Outcomes and Prognostic Factors in Patients with Hematologic Malignancies in the Intensive Care unit: A Single-Center Cohort Study of 233 Cases in Taiwan

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Research

Abstract

Background

Patients with a hematologic malignancies (HM) have one of the highest mortality rates among cancer patients admitted to the medical intensive care unit (ICU). The aim of this study was to identify outcomes and risk factors that predict the prognosis of critically ill patients with HM in the ICU.

Methods

A retrospective observational study was conducted in a tertiary referral hospital in Taiwan over 40 months (January 1, 2017–April 30, 2020). All adult patients with HM who were admitted to medical ICU were enrolled. Clinical data upon hospital and ICU admission were collected. The predictors of ICU mortality were evaluated using a multivariate analysis.

Results

A total of 233 patients with HM met the inclusion criteria. The median age (SD) was 59.3 (15.1) years, and 76% of the HMs were classified as high-grade disease. The median (IQR) Sequential Organ Failure Assessment (SOFA) score at ICU admission was 11 (9–15); Simplified Acute Physiology Score II, 64 (51–80); and Acute Physiology and Chronic Health Evaluation II score, 28 (23–34). The most common reasons for ICU admission were acute respiratory failure (63.1%) and septic shock (19.7%). The ICU and hospital mortality rates were 54.1% and 67.8%, respectively. A multivariate analysis revealed that the initiation of renal replacement therapy in the ICU (odds ratio [OR], 3.88; 95% CI, 1.66–9.08) and SOFA score (OR, 1.16; 95% CI, 1.03–1.31) were independently associated with ICU mortality.

Conclusions

The ICU and hospital outcomes of critically ill patients with HM are improving. Performance status, cancer status, invasive mechanical ventilation, severe neutropenia, and transplantation status were not identified as predictive factors of ICU outcome. Initiation of renal replacement therapy in the ICU and the SOFA score upon ICU admission were independently associated with ICU mortality. We suggest early and timely ICU admission of patients at risk of multiorgan failure.

Background

Cancer survival has been steadily improving over the last few decades, and more patients have been admitted to the intensive care unit (ICU) for the management of critical illnesses related either directly or indirectly to cancer (1). Compared with other patients with cancer who are admitted to the ICU, patients with hematologic malignancies (HMs) are generally more ill and have a higher mortality rate (2, 3). Recent advances in diagnosis, chemotherapy and conditioning regimes, innovative treatment regimens and targeted therapies, and general ICU care have led to better outcomes in these patients (4–6). As a result, physicians are now less reluctant to admit hematologic patients to the ICU than in the 1990s (7, 8).

Previous studies identified several indicators of poor prognosis, including older age (9), neutropenia (10–12), disease progression (13), allogeneic hematopoietic stem cell transplantation (HSCT) (14, 15), graft versus host disease (GVHD) (16), high Sequential Organ Failure Assessment (SOFA) score (17), high Simplified Acute Physiology Score (SAPS) II (12, 18, 19), high Acute Physiology and Chronic Health Evaluation (APACHE) II score (9, 10, 12, 20), invasive mechanical ventilation (10, 15, 17, 21), renal replacement therapy (19, 20), hepatic dysfunction (18, 20), and invasive fungal infection (14). However, the prognostic significance of some variables has changed in the last few years, and published studies have yielded conflicting results (15, 22).

Few studies have been conducted for this patient group in the Asian population. With substantial improvement in supportive care and cancer treatment in recent years, we aimed to evaluate the outcome of patients with HM admitted to ICU in Taiwan and identify predictors of ICU mortality.

Methods

Patients and setting

This retrospective single-center observational study was conducted in a tertiary referral hospital in mid-Taiwan, which is a 1722-bed hospital with a 45-bed adult medical intensive care unit and 7-bed bone marrow transplantation facility. Approximately 80 HSCT procedures are performed annually in the hospital.

This study was approved by the institutional review board of China Medical University Hospital (CMUH109-REC3-137), and informed consent was waived because of the retrospective nature of the study and the data gathered did not include any personally identifiable information. Data were collected on all adult patients admitted to the ICU with HM as the primary diagnosis or a concurrent comorbidity over a 40-month period (January 1, 2017–April 30, 2020). The hospital information system and medical records were reviewed. Patients transferred from the respiratory care ward (RCW) and admitted to the ICU for surgical indications or postoperative monitoring were excluded from the study. If the patient was admitted to the ICU more than once in a 28-day period, the first admission was included (Fig. 1).

