

Long-Term Outcome of Patients With a Hematologic Malignancy and Multiple Organ Failure Admitted at the Intensive Care

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Objectives: Historically, patients with a hematologic malignancy have one of the highest mortality rates among cancer patients admitted to the ICU. Therefore, physicians are often reluctant to admit these patients to the ICU. The aim of our study was to examine the survival of patients who have a hematologic malignancy and multiple organ failure admitted to the ICU.

Design: This retrospective cohort study, part of the HEMA-ICU study group, was designed to study the survival of patients with a hematologic malignancy and organ failure after admission to the ICU. Patients were followed for at least 1 year.

Setting: Five university hospitals in the Netherlands.

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All participating investigators are listed in Appendix 1.

The authors have disclosed that they do not have any potential conflicts of interest.

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Patients: One-thousand ninety-seven patients with a hematologic malignancy who were admitted at the ICU.

Interventions: None.

Measurements and Main Results: Primary outcome was 1-year survival. Organ failure was categorized as acute kidney injury, respiratory failure, hepatic failure, and hemodynamic failure; multiple organ failure was defined as failure of two or more organs. The World Health Organization performance score measured 3 months after discharge from the ICU was used as a measure of functional outcome. The 1-year survival rate among these patients was 38%. Multiple organ failure was inversely associated with long-term survival, and an absence of respiratory failure was the strongest predictor of 1-year survival. The survival rate among patients with 2, 3, and 4 failing organs was 27%, 22%, and 8%, respectively. Among all surviving patients for which World Health Organization scores were available, 39% had a World Health Organization performance score of 0–1 3 months after ICU discharge. Functional outcome was not associated with the number of failing organs.

Conclusions: Our results suggest that multiple organ failure should not be used as a criterion for excluding a patient with a hematologic malignancy from admission to the ICU. (*Crit Care Med* 2019; 47:e120–e128)

Key Words: hematologic malignancy; intensive care unit; multiple organ failure/mortality; organ failure; prognosis

The mortality rate among patients with various types of malignancies has decreased in recent years, presumably due in part to the development of new targeted treatment options and improved supportive care (1). However, aging of our general population has led to an overall increase in the number of oncology patients (2, 3), with a resulting increase in the number of patients with a hematologic malignancy admitted to the ICU (4, 5). The risk of ICU admission

is particularly high among patients with a hematologic malignancy due to their immunocompromised status, and sepsis (including neutropenic sepsis) is the most common reason for ICU admission (6). Compared with other cancer patients admitted to the ICU, patients with a hematologic malignancy are generally more ill, have a higher mortality rate, and have a poorer quality of life measured 1 year after discharge from the ICU (7–9). Despite their more vulnerable status, physicians today are less reluctant to admit hematologic patients to the ICU compared with the 1990s (10). Indeed, ICU survival rates have improved due in part to improved treatment of hematologic malignancies and improved ICU care (11, 12). However, a prospective study of the efficacy of triaging patients with a hematologic malignancy for possible ICU admission found that 20% of patients who were considered “not sick enough” to benefit from ICU support died before hospital discharge (13). In the same study, 25% of patients who were considered “too sick” to benefit from ICU support survived (13). These statistics indicate that restrictive judgment by clinicians in terms of ICU admission can be an alternative explanation for the improvement in ICU survival rates.

A reliable prognostic model for patients with a hematologic malignancy is still lacking, and recent studies found conflicting results with respect to the value of prognostic factors for mortality in critically ill patients with a hematologic malignancy. These factors include neutropenia/leukopenia, the Acute Physiology and Chronic Health Evaluation (APACHE) II score, and stem cell transplantation status. Consequently, it is currently unclear which variables can be used to predict the mortality rate of patients with a hematologic malignancy after admission to the ICU (14–19).

Organ failure is a well-recognized predictor of ICU-related mortality among this patient population (5, 15, 20), and the Sequential Organ Failure Assessment (SOFA) score has been reported to serve as an independent predictor of mortality among patients with a hematologic malignancy who are admitted to the ICU (14, 21–23). However, the aggregate SOFA score lacks information regarding the number of failing organs and the specific organ system(s) involved. In addition, most published studies that addressed the outcome of patients with a hematologic malignancy admitted to the ICU focused primarily on short-term survival (5, 7, 13, 24).

The aim of our study was to examine the 1-year survival rate and functional status of patients who have a hematologic malignancy and organ failure and were admitted to the ICU. By focusing on the contribution of different forms or combinations of nonhematologic organ failure, our results may provide a rational and reliable decision model that may help shape the policy regarding ICU admission for this patient population.

METHODS

Data Collection

We performed a multicenter retrospective observational study for the period from December 2002 to August 2015 using prospectively collected data in the Dutch National Intensive

Care Evaluation (NICE) registry and the Diagnosis Treatment Combination Healthcare Cost and Utilization databases at the participating medical centers. Where possible, any missing information was obtained retrospectively from the patient’s electronic medical records. The following five Dutch university hospitals participated in this study: the Academic Medical Center Amsterdam, Erasmus Medical Center (Rotterdam), Leiden University Medical Center, Radboud University Medical Center Nijmegen, and the University Medical Center Groningen. The participating ICUs were closed-format ICUs and held daily multidisciplinary meetings with the hematologist and intensivists. Ethics approval was obtained on August 23, 2016 from the Medical Ethics Committee of the University Medical Center Groningen (number METc 2016.396).

