the ICU.

Keywords: Cancer mortality; intensive care unit (ICU); clinical subtypes; scoring system; K-mean

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Introduction

Cancer is a common comorbidity in patients admitted to the intensive care unit (ICU). Approximately one in seven ICU patients have cancer comorbidity (1,2). Previous studies have explored the characteristics and outcomes of critically ill cancer patients and reported highly varied mortality for this population (3-5). These mortality-related variations indicate the difficulty of prognostication in critically ill cancer patients (6). Some exceptional research has specified criteria to select these patients such as postoperative admission after elective surgery (4,7). These studies always had similar outcomes, whereas others had quite different outcomes. The disparity in the mortality rates of ICU patients with cancer may imply some clinical subtypes that are so different in clinical features and prognoses that they cannot be regarded as a whole population, both in clinical practice and research. Therefore, to identify these subtypes may help explain the abovementioned disparity in mortality rates and facilitate prognostication in this specific population.

Furthermore, previous studies only revealed varied mortality among different types of cancer at organ level (8,9). Cancers at different locations within the same organ have distinct prognoses, such as for hilar versus peripheral lung cancer (10). Therefore, more detailed evidence, particularly on mortality at International Classification of Diseases (ICD) level, is needed.

We conducted this study to explore the characteristics and outcomes, particularly the ICD-level mortality rate, of patients with cancer in the ICU. Moreover, we introduced an unsupervised machine learning algorithm to identify different patient subpopulations through the analysis of cancer patients from two public ICU databases derived from large medical centers. We also evaluated the calibration of SAPS II and APACHE IV in this population. We present the following article in accordance with the STROBE reporting checklist (available at <http://dx.doi.org/10.21037/atm-20-4634>).

Methods

Data source

We extracted data from two large public databases: the Medical Information Mart for Intensive Care (MIMIC-III) Database (<https://mimic.physionet.org>) and eICU Collaborative Research Database (<https://eicu-crd.mit.edu>) (11,12). The MIMIC database contains medical records

of more than 50,000 distinct admissions in the critical care units of the Beth Israel Deaconess Medical Center that occurred between 2001 and 2012, whereas the eICU database collected medical records from over 200,000 admissions from multiple centers in 2014 and 2015.

Extraction criteria

The inclusion criteria were: (I) having diagnosis code of neoplasm (ICD-9 codes: 140–209) at any discharge diagnosis position; (II) the length of ICU stay was more than 4 hours; and (III) age between 16 and 89. We excluded ICU readmissions at the same hospital; in case of inter-ICU shift, only the first ICU stay was considered.

Data extraction and definition of variables

For both databases, the ICD-9 codes, along with their priority in each patient's diagnoses (a sequence in the MIMIC database, but classified as "primary," "main," "other" in the eICU database), were extracted to identify specific cancer types.

In the MIMIC database, we extracted data on demographics (age, sex, type of admission, and type of care unit), clinical service provider (surgical or medical), main comorbidities, vital signs, laboratory parameters reflecting illness severity, and organ-supporting treatment (mechanical ventilation, vasopressor, and renal replacement treatment) for analysis.

The clinical service referred to the service that a patient was admitted under. The main comorbidities were identified as previously described (13), and classified as congestive heart failure (CHF), atrial fibrillation (AFIB), liver disease, chronic obstructive pulmonary disease (COPD), chronic renal disease (CRD), coronary artery disease (CAD), stroke according to ICD-9 codes. The three abovementioned organ-supporting treatments were defined as binomial variables: whether they were used during the first 24 hours. Severity scoring systems, including the Simplified Acute Physiology Score II (SAPS II), Sequential Organ Failure Assessment (SOFA), and the Elixhauser Comorbidity Score, were calculated based on the respective published papers (14-16), with the code posted in the Github repository of the MIMIC database (17).

For the eICU database, the SAPS II score was calculated similarly as for the MIMIC database. However, the APACHE IV system was integrated in itself. Therefore, we extracted the APACHE IV score, predictive hospital

mortality based on APACHE IV, the calculated SAPS II scores, and actual hospital mortality from the eICU database.

Outcomes

The main outcome in the study was hospital mortality; length of ICU stay was demonstrated during the comparison of clinical subtypes.

Statistical analysis

The morbidity and mortality of cancer patients in the ICU were calculated within ICD-9 level and visualized by a histogram. For each type of cancer, the diagnostic priority was demonstrated by a heatmap. As all patient diagnoses were sequenced in the MIMIC database, we normalized the diagnostic space into 10 segments (0%~, 10%~, ...) and assigned those diagnoses into segments by their priority—that is, the primary diagnosis was at the 0%-segment and the last diagnosis was at the 90%-segment. Diagnostic priority was normalized by the Eq. [1]:

$$p_N = \begin{cases} 0\%(p_{max}=1) \\ \frac{p-1}{p_{max}-1} \times 100\%(p_{max}>1) \end{cases} \quad [1]$$

Where p_N refers to the normalized priority of the diagnosis, p_{max} refers to the total number of the patient's diagnoses, and p refers to the priority of the diagnosis before they were normalized. For each type of cancer, the sum of diagnoses in each segment was calculated. When visualized on the heatmap, the sum of diagnoses of each segment was normalized by the maximal value of all segments, as shown in Eq. [2]:

$$S_N = \frac{S}{S_{max}} \quad [2]$$

Where S_N refers to the normalized sum of diagnoses in each segment, S refers to the actual sum of diagnoses in each segment, and S_{max} refers to the sum of diagnoses in the segment with the largest number of diagnoses.

For the eICU database, we repeated the process above, but retained the three original diagnostic priorities (“primary,” “main,” and “other”) instead of ten segments.