Data collection

The variables recorded were patient characteristics, performance status at hospital admission using the Eastern Cooperative Oncology Group scale, type of HM, disease status at the time of admissions, previous HSCT, presence of GVHD, severe neutropenia, reason for ICU admission, whether invasive mechanical ventilation was needed, and whether renal replacement therapy was initiated in the ICU. The severity of illness at ICU admission was assessed using the SOFA score, SAPS II, and APACHE II score. All the scores were calculated using the patient data collected at the time of ICU admission or within 24 hours of ICU admission.

Definitions

HMs were categorized as follows: acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphoblastic leukemia (CLL), chronic myeloid leukemia (CML), Hodgkin's lymphoma (HL), aggressive non-Hodgkin's lymphoma (NHL), indolent NHL, and multiple myeloma (MM). AML, ALL, and aggressive non-Hodgkin's lymphoma were classified as high grade diseases (3).

Disease status was defined as complete remission (CR), partial remission (PR), stable disease (SD), and relapsed or refractory disease. In patients with newly diagnosed HM without treatment or unexpected hospital admission prior to the assessment of tumor response to cancer therapeutics, disease status was labeled as "non-evaluable."

Statistical Analyses

Statistical analyses were completed using SPSS version 25 (SPSS Inc., Chicago, IL, USA). The normality of all the variables was studied using the Kolmogorov-Smirnov test. Data are expressed as mean with standard deviations or median and interquartile range (IQR) for variables with and without a normal distribution, respectively. Continuous data with normal distributions were analyzed using a t test. For ordinal data and data that are not normally distributed, differences between groups were assessed using a Mann-Whitney U test. The categorical variables were presented as numbers and percentages and analyzed using the chi-square test. A univariate analysis was used to calculate the odds ratio (OR) of mortality, and the statistically significant variables were used in the multivariate logistic regression model analysis. The strength of association was presented as OR and 95% confidence interval (CI). All the tests were two-sided, and a p value of < 0.05 was considered to indicate a statistically significant difference.

Results

During the study period, 4521 patients were admitted to the medical ICU and 1194 patients (26.4%) had an underlying or current diagnosis of any type of malignancy, including 252 patients with HM. After excluding patients admitted for surgical indications, postoperative monitoring, RCW cases, and readmission to the ICU in a 28-day period, 233 patients, representing 5.2% of all ICU admissions, were evaluated.

Patient characteristics

The patients' mean (SD) age was 59.2 years (15.1), and 39.5% of the patients were female (Table 1). Of the patients, 25.8% (60) had a performance status of 0–2 at hospital admission; 42.1%, 3; and 32.2%, 4. All the patients had a confirmed HM based on pathological examination results or medical records, including 46% with leukemia, 41% with lymphoma; and 13% with plasma cell dysplasia (Fig. 2). Seventy-six percent of the HMs were classified as high-grade disease. Twenty-four percent of the patients received allogeneic HSCT, and 4.7% underwent autogenic HSCT, of which 14.2% had GVHD. A total of 81 patients (34.8%) had a relapsed or refractory disease. Notably, 31 patients (13.3%) had a newly diagnosed HM in the ICU.

The median (IQR) time in hospital before ICU admission was 5 days (0–24 days). Nearly 30% of patients were admitted to the ICU directly from the emergency department. The most frequent reasons for ICU admission were acute respiratory failure (63.1%) and septic shock (19.7%). Most patients (88.8%) required invasive mechanical ventilation, and 32.2% of the patient had initiation of renal replacement therapy in the ICU. The median durations of ICU and hospital stays were 8 days (IQR: 3–16 days, range: 1–51 days) and 27 days (IQR: 15–52 days, range: 1–168 days), respectively.

The illness severity scores were calculated at the time of ICU admission or within 24 hours of admission to the ICU for each case. The median (IQR) SOFA score was 11 (9–15); SAPS II score, 64 (51–80); and APACHE II score, 28 (23–34) (Table 2).