We included only patients with a clinically confirmed hematologic malignancy who were admitted to the ICU with an acute medical or surgical indication. Patients who were admitted after elective surgery or for a diagnostic procedure (e.g., bronchoscopy) were excluded. Only first ICU admissions were included in our analysis. To further exclude nonacute reasons for ICU admission, we also excluded all patients who were discharged from the ICU within 24 hours of admission.

We collected the following baseline characteristics: age at the time of admission to the ICU, gender, malignancy type, disease status at the time of admission, whether mechanical ventilation was needed, the use of vasoactive medication, the reason for admission to the ICU, previous stem cell transplantation, renal replacement therapy, length of stay at the hospital prior to ICU admission, and the presence of infection. Laboratory values obtained at the time of ICU admission included bilirubin level, creatinine level, neutrophil count, and platelet count. Severity of illness within the first 24 hours of ICU admission was assessed using the APACHE II score (25).

Survival was measured for up to 1 year. World Health Organization (WHO) performance scores were collected 3 months after ICU discharge at two (Academic Medical Center, University of Amsterdam and University Medical Center Groningen) of the five participating centers and were used to analyze performance at 3 months.

Definitions

Hematologic malignancies were categorized as follows: acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphoblastic leukemia, chronic myeloid leukemia, Hodgkin’s lymphoma (HL), non-HL (NHL), and multiple myeloma (MM). Disease status was defined as either active disease or complete remission, with active disease defined as either a lack of complete remission or a relapse.

Patients were categorized based on their reason for admission to the ICU as follows: disease-related, sepsis, anaphylactic shock, intestinal perforation, pulmonary embolus, neurologic indication, severe hemorrhaging, treatment-related toxicity, or other.

We focused on four types of organ failure based on the NICE criteria used to define organ failure (26, 27). Acute kidney injury was defined as the need for renal replacement therapy or a creatinine level greater than 133 $\mu\text{mol/L}$ in combination

with oliguria within 24 hours of admission to the ICU. Hepatic failure was defined as a bilirubin level greater than 102 $\mu\text{mol/L}$ within 24 hours of admission to the ICU. Respiratory failure was defined as the need for mechanical ventilation within 24 hours after admission to the ICU. Finally, hemodynamic failure was defined as the need for vasoactive medication within 24 hours of admission to the ICU.

We categorized patients with one or more failing organs into four main groups based on the number of failing organ systems (i.e., 1, 2, 3, or 4 failing organ systems). Multiple organ failure (MOF) was defined as the occurrence of two or more failing organ systems. In addition, we divided the main groups into subgroups based on the type(s) of organ failure, using a two-step procedure. First, we grouped patients according to the number of (nonhematologic) failing organs. We subsequently grouped patients according to the specific failing organ system(s). For example, patients with acute kidney injury and respiratory failure but not hemodynamic failure or hepatic failure formed one subgroup.

WHO performance score uses a five-point scale ranging from 0 to 4, with 0 defined as “able to carry out all normal activity without any restriction” and 4 defined as “completely disabled” (28).

Neutropenia was defined as a neutrophil count less than 0.5×10^9 cells/L. Infection was defined as the presence of a confirmed or suspected infection at the time of admission to the ICU or within the first 24 hours after admission; this was based on the results of a culture test, a positive Gram stain, perioperative findings, or the physician’s judgment.

We considered hematologic failure to be present in virtually all of our patients and therefore did not enter it as a distinguishing characteristic or type of organ failure. Thus, our study assessed the association between nonhematologic organ failure and outcome in this high-risk patient population.

Statistical Analyses

Normally distributed continuous data are presented as the mean \pm SD; categorical data are presented as the number of patients with the corresponding percentage. We used descriptive statistics for survival rate.

The primary outcome was survival 1 year after ICU admission. To compare the association between putative predictors of survival, we used the chi-square test (for dichotomous variables), the Mann-Whitney *U* test (for nominal variables and nonnormally distributed continuous variables), or the Student *t* test (for normally distributed continuous data). All tests were two-sided, and a *p* value of less than 0.05 was considered to indicate a statistically significant difference. To determine the quality of life of the surviving patients, we examined WHO scores obtained by two participating centers 3 months after discharge from the ICU. To test whether MOF was related to the 3-month WHO score, we performed a landmark analysis using an one-way analysis of variance. For this analysis, we included only the patients who survived the hospital stay; in addition, we classified any patients who died within 3 months of discharge from the ICU as “completely disabled” (i.e., a WHO performance score of 4).

We studied the association between MOF and survival using binary logistic regression, yielding a crude odds ratio (OR) with corresponding 95% CI. We ran bivariate analyses with all possible confounders and each combination of organ failure in order to select variables for our multivariate analyses. If the OR of organ failure/MOF in the bivariate analyses did not change more than 10% for any of variable used, we considered that organ failure/MOF to be an independent predictor of survival.

To identify which type of organ failure was most strongly associated with long-term outcome, we performed a Classification and Regression Tree (CRT) analysis in order to create a decision tree, providing a model that predicts the value of the dependent variable (i.e., long-term outcome) based on the values of the independent variables. The nodes of the CRT identify which variables are the most useful for predicting survival or mortality and what the survival rate is in several scenarios. To measure the fraction of patients who were still alive up to 1 year after ICU admission, and the effect of MOF on survival, we generated Kaplan-Meier survival curves and compared these curves using a log-rank test.

Missing values were considered as missing in our analyses.

