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Original Article

Factors affecting the prognosis of cancer patients in general intensive care units in a Chinese population

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Abstract: Background: More and more cancer patients are admitted to intensive care units (ICUs) with acute life-threatening conditions. In West, the mortality of cancer patients admitted to ICUs has been substantially reduced thanks to advances in diagnosis and treatment. However, there is a paucity of data regarding the current situation of cancer patients admitted to ICUs in China. Methods: We performed a detailed retrospective review of 255 cancer patients admitted to the ICUs of three university-affiliated hospitals in Hunan province over a five-year period. Outcome measure was ICU mortality rate, and was correlated with physiologic and therapeutic factors. We also evaluated the performance of two severity-of-illness scoring systems in this population. Results: During the studying period, the medical ICU plus Respiratory ICU (RICU) beds occupied 1.02% of all inpatients beds and received 1.8% of all inpatient admissions. The rates for ICU, one-month and six-month mortalities were 49.0%, 75.7% and 85.1%, respectively. Patients with lung cancer had better prognosis than other malignancies. No change or increased Sequential Organ Failure Assessment (SOFA) score, higher Acute Physiology and Chronic Health Evaluation (APACHE II) score at admission, and the need for invasive mechanical ventilation (IMV) and vasopressors were independently associated with ICU mortality. Conclusions: Cancer patients had less access to the intensive care resources in Hunan province of China than western countries. Both systemic illness and requirement for specific measures for organ failure predicted ICU mortality in this population. Based on our results, we proposed a set of clinical parameters to guide patient management when considering ICU transfers.

Keywords: Intensive care, cancer, prognostic factors, mortality, access to care, China

Introduction

Worldwide each year, approximately 12.7 million people are diagnosed with cancer and 7.6 million die from it [1]. Cancer is also becoming the leading cause of death and disability among Chinese adults [1, 2]. Inadequate healthcare infrastructure and inequity in the distribution of medical resources further complicates the attempt to decrease the disease burden of cancer in developing countries [3, 4].

Early diagnosis and effective treatment have substantially improved the average survival time for some cancer patients in the last two decades [3]. For instance, the survival for non-Hodgkin's lymphoma and leukemia has significantly increased [5]. On the flip side, more and more cancer patients encounter life-threatening situations after aggressive treatment such as high-dose chemo-radiation and complication rates are higher in patients with chronic comorbidities [6]. Cancer patients often require intensive care when admitted in the above settings.

Cancer patients consume more critical care resources than non-oncological patients [7]. So finding out the important prognostic factors for cancer patients in ICU is very important for both physicians and patients and their family members. Previous studies identified several important prognostic factors for cancer patients in the ICU, including disease status, systemic illness severity, shock, neutropenia, mechanical ventilation, and vasopressor use et al. [8-10]. There are also some studies revealed the prognosis of cancer patients in Chinese population.

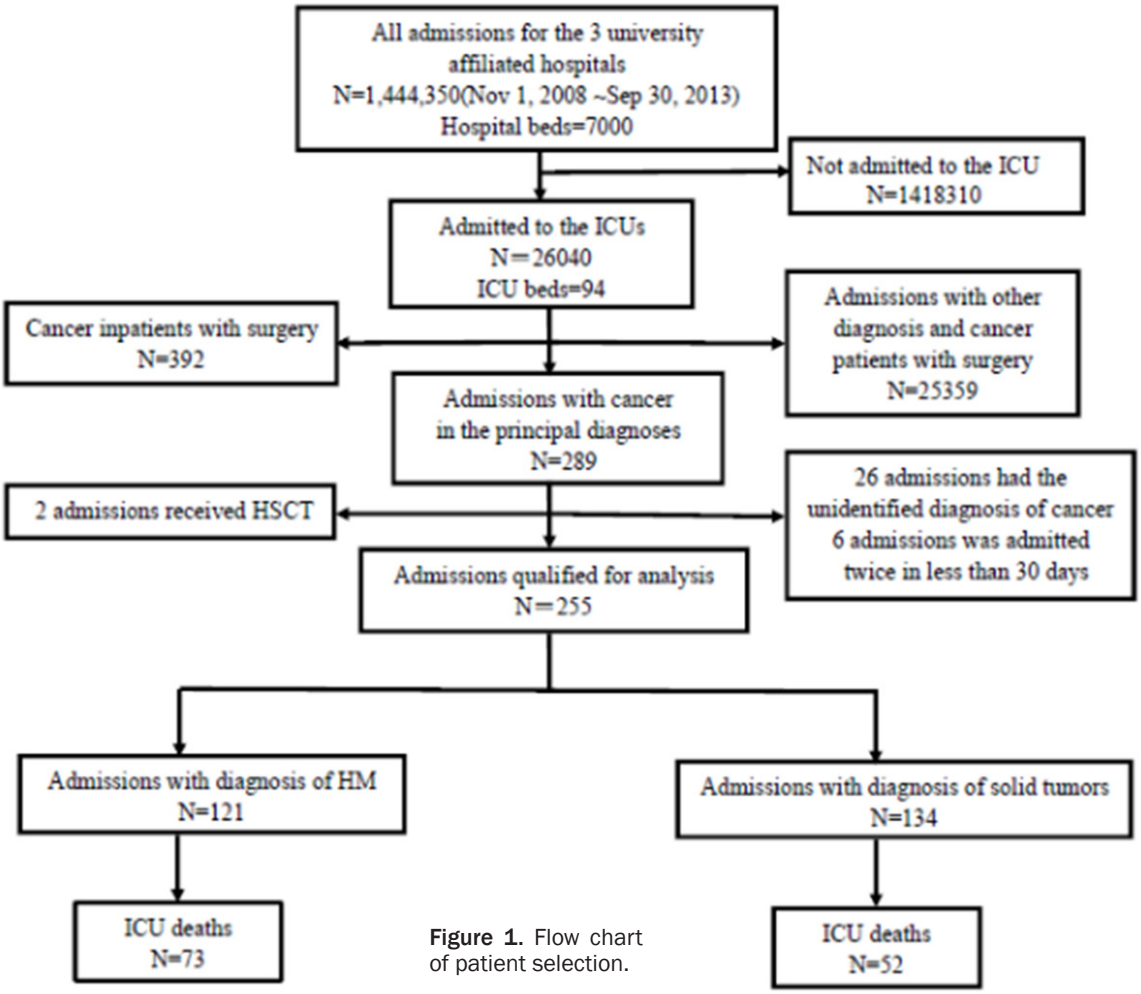

Figure 1. Flow chart of patient selection.

