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ORIGINAL REPORT

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

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ABSTRACT

Purpose
Patients with hematologic malignancies are increasingly admitted to the intensive care unit (ICU) when life-threatening events occur. We sought to report outcomes and prognostic factors in these patients.

Patients and Methods
Ours was a prospective, multicenter cohort study of critically ill patients with hematologic malignancies. Health-related quality of life (HRQOL) and disease status were collected after 3 to 6 months.

Results
Of the 1,011 patients, 38.2% had newly diagnosed malignancies, 23.1% were in remission, and 24.9% had received hematopoietic stem-cell transplantations (HSCT, including 145 allogeneic). ICU admission was mostly required for acute respiratory failure (62.5%) and/or shock (42.3%). On day1, 733 patients (72.5%) received life-supporting interventions. Hospital, day-90, and 1-year survival rates were 60.7%, 52.5%, and 43.3%, respectively. By multivariate analysis, cancer remission and time to ICU admission less than 24 hours were associated with better hospital survival. Poor performance status, Charlson comorbidity index, allogeneic HSCT, organ dysfunction score, cardiac arrest, acute respiratory failure, malignant organ infiltration, and invasive aspergillosis were associated with higher hospital mortality. Mechanical ventilation (47.9% of patients), vasoactive drugs (51.2%), and dialysis (25.9%) were associated with mortality rates of 60.5%, 57.5%, and 59.2%, respectively. On day 90, 80% of survivors had no HRQOL alterations (physical and mental health similar to that of the overall cancer population). After 6 months, 80% of survivors had no change in treatment intensity compared with similar patients not admitted to the ICU, and 80% were in remission.

Conclusion
Critically ill patients with hematologic malignancies have good survival, disease control, and post-ICU HRQOL. Earlier ICU admission is associated with better survival.

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INTRODUCTION

Cancer is a leading cause of death in North America and Europe.[1,2] Hematologic malignancies account for 20% of cancer diagnoses, with about 900,000 patients diagnosed in 2008 worldwide, a number similar to that of patients with prostate cancer.[1,2]

Over the last two decades, patients with hematologic malignancies have benefitted considerably from therapeutic advances.[3-7] As a result, a growing number of people are living with active hematologic malignancies.[1,7,8] These patients are at risk for life-threatening acute illness as a result of infection,[9] toxicity of intensive treatments[10,11] and targeted therapies,[3,12] and decompensation of comorbid conditions.[13] Reluctance to admit patients with hematologic malignancies and life-threatening acute events is eroding[14,15] as evidence accumulates that outcomes are not influenced by a need for intensive care unit (ICU) admission[16] and that ICU mortality rates have declined significantly over the last two decades.[17-19]