RESULTS

A total of 1,097 patients were included in our study. The mean age was 55 years, and 37% of patients were female (Table 1). All patients had a confirmed hematologic malignancy, with AML (35%), NHL (30%), and MM (13%) comprising the most prevalent types of malignancy. The survival rates of the ALL, HL, and MM patient groups were significantly higher than the average survival rate for the entire study population, due in part to the relatively low survival rate among patients with AML. A total of 693 patients (63%) had active disease, which was associated with decreased survival. Respiratory failure was the most prevalent form of organ failure, occurring in 700 patients (64%); hemodynamic failure occurred in 552 of patients (50%), acute kidney injury occurred in 167 patients (15%), and hepatic failure occurred in 114 patients (10%). Only 12 of the 1,097 patients (1.1%) had organ failure involving all four nonhematologic organ systems.

Outcome

The survival rate 28 days, 3 months, and 1 year after ICU admission was 56% (618 patients), 48% (524 patients), and 38% (413 patients), respectively. We found no significant difference between the five participating centers with respect to survival. Although the average age of the survivors was slightly lower than the nonsurvivors, neither age nor gender was associated with survival. Sepsis was the most common reason for admission to the ICU but was not associated with survival. Approximately one fifth of the patients (21%) received an allogeneic stem cell transplantation prior to admission to the ICU, and this was associated with decreased survival. Compared with nonsurvivors, the survivors had a significantly lower APACHE II score, with a mean overall score of 26.

TABLE 1. Baseline Characteristics of All 1,097 Patients at Baseline and the Surviving and Nonsurviving Patients at 1 Year

Characteristic	Baseline, <i>n</i> = 1,097	Survivors at 1 yr, <i>n</i> = 413	Nonsurvivors, <i>n</i> = 684	<i>p</i>
Hospital				0.31
Female, <i>n</i> (%)	401 (37)	152 (38)	249 (62)	0.87
Mean age, yr, mean ± SD	55 ± 15	54 ± 15	56 ± 14	0.09
Malignancy, <i>n</i> (%)				< 0.01
Acute lymphoblastic leukemia	76 (7)	37 (49)	39 (51)	
Acute myeloid leukemia	387 (35)	118 (30)	269 (70)	
Chronic lymphoblastic leukemia	68 (6)	24 (35)	44 (65)	
Chronic myeloid leukemia	47 (4)	15 (32)	32 (68)	
Hodgkin's lymphoma	44 (4)	24 (55)	20 (45)	
Non-Hodgkin's lymphoma	329 (30)	123 (37)	206 (63)	
Multiple myeloma	146 (13)	74 (49)	72 (51)	
Organ failure, <i>n</i> (%)				
Hepatic failure ^a	114 (10)	32 (28)	82 (72)	0.01
Acute kidney injury	167 (15)	39 (23)	128 (77)	< 0.01
Respiratory failure	700 (64)	201 (29)	499 (71)	< 0.01
Hemodynamic failure	552 (50)	175 (32)	377 (68)	< 0.01
Active disease, <i>n</i> (%)	693 (63)	231 (33)	462 (67)	< 0.01
Platelet count, × 10 ³ /μL, mean ± SD	90 ± 121	116 ± 135	75 ± 109	< 0.01
Neutropenia, <i>n</i> (%)	309 (28)	108 (35)	201 (65)	0.17
APACHE II score, mean ± SD	26 ± 18	23 ± 15	27 ± 19	< 0.01
High APACHE II score (> 22), <i>n</i> (%)	520 (47)	163 (31)	357 (69)	< 0.01
Reason for admission to the ICU, <i>n</i> (%)				
Disease related	199 (18)	67 (34)	132 (66)	0.15
Sepsis	543 (50)	206 (38)	337 (62)	0.82
Anaphylactic shock	12 (1)	9 (75)	3 (25)	0.01
Intestinal perforation	34 (3)	13 (38)	21 (62)	0.94
Pulmonary embolus	15 (1)	8 (53)	7 (47)	0.21
Neurologic indication	75 (7)	30 (40)	45 (60)	0.66
Hemorrhage	71 (7)	16 (23)	55 (77)	0.01
Treatment-related toxicity	32 (3)	11 (34)	21 (66)	0.70
Other	115 (11)	53 (46)	62 (54)	0.05
Stem cell transplantation, <i>n</i> (%)	307 (28)	108 (35)	199 (65)	0.02
Allogeneic	226 (21)	70 (31)	156 (69)	0.02
Autologous	81 (7)	38 (47)	43 (53)	0.07
Infection, <i>n</i> (%)	499 (46)	163 (33)	336 (67)	< 0.01
Length of hospital stay prior to ICU admission, d ^b , mean ± SD	11 ± 14	9 ± 12	12 ± 14	< 0.01

APACHE = acute physiology and chronic health evaluation.

^aHepatic failure values were missing for 91 patients.^bValues were missing for 280 patients; therefore, these data are shown for illustration purposes only and were not used for further analyses.Boldface values indicate *p* < 0.05 (statistically significant difference).

