Outcome and early prognostic indicators in patients with a hematologic malignancy admitted to the intensive care unit for a life-threatening complication*

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Objectives: **To assess the outcome and to identify early prognostic indicators in a global population of patients with hematologic malignancy admitted to the intensive care unit for a life-threatening complication.**

Design: **Retrospective observational study.**

Setting: **Medical intensive care unit at a tertiary university hospital.**

Patients: **A total of 124 consecutive critically ill patients with a hematologic malignancy admitted to the intensive care unit during a 3.5-yr period.**

Measurements: **We collected variables at admission and during admission and identified predictors of in-hospital mortality by stepwise logistic regression analysis.**

Main Results: **Mean Acute Physiology and Chronic Health Evaluation II score was 26 ± 7.7. Sixty-one percent had a high-grade malignancy, and 27% had active disease. Thirty-five percent were leukopenic (leukocyte count, $<1.0 \times 10^9$/L) at admission. Respiratory failure (48%), sepsis (18.5%), and neurologic impairment (17%) were the major reasons for admission at the intensive care unit. Seventy-one percent of the patients required ventilatory support for a median duration of 6 (3–17) days, 46% received vasopressors at admission, and 26.6% needed renal replacement therapy during their intensive care unit stay. A recent bacteremia precipitating intensive care unit admission was found in 21.8% of the patients. Crude intensive care unit, in-hospital, and 6-month mortality rates were 42%, 54%, and 66%, respectively. Four variables were independently associated with outcome in a multivariate logistic regression analysis: leukopenia (odds ratio, 2.9; 95% confidence interval, 1.1–7.7), vasopressors (odds ratio, 3.74; 95% confidence interval, 1.4–9.8), and urea of >0.75 g/L (>12 mmol/L) (odds ratio, 9.4; 95% confidence interval, 4.2–26) at admission were associated with poor outcome, whereas recent bacteremia (odds ratio, 0.17; 95% confidence interval, 0.05–0.58) was associated with better prognosis. Using these variables, we arbitrarily categorized our population into three groups for survival analysis: a low-risk group (low urea with or without either leukopenia or vasopressors, n = 60), an intermediate-risk group (high urea or a combination of leukopenia and vasopressors, n = 34), and a high-risk group (high urea in combination with leukopenia or vasopressors, n = 27). Patients with a bacteremia prompting intensive care unit admission were allocated to a one-step-lower risk group. Survival probabilities at 30 days and 6 months were 75% and 55% in the first group, 35% and 21% in the second group, and 4% and 0%, respectively, in the third group ($p < .001$).**

Conclusion: **The general reluctance to admit patients with a hematologic malignancy to the intensive care unit, even with severe critical illness, is unjustified. However, we identified four early predictors of outcome that may be of value in deciding in which patients advanced or prolonged support should not be continued. (Crit Care Med 2003; 31:104–112)**

KEY WORDS: hematologic malignancy; intensive care unit; outcome; urea; bacteremia

Over the past two decades, the survival of patients with a hematologic malignancy has substantially improved, particularly because of new and intensive chemotherapeutic regimens, eventually followed by bone marrow or peripheral stem cell rescue on one hand, and better supportive measures on the other hand. Unfortunately, the use of aggressive chemotherapeutic regimens frequently results in life-threatening complications, requiring transfer to the intensive care unit (ICU) for monitoring or advanced support (1). Once a patient with a hematologic malignancy requires advanced intensive care support, the prognosis is particularly poor (2–29). Mortality rates of 75–85% have been reported in patients with respiratory failure requiring mechanical ventilation (13–18), and these rates increase to 83–97% in patients who have undergone an allogeneic bone marrow transplantation (19–29) or who develop multiple organ failure during their ICU stay (8–10, 15). This limited survival is achieved at considerable costs (30) because the majority of ICU days, ventilation days, and use of blood products are accounted for by nonsurvivors (21, 30).

Because of the poor prognosis, the considerable costs, the substantial emotional burden endured by these patients and their relatives, and the resulting general reluctance of many intensivists to admit patients with a hematologic malignancy to the ICU, early prognostic indicators should be identified to discrimi-

***See also p. 320.**

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DOI: 10.1097/01.CCM.0000038213.27741.30

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nate patients who are more likely or less likely to benefit from advanced or prolonged ICU support. Prediction of mortality in an individual patient is unrealistic; however, early identification of a subgroup of patients whose survival is so low that advanced ICU support should not be continued without compromising the chances of potential survivors is a more reasonable goal (26).

Several severity of illness scores, such as Acute Physiology and Chronic Health Evaluation (APACHE) II, Simplified Acute Physiology Scale (SAPS) II, and Mortality Probability Model II have been used for the stratification of critically ill patients with a solid cancer or a hematologic malignancy and yield conflicting results (5, 9, 10, 16, 23, 27, 28, 31, 32). Although these scoring systems have a prognostic value, they generally underestimate mortality or fail to predict the individual outcome satisfactorily in the subpopulation of patients with a hematologic malignancy (12, 21, 25, 26). Other scoring systems have been developed but are rather complex to use in daily clinical practice (33, 34) or are based on a heterogeneous population of medical and surgical patients with a hematologic malignancy or solid tumor (34).

The aim of this study was to assess the outcome of patients with a hematologic malignancy admitted to the ICU for a life-threatening complication, to determine whether the general reluctance to admit these patients to the ICU is justified, and to identify simple and readily available early prognostic indicators in this population.