We used an unsupervised machine-learning method, K-means clustering, to cluster the patient population into subtypes (18). Briefly, K-means clustering aims to partition n observations into k clusters according to the

nearest Euclidean distance to the centroid of the belonging cluster (18). The centroid of each cluster, which is randomized at first, iteratively updates by calculating the average point of each cluster. Finally, observations with similar patterns are partitioned into the same cluster. Most of the abovementioned variables were used in the K-means model except for the severity-scoring systems and outcomes. Unlike variables calculated in the severity-scoring systems, we used the mean values of vital signs and laboratory parameters in the first 24 hours of ICU admission rather than the worst values. Missing values of variables fed into the K-means model were imputed with a logistic regression algorithm that predicted the missing value by other variables fed into the K-means model.

An “elbow plot” was drawn to help determine the best number of clusters. If failed, we would select it from different total numbers [2–4] of clusters (19). The results of the K-means clustering were visualized by a heatmap that demonstrated the relative values of all variables. Then, with an algorithm named principal component analysis (PCA) (20), all variables of each patient were compressed into two components (PCA1 and PCA2), whereby patients were visualized on a scatterplot with two dimensions that indicated the relationship between patients and clusters.

As the MIMIC database provided more detailed clinical data, we used the K-means method only for MIMIC database, and considered the eICU as the validation database. After clustering, variables were compared among different clusters, which implied different clinical subtypes. Variables that were closely related to the clusters were used as instrumentation variables to identify different clinical subtypes. We evaluated the interactions of clinical subtype, the severity scoring system, and outcomes by using the standard mortality ratio (SMR), calibration graph, and Hosmer-Lemeshow C statistic (21). The SMR was calculated by a ratio of the observed mortality divided by predicted mortality; 95% confidence intervals were calculated by Vandembroucke method (22).

In this study, continuous and categorical data were summarized as mean (SD) and number (percentage) respectively. One-way Analysis of variance (ANOVA) and chi-square test were used for statistical inferences of continuous and categorical data. A P value less than 0.05 was considered indicative of statistically significant differences. Databases were created locally with Postgresql (version 10.0) and accessed by structured query language integrated into a Python 3.7 notebook, on which run all the data-analysis codes used in the study. The notebook was

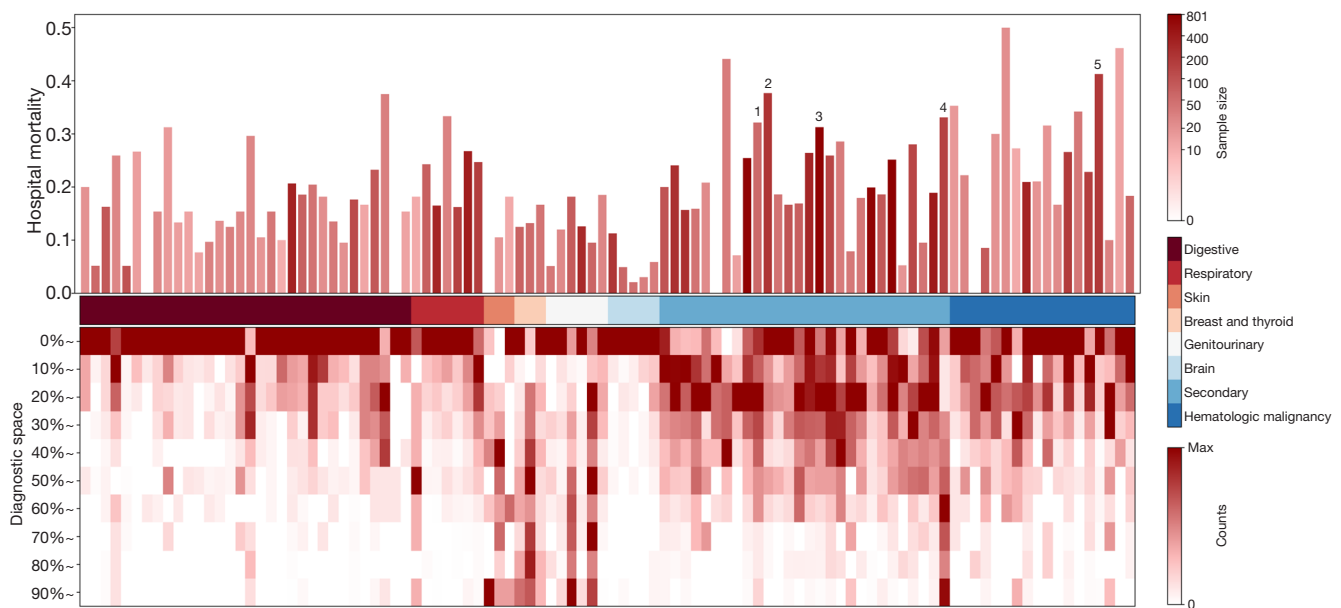


Figure 1 The mortality and distribution of positions of ICD-level diagnoses of the MIMIC database. In the top part of the figure, the depth of red color corresponds to the number of patients with a specific cancer. In the middle, the color blocks refer to the manually classified cancers according to the location or organ system. In the bottom part of the figure is a heatmap. The diagnostic space of each patient was divided into 10 segments, and the color in each segment refers to the frequency of the diagnosis occurring in that segment. The annotations were: 1, secondary malignant neoplasm of the mediastinum; 2, secondary malignant neoplasm of the pleura; 3, malignant neoplasm of the liver, secondary; 4, other malignant neoplasm without specification of the site; 5, acute myeloid leukemia, without details of having achieved remission. ICD, International Statistical Classification of Diseases and Related Health Problems; MIMIC, Medical Information Mart for Intensive Care.

uploaded on the Github for maintaining reproducibility (https://github.com/gscfwid/Cancer_ICU).