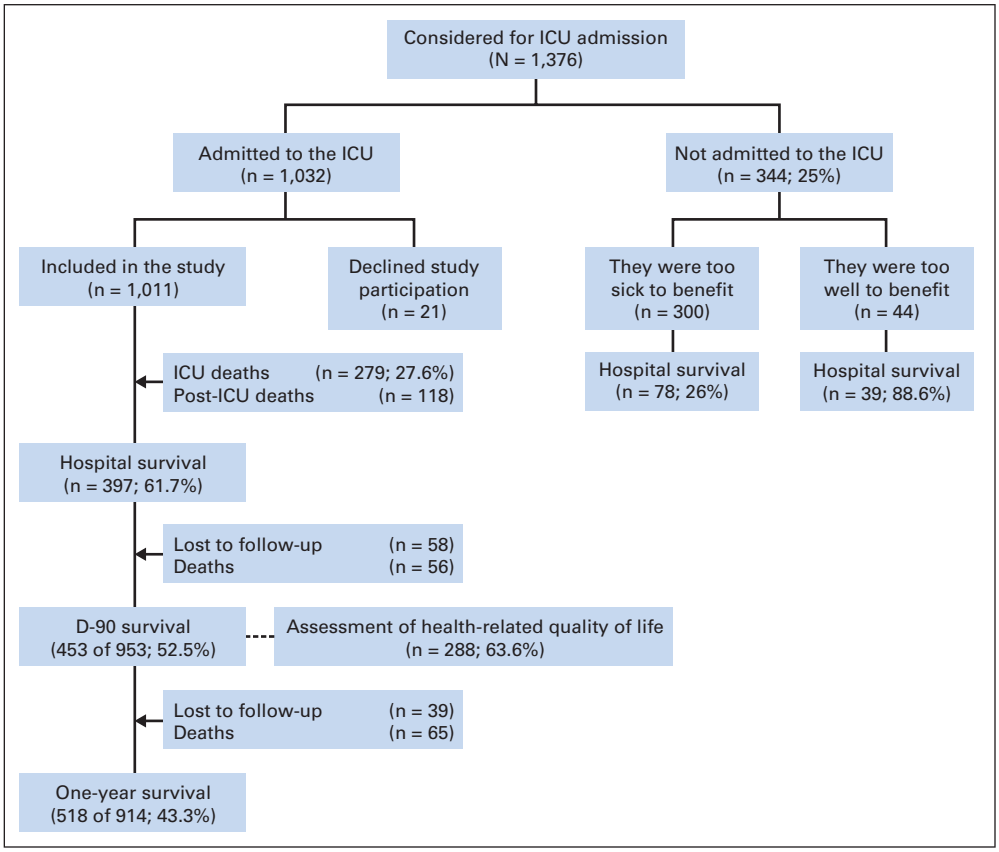

Fig 1. Patient flow diagram. D-90, day 90; ICU, intensive care unit.

Outcomes in critically ill hematology patients have been assessed in several studies. However, most of these studies were either retrospective,[17,19-21] mixed patients with hematologic malignancies and solid tumors, or focused on specific complications such as acute respiratory failure, kidney injury, or septic shock.[21-23] Furthermore, most of these studies included patients admitted to the ICU up to 15 years ago[24] and therefore did not reflect recent improvements in the management of acute respiratory failure,[25,26] kidney injury,[23] tumor lysis syndrome,[27,28] sepsis,[29] and septic shock.[19,21] Also, the recent broadening of ICU admission policies for hematology patients, which helps explain the increased number of admitted patients[14,15,30,31] and would result in earlier ICU admissions,[32] may have translated into changes in outcomes that need to be clarified. Mortality according to time in the ICU at initiation of life-supporting interventions[22] and mortality according to the number of days spent with a given life-supporting intervention need to be assessed in a large cohort of patients managed in different ICUs. Finally, most studies reported ICU or hospital mortality rates[20,22,33,34] but obtained no information on outcomes several months after ICU discharge, particularly regarding maintenance of cancer chemotherapy, disease control, and quality of life.

To address these issues with the goal of obtaining data for guiding therapeutic decisions, we performed a prospective, observational cohort study in 17 centers in France and Belgium. Only patients with hematologic malignancies managed in 2010 to 2011 were studied. In all 17 centers, patients were managed jointly by hematologists and intensivists. ICU patients received follow-up for 1 year after ICU discharge, with a telephone interview to assess health-related quality of life (HRQOL) and disease status.

PATIENTS AND METHODS

The study was approved by the appropriate ethics committees in France and Belgium. All patients or relatives were informed and consented to participate in the study. The study was carried out in 17 university or university-affiliated centers in France and Belgium that belonged to a research network instituted in 2005.[25] In all 17 centers, a senior intensivist and a senior hematologist are available around the clock and make ICU-admission decisions together.

From January, 1, 2010, to May, 1, 2011, consecutive patients having hematologic malignancies who were admitted to the participating ICUs for any reason were included. Exclusion criteria were complete cure of the malignancy for more than 5 years, ICU admission only to maximize safety of a procedure, and age younger than 18 years. In each center, an investigator used a standardized electronic case-report form to collect the study data. Data were also collected on patients with hematologic malignancies who were refused ICU admission (Fig 1). In each center, we reported the ICU refusal rate (number of patients considered for ICU admission but not admitted/number of patients admitted to the ICU throughout the study period).

Ninety days after ICU discharge, HRQOL was assessed by asking the patients to complete the short-form 36 questionnaire (SF-36)[35,36] during a telephone interview by a trained social worker. Results were compared with cancer patients who were not admitted to the ICU.[37] Six months after ICU discharge, the hematologists in charge of the patients were asked whether the ICU admission changed the patient's therapeutic intensity (compared with the standard optimal chemotherapy treatment protocol for the relevant disease, stage, and comorbidity profile) and disease status.