Outcomes

The ICU and hospital mortality rates were 54.1% and 67.8%, respectively. Although the overall mortality remained high, the ICU mortality rate decreased during the years of observation (Fig. 2), but the difference was not statistically significant.

Poor performance status, high-grade HM, relapsed or refractory disease, increased time in hospital before ICU admission, initiation of renal replacement therapy in the ICU, and high SOFA, SAPS II, and APACHE II scores were associated with ICU mortality (Table 3). When all of the above-mentioned variables were included, only the initiation of renal replacement therapy in the ICU (OR, 3.88; 95% CI, 1.66–9.08) and SOFA scores (OR, 1.16; 95% CI, 1.03–1.31) were independently associated with ICU mortality (Table 4). The area under the receiver-operating characteristic (ROC) curve to predict ICU mortality was 0.81 (95% CI, 0.75–0.87) when the two variables were used in one model (Table 2).

Discussion

This study is one of the largest single-center studies of ICU patients with HM and includes a considerable proportion of patients with HSCT. To the best of our knowledge, this is the first study in Taiwan to report the prognostic factor related to short-term outcomes in critically ill patients with HM.

The ICU and hospital mortalities in our study were 54.1% and 67.8%, respectively. A recent single-center study from Germany reported ICU mortalities rates of 45.2% (in 2009–2012 cohort) and 66.7% (in 2013–2016 cohort) at different time periods (23). To a wider extent, the previously published ICU and hospital mortality rates in patients with HM who were admitted to the ICU ranged from 24.8–66% and from 43–77%, respectively (15). The differences in mortality observed between studies including ours may be

explained by variations in disease severity, admission and discharge criteria, treatment decisions, and the implementation of end-of-life decisions. Notably, the disease severity at ICU admission was higher in our patient than those reported in previous studies. With persisting high overall mortality, the ICU mortality decreased during the years of observation (Fig. 3), which may be attributable to better supportive care, improved management of sepsis (24), and acute respiratory distress syndrome (ARDS) (25). Although this finding was not statistically significant, the trend of decreased ICU mortality was consistent with previous studies (4–6).

Several prognostic factors for critically ill patients with HM were published by previous studies, and some were considered "classical" risk factors. Neutropenia, poor performance status, advanced cancer status, invasive mechanical ventilation, vasopressors, renal replacement therapy, HSCT, and increasing time in hospital before ICU admission have been shown to be useful predictors of ICU and hospital mortality rates in previous studies. Scoring systems such as the APACHE II and SAPS II were widely validated in previous studies. However, in our study, only the initiation of renal replacement therapy in the ICU and SOFA scores were independently associated with ICU mortality. The area under the ROC curve to predict ICU mortality increased to 0.81 (95% CI, 0.75–0.0.87) when the two variables were combined. This result was consistent with previous results that the presence of organ failure was the major factor of poor outcome (10, 14, 17, 20, 22, 26). In previous studies, the SOFA score was less validated in predicting the ICU outcome of critically ill patients with HM than the APACHE II and SAPS II. However, the SOFA scoring system is a less cumbersome tool in clinical practice and had been applied in determining the duration of time-limited trials of intensive care for critically ill patients with cancer (27). Our result encourages clinicians to use the SOFA score for triage decisions and time-limited trial in the patient group.

Early ICU admission of patients identified as being at risk of multiorgan failure had been recommended (4), and early intervention before ICU admission in critically ill cancer patients was proved to decrease in-hospital mortality (28). In our study, 68 patients (29.2%) were admitted to the ICU directly from the emergency department, of whom 49 survived the ICU stay. Time in hospital before ICU admission was significantly higher in the non-survivor group. Although we could not clarify the relationship between time in hospital before ICU admission and delayed ICU admission, our data supports the concept that early and timely admission to the ICU in patient identified as high risk of severe organ dysfunction (29). Thus, underlying HM disease, neutropenia, and even post HSCT status should not be considered as a reason for delayed endotracheal tube intubation or ICU admission.

Thirty-one patients (13.3%) had pathologically confirmed HMs in the ICU, and in 15 patients, administration of antineoplastic agents was initiated as a first-line treatment in the ICU. Of all the patients, 11 survived the ICU stay and 6 were still alive 180 days after ICU discharge. It is crucial that a hematologic specialist is involved in the ICU management (30). With the emergence of novel agents for treating HMs, specific therapies under the recommendation of a hematologic specialist may lead to improved outcome and long-term survival (31).