Xing et al. had reviewed the data of 190 critically ill cancer patients with postoperative respiratory insufficiency in China [11]. In addition, results of a observational retrospective study analysed the score ability in predicting in-hospital mortality of critically ill cancer patients, but most of the patients were mainly underwent scheduled surgery (92.9%) [12]. However, the physiological and physical characteristics are totally different from cancer patients who can suffer from surgery or not. Moreover, little is known about the ICU course and prognosis of critically ill cancer patients who were not able to endure surgery in China.

We had previously investigated the prognostic factors and mortality outcomes in patients with hematological malignancies (HM) in three university-affiliated hospitals in Hunan province of China [13]. The study revealed significant clinical outcome predictors and showed that patients in this region had relatively little access to intensive care resources and high mortality compared to some results revealed by western researches [13]. However, the population of HM only accounts for less than 10% of all the cancer patients [14]. Therefore we wanted to evaluate the access to intensive care and prognostic factors for critically ill patients with other malignancies in Hunan province

Methods

Patients and setting

This study was deemed exempt from a formal review by the Ethics Committee of Central South University as no personally identifiable information would be collected. We conducted a detailed retrospective chart review of patients admitted from three university-affiliated hospitals in Hunan, China, from November 2008 to September 2013. The catchment area of these three hospitals spans Hunan province serving

amount of 60 million patients with diverse socioeconomic backgrounds. The three hospitals have about 25,000 cancer inpatient admissions each year. In addition to the general medical ICUs (MICU), all three hospitals have specialized ICUs such as coronary care units, neuroscience ICUs, pediatric ICUs, newborn ICUs, and respiratory ICUs (RICU) where lung cancer patients are admitted. As regional referral centers, the MICUs (77 beds total) and RICUs (15 beds total) of these hospitals admit over 5,000 critically ill patients each year. The equipment of these units are in accordance with our previously descriptions [13]. The same admission and transfer criteria were applied to cancer patients and other critically ill patients. ICU-level care was considered when a patient required frequent, close monitoring and the support of special equipment such as mechanical ventilation, continuous blood purification and intensive medication. The decision to admit or transfer to the ICU was made by the referring departments in collaboration with the intensive care specialists and required consent from the patient and/or family member. The same ICU admission protocol was used in all three hospitals and there was no substantial difference in the admission policy between MICUs and RICUs.

The flow chart in **Figure 1** shows the process of case selection for the chart review. A total of 92 MICU and RICU beds (1.02% of all inpatient beds) received 26,040 inpatient admissions (1.8% of all inpatient admissions) in the study period. Among them, 289 admissions without surgical interventions listed cancer as the principal diagnosis; 392 additional cancer admissions involving surgery were excluded. Thirty-four admissions were excluded because the patients received hematopoietic stem cell transplant (HSCT, 2 admissions), had non-specific diagnoses of cancer (26 admissions), or were readmissions within 30 days (6 admissions). Finally 255 admissions with cancer qualified for analysis.

For patients who had multiple readmissions to the same ICU, each admission was counted separately, unless it occurred within 30 days from the previous admission.

Data collection

The following background data were collected for each ICU admission: age, sex, principal diagnoses, disease status, timing and reason for ICU admission, lengths of ICU and hospital stays, time-lapse between diagnosis and admission, treatment regimen prior to ICU admission, and the presence or absence of organ failures. Disease status was coded into three categories: controlled, defined as those who had undergone previous treatments (including chemotherapy, radiotherapy, etc) and had no sign of recurrence; newly diagnosed, defined as those who had been diagnosed with cancer in the last three months; recurrence/progression, defined as those with active disease status accessed by the hematology-oncology attending physician or persistent disease insensitivity to standard chemotherapy. The definition of complete/partial remission of HM is the same as our previous study [13] and NCCN guidelines were also used to evaluate the disease status of each patient [15] (Supplement Table 1).

In this study, we used two scoring systems to assess systemic illness-Acute Physiologic and Chronic Health E-valuation II (APACHE II) and Sequential Organ Failure Assessment (SOFA) [13]. The outcome measure was ICU mortality. The categorization of other clinical factors were described previously [13].

We also collected selected socioeconomic factors, including the type of medical insurance, the place of residence (urban or rural), and the total cost of the hospital stay. Three main types of insurance were in wide use in Hunan province during the study-Urban Resident Basic Medical Insurance (URBMI), Urban Employee Basic Medical Insurance (UMBMI) and New Rural Cooperative Medical Insurance Scheme (NRCMS), each with different out-of-pocket expense ratios [16].

Data analysis

The statistical analysis was done with SPSS, version 17.0. Continuous variables were reported as mean ± standard deviation (SD) or standard error of mean (SEM) when appropriate. Proportions were presented as percentages. Inter-group comparison was performed with Student's t-test, one-way ANOVA, and chi-square test. We used logistic regression to estimate the relationship between multiple variables and ICU survival. Wald statistic was used to denote strength of association and Pearson's coefficient was used to evaluate correlation between parameters (Supplement Table 2).