MATERIAL AND METHODS

Data were retrospectively collected on 146 consecutive patients with a hematologic malignancy or aplastic anemia who were admitted with a life-threatening complication to the Ghent University Hospital medical ICU between January 1, 1997, and June 30, 2000. This 14-bed unit admits critically ill patients who are at least 15 yrs old. The medical management of patients with a hematologic malignancy is undertaken by two intensive care staff members trained in hemato-oncology (D. Benoit, K. H. Vandewoude) in collaboration with the attending hematologists. Four patients who were in complete remission for >5 yrs, two patients who were admitted for monitoring, one patient who was transferred after 24 hrs of admission from another hospital ICU, one Jehovah's Witness who refused blood transfusions, four patients who had incomplete or missing charts, and four patients who were already moribund at admission were excluded from further analysis. For another six patients who were readmitted to the medical ICU within 1 month after discharge, only the first admission was used for analysis. Three patients who were readmitted after, respectively, 1½, 3, and 5 months with a complication unrelated to their first admission were included in this cohort, yielding a total sample of 124 admissions for analysis. We reviewed the charts and the computerized hospital laboratory and the administrative database of this cohort and collected variables at admission and during ICU stay. Variables collected within 24 hrs of admission included age, sex, type of hematologic malignancy, disease status, type of recent chemotherapy or bone marrow transplantation, number of weeks since transplant, major reason for ICU admission, need for ventilation, use of vasopressors, use of a pulmonary artery catheter, and, if available, duration of leukopenia before admission. Laboratory data included white blood cell count, urea, creatinine, total bilirubin, prothrombin time, and Pao_2/Fio_2. Other laboratory variables and physiologic variables were collected only to calculate the severity of illness scores. Two severity of illness scores at admission, the Acute Physiology and Chronic Health Evaluation (APACHE) II and the Simplified Acute Physiology Scale (SAPS) II, were calculated for each patient using the appropriate formulas (31, 32). We used the most unfavorable values available for the first 24 hrs in the ICU. The Glasgow Coma Score was routinely available in patients with a serious neurologic disorder. All other patients were considered to have a normal mental state. Positive blood cultures drawn at <48 hrs before or at admission were also noted. Variables collected after admission included need for ventilation after 24 hrs, need for renal replacement therapy, duration of leukopenia, duration of ventilation, and length of stay. ICU, 30-day, and 6-month mortalities and total days of survival since ICU admission were also noted.

Definitions. The type of hematologic malignancy was categorized into high-grade malignancies, including acute myelogenous leukemia, acute lymphoblastic leukemia, and high-grade non-Hodgkin lymphoma, and into low-grade malignancies, including all other types of hematologic malignancies and aplastic anemia. Disease status was categorized into active or stable disease. Patients with a relapse or disease progression who needed or who received chemotherapy at least 4 wks before admission were categorized as having active disease. Hence, patients in stable partial remission were not considered to have active disease. Patients who received myeloablative therapy in the context of bone marrow or peripheral stem cell transplantation or who received >2 g cytosine arabinoside m^2 at least 4 wks before admission were defined as having received high-dose therapy. Leukopenia was defined as a total white blood cell count of $<1.0 \times 10^9$/L. Ventilation included noninvasive and invasive mechanical ventilation. The use of vasopressors was defined as any vasopressor or inotropic drug that was started within 24 hrs of admission. At our department, the use of vasopressors and inotropics is restricted to patients with hypotension not responding to a fluid challenge or to patients with proven cardiac failure on echocardiography or pulmonary artery catheterization and signs of organ failure (i.e., oliguria, renal failure, neurologic impairment, lactic acidosis). Oliguria was defined as a urinary output of <500 mL/24 hrs. Recent bacteremia was defined as at least two positive blood cultures for coagulase-negative *Staphylococci* or *Corynebacterium* species or at least one positive blood culture for other bacteria <48 hrs before admission or on the day of admission, with signs of sepsis.

Statistical Analysis. Values are expressed as mean ± SD, as median (interquartile range), or as percentage when appropriate. The major response variable used in the analyses was vital status (alive or dead) at hospital discharge. Both groups were compared by the Student's *t*-test or Mann-Whitney U, depending on the distribution for continuous variables and by the Fisher-exact test for categorical variables. Logistic regression analysis was used to assess the multivariate relationship between multiple patient characteristics and the probability of in-hospital mortality. For this analysis, each continuous laboratory variable was dichotomized by replacing it with an indicator of whether it was above or below its median value. For laboratory values in which the median fell between normal values, we used the upper normal laboratory value or a clinical relevant value (see "RESULTS") as a cutoff point. Stepwise forward and backward elimination regression procedures were used. Using the independent variables found by multiple regression analysis, we classified our population into different risk groups for survival analysis. Kaplan-Meier survival probabilities were compared by a log-rank test. To compare differences between groups, we used a one-way analysis of variance test or Kruskal-Wallis test for continuous variables, depending on the distribution, and a chi-square test for categorical variables. All reported *p* values are two-tailed. When appropriate, odds ratio (OR) and 95% confidence intervals (95% CI) are reported. All statistical analyses were carried out with SPSS 9.0 (SPSS Inc, Chicago, IL).