This study has several limitations. First, this was a retrospective single-center study. However, it analyzed data collected over 40 months from one of the largest medical centers in Taiwan and enrolled a considerable number of patients. Second, the mortality rate was higher in our patients than in those in previous studies (15). However, the severity index was higher in our patients, and the crude mortality was difficult to compare from those in other studies because of the variations in admission and discharge criteria. Third, we could not demonstrate the impact of time-limited trials, which was a widely known concept in the management of critically ill patients with cancer (27). The decision of whether to treat these patients in the ICU remains difficult and needs evaluation on a patient-to-patient basis. A recent multicenter retrospective cohort study with 1097 patients in the Netherlands suggested that even in multiorgan failure, it should not be used as a criterion for excluding patients with HMs from admission to the ICU (8).

Future studies should focus on ICU-acquired infections in this patient group; further clarifying the relationship between time in hospital before ICU admission and delayed ICU admission; long-term outcomes after ICU discharge, including quality of life; and new epidemiology and challenges in ICU admission in the era of immunotherapy.

Conclusion

With the persistently high overall mortality, a trend of decreasing ICU mortality was observed in our study, which may be attributable to the improved general ICU care. Risk factors, including poor performance status, advanced cancer status, mechanical ventilation, severe neutropenia, transplantation status, and GVHD, and the widely used risk scores, including SAPS II score and APACHE II, were not predictive of ICU outcome. Initiation of renal replacement therapy in the ICU and the SOFA score upon ICU admission were independently associated with ICU mortality. We suggest early and timely ICU admission of patients identified as at risk of multiorgan failure.

Abbreviations

ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
APACHE	Acute Physiology and Chronic Health Evaluation
ARDS	Acute respiratory distress syndrome
CI	Confidence interval
CLL	Chronic lymphoblastic leukemia
CML	Chronic myeloid leukemia
CR	Complete remission
ECOG	Eastern Cooperative Oncology Group
GVHD	Graft Versus Host Disease
HL	Hodgkin's lymphoma
HM	Hematologic malignancy
HSCT	Hematopoietic stem cell transplantation
ICU	Intensive care unit
IQR	Interquartile range
MM	Multiple myeloma
MV	Mechanical ventilation
NHL	Non-Hodgkin's lymphoma
OR	Odds ratio
PR	Partial remission
RCW	Respiratory care ward
ROC	Receiver operating characteristic
RRT	Renal replacement therapy
SAPS II	Simplified Acute Physiology Score II
SD	Stable disease, Standard deviation
SOFA	Sequential Organ Failure Assessment
Declarations	

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of China Medical University Hospital (CMUH109-REC3-137), and informed consent was waived because of the retrospective nature of the study and the data gathered did not include any personally identifiable information.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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None.

Authors' contributions

BRW and WCL designed the study and were guarantor of the paper. CLC and STW were involved in clinical data collection and arrangement. WCC and CYC helped with data analysis and interpretation of the results. CLC and STW prepared the draft and finalized the manuscript. WCC and YCL also reviewed the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1 Patient characteristics

	N=233
Age (years)	59.2 ± 15.1
Female	92 (39.5%)
Body weight	60.5 ± 11.5
ECOG Performance Status at admission	
0	2 (0.9%)
1	15 (6.4%)
2	43 (18.5%)
3	98 (42.1%)
4	75 (32.2%)
Cancer type	
Leukemia	108 (46.4%)
Lymphoma	95 (40.8%)
Plasma cell dysplasia	30 (12.9%)
High grade hematological malignancies	177 (76%)
Hematopoietic stem cell transplantation	
Allogeneic	56 (24%)
Autogenic	11 (4.7%)
Graft versus host disease	33 (14.2%)
Cancer status	
Complete remission (CR)	34 (14.6%)
Partial remission (PR)	14 (6%)
Stable disease (SD)	11 (4.7%)
Relapsed or refractory	81 (34.8%)
Non-evaluable	93 (39.9%)
Newly diagnosed malignancy	75 (32.2%)
Cancer diagnosed in ICU	31 (13.3%)