Table 1. Characteristics of cancer admissions and variables associated with ICU mortality (N (%) or mean ± SEM)

	All (n=255)	Survivors (n=130)	Non-survivors (n=125)	Subgroup mortality
Age	55.78±1.13	57.16±1.42	54.34±1.77	
Male sex	185 (72.5%)	90 (69.2%)	95 (76.0%)	51.4%
Disease status				
Newly diagnosed	172 (67.5%)	90 (69.2%)	82 (65.6%)	47.7%
Controlled	27 (10.6%)	15 (11.5%)	12 (9.6%)	44.4%
Recurrence/progression	56 (21.9%)	25 (19.2%)	31 (24.8%)	55.4%
Underlying malignancy				
Hematologic	121 (47.5%)	48 (36.9%)	73 (58.4%)	60.3%
Lung	101 (39.6%)	67 (51.5%)	34 (27.2%)	33.7%*
Gastrointestinal	17 (6.7%)	5 (3.8%)	12 (9.6%)	70.6%
Other solid tumors	16 (6.3%)	10 (7.7%)	6 (4.8%)	37.5%
Reason for ICU admission				
Acute respiratory failure	157 (61.6%)	82 (63.1%)	75 (60%)	47.8%
Shock	28 (11.0%)	14 (10.8%)	14 (11.2%)	50.0%
Heart failure	10 (3.9%)	6 (4.6%)	4 (3.2%)	40.0%
Coma	40 (15.7%)	15 (11.5%)	25 (20.0%)	62.5%
Acute renal failure	2 (0.8%)	2 (1.5%)	0	0
Others	18 (7.0%)	11 (8.5%)	7 (5.6%)	38.9%
Time from diagnosis to ICU admission (d)	262.89±39.77	204.14±47.50	324.00±64.09	
Time between hospital and ICU admission <24 hours	107 (42.0%)	59 (45.4%)	48 (37.4%)	44.9%
Chemotherapy in past month	79 (31.0%)	37 (28.5%)	42 (33.6%)	53.2%
Life support intervention				
Ventilatory support				
Oxygen only	72 (28.2%)	63 (48.5%)	9 (7.2%)	12.5%
Noninvasive mechanical ventilation	38 (14.9%)	30 (23.1%)	8 (6.4%)	21.1%
Invasive mechanical ventilation	145 (56.9%)	37 (28.5%)	108 (86.4%)	74.5%*
Vasopressors	144 (56.5%)	36 (27.7%)	108 (86.4%)	74.5%*
Dialysis	26 (10.2%)	9 (6.9%)	17 (13.6%)	65.4%
Positive sputum culture	71 (27.8%)	32 (24.6%)	39 (31.2%)	54.9%
Positive blood culture	23 (9.0%)	12 (9.2%)	11 (8.8%)	47.8%
Laboratory values				
PH	7.37±0.01	7.42±0.01	7.32±0.02	*
PCO_2 (mmHg)	40.36±1.23	36.70±1.16	44.17±2.16	*
PO_2 (mmHg)	85.50±3.01	89.43±3.92	81.42±4.58	
Cr (mg/dL)	113.0±7.50	103.14±11.25	123.25±9.82	
BUN (mmol/L)	9.91±0.45	8.52±0.54	11.37±0.69	*
Scoring systems				
SOFA score on day 1	8.78±0.34	6.45±0.39	11.20±0.48	*
Any SOFA score ≥15 in first week	79 (31.0%)	18 (13.8%)	61 (48.8%)	77.2%*
Any SOFA score ≥12 at admission	73 (28.6%)	20 (15.4%)	53 (42.4%)	72.6%*
No change/increased SOFA score during ICU admission	190 (74.5%)	70 (53.8%)	120 (96.0%)	63.2%*
SOFA score increase 48 hours later	107 (42.0%)	52 (40.0%)	55 (44.0%)	51.4%*
APACHE II score on day 1	16.12±0.46	12.18±0.51	20.22±0.59	*
Social factors				
Insurance type				
NRCMS	99 (38.8%)	54 (41.5%)	45 (36.0%)	
URBMI	44 (17.3%)	21 (16.2%)	23 (18.4%)	
UMBMI	112 (43.9%)	55 (42.3%)	57 (45.6%)	
Cost of hospital stay (*10^4RMB)	5.09±0.40	4.23±0.35	5.99±0.71	*
Outcome measures				
ICU mortality	49.0%			

Abbreviations: Intensive Care Unit (ICU); Standard Error of Mean (SEM); Creatinine (Cr); Blood Urea Nitrogen (BUN); Sequential Organ Failure Assessment (SOFA); Acute Physiology and Chronic Health Evaluation (APACHE); Urban Resident-based Basic Medical Insurance (URBMI); the Urban Employee Basic Medical Insurance (UMBMI); New Rural Cooperative Medical Insurance Scheme (NRCMS); *P<0.05.