Results

According to extractive criteria, we extracted data on 6,505 (13.8%) patients with cancer from 46,998 patients with non-specific diagnosis from the MIMIC database. Among these cancer patients, cancer-related diagnostic codes were counted 11,174 times. While in the eICU database, up to 7,351 (4.9%) patients with cancer were extracted from 148,532 patients with nonspecific diagnoses, and the cancer-related diagnosis was counted 7,893 times. The most common cancer types based on the ICD-9 system were metastatic cancer of bone/bone marrow in MIMIC and lung cancer in the eICU database. Moreover, the diagnosis with the highest mortality (for cancer type with more than 10 patients) was mycosis fungoides in the MIMIC database, and metastatic adenocarcinoma of unknown primary in the eICU database. The top 10 most common and most

fatal cancer types in the ICD level were summarized in the [Tables S1,S2](#).

Mortality and diagnostic priority of different cancer types that had more than 10 victims are shown in [Figure 1](#). The top part of [Figure 1](#) depicts the mortality rates of all types of cancer. The top 5 cancer types with the highest mortality that had at least 50 victims were annotated. The middle of the figure lists manually classified cancer types according to the organ or system, and this manual classification is listed respectively in [Tables S3,S4](#) in the MIMIC and eICU databases, respectively. The priorities for each diagnosis were illustrated in the bottom part of [Figure 1](#). We analyzed the eICU database in a similar way ([Figure S1](#)). Generally, for both databases, ICU patients with metastatic cancer, hematologic malignancy had higher mortality rates than others; they were less likely to be the primary diagnosis, except in metastatic brain tumor. Moreover, in the MIMIC database, most non-metastatic solid cancers held the first position at diagnosis.

As the elbow plot hardly provided the best cluster

number (Figure S2), we conducted a spectrum of K-means clustering with different cluster numbers [2–4] for the MIMIC database, as illustrated in Figure 2A and Figures S3,S4. The boundary of all 4 clusters were relatively clear (Figure 2B). Variables that were mostly associated with different clusters were admission type (elective or emergency) and clinical service provider (surgical or medical). We noticed that nearly all patients in the first cluster from the clustering of K=4 (Figure 2) were elective admissions (99.1%), whereas in the rest of the clusters, most were emergency admissions (93.7%). Most surgical patients were in the 1+2 clusters (92.0%) and most medical patients were in the 3+4 clusters (93.5%). Detailed disparities of the characteristics and outcomes from all four clusters are summarized in Table 1.

When comparing the clusters with different K numbers (Figure 2A, Figures S3 and S4), an evolutionary process could be observed. When K=2, it reflected the differences between clinical service providers (surgical or medical). When K=3, a new cluster was generated and featured worse cardiac and renal function. Finally, in the clustering of K=4, the cluster that featured with surgical service was divided into elective and emergency admissions.

Interestingly, although we did not use any outcome data or severity scoring data in the K-means model, the clusters were extremely associated with outcomes. The mortality rates of the four clusters were 4.0%, 11.8%, 20.4%, and 46.5%, which showed similar discrimination to the SAPS II system (4.8%, 8.5%, 20.1%, and 50.8%), as illustrated in Figure 2C. Here, we sorted all patients according to the SAPS II score in ascending order and divided them into four groups which had the same sizes with the K-means clusters. The mortality and SAPS II score were compared between these two systems. Except for the fourth cluster, we noticed similar SAPS II scores but distinct mortality among the clusters. Especially in the second and third clusters, the median and interquartile range of the SAPS II score was very close {37 [30–45] vs. 38.5 [31–47]}, but the mortality of the second cluster was nearly half that of the third cluster (11.8% vs. 20.3%; Figure 2C).

Furthermore, we validated the abovementioned findings in the eICU database. Because the clinical subtypes of cancer patients in the ICU were actually based on the clinical service provider, we classified patients of the eICU database into surgical and non-surgical groups based on the ICU admission resource: patients from the operation room were identified as belonging to the surgical group; otherwise, they were assigned to the non-

surgical group, corresponding to clusters 1+2 and 3+4 in the MIMIC database. The SMR, Hosmer–Lemeshow C statistic, and calibration graph were conducted on the basis of different scoring systems (Table 2 and Figure 3), and the corresponding number of patients in each risk decile were plotted in Figure S5. The calibration of SAPS II for both databases were poor (C=628.07, P<0.001 for the MIMIC database; C=827.64, P<0.001 for the eICU database; as shown in Table 2 and Figure 3A,3B). However, the calibration of APACHE IV in the eICU database was relatively better, despite a P value less than 0.05 (C=87.84, P<0.001; as shown in Table 2, Figure 3C,3D). Furthermore, the SMRs of the surgical groups (cluster 1+2 in the MIMIC database) were lower than those in the non-surgical groups (cluster 3+4 in the MIMIC database) for all comparisons (Table 2 and Figure 3).

The number of patients in each risk decile of the APACHE IV were imbalanced: numbers in high-risk deciles were fewer (Figure S5). Therefore, we compared the actual and predicted mortality for lower risk subgroups (Figure 4). The population of each database was divided into segments according to different SPAS II or APACHE IV scores, and the actual mortality, with 95% CIs, of the surgical and non-surgical group in each segment were compared, along with the predicted mortality by scoring systems.

For both databases, the mortality of the surgical group (cluster 1+2 in MIMIC database) was significantly lower than that of the non-surgical group (cluster 3+4 in MIMIC database; Figure 4A,4B). However, as the mortality predicted by the APACHE IV was calculated by the APACHE score and admission information, including diagnoses and admission information, surgical and non-surgical groups had different predicted mortality (Figure 4C). As shown in Figure 4C, the actual mortality was close to the mortality predicted by APACHE IV in these lower risk segments (the mortality of those segments was less than 0.25).