Admitted to ICU directly from Emergency room	68 (29.2%)
Time in hospital before ICU admission (day)	5 (0-24)
Main reason for ICU admission	
Acute respiratory failure	147 (63.1%)
Septic shock	46 (19.7%)
Cardiac arrest	15 (6.4%)
ICU intervention	
Invasive mechanical ventilation	207 (88.8%)
Initiation of renal replacement therapy	75 (32.2%)
ECMO	6 (2.6%)
Antineoplastic treatment in ICU	54 (23.2%)
Abbreviations: ECOG = Eastern Cooperative Oncology Group; ICU = Intensive care unit; ECMO = Extracorporeal membrane oxygenation	

Table 2 Severity of illness scores upon admission to the ICU

Severity of illness score	Score Median (IQR)	Area under the (ROC) curve to predict ICU mortality
SOFA score at ICU admission	11 (9-15)	0.769
SAPS II at ICU admission	64 (51-80)	0.768
APACHE II at ICU admission	28 (23-34)	0.721
SOFA score + initiation of hemodialysis in ICU	-	0.809
Abbreviations: ICU = Intensive care unit; ROC = Receiver operating characteristic; SOFA = Sequential Organ Failure Assessment; SAPS = Simplified Acute Physiology Score; APACHE = Acute Physiology and Chronic Health Evaluation		

**Table 3** Comparisons between ICU survivors and non-survivors with hematological malignancies

Characteristics	Survivors (N=107)	Non-survivors (N=126)	p value
Age	59.4 ± 15.4	59.0 ± 14.9	0.832
Female	44 (41.1%)	48 (38.1%)	0.638
Body mass index	22.7 ± 4.0	22.5 ± 3.4	0.742
ECOG Performance Status at admission			**<0.001**
0-2	24 (22.4%)	36 (28.6%)	
3[#]	32 (29.9%)	66 (52.4%)	
4[#]	51 (47.7%)	24 (19.0%)	
Newly diagnosed malignancy	31 (29%)	44 (34.9%)	0.333
High grade hematological malignancies	69 (64.5%)	108 (85.7%)	**<0.001**
Cancer status			**0.022**
Non-progressive (CR, PR, SD) [a]	35 (32.7%)	24 (19.0%)	
Relapsed or refractory [a]	29 (27.1%)	52 (41.3%)	
Non-evaluable	43 (40.2%)	50 (39.7%)	
HSCT			0.699
No	79 (73.8%)	87 (69.0%)	
Allogeneic	23 (21.5%)	33 (26.2%)	
Autogenic	5 (4.7%)	6 (4.8%)	
GVHD	13 (12.1%)	20 (15.9%)	0.417
Duration of neutropenia [b] (day)	7 (3-24)	9 (2.25-23.75)[c]	0.889
CRP at ICU admission (mg/dL)	20.96 (8.19-30.49)	18.57 (6.02-29.3)	0.07
Albumin at ICU admission (g/dL)	2.7 (2.2-3.8)	2.9 (2.53-3.1)	**<0.001**
Time in hospital before ICU admission (day)	0 (0-19)	23 (2.25-42.25)	**<0.001**
Respiratory support at ICU admission			**0.046**
Oxygen support [a]	11 (10.3%)	4 (3.2%)	
NIV	3 (2.8%)	8 (6.3%)	
MV	93 (86.9%)	114 (90.5%)	

Initiation of RRT in ICU	13 (12.1%)	62 (49.2%)	**<0.001**
Mechanical support (ECMO)	0	6 (4.8%)	**0.032**[d]
Antineoplastic treatment in ICU	23 (21.5%)	30 (23.8%)	0.675
SOFA score at ICU admission	12 (8-13)	14 (11-15)	**<0.001**
SAPS II at ICU admission	63 (43-66)	67.5 (52.25-88)	**<0.001**
APACHE II at ICU admission	24 (20-35)	28 (24.25-38)	**<0.001**

a: The adjusted standardized residual was greater than 2 which indicates the column proportions were significantly different at p<0.05 level

b: Severe neutropenia was defined as absolute neutrophil count (ANC) < 500/uL

c: Duration of neutropenia was underestimated in 44.3% patients (N=51) with severe neutropenia (N=115)

d: Fisher's exact test

Abbreviations: ECOG = Eastern Cooperative Oncology Group; ICU = Intensive care unit; CR = Complete remission; PR = Partial remission; SD = Stable disease; PD = disease progression; HSCT = Hematopoietic stem cell transplantation; GVHD = Graft versus host disease; NIV = Non-invasive ventilation; MV = Mechanical ventilation; RRT = Renal replacement therapy; ECMO = Extracorporeal membrane oxygenation; CRP = C-Reactive protein; PCT = Procalcitonin; SOFA = Sequential Organ Failure Assessment; SAPS = Simplified Acute Physiology Score; APACHE = Acute Physiology and Chronic Health Evaluation