RESULTS

Patient Population. Of the 124 patients with a hematologic malignancy who were admitted to the ICU for a life-threatening complication, 68 (55%) were men and 56 (45%) women (Table 1). The median age was 56 (40–68) yrs. Sixty-one

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percent had a high-grade malignancy, and the majority of all 124 patients (73%) were in remission. Fifty-two patients (42%) received chemotherapy in the weeks before admission, and 44 patients (35%) were still leukopenic at admission. Thirty-seven of these patients (84%) had or developed a leukocyte count of $<0.5 \times 10^9$/L in the first days of ICU admission. Twenty-two patients (19%) received high-dose chemotherapy within 4 wks before admission, followed by allogeneic bone marrow or peripheral stem cell transplantation in nine of them. Mean duration of leukopenia before admission was 11.5 ± 6.5 days. Mean APACHE II and SAPS II scores at admission were 26 ± 7.7 and 53 ± 17.8, respectively. Table 2 summarizes the general categories of admission reasons to the medical ICU as noted on the charts and the observed mortalities in these subgroups. Respiratory failure (49 patients, 39.5%), sepsis (23, 18.5%), and neurologic impairment (21, 17%) were the most common, followed by cardiac failure (16, 12.9%), metabolic disorder (8, 6.5%), gastrointestinal bleeding (3, 2%), and cardiopulmonary resuscitation (3, 2%). Only one patient was admitted to the medical ICU postoperatively after resection of a pulmonary aspergilloma. It is important to note that most patients had a combination of admission reasons. Of the 124 patients, 88 (71%) needed ventilation. Six of them were not intubated because of a written do-not-resuscitate order, 55 (66%) were ventilated within 24 hrs of admission, and 30 (44%) were ventilated after 24 hrs. Noninvasive ventilation was started in 16 patients (18%) and was successful in six. Median duration of ventilation was 6 (3–17) days. Fifty-seven patients (46%) received vasopressors at admission, and 33 (26.6%) needed renal replacement therapy during their ICU stay. A pulmonary artery catheter was placed in 36 patients (29%) within 24 hrs of admission. Oliguria was seen in 20 patients (16%). Twenty-seven patients (21.8%) had a recent bacteremia. Fifteen (55.6%) of them had a Gram-positive bacteremia, nine (33.3%) a Gram-negative bacteremia, and three (11.1%) a polymicrobial bacteremia.

Outcome. The overall in-hospital mortality was 54% (67 deaths); fifty-two patients (42%) died in the ICU, ten patients died shortly after ICU discharge, and another five patients died within 3 wks after ICU discharge. Three of the 57 survivors were readmitted to the medical ICU after, respectively, 1½, 3, and 5 months with a

Table 1. Patients' characteristics at admission (n = 124)

	Patients	
	No.	Percentage
Demographics		
Age, yr, median (interquartile range)	56 (40–68)	
Sex, male	68	55
Severity of illness		
APACHE II score	26 ± 7.7	
SAPS II score	53 ± 17.8	
Type of hematologic malignancy		
High-grade malignancy	76	61
Acute myelogenous leukemia	35	28
Acute lymphoblastic leukemia	14	11
High-grade NHL	27	22
Low grade malignancy/chronic disease	48	39
Chronic myelogenous leukemia	2	2
Chronic lymphocytic leukemia/low-grade NHL	10	8
Hodgkin disease	8	6
Multiple myeloma	19	15
Myelodysplastic syndrome	4	3
Myelofibrosis with myeloid metaplasia	2	2
Aplastic anemia	3	2
Disease status		
Recently diagnosed	35	28
Complete remission	28	23
Partial remission	32	26
Chronic disease	29	23
Relapse/active disease	34	27
Therapy-related characteristics		
Leukopenia at admission	44	36
Recent high-dose therapy	23	19
Allogeneic-BMT/PBSCT	22	18
<30 days	9	7
30–90 days	3	2
>90 days	10	8

APACHE, Acute Physiology and Chronic Health Evaluation; SAPS, Simplified Acute Physiology Scale; NHL, non-Hodgkin lymphoma; BMT, bone marrow transplantation; PBSCT, peripheral blood stem cell transplantation.

Table 2. Major reasons for admission to the medical intensive care unit

	No. (%) of Deaths Per Total in Subgroups
Respiratory failure	29/49 (59.1)
Pneumonia	13/21
ARDS/interstitial pneumonitis	15/25
Pulmonary hemorrhage	1/1
Pulmonary embolus	0/1
Airway obstruction	0/1
Sepsis	9/23 (39.1)
Neurologic disease	7/21 (33.3)
Metabolic encephalopathy	0/3
Seizures	0/4
Meningitis/cerebritis	1/5
Malignancy	1/3
Intracerebral hemorrhage	3/4
Cerebral infarction	2/2
Congestive heart failure	13/16 (81.2)
Metabolic impairment	3/8 (37.5)
Diabetic ketoacidosis	0/2
Hypoglycemia	0/1
Hypercalcemia	0/2
Hepatic failure	1/1
Malignant lactic acidosis	1/1
Transplant-related TTP	1/1
Gastrointestinal hemorrhage	3/3 (100)
Cardiopulmonary resuscitation	3/3 (100)
Postoperative admission	0/1 (0)

ARDS, acute respiratory distress syndrome; TTP, thrombotic thrombocytopenic purpura.

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complication unrelated to their first admission. All of these three patients were long-term survivors. Fifteen additional patients died during the 6-month follow-up period, which constitutes an overall 6-month mortality of 66%. The median length of stay in the ICU was 7 (3–15) days. A do-not-resuscitate order was written in 25 patients (20.2%) at a median stay of 7 (2–11.5) days into their ICU course. Five do-not-resuscitate orders (4%) were written within 24 hrs of admission. Among the subgroups, the ICU, in-hospital, and 6-month mortality rates were 59%, 69%, and 79%, respectively, in ventilated patients and 50%, 66%, and 73% in leukopenic patients.