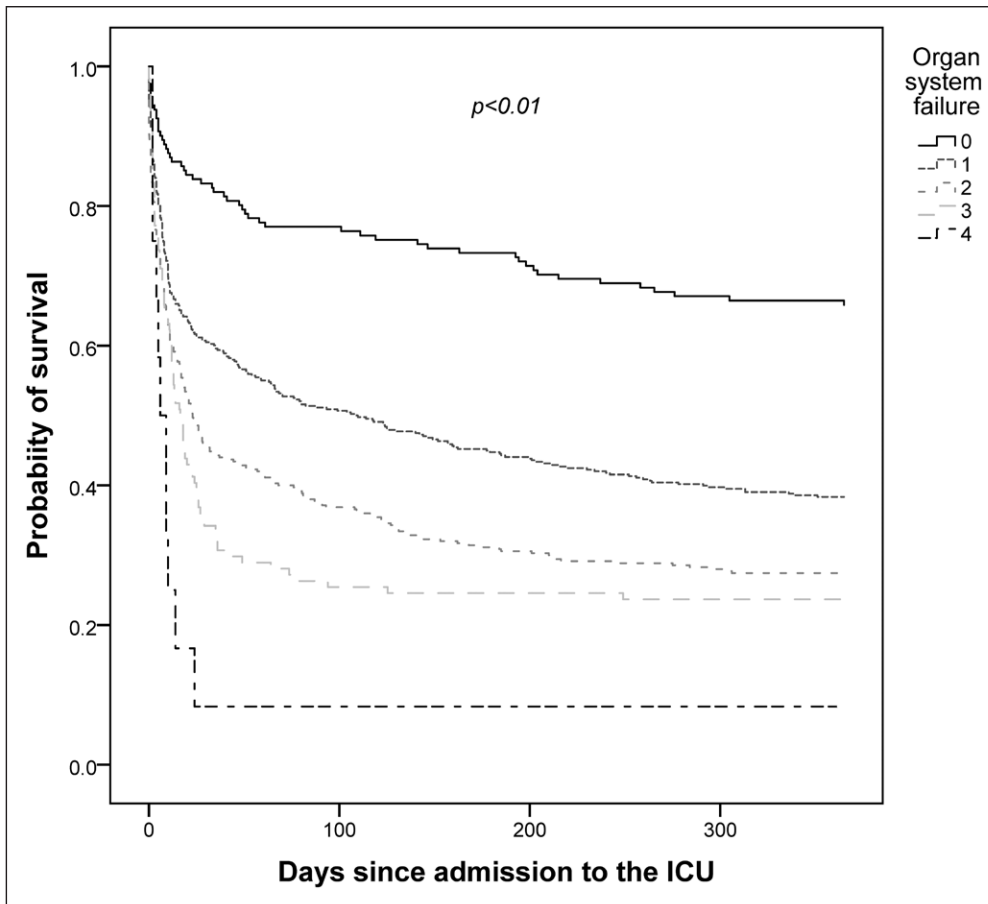


Figure 1. Kaplan-Meier survival curve for patients with 0, 1, 2, 3, or 4 failing organ systems.

WHO performance score was available for 493 patients. Among the patients who survived their hospital stay, 39% had a WHO performance score of 0 or 1 3 months after discharge from the ICU, with a mean score of 1.83. Although the number of failing organ systems was inversely associated with survival (**Fig. 1**), it was not associated with the WHO performance score measured 3 months after ICU discharge ($p = 0.42$).

Among the patients with “only” one failing organ, the 1-year survival rate was similar to the overall 1-year survival rate (i.e., 38%). However, having “at least” one or more failing organs was strongly inversely associated with survival, and the survival rate in these patients depended largely on the specific combination of failing organs (**Fig. 2** and **Table 2**). (**Table 3**)