Table 4 Univariate analysis and multivariate logistic regression analysis of the prognostic variables for ICU mortality

Variables	Univariate analysis with logistic regression analysis			Multivariate analysis with logistic regression analysis		
	OR	95% CI	*p* value	OR	95% CI	*p* value
ECOG Performance Status at admission						
0-2	1	-	-	1	-	-
3	1.38	0.71-2.68	0.349	2.01	0.80-5.09	0.139
4	0.31	0.15-0.64	**0.001**	0.54	0.19-1.59	0.265
High grade hematological malignancies	3.30	1.75-6.25	**<0.001**	2.31	0.95-5.62	0.065
Cancer status						
Non-progressive (CR, PR, SD)	1	-	-	1	-	-
Relapsed or refractory	2.62	1.31-5.21	**0.006**	1.60	0.61-4.18	0.336
Non-evaluable	1.70	0.88-3.28	0.117	0.80	0.31-2.03	0.634
Albumin at ICU admission (g/dL)	0.34	0.21-0.56	**<0.001**	0.54	0.29-1.03	0.059
Time in hospital before ICU admission (day)	1.01	1.00-1.03	**0.021**	1.01	0.99-1.02	0.509
Respiratory support at ICU admission						
Oxygen support	1	-	-	1	-	-
NIV	7.33	1.27-42.29	**0.026**	4.29	0.36-50.75	0.249
MV	3.37	1.04-10.93	**0.043**	1.55	0.32-7.40	0.584
Initiation of RRT in ICU	7.00	3.56-13.79	**<0.001**	3.88	1.66-9.08	**0.002**
SOFA score at ICU admission	1.33	1.21-1.45	**<0.001**	1.16	1.03-1.31	**0.017**
SAPS II at ICU admission	1.06	1.04-1.08	**<0.001**	1.04	1.00-1.08	0.059
APACHE II at ICU admission	1.12	1.07-1.16	**<0.001**	0.97	0.89-1.06	0.471

Abbreviations: ECOG = Eastern Cooperative Oncology Group; ICU = Intensive care unit; CR = Complete remission; PR = Partial remission; SD = Stable disease; PD = disease progression; NIV = Non-invasive ventilation; MV = Mechanical ventilation; RRT = Renal replacement therapy; SOFA = Sequential Organ Failure Assessment; SAPS = Simplified Acute Physiology Score; APACHE = Acute Physiology and Chronic Health Evaluation