Prognostic Indicators of Outcome. Survivors had a lower APACHE II and SAPS II scores (22 ± 5.9 and 43 ± 13.2, respectively) compared with nonsurvivors (29 ± 7.4 and 60 ± 16.7, respectively; $p < .001$ for both). There was no difference in age or in length of stay between the two groups. Because we were interested in groups of patients, all continuous laboratory variables were dichotomized by replacing them with indicators of whether they were above or below their median value. Because the median of bilirubin and prothrombin time fell between the normal laboratory values, the cutoff point of bilirubin was adjusted to a clinically significant value of 2 mg/dL (>34 μmol/L, to exclude a clinically insignificant rise in indirect serum bilirubin due to Gilbert disease or posttransfusion hemolysis), and the prothrombin time was adjusted to <50% (>15 secs). Among all categorical variables recorded, the following seemed to be significant prognostic factors related to the in-hospital mortality in an univariate analysis (Table 3): ventilation (OR, 3.2; 95% CI, 1.5–6.7), use of vasopressors (OR, 3.5; 95% CI, 1.6–7.4), urea > 0.75 g/L (12 mmol/L; OR, 7.4; 95% CI, 3.3–15.6), creatinine > 1.2 mg/dL (>106 μmol/L; OR, 2.3; 95% CI, 1.1–4.8), oliguria (no survivor), bilirubin > 2 mg/dL (>34 μmol/L; OR, 3.46; 95% CI, 1.4–8.2), and a prothrombin time <50% (>15 secs; OR, 4.3; 95% CI, 1.8–10.2) for factors at admission. There was only a trend to a statistically significant higher mortality in leukopenic patients (OR, 2.14; 95% CI, 1–4.6). Need for ventilation (OR, 7.6; 95% CI, 3.1–18.8) and renal replacement therapy (OR, 10.1; 95% CI, 3.2–31.2) during admission were also significant prognostic indicators. The result of the multivariable logistic regression analysis based on all variables recorded at admission and bacteremia are listed in Table 4. Because no patient with oliguria survived, this variable was not included in the multivariable analysis to avoid unstable model fits. Only four variables were independently associated with outcome: leukopenia (OR, 2.9; 95% CI, 1.1–7.7), vasopressors (OR, 3.7; 95% CI, 1.4–9.8), and urea > 0.75 g/L (>12 mmol/L; OR, 9.4; 95% CI, 3.6 - 24.4) were

Table 3. Number and percentage of patients who lived and who died by level of categoric variables (n = 124)

Variables	Lived, n (%)	Died, n (%)	p Value
Factors at admission			
Sex			
Male	27 (39.7)	41 (60.3)	.15
Female	30 (53.6)	26 (46.4)	
Age >55 yrs			
Yes	26 (40.6)	38 (59.4)	.28
No	31 (51.6)	29 (48.4)	
High-grade malignancy			
Yes	35 (46)	41 (54)	.99
No	22 (45.8)	26 (54.2)	
Active disease			
Yes	13 (38.2)	21 (61.8)	.32
No	44 (48.8)	46 (51.2)	
Recent high-dose therapy			
Yes	6 (27.2)	16 (72.8)	.06
No	51 (50)	51 (50)	
Bone marrow transplantation			
Yes	8 (36.4)	14 (63.6)	.35
No	49 (48)	53 (52)	
Leukopenia at admission			
Yes	15 (34.1)	29 (65.9)	.06
No	42 (52.5)	38 (47.5)	
Ventilation			
Yes	18 (31)	40 (69)	.002
No	39 (59)	27 (41)	
Pa_{O_2}/F_{IO_2} <170			
Yes	24 (39.3)	37 (60.7)	.15
No	33 (52.4)	30 (47.6)	
Use of vasopressor			
Yes	17 (29.8)	40 (70.2)	.001
No	40 (59.7)	27 (40.3)	
Oliguria			
Yes	0 (0)	20 (100)	<.001
No	57 (54.8)	47 (45.2)	
Urea of >12 mmol/L			
Yes	13 (22)	46 (78)	<.001
No	44 (67.6)	21 (32.4)	
Creatinine of >160 μmol/L			
Yes	23 (35.9)	41 (64.1)	.03
No	34 (56.6)	26 (43.4)	
Bilirubin of >34 μmol/L[a]			
Yes	9 (25)	27 (75)	.003
No	45 (53.6)	39 (46.4)	
Prothrombin time, <50%			
Yes	9 (23.1)	30 (66.9)	
No	48 (56.4)	37 (43.6)	.001
Positive blood culture			
Yes	17 (62.9)	10 (36.1)	
No	40 (41.2)	57 (58.8)	.052
Factors during admission			
Ventilation			
Yes	28 (32.2)	59 (67.8)	
No	29 (78.4)	8 (21.6)	<.001
Renal replacement therapy			
Yes	4 (12.1)	29 (87.9)	
No	53 (58.2)	38 (41.8)	<.001
Leukopenia during admission			
Yes	19 (38)	31 (62)	
No	38 (51.3)	36 (48.7)	.2

[a]Bilirubin at admission was not determined in four patients.

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Table 4. Results from stepwise logistic regression analysis for probability of in-hospital mortality

Variable	Variables in the Equation				
	Coefficient	SE	*p* Value	OR	95% CI
Leukopenia	1.070	0.5	.032	2.9	1.1–7.8
Vasopressor need	1.319	0.5	.008	3.7	1.4–9.8
Urea of >12 mmol/L	2.236	0.48	<.001	9.4	3.6–24.4
Bacteremia	−1.787	0.64	.005	0.2	0.05–0.6

OR, odds ratio; CI, confidence interval.
Goodness-of-fit test, chi-square = 9.4, $df = 7$, $p = .216$.

associated with an increased risk of death, whereas recent bacteremia (OR, 0.2; 95% CI, 0.05–0.6) was associated with a lower one. The area under the receiver operating characteristic curve and the goodness-of-fit chi-square statistics were 0.83 (SE = 0.038) and 9.4, $df = 7$, $p = .216$ for our model, 0.712 (SE = 0.043), 5.12, $df = 5$, $p = .39$ for the APACHE II score, and 0.765 (SE = 0.043) and 3.63, $df = 5$, $p = .6$, respectively, for the SAPS II score. Among the subpopulation of ventilated patients, the duration of ventilation, 5.5 (3–18.7) days vs. 6 (3–15) days, respectively ($p = .72$), and the PaO_2/FIO_2, 204 (97.7–387) vs. 134 (82.5–275.2), respectively ($p = .054$), were not significantly different between survivors and nonsurvivors. Among the leukopenic patients, neither the duration of leukopenia before admission, 8.3 ± 7.3 vs. 12.7 ± 8.9 days ($p = .13$), or the duration of leukopenia during admission, 2.5 (1–4.2) vs. 5 (2–7.7) days ($p = .11$), were significantly different between survivors and nonsurvivors.