Discussion

The present study showed that, according to the ICD-level mortality (Figure 1, Figure S1), secondary and hematologic malignancies have worse outcomes. Moreover, among the top 5 diagnoses that had the highest mortality rates in the two databases, three of the diagnoses were the same: (I) metastasis involving pleura; (II) metastasis involving the liver; and (III) acute myeloid leukemia. This is consistent with the mainstream opinion that metastatic cancer and hematologic malignancy are independent prognostic

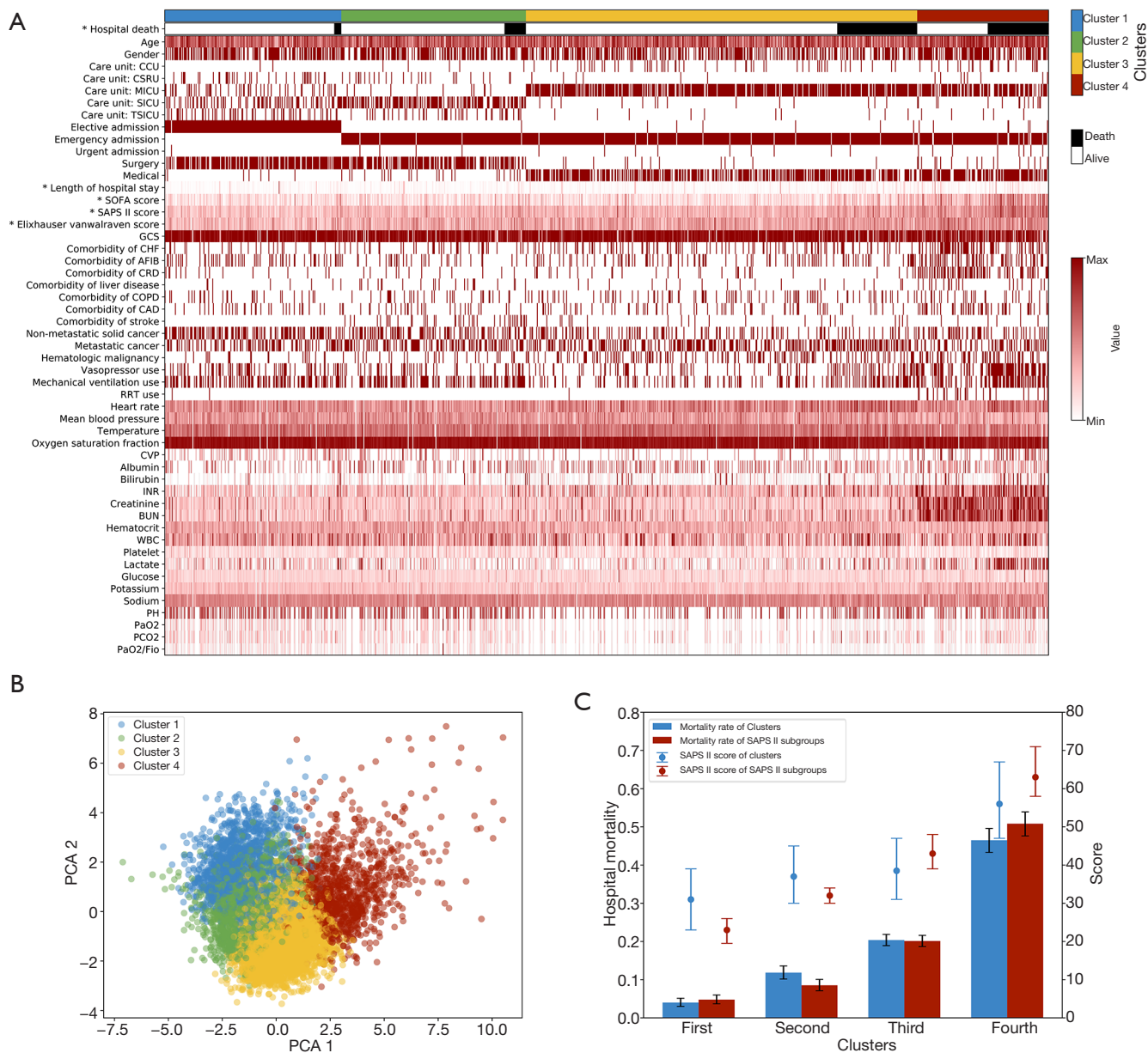


Figure 2 K-means clustering revealed four clinical subtypes (cluster 1-4) (A,B) and their associations with hospital mortality as compared with the SAPS II system (C). In Subplot A, the depth of red color in the heatmap referred to the relative value of the variables, and their names are annotated on the left. Variables marked by asterisk were not entered into the K-means model. The Subplot B refers to the visualization of Principal Component Analysis (PCA), and PCA1 and PCA2 are the two largest components. Each point represents an individual patient. The mortality of the four clusters are illustrated in Subplot C, compared with the four groups divided by the SAPS II score (the four SAPS II groups had the same sizes as those four clusters and their SAPS scores were sorted in an ascending order). CCU, cardiac care unit; CSRU, Cardiac surgery recovery unit; MICU, medical intensive care unit; SICU, surgery intensive care unit; TSICU, trauma/surgical intensive care unit; SOFA, sequential organ failure assessment; SAPSII, Simplified Acute Physiology Score II; GCS, Glasgow Coma Scale; CHF, chronic heart failure; AFIB, atrial fibrillation; CRD, chronic renal disease; COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease; RRT, renal replacement treatment; CVP, central venal pressure; INR, international normalized ratio; BUN, blood urea nitrogen; WBC, white blood cells; PaO2, artery partial pressure of oxygen; PCO2, partial pressure of carbon dioxide; FiO2, fraction of inspired oxygen.