Figures
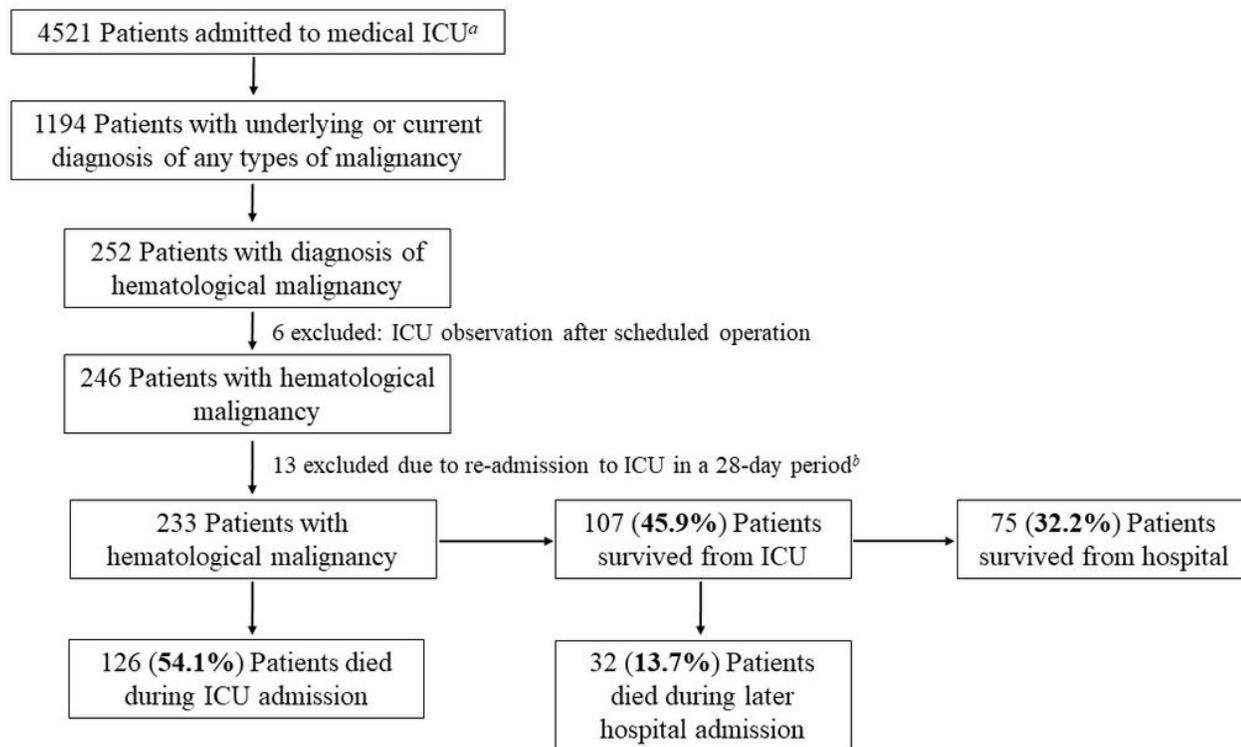
a: not including cardiovascular care unit
b: If the patient was admitted to the ICU more than once in a 28-day period, the first admission was included
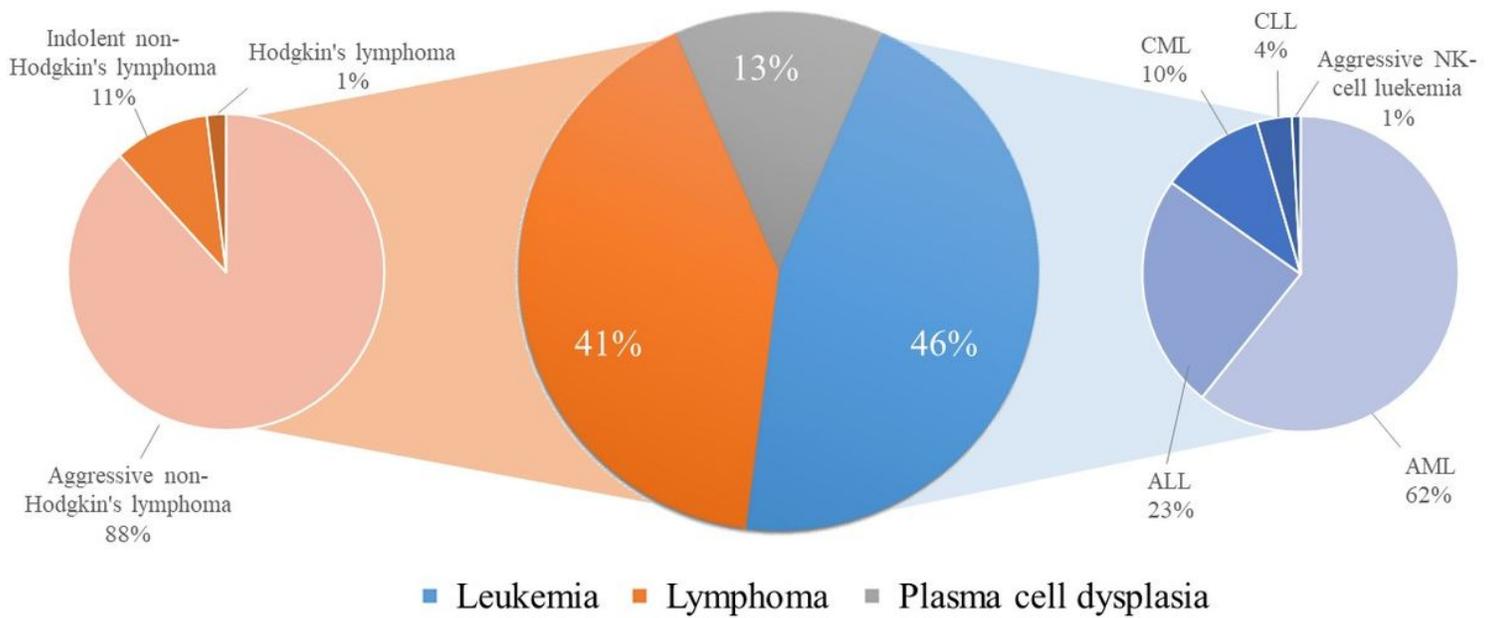
Figure 1