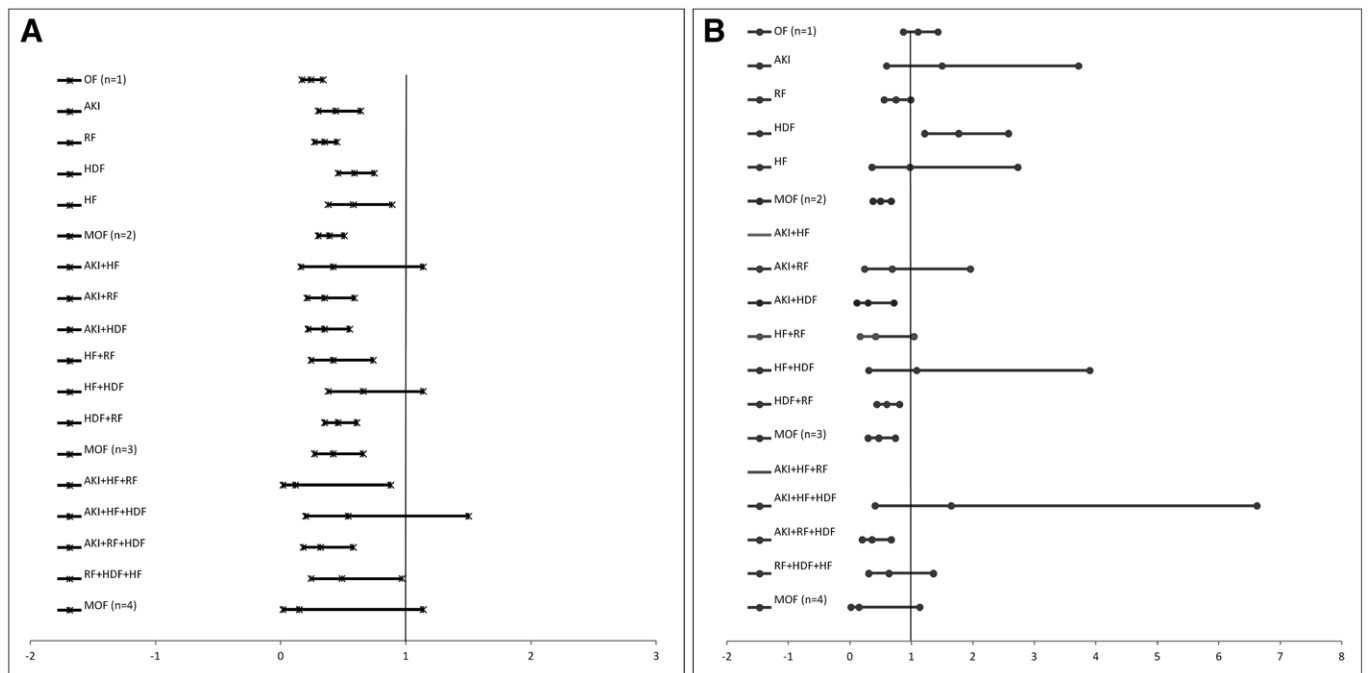


Figure 2. Forest plot showing the odds ratio (OR) and corresponding 95% CI for 1-yr survival in patients with either single organ failure (OF) or multiple OF (MOF). **A.** OR for patients with at least the indicated type of single OF or MOF; for example, a patient with acute kidney injury (AKI) also includes patients with AKI and hepatic failure (HF). **B.** OR for patients with exactly the indicated type of OF. Note that one patient with exactly AKI + HF and the three patients with exactly AKI + HF + respiratory failure (RF) had a 0% survival rate; thus, an OR could not be calculated for these two type of MOF. See also Table 2. HDF = hemodynamic failure.

TABLE 2. Survival Rate and Odds Ratio 1 Year After ICU Admission for All Possible Combinations of Organ Failure Compared With the Entire Study Population

Failing Organ(s)	With at Least This Type of Organ Failure or MOF Combination			With Exactly This Type of Organ Failure or MOF Combination		
	<i>n</i>	Survival Rate, %	OR (95% CI)	<i>n</i>	Survival Rate	OR (95% CI)
One failing organ	916	32	0.24 (0.17–0.34)	438	38	1.11 (0.87–1.43)
AKI	167	23	0.44 (0.30–0.64)	19	47	1.50 (0.60–3.72)
RF	700	29	0.35 (0.27–0.45)	279	33	0.75 (0.56–0.99)
HDF	552	32	0.59 (0.46–0.75)	124	50	1.77 (1.22–2.58)
HF	114	27	0.58 (0.38–0.89)	16	38	0.98 (0.36–2.73)
Two failing organs	478	26	0.39 (0.30–0.51)	351	27	0.50 (0.38–0.67)
AKI+ HF	24	21	0.42 (0.16–1.14)	1	0	NA
AKI + RF	101	19	0.35 (0.21–0.59)	17	29	0.69 (0.24–1.96)
AKI + HDF	127	19	0.35 (0.22–0.55)	38	16	0.30 (0.12–0.72)
HF + RF	79	22	0.42 (0.24–0.74)	29	21	0.42 (0.17–1.04)
HF + HDF	65	29	0.66 (0.38–1.14)	10	40	1.09 (0.31–3.90)
HDF + RF	372	26	0.46 (0.35–0.61)	256	29	0.60 (0.44–0.81)
Three failing organs	127	22	0.42 (0.27–0.66)	115	22	0.47 (0.30–0.74) ^a
AKI + HF + RF	15	7	0.12 (0.02–0.88)	3	0	NA
AKI + HF + HDF	20	25	0.54 (0.20–1.50)	8	50	1.65 (0.41–6.62)
AKI + RF + HDF	81	17	0.32 (0.18–0.58)	69	19	0.36 (0.20–0.67)
RF + HDF + HF	47	23	0.49 (0.24–0.97)	35	29	0.64 (0.31–1.36)
Four failing organs						
AKI + HF + RF + HDF	12	8	0.15 (0.02–1.14)	12	8	0.15 (0.02–1.14)

AKI = acute kidney injury, HDF = hemodynamic failure, HF = hepatic failure, MOF = multiple organ failure, NA = not applicable, OR = odds ratio, RF = respiratory failure.

^aOR (95% CI) changed to 0.53 (0.33–0.86) when platelet count was included in the analysis. Thus, the survival rate with exactly 3 failing organs is only 14% when combined with a platelet count of $< 44 \times 10^3/\mu\text{L}$.

Among the patients with two failing organs, the 1-year survival rate was 27%. The survival rate was similar for all patients with two or more failing organs (26%), and this decreased only slightly (to 22%) for patients with three failing organs. As mentioned above, only 12 patients had four failing organ systems, and the 1-year survival rate was 8%; however, it should be noted that only one of the 12 patients with four failing organ systems survived the ICU and was discharged. This patient had a 3-month WHO performance score of 2, indicating that he/she was ambulatory, able to care for himself/herself, and up and about more than 50% of the waking hours but was unable to hold employment.

Our analysis revealed that MOF is an independent predictor of survival. Platelet count was the only factor that affected survival among patients with three failing organs; specifically, survival decreased from 22% to 14% when these patients had a concomitant platelet count below the median value of $44 \times 10^3/\mu\text{L}$. The nodes in the CRT analysis were split based only on significant predictors, starting with the most

important predictor as the parent node (**Fig. 3**). The need for mechanical ventilation was the strongest predictor of survival. The lowest survival rate was seen in node 6, with only 19% of patients in this node (i.e., both respiratory failure and acute kidney injury) surviving. In contrast, the lowest mortality rate was seen in node 7 (i.e., patients who did not have respiratory failure, kidney failure, or hemodynamic failure), with a 1-year survival rate of 65%.