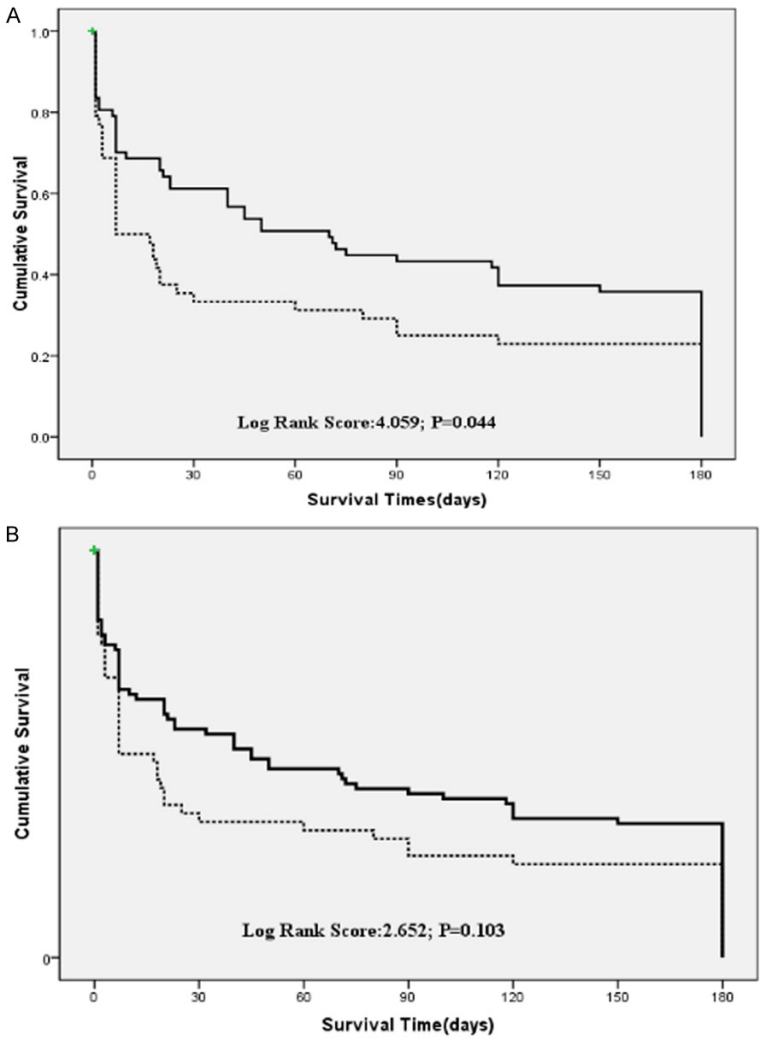

Figure 2. A. Kaplan-Meier curves for survival. Haematological malignancy (Dotted line); lung cancer (Bolded line); B. Kaplan-Meier curves for survival. Haematological malignancy (Dotted line); solid tumour (Bolded line).

Parameters that were statistically significant in the univariate analysis (P<0.05) were entered into the multivariate model in a stepwise manner and P<0.05 was required for the variable to retain itself within the model. A final bootstrap analysis was performed to confirm the conclusions.

Results

Patient characteristics and comparison between ICU survivors and non-survivors

Table 1 shows the demographic and clinical data of the 255 ICU admissions involving cancer patients. The majority of the patients (185, 72.5%) was male and the mean age was 55.78±1.13 years. HM accounted for 47.5% of the admissions, while lung cancer (101/134, 75.3%) was the most common solid tumor diagnosis. Acute respiratory failure (61.6%) was the most common reason for ICU admission; followed by coma (15.7%), shock (11.0%), heart failure (3.9%), and acute renal failure (0.8%). About two-thirds (172, 67.5%) of the cases were newly diagnosed. The disease was controlled in only 27 (10.6%) admissions. In 79 admissions (31.0%), the patients had undergone chemotherapy in the prior month. The proportion of chemotherapy was lower in solid tumors than HM [13]. In the ICU, 145 patients (56.9%) required invasive mechanical ventilation (IMV), 144 patients (56.5%) needed vasopressors and 26 (10.2%) required dialysis. In addition, the ICU mortality rate was 74.5% (P<0.05) in patients who received IMV or vasopressors. Seventy one (27.8%) patients had positive sputum cultures and 23 (9.0%) had positive blood cultures. The average SOFA and APACHE II score on day 1 were 8.78±0.34 and 16.12±0.46, respectively.

The rates for ICU mortalities was 49.0%. Compared to ICU survivors, patients who died in the ICU had significantly lower pH (7.32±0.02 vs. 7.42±0.01, P<0.001), higher pCO_2 (44.17±2.16 vs. 36.70±1.16, P=0.004), and higher BUN (11.37±0.69 vs. 8.52±0.54, P=0.002). Non-survivors had significantly (P<0.05) higher APACHE-II and SOFA scores compared with the survivors. In addition, ICU non-survivors had a higher hospital cost ($5.99±0.71*10^4$ RMB vs $4.23±0.35*10^4$ RMB, P<0.05).

Comparison between patients with HM and solid tumors

In the initial analysis (**Table 1**), we noted that patients with lung cancer had better ICU survival rates than patients with HM. The longer

Table 2. The comparison between patients with HM and lung cancer patients (n% or ± SEM)

	HM (n=121)	Lung cancer (n=101)	OR	95% CI	*P* value
Age	46.93±1.63	64.50±1.21			<0.001
Sex (male)	87 (71.9%)	74 (73.3%)	1.071	0.592~1.938	0.820
Disease Status					0.146
Reason for ICU admission					0.148
Organ failure support					
IMV	79 (65.3%)	44 (43.6%)	0.410	0.238~0.706	<0.001
Vasopressors	82 (67.8%)	40 (39.6%)	0.312	0.180~0.541	<0.001
Laboratory values					
Cr (mg/dL)	123.62±12.08	95.71±10.15			0.078
BUN (mmol/L)	11.15±0.73	8.52±0.58			0.005
SOFA score on admission	10.75±0.48	6.21±0.42			<0.001
APACHE II score on admission	20.84±0.89	13.72±0.67			<0.001

Abbreviations: Hematological Malignancies (HM); Standard Error of Mean (SEM); Creatinine (Cr); Blood Urea Nitrogen (BUN); Sequential Organ Failure Assessment (SOFA); Acute Physiology and Chronic Health Evaluation (APACHE).

survival was also better in patients with lung cancer (P=0.044) and there was no significantly difference between patients with hematological malignancies or solid tumors (P=0.103) (**Figure 2A**, **2B**). The better outcome prompts comparing between the two groups in detail (**Table 2**). The two groups did not differ significantly in gender, disease status, or the reason for ICU admission. Patients with lung cancer were significantly older than patients with HM. More HM patients suffered from renal failure and required IMV and vasopressors support. HM patients also had higher SOFA and APACHE II scores on ICU admission.