Table 1 Comparison of the characteristics and outcomes of the four clusters from the K-means clustering

	Missing	Cluster 1	Cluster 2	Cluster 3	Cluster 4	P value
n		1,307	1,379	2,785	1,034	
Age ^a	0	64.3 (12.4)	64.5 (13.2)	64.3 (13.9)	69.9 (12.7)	<0.001
Gender (M) ^a	0	796 (60.9)	831 (60.3)	1,528 (54.9)	700 (67.7)	<0.001
Care unit ^b	0					<0.001
CCU		15 (1.1)	34 (2.5)	327 (11.7)	119 (11.5)	
CSRU		235 (18.0)	168 (12.2)	16 (0.6)	23 (2.2)	
MICU		239 (18.3)	67 (4.9)	2,370 (85.1)	785 (75.9)	
SICU		530 (40.6)	825 (59.8)	42 (1.5)	81 (7.8)	
TSICU		288 (22.0)	285 (20.7)	30 (1.1)	26 (2.5)	
Admission type ^b	0					<0.001
Elective		1,258 (96.3)	1 (0.1)	56 (2.0)	59 (5.7)	
Emergency		1 (0.1)	1,367 (99.1)	2,674 (96.0)	951 (92.0)	
Urgent		48 (3.7)	11 (0.8)	55 (2.0)	24 (2.3)	
Service provider ^b	0					<0.001
Surgery		1,043 (79.8)	900 (65.3)	95 (3.4)	77 (7.4)	
Medical		35 (2.7)	196 (14.2)	1,957 (70.3)	790 (76.4)	
Unclear		229 (17.5)	283 (20.5)	733 (26.3)	167 (16.1)	
SOFA score ^a	0	3.4 (2.4)	3.3 (2.5)	3.6 (2.6)	8.0 (3.8)	<0.001
SAPS II score ^a	0	31.6 (12.5)	38.5 (12.0)	39.1 (11.3)	57.6 (15.5)	<0.001
Elixhauser Vanwalraven score ^a	10	8.8 (7.5)	12.3 (8.1)	14.3 (7.8)	19.1 (8.5)	<0.001
GCS ^a	102	14.1 (2.1)	13.6 (2.6)	14.1 (2.1)	13.2 (3.1)	<0.001
Comorbidity of ^b						
CHF	0	149 (11.5)	146 (10.7)	577 (20.0)	408 (42.1)	<0.001
AFIB	0	309 (23.8)	222 (16.3)	626 (21.8)	344 (35.5)	<0.001
CRD	0	67 (5.2)	59 (4.3)	179 (6.2)	383 (39.6)	<0.001
Liver disease	0	42 (3.2)	144 (10.6)	129 (4.5)	96 (9.9)	<0.001
COPD	0	181 (13.9)	153 (11.2)	487 (16.9)	167 (17.3)	<0.001
CAD	0	196 (15.1)	182 (13.4)	386 (13.4)	232 (24.0)	<0.001
Stroke	0	29 (2.2)	206 (15.1)	118 (4.1)	30 (3.1)	<0.001
Non-metastatic solid cancer ^b	0	688 (53.0)	565 (41.5)	731 (25.4)	290 (30.0)	<0.001
Metastatic cancer ^b	0	525 (40.4)	646 (47.5)	1,340 (46.6)	360 (37.2)	<0.001
Hematologic malignancy ^b	0	94 (7.2)	153 (11.2)	822 (28.6)	324 (33.5)	<0.001
Vasopressor use ^b	0	403 (30.8)	320 (23.2)	469 (16.8)	544 (52.6)	<0.001
Mechanical ventilation use ^b	0	653 (50.0)	740 (53.7)	745 (26.8)	512 (49.5)	<0.001
RRT use ^b		5 (0.4)	4 (0.3)	11 (0.4)	152 (15.7)	<0.001

Table 1 (continued)

Table 1 (continued)

	Missing	Cluster 1	Cluster 2	Cluster 3	Cluster 4	P value
Heart rate ^a (bpm)	87	86.6 (14.2)	84.2 (15.5)	92.1 (17.1)	92.4 (18.2)	<0.001
Mean blood pressure ^a (mmHg)	89	78.1 (9.5)	81.3 (10.6)	77.4 (10.8)	72.1 (11.1)	<0.001
Temperature ^a (°C)	137	36.9 (0.6)	36.8 (0.6)	36.8 (0.6)	36.5 (0.7)	<0.001
Oxygen saturation fraction ^a (%)	98	97.5 (1.7)	97.6 (1.7)	96.6 (2.0)	95.7 (4.5)	<0.001
CVP ^a (mmHg)	4,927	9.7 (5.2)	9.8 (5.0)	10.8 (6.1)	16.8 (8.2)	<0.001
Albumin ^a (g/dL)	3,834	2.8 (0.6)	3.1 (0.7)	3.0 (0.6)	2.7 (0.6)	<0.001
Bilirubin ^a (mg/dL)	3,277	2.2 (2.9)	1.9 (2.9)	1.7 (3.3)	3.5 (6.3)	<0.001
INR ^a	877	1.3 (0.3)	1.3 (0.4)	1.4 (0.6)	2.0 (1.7)	<0.001
Creatinine ^a (mg/dL)	56	1.0 (0.7)	0.9 (0.5)	0.9 (0.5)	2.9 (2.4)	<0.001
BUN ^a (mg/dL)	59	18.4 (10.0)	18.9 (10.0)	21.3 (12.4)	54.0 (28.6)	<0.001
Hematocrit ^a (%)	59	32.2 (4.4)	32.8 (5.3)	30.3 (5.2)	30.4 (5.3)	<0.001
WBC ^a (1,000/uL)	78	12.4 (6.1)	11.9 (7.9)	12.0 (16.4)	19.2 (41.0)	<0.001
Platelet ^a (1,000/uL)	76	232.5 (110.5)	242.5 (129.8)	235.3 (161.4)	195.6 (131.6)	<0.001
Lactate ^a (mmol/L)	2,460	2.2 (1.4)	2.3 (1.5)	1.9 (1.0)	3.8 (3.3)	<0.001
Glucose ^a (mg/dL)	43	143.4 (32.5)	143.8 (43.5)	134.1 (47.4)	150.5 (73.1)	<0.001
Potassium ^a (mmol/L)	48	4.2 (0.4)	4.1 (0.4)	4.0 (0.5)	4.7 (0.8)	<0.001
Sodium ^a (mmol/L)	56	137.8 (3.0)	137.7 (4.0)	137.4 (4.7)	136.9 (6.0)	<0.001
pH ^a	3,813	7.4 (0.1)	7.4 (0.1)	7.4 (0.1)	7.3 (0.1)	<0.001
PaO ₂ ^a (mmHg)	3,813	171.4 (66.8)	211.9 (89.7)	127.2 (59.8)	130.4 (62.6)	<0.001
PCO ₂ ^a (mmHg)	3,813	42.1 (6.9)	40.4 (7.2)	43.3 (12.4)	40.8 (11.9)	<0.001
PaO ₂ /FiO ₂ ^a	3,813	291.4 (120.9)	344.5 (148.3)	217.5 (110.6)	203.3 (110.4)	<0.001
Length of hospital stay ^a (d)	0	3.8 (6.1)	3.6 (4.6)	3.6 (5.1)	5.1 (7.2)	<0.001
Hospital death ^a	0	56 (4.3)	162 (11.7)	550 (19.7)	481 (46.5)	<0.001