Urea as the Most Important Predictor of Adverse Outcome. As urea of >0.75 g/L (12 mmol/L) proved the most important independent predictor of outcome in our cohort, we searched for factors associated with a high urea. Patients with a high urea had more frequently active disease (40.6% vs. 15.3%, $p < .001$), had more frequently undergone an allogeneic bone marrow transplantation (28.8% vs. 0.07%, $p = .004$), were more frequently ventilated within 24 hrs of admission (57.6% vs. 36.9%, $p = .03$) but not during admission (72.8% vs. 67.7%, $p = .33$), more frequently needed vasopressors (59.3% vs. 33.8%, $p = .007$), and had serum creatinine levels more frequently >1.2 mg/dL (>106 μmol/L; 84.7% vs. 21.3%, $p < .001$), serum bilirubin of >2 mg/dL (> 34 μmol/L, 46.5% vs. 14.5%, $p < .001$), and a prothrombin time <50% (>15 secs, 49.1% vs. 15.4%, $p < .001$) compared with patients with low urea. The results of the logistic regression analysis of the association of possible risk factors with a high urea, including all variables except oliguria, are listed in Table 5.

Bacteremia as a Predictor of Favorable Outcome. Because we did not expect bacteremia to be related to better outcome, we further analyzed the differences between patients with a Gram-positive (n = 15), Gram-negative, or polymicrobial bacteremia (n = 12) and patients without proven bacteremia (n = 97). Because of the limited number of patients, these results should be interpreted with caution. Although patients with a Gram-positive bacteremia had a significantly lower mortality compared with the two other groups (20% vs. 58.3% and 59%, respectively, $p = .02$), we found no significant difference in severity of illness according to the APACHE II (27 vs. 30 and 25, $p = .16$) and SAPS II (52 vs. 64 and 52, $p = .11$) scores, nor did we find a difference in the proportion of patients ventilated at admission (60% vs. 50% and 44.3%, $p = .51$) or during admission (80% vs. 66.6% and 69%, $p = .66$) among these three groups. However, patients with Gram-negative bacteremia were more likely to have a high-grade malignancy (33.3% vs. 83.3% vs. 62.8%, $p = .02$), to be leukopenic at admission (6.6% vs. 75% vs. 35%, $p = .005$), and to need vasopressors (53.3% vs. 83.3% vs. 40.2%, $p = .02$) compared with the two other groups.

Risk Stratification and Survival Analysis. Using the early predictors of outcome found by multivariate analysis, we arbitrarily categorized our population into three groups for survival analysis. The survival analysis was based on 121 patients because three readmissions were excluded. Patients with a urea of <0.75 g/L (<12 mmol/L) with or without either leucopenia or vasopressors were categorized into group I (low-risk group, n = 60), patients with a urea of >0.75 g/L (>12 mmol/L) or with a combination of vasopressors and leukopenia were categorized into group II (intermediate-risk group, n = 34), and patients with urea of >0.75 g/L (>12 mmol/L) in combination with leukopenia or vasopressors were categorized into group III (high-risk group, n = 27). Patients who had a bacteremia prompting ICU admission were allocated to a one-step-lower risk group. For example, a patient with all risk factors and bacteremia was categorized into group II instead of group III. Survival analysis on the basis of this risk stratification is shown in Figure 1.

Cumulative probabilities of survival at 30 days and 6 months were 75% and 55% in group I, 35% and 21% in group II and, 4% and 0%, respectively, in group III ($p < .001$). Only one patient in group III with refractory lymphoblastic leukemia admitted to the ICU with an interstitial pneumonitis to start noninvasive ventilation in case of deterioration (do-not-intubate order) could be discharged from the hospital, but the patient died 60 days later of refractory disease. For a better understanding of the difference in mortality between the three groups, we further analyzed the differences between these groups for variables at admission not included in the logistic regression analysis and variables during admission. The APACHE II scores (23, 27, and 32, respectively in group I, II, and III) and SAPS II scores (47, 54, and 67, respectively) were significantly different between groups ($p < .001$). Patients with a neurologic impairment were more likely to be categorized in group I than in the two other groups (28.3% vs. 5.9% and 7.4%, $p = .005$). We found no significant difference in the proportion of patients ventilated during admission among the three groups (60%, 68%, and 81%, $p = .14$); however, patients in group I were less frequently ventilated at admission than patients in the two other groups (25% vs. 44% and 68%, $p = .001$). Although we found no difference in duration of ventilation between the three groups ($p = .53$), ventilated patients categorized in group I had a significantly lower mortality compared with the two other groups (37.8% vs. 87% and 100%, $p = .001$). Furthermore, as expected by the results of the logistic regression analysis performed on urea, patients in group III had more frequently active disease (16.7% and 29.4% vs. 48.1%, $p = .009$) and were more frequently in severe septic shock and multiple organ failure compared with patients in group I and II. In

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Table 5. Results from stepwise logistic regression analysis for factors predicting urea of >12 mmol/L

Variable	Variables in the Equation				
	Coefficient	SE	*p* Value	OR	95% CI
Active disease	2.249	0.72	.002	9.5	2.3–38.8
Ventilation at admission	1.407	0.57	.014	4.1	1.3–12.5
Creatinine, >106 μmol/L	3.542	0.64	<.001	34.5	9.9–120
Bilirubin, >34 μmol/L	1.722	0.64	.007	5.6	1.6–19.8

OR, odds ratio; CI, confidence interval.