Factors affecting ICU mortality

Tables 3 and **4** show the results of the univariate and multivariate logistic regression analysis of factors contributing to ICU mortality. Conditions shown to be significant (P<0.05) in the univariate analysis were incorporated into the multivariate model. Patient's age, disease status, reason for ICU admissions, time-lapse between hospital and ICU admission and ICU length of stay did not significantly affect ICU mortality. In addition, some socioeconomic factors such as gender and type of medical insurance were not associated with the outcome. Patients with the lung cancer had significantly lower ICU mortality than patients with other malignancies (OR 0.334, 95% CI 0.192-0.579, P<0.001). Patients receiving IMV (OR 20.432, 95% CI 9.255-45.109, P<0.001) and vasopressors (OR 16.588, 95% CI 8.750-31.447, P<0.001) had significantly higher ICU mortality rates. Moreover, the cost of ward stay were associated with the ICU mortality (P=0.033). We assessed SOFA scores at several different time points and calculated the trend of change during the ICU stay. All of the SOFA measurements had significant correlation with ICU mortality, but the overall trend had the highest odds ratio and was incorporated into the multivariate model. After correcting for age and sex, the model had excellent goodness-of-fit (Cox and Snell R^2=0.549, Nagelkerke R^2=0.732, Chi-square=4.885, P=0.770). In our model, no change or increased in SOFA score, APACHE II score at admission, the need for invasive mechanical ventilation, and the need for vasopressors were independent prognostic factors associated with ICU mortality.

Discussion

This study aimed to evaluate the access to intensive care and prognostic factors affecting cancer patients admitted to the ICU in a Chinese population. Our previous work had shown that compared to some results of Western studies, patients with hematologic malignancies had poor access to intensive care resources and experienced relatively high mortality rates during and after ICU admission in Hunan province of China [13]. In the current study, we wanted to see if what we observed with HM patients was representative of other cancer patients.

We found that cancer patients in general had poor access to the medical ICUs in the three

Table 3. Univariate analysis of factors associated with ICU mortality

	OR	95% CI	Wald	*P*
Age	0.991	0.978-1.005	1.551	0.213
Male sex	1.407	0.809-2.450	1.460	0.227
Disease status				
Newly diagnosed	1.000			
Controlled	0.878	0.388-1.986	0.098	0.755
Recurrence/progression	1.167	0.862-1.579	0.994	0.319
Underlying malignancy				
Hematological malignancies	1.000			
Lung cancer	0.334	0.192-0.579	15.275	<0.001
Gastrointestinal tumors	1.256	0.723-2.183	0.655	0.418
Other solid tumors	0.733	0.512-1.050	2.872	0.090
Reason for ICU admission				0.552
Time from diagnosis to ICU admission(/d)				0.146
Time between hospital and ICU admission <24 hours	0.750	0.455-1.236	1.274	0.259
Chemotherapy in past month	1.272	0.747-2.165	0.786	0.375
Life support intervention				
Ventilatory support				
Oxygen only	1.000			
Noninvasive mechanical ventilation	0.536	0.188-1.526	1.365	0.243
Invasive mechanical ventilation	20.432	9.255-45.109	55.754	<0.001
Vasopressors	16.588	8.750-31.447	74.074	<0.001
Dialysis	2.116	0.906-4.944	2.998	0.083
Laboratory values				
pH				<0.001
pCO_2 (mmHg)				0.004
pO_2 (mmHg)				0.190
Cr (mg/dL)				0.193
BUN (mmol/L)				0.002
Scoring systems				
SOFA score on day 1	1.221	1.148-1.298	40.328	<0.001
Highest SOFA score in first week	1.048	1.009-1.088	5.960	0.015
Any SOFA score ≥15 in first week	5.931	3.226-10.902	32.837	<0.001
Any SOFA score ≥12 at admission	4.049	2.235-7.333	21.290	<0.001
No change/increased SOFA score during ICU admission admission	20.571	7.886-53.659	28.214	<0.001
SOFA score increase during the first 48 hours	4.080	2.027-8.211	15.522	<0.001
APACHE II score on day 1				<0.001
Social factors				
Insurance type				
URBMI	1.000			
UMBMI	1.314	0.645-2.678	0.567	0.452
NRCMS	1.115	0.850-1.462	0.622	0.430
Cost of ward stay (*10^4RMB)				0.033
ICU stay (/d)				0.561

Abbreviations: Intensive Care Unit (ICU); Odds Ratio (OR); Confidential Interval (CI); Creatinine (Cr); Blood Urea Nitrogen (BUN); Sequential Organ Failure Assessment (SOFA); Acute Physiology and Chronic Health Evaluation (APACHE); Urban Resident-based Basic Medical Insurance (URBMI); the Urban Employee Basic Medical Insurance (UMBMI); New Rural Cooperative Medical Insurance Scheme (NRCMS).