^a, continued value summarized as mean (SD); ^b, categorical value summarized as number (percentage). CCU, cardiac care unit; CSRU, Cardiac surgery recovery unit; MICU medical intensive care unit; SICU, surgery intensive care unit; TSICU, trauma/surgical intensive care unit; SOFA, sequential organ failure assessment; SAPS Simplified Acute Physiology Score; GCS, Glasgow Coma Scale; CHF, chronic heart failure; AFIB atrial fibrillation; CRD chronic renal disease; COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease; RRT, renal replacement treatment; CVP, central venal pressure; INR, international normalized ratio; BUN, blood urea nitrogen; WBC, white blood cells; PaO₂, artery partial pressure of oxygen; PCO₂, partial pressure of carbon dioxide; FiO₂, fraction of inspired oxygen.

factors (23,24). In the SAPS II system, metastatic cancer was assigned an increasing score of 9 whereas hematologic malignancy was scored as 10 (14).

Generally, the primary diagnosis is always the main reason for ICU admission. As shown in *Figure 1*, most non-metastatic solid cancer held the first position of diagnosis. And in *Figure 2*, non-metastatic solid cancer more frequently occurs in cluster 1 and 2, which were featured as surgical patients. All the above imply that these patients

were admitted to ICU for postoperative monitoring. On the contrary, metastatic cancer and hematologic malignancy are less likely to be the primary diagnosis, which implies that its complications, rather than the cancer itself, necessitated ICU admission for these patients.

We found that different clinical subtypes could be simply identified by the admission information. Hospital mortality varied among these subtypes, and this was consistent with the variation of prognoses reported by previous studies

Table 2 The standard mortality ratio and Hosmer–Lemeshow C statistic of different groups by different severity-scoring systems

	SMR (95% CIs)	H–L C statistic	P value
Cluster 1+2 (MIMIC) to SAPS II	0.37 (0.33–0.43)	409.22	<0.001
Cluster 3+4 (MIMIC) to SAPS II	0.76 (0.72–0.81)	315.15	<0.001
Whole population (MIMIC) to SAPS II	0.65 (0.61–0.68)	628.07	<0.001
Surgical group (eICU) to SAPS II	0.32 (0.25–0.39)	209.53	<0.001
Non-surgical group (eICU) to SAPS II	0.67 (0.63–0.71)	679.19	<0.001
Whole population (eICU) to SAPS II	0.63 (0.59–0.67)	827.64	<0.001
Surgical group (eICU) to APACHE IV	0.76 (0.60–0.95)	31.53	<0.001
Non-surgical group (eICU) to APACHE IV	1.07 (1.01–1.14)	99.19	<0.001
Whole population (eICU) to APACHE IV	1.05 (0.99–1.11)	87.84	<0.001

SMR, standard mortality ratio; H-L Hosmer–Lemeshow; MIMIC, medical information mart for intensive care; SPAS, Simplified Acute Physiology Score; APACHE, acute physiology and chronic health evaluation.

(6,25). The reported hospital mortality rates could be as low as 10%, often in postoperative monitoring cohorts (4,8), and as high as 50% or more, often in non-surgical diagnoses (3,9). This disparity cannot be explained only by illness severity but may indicate a different association of mortality other than that mentioned in the traditional severity scoring systems. One reason for this disparity may be that the acute postoperative stress status (tachycardia, intubation, and so on) causes a deterioration of the score evaluated in the first 24 hours in the ICU. However, more research is needed to validate this rationale.

The SAPS II scoring system didn't perform well in calibration even though it considered the influence of admission type, partially due to its older age (introduced in 1993). The APACHE IV system takes the admission type and diagnosis into account when predicting mortality according to the APACHE score (26). The system performed well for cancer patients at low risk of mortality in the eICU database of the present study. However, as the number of ICU cancer patients at high risk of mortality in the present study (especially the surgical group) was too low to generate credible conclusions, more evidence is needed. Previous studies have found an apriority of APACHE IV compared to SAPS II in many ICU conditions (27,28), but the evidence in cancer patients was insufficient. The application of the APACHE IV system is limited by its complexity. However, as data science develops, the complexity of this system could be overcome by electronic recording techniques and massive computing power.