DISCUSSION

In our cohort of more than 1,000 patients with a hematologic malignancy admitted to the ICU, we found that MOF was inversely associated with survival, although the survival rate was relatively high and nearly half of the survivors had a good WHO performance score. The specific combination of organ systems that fail can help the clinician identify the patient groups with the highest and lowest survival rates. Respiratory failure appeared to be the most important determinant of survival. For example, patients with both respiratory failure and

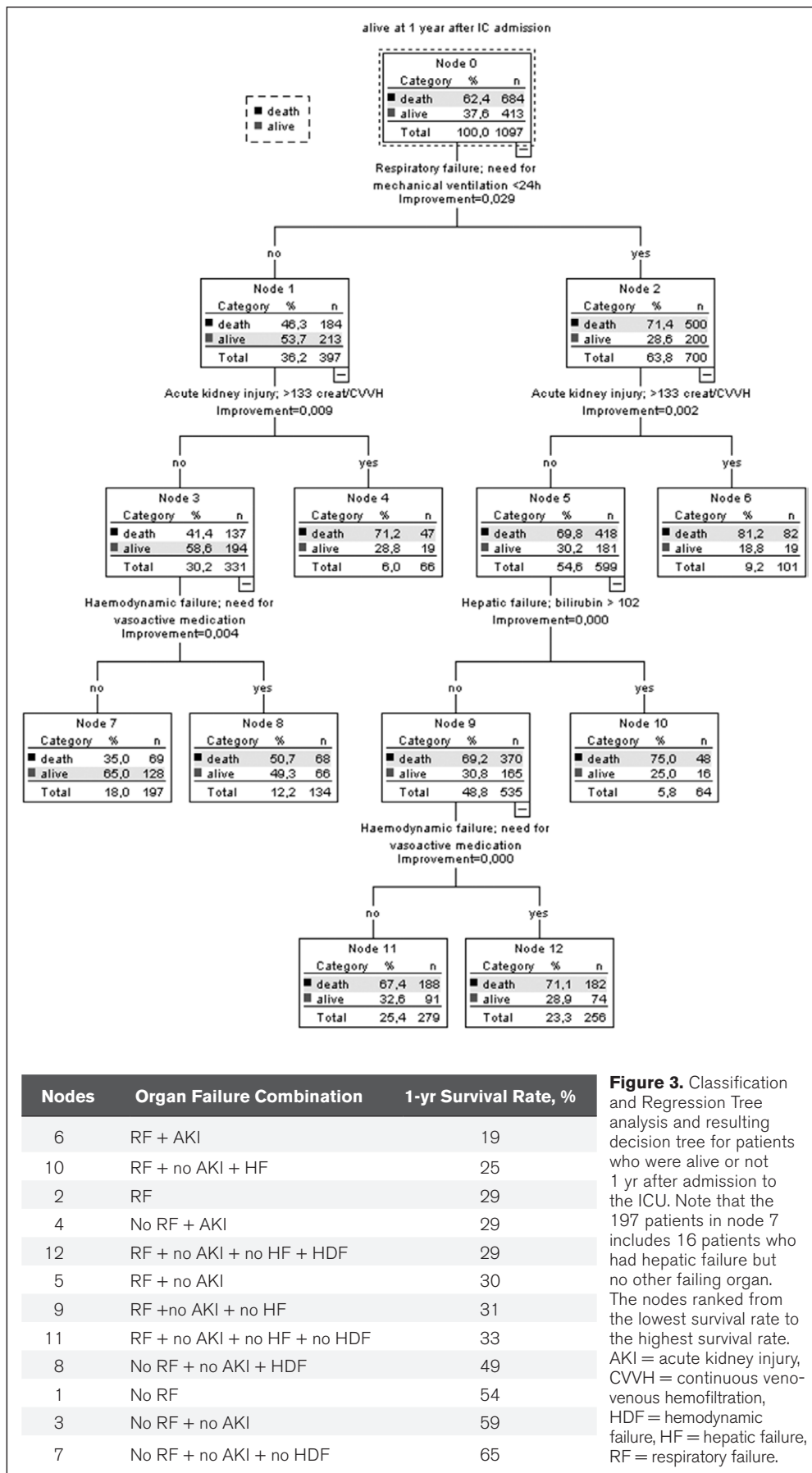


Figure 3. Classification and Regression Tree analysis and resulting decision tree for patients who were alive or not 1 yr after admission to the ICU. Note that the 197 patients in node 7 includes 16 patients who had hepatic failure but no other failing organ. The nodes ranked from the lowest survival rate to the highest survival rate. AKI = acute kidney injury, CVVH = continuous venovenous hemofiltration, HDF = hemodynamic failure, HF = hepatic failure, RF = respiratory failure.

acute kidney injury had only a 19% survival rate, compared with 54% of patients without respiratory failure. Importantly, the overall 38% 1-year survival rate is encouraging, particularly given that up to 84% of these survivors had at least one failing organ system. The average survival rate, APACHE II score, age, and baseline characteristics of our patient cohort were consistent with previous European studies (5,9,12,16,20,21,24,29); thus, we conclude that the large, heterogeneous population in this multicenter study likely reflects the general population, indicating that our results provide added value with respect to clinical decision-making.