Table 4. Multivariate analysis of factors affecting ICU mortality

	B	*P* value	Wald	OR	95% CI
Male sex	0.738	0.147	2.101	2.092	0.771-5.673
Age	-0.010	0.455	0.559	0.990	0.965-1.016
Cost of Ward stay (*10^5 RMB)	0.000	0.750	0.102	1.000	1.000-1.000
Lung cancer	-0.537	0.293	1.107	0.584	0.215-1.590
PH	-3.863	0.150	2.072	0.021	0-4.044
PCO_2 (mmHg)	0.012	0.458	0.551	1.012	0.981-1.043
BUN (mmol/L)	-0.020	0.570	0.323	0.981	0.916-1.049
Invasive Mechanical Ventilation	1.480	0.003	8.998	4.394	1.670-11.558
Vasopressors	1.917	<0.001	14.715	6.803	2.554-18.121
No change/increased SOFA score	3.232	<0.001	20.638	27.753	6.616-116.413
APACHE II score on day 1	0.168	<0.001	15.319	1.182	1.087-1.286

Abbreviations: Intensive Care Unit (ICU); Odds Ratio (OR); Confidential Interval (CI); Blood Urea Nitrogen (BUN); Sequential Organ Failure Assessment (SOFA); Acute Physiology and Chronic Health Evaluation (APACHE).

university-affiliated hospitals in Hunan province. During our study period, 26,040 patients (1.8% of all admissions) stayed in the 92 MICU and RICU beds (1.02% of all inpatient beds). Our data were similar to another multicenter study in China, in which medical ICU beds accounted for 1.26% of all inpatient beds [17]. Compared to Western countries, where medical ICU beds occupy 1.8%-5% of all inpatient beds and received 1.99%-4.1% of inpatient admissions [18, 19], the availability of Hunan's medical intensive care resources is limited. In our study, only 681 (**Figure 1**) ICU admissions, including those for post-operative care, involved patients with cancer. Cancer was the primary diagnosis in less than 3% of all ICU admissions, much lower than what was observed previously [7, 20]. This points to the fact that patients with cancer have reduced access to intensive care in Hunan province. In addition to the scarcity of intensive care resources, we speculate that presumed poor prognosis for cancer patients, coupled with the high cost of care and associated out-of-pocket expenses, may be preventing medical providers and families from transferring patients to the ICU [21]. These results suggested that it would be necessary to improve ICU admission by carrying better insurance, by increasing the availability of hospital ICU beds, or by stretching the criteria of admission to ICU.

We observed that patients with solid tumors, particularly lung cancer, had considerably better prognosis than patients with HM, consistent with previous studies [10, 22]. Comparing the two groups revealed that more patients with HM experienced renal failure, need IMV and vasopressors, and had higher SOFA and APACHE II scores on ICU admission. Patients with HM also more frequently suffered severe sepsis and required rigorous treatments [13], which may be associated with complications and organ failures [7]. Furthermore, solid tumors were often regarded as chronic diseases and the health profiles of these patients were similar to the non-cancer populations [10], associated with better outcomes. In contrast, HM admissions to the ICU often resulted from acute deteriorations such as blast crisis, aplastic crisis, and neutropenia [13]. Lastly, the three academic hospitals in our study had specialized respiratory ICUs that enabled prompt admission and treatment of lung cancer patients. To some extent, RICUs are an example of broadened ICU access for cancer patients. Optimizing ICU admission policies for HM patients may be needed to improve their survival.

In our sample, trends of SOFA scores, APACHE II scores at admission, the need for invasive mechanical ventilation, and vasopressor use were independently associated with increased ICU mortality of cancer patients. Other clinical parameters, such as disease status, reason for ICU admission, and time-lapse between hospital and ICU admission, did not have significant correlation with outcomes. These results are consistent with some early studies from our and other groups [7-9, 13, 23]. The predictive effect of vasopressor use was not observed in

our previous study of HM patients, even though the ICU mortality was non-significantly elevated in patients on vasopressors [13]. The larger sample size in the current study may have helped reveal vasopressor use as an independent predictor. Since vasopressor use is a surrogate for the hemodynamic changes caused by heart failure or septic shock [24, 25], monitoring and assessment of the hemodynamic state of cancer patients would be crucial for management decisions in the ICU.

In addition to clinical parameters, we also evaluated the contribution of socioeconomic factors to patient outcome. Gender, type of medical insurance, and cost of hospitalization did not have significant effect on the ICU mortality of the cancer patients. Even though non-survivors incurred higher cost during the ICU stay (5.99±0.71*10^4 RMB VS 4.23±0.35*10^4 RMB, P=0.033), cost lost significance when entered into the model with clinical factors. However we noted that our study sample was predominantly male carrying urban insurance policies, suggesting that socioeconomic factors may play into the decision of ICU admission and patients' access to intensive care resources.

Our study had several limitations. The retrospective study design prevented more detailed data collection to include other physiologic and social characteristics which may be pertinent to the outcomes. And also the data is limited (only 255 cases) for more detailed group analysis. But to our knowledge, this is the first study to investigate the prognostic factors for Chinese cancer patients without surgery admitted to the ICU. We believe it at least represents part of the current situation in Chinese cancer patients' intensive care. We hope the series of clinical determinants reported here could offer guidance help for Chinese physicians to make clinically appropriate and cost effective decisions about ICU admissions.

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Disclosure of conflict of interest

None.

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References

[1] Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011; 61: 69-90.

[2] He J, Gu D, Wu X, Reynolds K, Duan X, Yao C, Wang J, Chen CS, Chen J, Wildman RP, Klag MJ, Whelton PK. Major causes of death among men and women in China. N Engl J Med 2005; 353: 1124-1134.

[3] Hvistendahl M. China. World's biggest health care system goes under the knife. Science 2013; 339: 505-507.

[4] Brenner H. Long-term survival rates of cancer patients achieved by the end of the 20th century: a period analysis. Lancet 2002; 360: 1131-1135.

[5] Brenner H, Gondos A and Arndt V. Recent major progress in long-term cancer patient survival disclosed by modeled period analysis. J Clin Oncol 2007; 25: 3274-3280.