The present study supports the theory that cancer patients in the ICU need to be considered separately

according to the admission type and clinical service provider. A similar opinion was proposed by Weissman and his colleagues based on their experience and intuition (29). They found significant differences between elective and emergency postoperative patients in the ICU, which corresponds to the first and second clusters in our study. However, our study used a method of machine learning to deal with the high-dimensional clinical data, based on the theory that data intracusters were more consistent than interclusters. Furthermore, The K-mean algorithm tells us the distance among different clusters. When K=2 we have surgical and medical groups; until K=4 we get elective and emergent/urgent subgroups. It implies that the differences between surgical and medical groups are more obvious than those between elective and emergent/urgent subgroups. Separately analysing the surgical and medical patients (or elective and emergent/urgent surgical) with cancer in ICU can decrease heterogeneity. Some studies addressed this concern and specified patient-selection criteria (7,30,31), but others lacked this additional measure and only treated it as a variable for analysis (1,2,32). This is because there are some other concerns (e.g., sample size, study purpose) to take into account besides heterogeneity for observational research as well as systematic review or meta-analysis.

Puxty and colleagues conducted excellent work on a comprehensive meta-analysis for ICU patients with solid cancers (25). They found that cancer patients admitted as medical patients had increased risk (2- to 4-fold higher) of ICU mortality, and increased risk of in-hospital mortality (6- to 8-fold higher) compared with cancer patients who were surgical admissions; however, they only specified

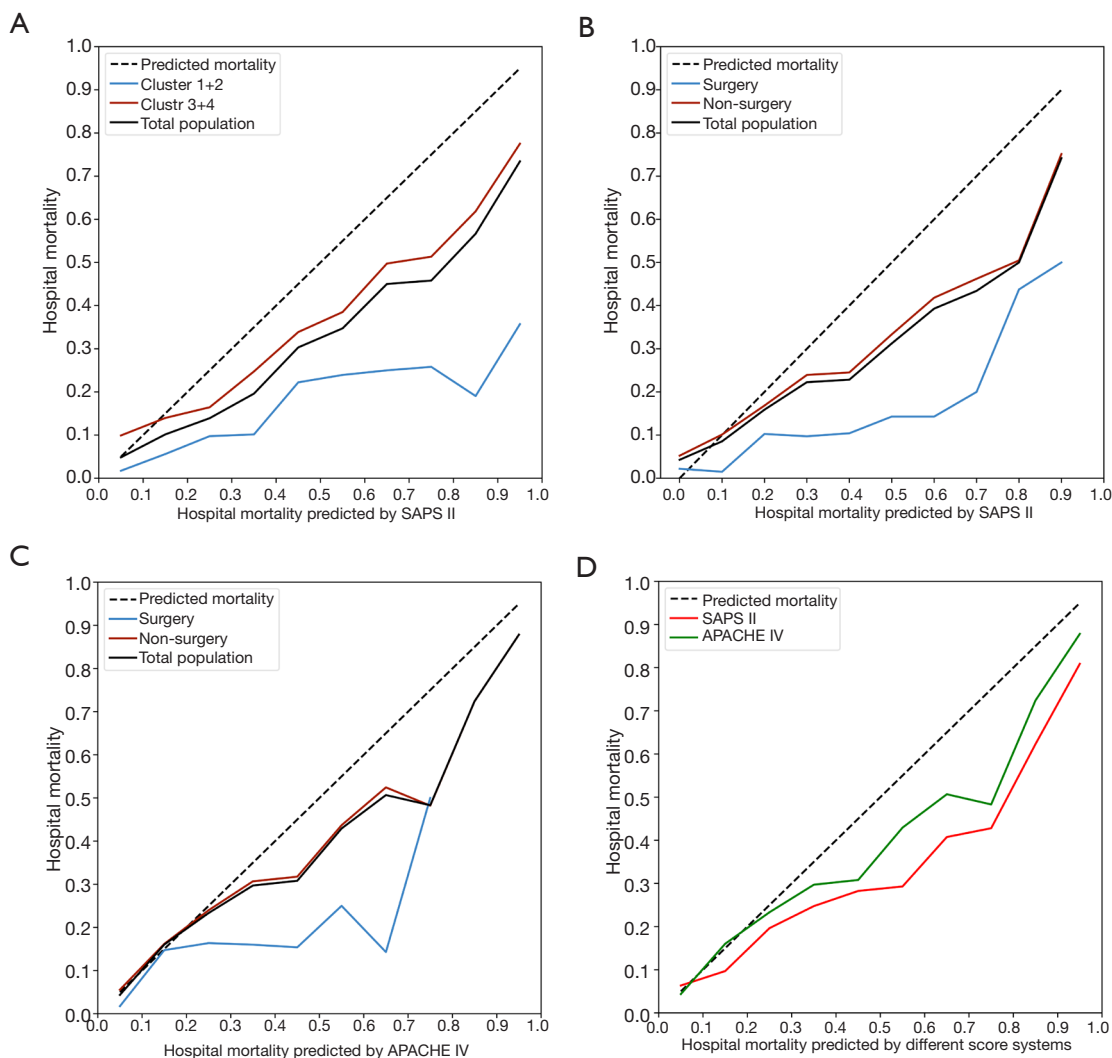


Figure 3 The graphs show the calibration of SAPS II and APACHE IV in the MIMIC and eICU databases: (A) SAPS II in the MIMIC database; (B) SAPS II in the eICU database; (C) APACHE IV in the eICU database; (D) the comparison of the total population for the two score systems in eICU database. MIMIC, Medical Information Mart for Intensive Care; SPAS, Simplified Acute Physiology Score; APACHE, Acute Physiology and Chronic Health Evaluation.

group stratification by different cancer sites. Furthermore, we noticed an outstanding variation among the enrolled studies for both hospital mortality ($I^2=98.8\%$, $P<0.001$) and ICU mortality ($I^2=99.1\%$, $P<0.001$). Therefore, the admission type should have been considered for stratified analysis in Puxy’s research, which may have also improved the heterogeneity of the enrolled studies.