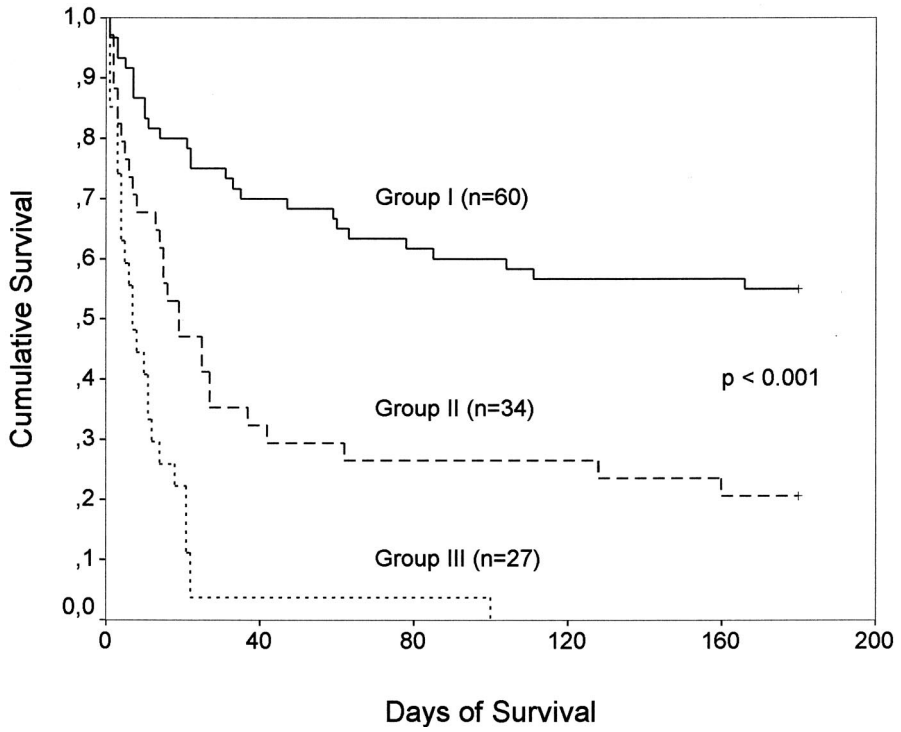

Figure 1. Risk stratification and survival analysis. Group I are patients with a low urea (<12 mmol/L) with or without either leucopenia or vasopressor need. Group II are patients with a high urea (>12 mmol/L) or combination of leukopenia and vasopressors. Group III are patients with a high urea in combination with leukopenia or use of vasopressors. Patients with bacteremia prompting intensive care unit admission are allocated to a one-step lower risk group.

this group, there was a higher proportion of patients with severe acute renal failure at admission (oliguria, 1.7% and 20.6% vs. 40.7%, $p < .001$) and need for renal replacement therapy during admission. (6.7% and 44.1% vs. 48.1%, $p < .001$).

DISCUSSION

In this study of 124 patients with a hematologic malignancy who were admitted to the ICU for a life-threatening complication, crude ICU and in-hospital mortality rates were 42% and 54%, respectively, which is comparable with the mortality rates reported in two recently published series (12, 34). However, although it is difficult to compare outcomes between series, our patient population was probably more severely ill compared with the subpopulation of patients with a hematologic malignancy in the study by Staudinger et al. (12), as suggested by the higher prevalence of ventilation, use of vasopressors, and need for renal replacement therapy during ICU stay and the longer duration of ventilation and length of stay. Considering the low number of do-not-resuscitate orders within 24 hrs of admission and the absence of influence of active disease on mortality in our study, we must conclude that this relatively good outcome must in part be attributed to a good selection of patients who could benefit from ICU admission. Only patients who had a potential long-term survival or treatable relapse were admitted to the ICU. This may have influenced the long-term outcome and also the short-term outcome by stimulating the physicians and nurses to treat this patient population as other critically ill patients without a hematologic malignancy. By this admission policy and by giving advanced and prolonged supportive care to these patients, we achieved a 6-month survival of 34%, which is considerably better than the 6-month survival of 20% observed in a general ICU population with acute renal failure who needed renal replacement therapy at our center (35). In these conditions and because the mortality rates in our population are comparable with other critically ill nonhematologic cancer patients (36–38), general reluctance to admit patients with hematologic malignancy to the ICU, even with serious critical illness, is unjustified. However, using logistic regression analysis, we identified four simple and readily available early predictors of outcome that may be of value in deciding in which patients prolonged intensive care support might not be given. Leukopenia, use of vasopressors, and urea of >0.75 g/L (>12 mmol/L) at admission were associated with poor outcome, whereas recent bacteremia was associated with better survival.

The importance of leukopenia as a risk factor for mortality in critically ill patients with a hematologic malignancy is controversial. Many studies have reported a higher mortality in patients with (prolonged) leukopenia (3, 6, 7, 11, 13), especially when mechanical ventilation is required; however, this has not been confirmed by other studies (5, 8, 14, 17, 34). In our analysis, leukopenia at admission, which was in most cases chemotherapy-related, was an independent risk factor for adverse outcome. However, as previously reported (5, 8, 27), the higher mortality in this subgroup of patients was not related to the duration of leukopenia before or during admission. In fact, three of five patients who were leukopenic for over 10 days during admission survived to discharge; all were alive at 6 months. Whether the higher risk of death in this subpopulation may only be attributed to a higher susceptibility for Gram-negative or fungal infection or to concomitant chemotherapy-induced organ toxicity remains to be evaluated in future studies.