[6] Torheim H and Kvangarsnes M. How do patients with exacerbated chronic obstructive pulmonary disease experience care in the intensive care unit? Scand J Caring Sci 2014; 28: 741-748.

[7] Merz TM, Schar P, Buhlmann M, Takala J, Rothen HU. Resource use and outcome in critically ill patients with hematological malignancy: a retrospective cohort study. Crit Care 2008; 12: R75.

[8] Azoulay E, Moreau D, Alberti C, Leleu G, Adrie C, Barboteu M, Cottu P, Levy V, Le Gall JR, Schlemmer B. Predictors of short-term mortality in critically ill patients with solid malignancies. Intensive Care Med 2000; 26: 1817-1823.

[9] Maschmeyer G, Bertschat FL, Moesta KT, Häusler E, Held TK, Nolte M, Osterziel KJ, Papstein V, Peters M, Reich G, Schmutzler M, Sezer O, Stula M, Wauer H, Wörtz T, Wischnewsky M, Hohenberger P. Outcome analysis of 189 consecutive cancer patients referred to the intensive care unit as emergencies during a 2-year period. Eur J Cancer 2003; 39: 783-792.

[10] Taccone FS, Artigas AA, Sprung CL, Moreno R, Sakr Y, Vincent JL. Characteristics and out-

comes of cancer patients in European ICUs. Crit Care 2009; 13: R15.
[11] Xing XZ, Gao Y, Wang HJ, Yang QH, Huang CL, Qu SN, Zhang H, Wang H, Xiao QL, Sun KL. Risk factors and prognosis of critically ill cancer patients with postoperative acute respiratory insufficiency. World J Emerg Med 2013; 4: 43-47.
[12] Xing X, Gao Y, Wang H, Huang C, Qu S, Zhang H, Wang H, Sun K. Performance of three prognostic models in patients with cancer in need of intensive care in a medical center in China. PLoS One 2015; 10: e131329.
[13] Liu J, Cheng Q, Yang Q, Li X, Shen X, Zhang L, Liu Z, Khoshnood K. Prognosis-related factors in intensive care unit (ICU) patients with hematological malignancies: A retrospective cohort analysis in a Chinese population. Hematology 2015; 20: 494-503.
[14] Ferlay J, Autier P, Boniol M, Heanue M, Colombet M, Boyle P. Estimates of the cancer incidence and mortality in Europe in 2006. Ann Oncol 2007; 18: 581-592.
[15] NCCN. The NCCN clinical practice guidelines in oncology (version 1.2014). http://www.nccn.org/professionals/physician_gls/f_guidelines.asp.
[16] Tang S, Tao J and Bekedam H. Controlling cost escalation of healthcare: making universal health coverage sustainable in China. BMC Public Health 2012; 12 Suppl 1: S8.
[17] Du B, An Y, Kang Y, Yu X, Zhao M, Ma X, Ai Y, Xu Y, Wang Y, Qian C, Wu D, Sun R, Li S, Hu Z, Cao X, Zhou F, Jiang L, Lin J, Chen E, Qin T, He Z, Zhou L. Characteristics of critically ill patients in ICUs in mainland China. Crit Care Med 2013; 41: 84-92.
[18] Bird GT, Farquhar-Smith P, Wigmore T, Potter M and Gruber PC. Outcomes and prognostic factors in patients with haematological malignancy admitted to a specialist cancer intensive care unit: a 5 yr study. Br J Anaesth 2012; 108: 452-459.
[19] Capelastegui A, Espana PP, Quintana JM, Areitio I, Gorordo I, Egurrola M, Bilbao A. Validation of a predictive rule for the management of community-acquired pneumonia. Eur Respir J 2006; 27: 151-157.
[20] Soares M, Salluh JI, Torres VB, Leal JV and Spector N. Short- and long-term outcomes of critically ill patients with cancer and prolonged ICU length of stay. Chest 2008; 134: 520-526.
[21] Varghese C, Carlos MC and Shin HR. Cancer burden and control in the Western pacific region: challenges and opportunities. Ann Glob Health 2014; 80: 358-369.
[22] Thiery G, Azoulay E, Darmon M, Mikane T, Oku S, Iwasaki E, Ishii M, Mieda H, Ishikawa T, Minami E, Schlemmer B. Outcome of cancer patients considered for intensive care unit admissin: a hospital-wide prospective study. J Clin Oncol 2005; 23: 4406-4413.
[23] Kress JP, Christenson J, Pohlman AS, Linkin DR and Hall JB. Outcomes of critically ill cancer patients in a university hospital setting. Am J Respir Crit Care Med 1999; 160: 1957-1961.
[24] Zechmeister C, Hurren J and McNorton K. Continuation of Statin Therapy and Vasopressor Use in Septic Shock. Ann Pharmacother 2015; 49: 790-5.
[25] Sasai T, Tokioka H, Fukushima T, Mikane T, Oku S, Iwasaki E, Ishii M, Mieda H, Ishikawa T, Minami E. Reliability of central venous pressure to assess left ventricular preload for fluid resuscitation in patients with septic shock. J Intensive Care 2014; 2: 58.