Our study provided ICD-level data on the mortality rate of cancer patients in the ICU from multiple resources, and emphasized the importance of differentiating between admission types and clinical service providers. We discussed

the calibration of different severity-scoring systems for cancer patients in the ICU across different clinical subgroups. However, this study has some limitations. First, selection bias might exist, especially in the eICU database, because there were fewer cancer patients in the ICU than reported on average by most studies (~15%). Second, unlike the eICU database, it was difficult to compare the two different severity-scoring systems in the MIMIC database, because the APACHE IV algorithm is only available online (33). Moreover, there were limits deriving from the retrospective nature of the analysis and relatively small

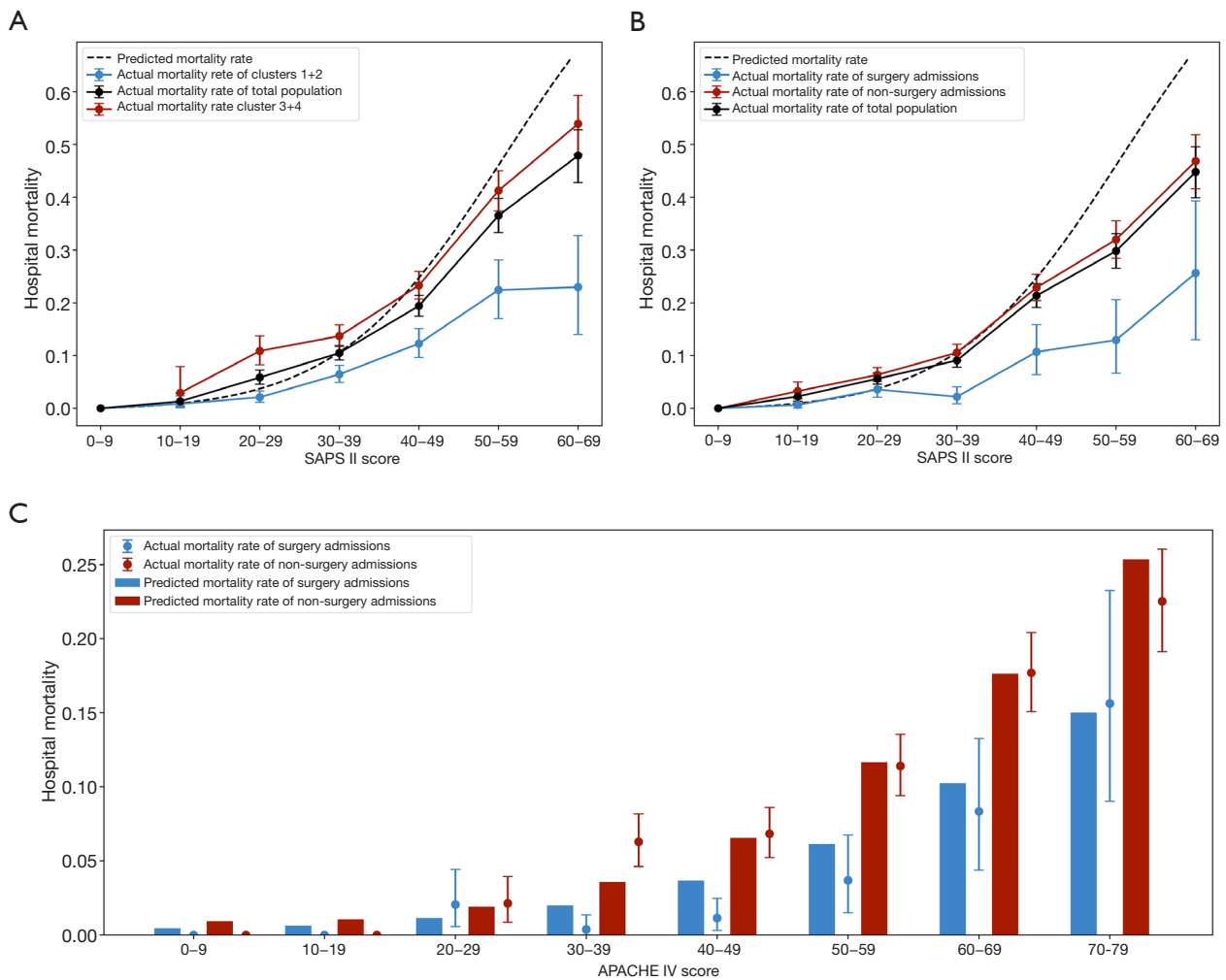


Figure 4 The comparison of mortality in different groups stratified by different intervals of severity score. (A) The population from the MIMIC database; (B,C) the population from the eICU database. MIMIC, Medical Information Mart for Intensive Care; SPAS, Simplified Acute Physiology Score; APACHE, Acute Physiology and Chronic Health Evaluation.

sample size for machine learning. Therefore, prospective studies with larger populations are needed in the future.

Conclusions

Similar mortality rates for a spectrum of ICD-level cancer diagnoses were observed within two large ICU databases. Different clinical subtypes of ICU patients with cancer can be well identified by admission type and clinical service provider, and caution should be exercised when considering these patients as a whole population, both in clinical practice and research. The system of APACHE IV performs better than SAPS II for cancer patients at low risk of mortality in the ICU, whereas the same conclusion for those at high risk

of mortality needs to be validated in further studies.

Data sharing and data accessibility

The datasets generated and/or analysed during the current study are available in the MIMIC-III v1.4 (<https://mimic.physionet.org>) and eICU (<https://eicu-crd.mit.edu/>).

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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