The survival rates associated with MOF in our patient cohort were higher than previous reports (7, 20, 24, 30), and our results obtained for patients with hemodynamic failure clearly support this higher rate; even though hemodynamic failure was a predictor of decreased survival, nearly one in three patients survived, even when combined with another type of organ failure. This finding is in contrast with previous studies in which none of the patients who were taking vasoactive medication and had both organ failure and leukopenia survived (16, 31). These data suggest that the occurrence of MOF should not necessarily be an exclusion criterion for admission to the ICU. Given that previous studies used the SOFA score to define organ failure, it is unclear which factor used to calculate the SOFA score was responsible for the association between SOFA score and mortality (14, 21–23). Furthermore, the value of using the SOFA score to predict survival can vary, as some studies found that the SOFA score was an independent predictor of ICU mortality, whereas other studies

found no such association (19, 24, 29). By defining organ failure using our specific criteria, we were able to examine the association between survival and specific forms and combinations of organ failure, providing added value compared with the prediction models used in other studies. Furthermore, our relatively large dataset enabled us to perform a CRT analysis, which can be helpful in clinical decision-making, as the effect of each variable can be measured and displayed clearly.

Another strength of our study is our concrete primary endpoint (1-yr survival), which was possible due to the relatively long-term follow-up period. Finally, the NICE registry is considered to be a reliable source of high-quality data (32).

Despite its strengths, our study had several limitations that warrant discussion. First, our retrospective evaluation of prospectively collected data could have led to selection bias. Although the mean APACHE score in our patient population was similar to other studies, we cannot rule out the possibility that some patients who were considered too sick were not admitted to the ICU. However, we do not believe this was likely a major issue in our analysis given the high average APACHE II scores in our patient population. Second, the relatively large time window (spanning approximately 13 yr) for the data included in our study may have influenced the results. However, the survival rates among our patients were similar—or higher—than previous studies. Third, complete functional outcome scores were not available for all patients. Finally, the definitions that we used for organ failure were based on the NICE criteria and therefore could have differed slightly from international definitions of organ failure such as the SOFA score (26, 27). Furthermore, the Glasgow Coma Score was not taken into account as a measure of a separate type of organ failure. However, we previously examined the association between CNS function and survival and found that patients with a history of hematologic malignancy who present with a critical neurologic event have a survival rate similar to other patients with a hematologic malignancy admitted to the ICU (33).

It would be interesting to expand the decision tree by adding additional relevant parameters such as duration of the hospital stay prior to admission to the ICU. The association between MOF and decreased survival indicates that the risk of developing MOF could serve as an indication to admit these patients to the ICU as early as possible; furthermore, previous studies found that a longer hospital stay prior to ICU admission is predictive of mortality (5, 24). We also found that the duration of time in the hospital prior to admission to the ICU was associated with survival (data not shown); however, due to missing values, we were unable to add this variable to the decision tree. In addition, the length of the stay in the ICU and the duration of life-supporting interventions could be relevant factors in determining and predicting survival. For example, the sooner the patient can be stabilized, the sooner the treatment for the underlying hematologic malignancy can resume; this will likely improve long-term survival, as recent studies showed that long-term survival among patients with a hematologic malignancy depends strongly on the ability of the patient to resume treatment for the underlying malignancy (34, 35).

Our study yielded additional findings that may be clinically relevant, including the presence of active disease, low platelet count (thrombocytopenia), and the type of hematologic malignancy. Our finding that active disease—an indicator of disease status—is correlated with a decreased 1-year survival rate is in contrast to other studies (36). Furthermore, thrombocytopenia—a common complication among patients with a hematologic malignancy due to chemotherapy, disseminated intravascular coagulation, or bone marrow failure—has been related to MOF (37).

CONCLUSIONS

Here, we provide clear evidence that organ failure is a predictor of decreased 1-year survival among patients with a hematologic malignancy in the ICU. In particular, the need for mechanical ventilation (i.e., respiratory failure) had the strongest inverse association with long-term outcome. Nevertheless, we believe that MOF should not be used as an exclusion criterion for admission to the ICU, as survival rate was still relatively high even among patients with two or more failing organ systems. Furthermore, with respect to long-term function, we found no difference in 3-month WHO performance scores between survivors with no organ failure and survivors who had multiple failing organ systems while in the ICU.

REFERENCES

1. 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
2. Ferlay J, Shin HR, Bray F, et al: Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010; 127:2893–2917
3. Pawelec G, Barnett Y, Forsey R, et al: T cells and aging, January 2002 update. *Front Biosci* 2002; 7:d1056–d1183
4. Haas LE, Karakus A, Holman R, et al: Trends in hospital and intensive care admissions in the Netherlands attributable to the very elderly in an ageing population. *Crit Care* 2015; 19:353
5. van Vliet M, Verburg IW, van den Boogaard M, et al: Trends in admission prevalence, illness severity and survival of haematological patients treated in Dutch intensive care units. *Intensive Care Med* 2014; 40:1275–1284
6. Pène F, Soares M: Can we still refuse ICU admission of patients with hematological malignancies? *Intensive Care Med* 2008; 34:790–792
7. Taccone FS, Artigas AA, Sprung CL, et al: Characteristics and outcomes of cancer patients in European ICUs. *Crit Care* 2009; 13:R15
8. Schellongowski P, Sperr WR, Wohlfarth P, et al: Critically ill patients with cancer: Chances and limitations of intensive care medicine—a narrative review. *ESMO Open* 2016; 1:e000018
9. Oeyen SG, Benoit DD, Annemans L, et al: Long-term outcomes and quality of life in critically ill patients with hematological or solid malignancies: A single center study. *Intensive Care Med* 2013; 39:889–898
10. Brunet F, Lanore JJ, Dhainaut JF, et al: Is intensive care justified for patients with haematological malignancies? *Intensive Care Med* 1990; 16:291–297
11. Bos MM, de Keizer NF, Meynaar IA, et al: Outcomes of cancer patients after unplanned admission to general intensive care units. *Acta Oncol* 2012; 51:897–905
12. Azoulay E, Mokart D, Pène F, et al: Outcomes of critically ill patients with hematologic malignancies: Prospective multicenter data from