Supplement Table 1. The definition of disease status in NCCN guidelines (Version 2014) [1, 2]

Solid tumors	Definition	
Lung cancer	The NCCN guidelines use the AJCC (7th edition) staging system for lung cancer. With the new staging, locally advanced disease is now stage III, advanced disease is now stage IV. Pathologic staging uses both clinical staging information and other invasive staging procedures.	
Colon cancer	The 7th edition of the American Jonit Committee on Cancer's (AJCC) includes the suggestion that patients with potentially convertable metastatic disease that is not responding to therapy. Poor prognostic features are poorly differentiated histology; lymphatic/vascular invasion; bowel obstruction; perineural invasion; localized perforation; close, indeterminate or positive margins.	
Rectal cancer	Some of the information are detailed in: grade of cancer; depth of penetration and extension to adjacent structures; number of regional lymph nodes evaluated; the presence of distant metastases to other organs or sites including non-regional lymph nodes and the response to treatment.	
Hematological malignancies		
Acute myeloid leukemia		
	Complete remission	Morphologic CR (patient independent of transfusions): Absolute neutrophil count >1000/mcL; Platelets ≥100,000/mcL; No residual evidence of extralmedullary disease. Cytogenetic complete response-cytogenetics normal (in those with previously abnormal cytogenetics). Molecular complete response- molecular studies negative.
	Partial remission	Decrease of at least 50% in the percentage of blasts to 5% to 25% in the bone marrow aspirate and the normalization of blood counts, as noted above. Patients failing to achieve a complete response are considered treatment failures. Relapse following complete response is defined as reappearance of leukemic blasts in the peripheral blood or the finding of more than 5% blasts in the bone marrow, not attributable to another cause or extramedullary relapse.
Acute lymphoblatic leukemia	Complete remission	No circulating blasts or extramedullary disease; trilineage hematopoiesis and <5% blasts; absolute neutrophil count >1000/microL; platelets >100,000/microL; no recurrence for 4 weeks.
	Refractory disease	Failure to achieve CR at the end of induction.
	Progressive disease	Increase of at least 25% in the absolute number of circulating or bone marrow blasts or development of extralmedullary disease.
	Relapsed disease	Reappearance of blasts in the blood or bone marrow (>5%) or in any extramedullary site after a CR.
Multiple Myeloma	Complete response	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and ≤5% plasma cells in bone marrow.
	Progressive disease	Requires any one or more of the following: increase of ≥25% from baseline in: serum M-component and/or (the absolute increase must be ≥0.5 g/dL); Urine M-component and/or (the absolute increase must be ≥200 mg/24 h); only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels. The absolute increase must be >10 mg/dl. Bone marrow plasma cell percentage: the absolute % must be >10%. Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas or definite increase in the size of ex siting bone lesions or soft tissue plamacytomas; development of hypercalsemia (corrected serum calcium >11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to the plasma cell proliferative disorder.
Non-Hodgkin's Lymphomas	Complete remission	Disappearance of all evidence of disease.
	Relapsed disease	Any new lesion or increase by ≥50% of previously involved sites from dadir.

[1] NCCN. The NCCN clinical practice guidelines in oncology (version 1.2014). http://www.nccn.org/professionals/physician_gls/f_guidelines.asp.

[2] Liu J, Cheng Q, Yang Q, Li X, Shen X, Zhang L, Liu Z, Khoshnood K. Prognosis-related factors in intensive care unit (ICU) patients with hematological malignancies: A retrospective cohort analysis in a Chinese population. Hematology 2015; 20: 494-503.

Supplement Table 2. Covariance between parameters in univariate analysis (P<0.05), checked with Pearson's correlation test

		Cost	Age	Sex	Lung cancer	pCO_2	Cr	BUN	IMV	Vaso-pressors	APACHE II on admission	No change/ increased SOFA score
Cost	Pearson correlation	1	.036	.033	-.217**	.020	-.008	-.052	.198**	.233**	.097	.085
	sig.(2-tailed)		.578	.612	.001	.761	.898	.424	.002	.001	.131	.190
Age	Pearson correlation	.036	1	.176**	.392**	.142*	.005	-.020	-.039	-.110	-.009	-.064
	sig.(2-tailed)	.578		.005	.001	.023	.933	.746	.538	.080	.889	.308
Sex	Pearson correlation	.033	.176**	1	.013	.033	.154*	.171**	.103	.045	.063	-.077
	sig.(2-tailed)	.612	.005		.836	.603	.014	.006	.101	.476	.319	.217
Lung cancer	Pearson correlation	-.217**	.392**	.013	1	.079	-.117	-.159*	-.217**	-.276**	-.264**	-.152*
	sig.(2-tailed)	.001	.001	.836		.208	.062	.011	.001	.001	.001	.015
PCO_2	Pearson correlation	.020	.142*	.033	.079	1	-.079	-.132*	.118	.092	.175**	.075
	sig.(2-tailed)	.761	.023	.603	.208		.209	.035	.059	.141	.005	.231
Cr	Pearson correlation	-.008	.005	.154*	-.117	-.079	1	.570**	.094	.188**	.231**	.088
	sig.(2-tailed)	.898	.933	.014	.062	.209		.001	.135	.003	.001	.160
BUN	Pearson correlation	-.052	-.020	.171**	-.159*	-.132*	.570**	1	.099	.263**	.291**	.125*
	sig.(2-tailed)	.424	.746	.006	.011	.035	.001		.113	.001	.001	.047
IMV	Pearson correlation	.198**	-.039	.103	-.217**	.118	.094	.099	1	.577**	.425**	.326**
	sig.(2-tailed)	.002	.538	.101	.001	.059	.135	.113		.001	.001	.001
Vasopressors	Pearson correlation	.233**	-.110	.045	-.276**	.092	.188**	.263**	.577**	1	.408**	.303**
	sig.(2-tailed)	.001	.080	.476	.000	.141	.003	.001	.001		.001	.001
APACHE II on admission	Pearson correlation	.097	-.009	.063	-.264**	.175**	.231**	.291**	.425**	.408**	1	.275**
	sig.(2-tailed)	.131	.889	.319	.001	.005	.001	.001	.001	.001		.001
No change/in-creased SOFA score	Pearson correlation	.085	-.064	-.077	-.152*	.075	.088	.125*	.326**	.303**	.275**	1
	sig.(2-tailed)	.190	.308	.217	.015	.231	.160	.047	.001	.001	.001	