Study design and flow chart

Figure 2

Patterns of hematologic malignancies of the study population Non-Hodgkin's lymphoma, acute myeloid leukemia, and acute lymphoblastic leukemia comprising the most prevalent types of malignancy. Seventy-six percent of the hematologic malignancies were classified as high-grade disease (3).

Abbreviations: ALL = Acute lymphoblastic leukemia; AML = Acute myeloid leukemia; CLL = Chronic lymphoblastic leukemia; CML = Chronic myeloid leukemia
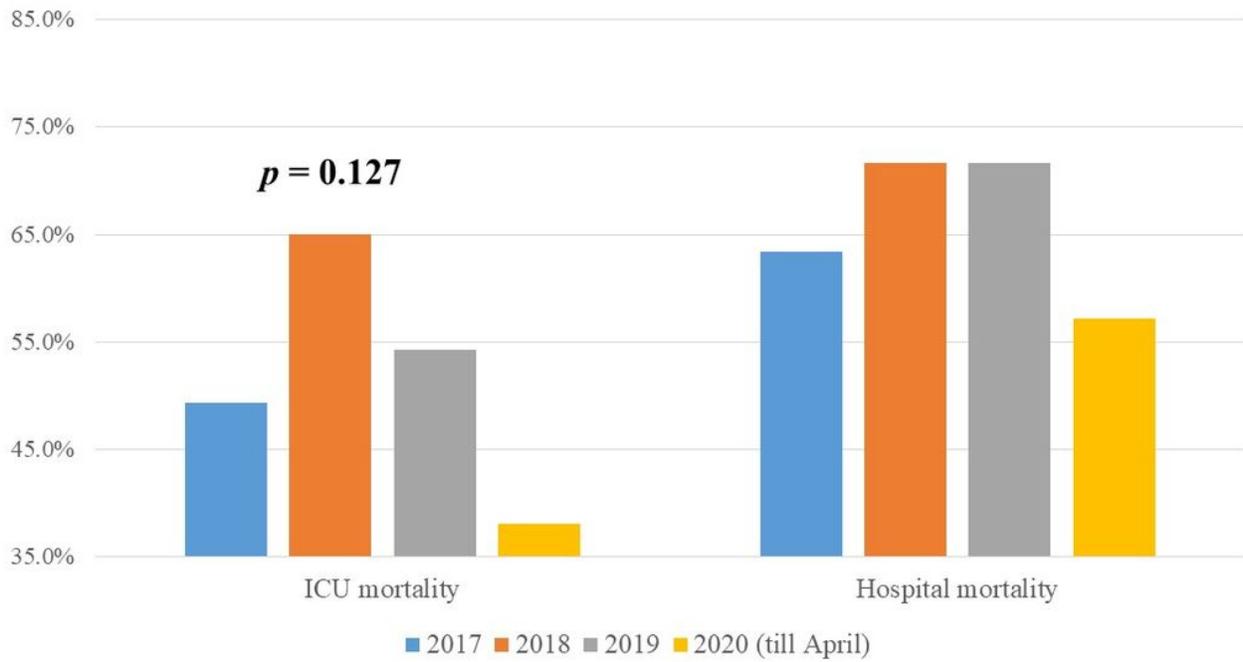
Figure 3

ICU and hospital morality rate There was a decrease ICU mortality during the years of observation; but it was not statistically significant