- France and Belgium—a groupe de recherche respiratoire en réanimation onco-hématologique study. *J Clin Oncol* 2013; 31:2810–2818
13. Thiéry G, Azoulay E, Darmon M, et al: Outcome of cancer patients considered for intensive care unit admission: A hospital-wide prospective study. *J Clin Oncol* 2005; 23:4406–4413
 14. Namendys-Silva SA, González-Herrera MO, García-Guillén FJ, et al: Outcome of critically ill patients with hematological malignancies. *Ann Hematol* 2013; 92:699–705
 15. Bird GT, Farquhar-Smith P, Wigmore T, et al: 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
 16. Benoit DD, Vandewoude KH, Decruyenaere JM, et al: Outcome and early prognostic indicators in patients with a hematologic malignancy admitted to the intensive care unit for a life-threatening complication. *Crit Care Med* 2003; 31:104–112
 17. Souza-Dantas VC, Salluh JI, Soares M: Impact of neutropenia on the outcomes of critically ill patients with cancer: A matched case-control study. *Ann Oncol* 2011; 22:2094–2100
 18. Cheng Q, Tang Y, Yang Q, et al: The prognostic factors for patients with hematological malignancies admitted to the intensive care unit. *Springerplus* 2016; 5:2038
 19. Darmon M, Vincent F, Canet E, et al: Acute kidney injury in critically ill patients with haematological malignancies: Results of a multicentre cohort study from the Groupe de Recherche en Réanimation Respiratoire en Onco-Hématologie. *Nephrol Dial Transplant* 2015; 30:2006–2013
 20. Grgić Medić M, Gornik I, Gašparović V: Hematologic malignancies in the medical intensive care unit—Outcomes and prognostic factors. *Hematology* 2015; 20:247–253
 21. Platon L, Amigues L, Ceballos P, et al: A reappraisal of ICU and long-term outcome of allogeneic hematopoietic stem cell transplantation patients and reassessment of prognosis factors: Results of a 5-year cohort study (2009-2013). *Bone Marrow Transplant* 2016; 51:256–261
 22. Lamia B, Hellot MF, Girault C, et al: Changes in severity and organ failure scores as prognostic factors in onco-hematological malignancy patients admitted to the ICU. *Intensive Care Med* 2006; 32:1560–1568
 23. Silfvast T, Pettilä V, Ihalainen A, et al: Multiple organ failure and outcome of critically ill patients with haematological malignancy. *Acta Anaesthesiol Scand* 2003; 47:301–306
 24. Hampshire PA, Welch CA, McCrossan LA, et al: Admission factors associated with hospital mortality in patients with haematological malignancy admitted to UK adult, general critical care units: A secondary analysis of the ICNARC Case Mix Programme Database. *Crit Care* 2009; 13:R137
 25. Knaus WA, Draper EA, Wagner DP, et al: APACHE II: A severity of disease classification system. *Crit Care Med* 1985; 13:818–829
 26. van de Klundert N, Holman R, Dongelmans DA, et al: Data resource profile: The Dutch National Intensive Care Evaluation (NICE) registry of admissions to adult intensive care units. *Int J Epidemiol* 2015; 44:1850–1850h
 27. National Intensive Care Evaluation (NICE). Data dictionary. Available at: <https://www.stichting-nice.nl/dd/#start>. Accessed May 1, 2016
 28. Gosney M, Harper A, Conroy S: Oxford Desk Reference: Geriatric Medicine. Oxford, England, Oxford University Press, 2012, pp 133
 29. Vandijck DM, Benoit DD, Depuydt PO, et al: Impact of recent intravenous chemotherapy on outcome in severe sepsis and septic shock patients with hematological malignancies. *Intensive Care Med* 2008; 34:847–855
 30. Azoulay E, Thiéry G, Chevret S, et al: The prognosis of acute respiratory failure in critically ill cancer patients. *Medicine (Baltimore)* 2004; 83:360–370
 31. Khassawneh BY, White P Jr, Anaissie EJ, et al: Outcome from mechanical ventilation after autologous peripheral blood stem cell transplantation. *Chest* 2002; 121:185–188
 32. Koetsier A, Peek N, de Jonge E, et al: Reliability of in-hospital mortality as a quality indicator in clinical quality registries. A case study in an intensive care quality register. *Methods Inf Med* 2013; 52:432–440
 33. Riedijk M, van den Bergh WM, van Vliet M, et al; HEMA-ICU study group: Characteristics and outcomes of patients with a haematological malignancy admitted to the intensive care unit for a neurological event. *Crit Care Resusc* 2015; 17:268–273
 34. Hamaker ME, Augschoell J, Stauder R: Clinical judgement and geriatric assessment for predicting prognosis and chemotherapy completion in older patients with a hematological malignancy. *Leuk Lymphoma* 2016; 57:2560–2567
 35. Hirakawa T, Yamaguchi H, Yokose N, et al: Importance of maintaining the relative dose intensity of CHOP-like regimens combined with rituximab in patients with diffuse large B-cell lymphoma. *Ann Hematol* 2010; 89:897–904
 36. Massion PB, Dive AM, Doyen C, et al: Prognosis of hematologic malignancies does not predict intensive care unit mortality. *Crit Care Med* 2002; 30:2260–2270
 37. Nguyen TC, Cruz MA, Carcillo JA: Thrombocytopenia-associated multiple organ failure and acute kidney injury. *Crit Care Clin* 2015; 31:661–674

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