Urea has been found of particular interest as a short-term and long-term predictor of outcome in several patient populations (39, 40) and is included in

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various severity of illness scores (32–34). Urea of >0.75 g/L (>12 mmol/L) was the most significant and most powerful independent predictor of adverse outcome in our cohort. Hospital mortality rates in patients with a low urea compared with those with a high urea were, respectively, 32.4% and 78% in the global population ($p < .001$), 44% and 91% in ventilated patients ($p < .001$), 43.4% and 90.5% in leukopenic patients ($p = .001$), and 40.9% and 80% in patients receiving vasopressors ($p = .003$). Patients with a high urea, especially in combination with vasopressor need or leucopenia, had a particularly grim prognosis because they were more likely to have severe septic shock, multiple organ failure, and to need ventilation or renal replacement therapy compared with patients with a low urea. In a logistic regression analysis, ventilation, creatinine of >1.2 mg/dL (>106 μmol/L), and bilirubin of >2 mg/dL (>34 μmol/L) at admission and active disease were independently associated with a high urea. So, it seems that in patients with a hematologic malignancy admitted to the ICU, urea of >0.75 g/L (>12 mmol/L) at admission should be regarded as a potential marker of serious critical illness or multiple organ failure. This explains the high mortality found in patients with a high urea. As reported in several previous studies, multiple organ failure (6–10, 15, 19, 25–28) and combined need for ventilation and renal replacement therapy (8, 11, 12, 26, 28) have a profound adverse effect on survival in hemato-oncologic patients. However, because we cannot exclude that other factors such as nephrotoxic drugs or use of corticosteroids had an influence on urea and subsequently on mortality and because the analysis of urea was not one of our end points in this cohort, factors influencing urea and the value of urea as a potential predictor of long-term outcome with respect to its relationship to active disease should be evaluated in future studies.

Another striking finding of our study was that bacteremia was associated with a better outcome. This is in contrast with the majority of previous reports in which infection is always considered as the most important direct or indirect cause of mortality in patients with a hematologic malignancy admitted to the ICU. However, the majority of these studies lacks the use of definition for infection or considered every pulmonary infiltrate as potentially infectious (3–5, 7, 8, 18, 24). Other authors did not differentiate bacterial infections from potentially more lethal infections such as invasive pulmonary aspergillosis or cytomegalovirus infection (3–5, 7, 8, 18, 24, 28), did not consider the time between the occurrence of infection and ICU admission (3–5, 7, 15, 18, 24, 28), or did not assess the relationship between infection and mortality (3–5, 7, 8, 13–16, 28). In immunocompromised patients, it is often difficult to distinguish between infectious and noninfectious pulmonary infiltrates (41), and the diagnosis of infection and especially of pneumonia is too often based on doubtful clinical or radiologic considerations (9, 27, 41). Because the exact cause of respiratory failure or pneumonia is often difficult to establish retrospectively, we used bacteremia as the most reliable sign of bacterial infection. Moreover, we only considered positive blood cultures at admission or <48 hrs before admission. By doing so, we selected a patient population with a clear documented and treatable bacterial infection on one hand and with a low probability of potentially more life-threatening infectious or noninfectious concomitant complication such as invasive pulmonary aspergillosis, viral pneumonitis, chemotherapy-induced cardiac or pulmonary injury, or intracerebral bleeding prompting ICU admission on the other hand. Several reports have shown a beneficial effect of the documentation of an infection on outcome. Reyes et al. (42) showed that mortality in a general ICU population was higher in septic shock patients without a clinically identifiable source of infection compared with those with an identified source of infection. This was recently confirmed by Hilbert et al. (43) in an immunosuppressed patient population with respiratory failure. In this study, hospital mortality rates in patients with documented pulmonary infection compared with those without documented infection were 29% and 89% ($p = .006$) in patients treated with noninvasive ventilation and 71% and 92%, respectively ($p = .21$), in patients who were intubated. As we considered only positive blood cultures at admission or <48 hrs before admission, we also potentially selected a population of patients who were referred to the ICU early in the evolution of their critical illness. We may then speculate that due to advanced ICU management, this patient subgroup did not develop intractable organ failure or had a more rapidly reversible multiple organ failure and therefore had a lower mortality compared with patients without bacteremia. As expected, the better outcome in patients with bacteremia in our study could mainly be attributed to a lower observed mortality in Gram-positive bacteremia compared with Gram-negative (and polymicrobial) bacteremia. However, the lower mortality in this group could not be explained by a high proportion of relatively minor Gram-positive infections, such as uncomplicated catheter-related bacteremia, as only 5 of 15 patients had coagulase-negative staphylococcal sepsis (data not shown). Moreover, four of these five patients were in shock and needed vasopressors at admission. From our data, it is unclear whether the higher mortality in patients with Gram-negative bacteremia was due to an intrinsic higher fatality rate as reported in *Pseudomonas* bacteremia (44) or to the higher proportion of leukopenia and use of vasopressors, two variables independently associated with mortality in this subgroup of patients. It is also unclear whether this finding can be extrapolated to all documented bacterial infections.

In accordance with previous studies, ventilation at admission had a profound adverse effect on outcome (1–4, 6–12, 25, 27, 28, 34). However, our data indicate that once urea is higher than 0.75 g/L (>12 mmol/L) at admission, the risk for fatal outcome is high regardless of the need for ventilation. Only when the whole population of patients ventilated at and during admission was considered, ventilation became independently related to outcome without excluding urea of >0.75 g/L from the model (data not shown). This is not surprising because we can expect that the majority of deteriorating patients are ventilated despite a grim prognosis. As previously reported (8, 14, 17, 23, 24), duration of ventilation was not predictive of hospital mortality in our study. In fact, six out of ten patients ventilated for >20 days survived to discharge, and five were still alive at 6 months.

Using the four independent predictors of outcome, we identified a subgroup of patients with particularly poor prognosis in whom advanced or prolonged life support must be questioned. Of the 39 patients with an urea of >0.75 g/L (>12 mmol/L) in combination with leukopenia or the use of vasopressors at admission, 4 of 12 patients (30%) with bacteremia survived to hospital discharge compared with only 1 of 27 patients (4%) without

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bacteremia ($p = .024$). Although the survival probability in this latter group was only 4% at 30 days, we do not think that these patients should not be offered advanced ICU support, at least for a limited time period to assess early evolution, because of the following reasons. First, we only treated a limited number of patients in this subgroup. Second, the prognosis of patients with a hematologic malignancy who are admitted to the ICU is improving over time. Rubenfeld et al. (26) found an increase in survival rate from 5% to 16% in the period between 1988 and 1992 in patients who had undergone an allogeneic bone marrow transplantation and who required mechanical ventilation. Azoulay et al. (45) found a ten-fold lower risk for death in patients with multiple myeloma who required ICU support between 1996 and 1998 as compared with the period between 1992 and 1995 and a four-fold lower risk for death in cancer patients who required mechanical ventilation between 1996 and 1998 as compared with 1990–1995 (46). These improvements in outcome could only be explained by an improvement in therapeutic strategies and supportive care. Third, recent advances in transplantation procedures such as the introduction of peripheral stem cell transplantation (28) and in ICU support with the use of noninvasive ventilation (43, 46) seem promising to further improve the survival of patients with a hematologic malignancy admitted to the ICU. Finally, as the microbiological examinations are rarely available within the first 24 hrs of admission and as differentiating between bacterial, nonbacterial, and noninfectious complication in immunocompromised patients is frequently difficult, supporting these patients for a limited time period enables one to assess the effect of antibiotic or other therapeutic strategies and to assess the reason that precipitated ICU admission. Therefore, even patients with all adverse risk factors should be offered advanced ICU support for a limited time period to avoid compromising the chances of potential survivors. Nevertheless, these risk factors can be used to inform the relatives about the severity of illness and their chances for recovery and to help to identify patients in whom prolonged advanced supportive therapy seems futile.

As we had only a limited number of patients from a single center, it was not our intention to make a scoring system with a high accuracy by fitting the variables to our study sample but simply to identify, early in the evolution of their critical illness, patients likely to do poorly. Despite this fact, our prognostic indicators were superior to the APACHE II and SAPS II in discriminating survivors from nonsurvivors. This again confirms the limited use of these scoring system for the assessment of prognosis in critically ill patients with a hematologic malignancy (12, 21, 25, 26) and the need for developing a new scoring system that is specifically designed for this population and that can easily be used at bedside.

Our study has several limitations. First, it is a retrospective analysis, and therefore, we cannot exclude that some variables are incorrect. To minimize the effect of this potential bias, we focused on laboratory variables collected from a computerized database and used a minimum of definitions for organ failures. Moreover, neither etiologic diagnosis nor scoring systems were used for the assessment of prognostic indicators. Second, it is important to note that the prognostic indicators are based on variables collected within 24 hrs of admission (with the exception of blood cultures, which were taken <48 hrs before or at admission) and that none of the patients who were admitted to ICU during the study period received renal replacement therapy before admission. Therefore, these prognostic indicators should be applied cautiously in other settings. Third, as we do not know when the positive cultures were known to the clinician, we cannot exclude that patients who had positive blood cultures within 24–48 hrs of admission were more likely to receive antibiotics to which the bacteria was sensitive than patients who did not have early positive blood cultures. However, as usual in immunocompromised patients and according to international guidelines, all patients with a presumed bacterial infection were treated with empirical, broad-spectrum antibiotic therapy, which was started at the ward or at admission. Subsequently, positive (blood) cultures were used to narrow the antibiotic coverage rather than to extend it. Therefore, it seems unlikely that the initial antibiotic treatment was less adequate in patients without (proven) bacteremia and that this was responsible for the higher mortality observed in this subgroup of patients. Finally, as it is a single-center study, we cannot exclude a selection bias due to admission and do-not-resuscitate order policy or treatment strategies. Therefore, our prognostic indicators need to be validated in a prospective multicenter study. Nevertheless, our results clearly show that the general reluctance to admit patients with a hematologic malignancy to the ICU, even with severe critical illness, is unjustified and that advanced ICU support for a prolonged period of time should be offered to patients with a clear bacterial infection precipitating ICU admission.

Our results clearly show that the general reluctance to admit patients with a hematologic malignancy to the intensive care unit, even with severe critical illness, is unjustified and that advanced intensive care unit support for a prolonged period of time should be offered to patients with a clear bacterial infection precipitating intensive care unit admission.

ACKNOWLEDGMENTS

We thank Dr. Luc Noens, Dr. Fritz Offner, and Dr. Ann Janssens, Department of Hematology, for the excellent collaboration and the trust they gave us in our taking care of their patients, Dr. Dirk Vogelaers, Department of Infectious Diseases, for his critical review of the manuscript, and George Van Maele, Department of Medical Informatics and Statistics, for his advice in the statistical analysis.

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