The data in the tables and figures were collected prospectively. Newly diagnosed malignancies were defined as diagnosed within the past 4 weeks. The Sepsis-Related Organ Failure Assessment (SOFA) score was computed at admission then daily throughout the patient's stay in the ICU[38]; this score provides an estimate of the risk of death based on organ dysfunction. The performance status[23] and Charlson comorbidity index were determined at ICU admission.[39] Both leukemia and lymphoma are already part of the Charlson index. Reasons for ICU admission were recorded based on the main symptoms at ICU admission. Acute respiratory failure was defined as oxygen saturation less than 90% or PaO_2 less than 60 mmHg on room air combined with severe dyspnea at rest with an inability to speak in sentences or a respiratory rate greater than 30 breaths per minute or clinical signs of respiratory distress.[25] Shock was defined as previously reported.[21] Life-supporting interventions, anti-infectious agents, prophylactic treatments, urate oxidase use, and diagnostic procedures were administered at the discretion of the attending intensivists, who followed best clinical practice and guidelines. Chemotherapy, corticosteroids, hematopoietic growth factors, immunosuppressive drugs, and other cancer-related treatments were prescribed by the hematologist in charge of each patient in accordance with institutional guidelines. Neutropenia was defined as a neutrophil count of less than 500/mm^3.

Etiologic diagnoses were made by consensus by the intensivists, hematologists, and consultants, according to recent definitions.[16,23,25] In particular, etiologies of pulmonary involvement were diagnosed based on predefined criteria[25]; for possible or probable invasive pulmonary aspergillosis, the most recent definitions were used.[40]

The primary outcome was vital status at hospital discharge. Results are described as medians and interquartile ranges (IQR) for quantitative variables and numbers and percentages for qualitative variables. Univariable prognostic analyses were based on the Wilcoxon rank-sum test or the Fisher's exact test. To identify independent predictors of hospital mortality, characteristics available at ICU admission associated with *P* values less than .1 by univariate analysis or deemed clinically relevant were included in a multivariable logistic regression model with backward selection. Non-log-linear continuous variables were dichotomized. Missing data were completed by multiple imputation with chained equations.[41] Results are reported with and without imputation. Goodness-of-fit of the model was assessed using the Le Cessie-van Houwelingen test on all imputed datasets.[42]

A secondary objective was to assess whether starting life-supporting interventions late during the ICU stay or using life-supporting interventions for prolonged periods was beneficial. The conditional survival probability associated with organ failure was estimated among patients requiring mechanical ventilation, vasoactive drugs, and/or renal replacement therapy (RRT) within 24 hours after ICU admission. It was computed for day X, as the percentage of patients alive at ICU discharge among patients alive after X days of organ failure. We also modeled the center effect using a logistic regression model with a random center effect on the intercept. Estimates were obtained using a maximum likelihood estimator (glmmML_0.82-1 *R*-package), and center effect has been tested using a permutation test as recommended by Lee and Braun.

All tests were two-sided, and *P* values less than .05 were considered significant. Analyses were done using *R* software version 2.14.2 (R Project for Statistical Computing, Wien, Austria).

RESULTS

As shown in Figure 1, 1,376 patients with hematologic malignancies were considered for ICU admission, of whom 1,032 patients (75%) were admitted to the ICU; 21 patients declined to participate, leaving 1,011 patients enrolled onto the study. ICU refusal rate was 0.25 (IQR, 0.22 to 0.27), ranging from 0.11 to 0.30.

ICU admission occurred 4 days (IQR, 1 to 6) after hospital admission; 451 patients (44.6%) were admitted within 1 day, including 267 patients (26%) admitted directly to the ICU. The main reasons for ICU admission were acute respiratory failure and shock (62.5% and 42.3% patients, respectively). ICU refusal rate was not different in patients admitted from the hematologic wards compared with patients admitted from the emergency department.

As listed in Table 1, non-Hodgkin's lymphoma, acute myeloid leukemia, and myeloma accounted for 71.3% of the total cohort. Median time since diagnosis of malignancy was 5.4 months (IQR, 0 to 33.5); 386 patients (38.2%) had newly diagnosed malignancies and 234 patients (23.1%) were in complete or partial remission. Only 27%

Table 1. Patient Characteristics at Intensive Care Unit Admission

Variable	No. of Patients	%
Age, years*		
Median	60	
IQR	49-70	
Sex, male	614	61
Underlying malignancy		
Non-Hodgkin's lymphoma	320	31.6
Hodgkin's disease	25	2.5
Acute myeloid leukemia	275	27.2
Acute lymphocytic leukemia	76	7.5
Myeloma	126	12.5
Chronic myeloid leukemia	19	1.9
Chronic lymphocytic leukemia	76	7.5
Myelodysplastic syndrome	46	4.5
Other	51	5
Days since diagnosis		
Median	166	
IQR	7-1,020	
Disease status at admission*		
Newly diagnosed	386	38.2
Complete or partial remission	234	23.1
Other	338	33.4
Unknown	53	5.2
BMT/HSCT recipient*	252	24.9
Autologous	107	10.6
Allogeneic	145	14.3
Poor performance status (bedridden/completely disabled)	195	19.3
Charlson comorbidity index*		
Median	4	
IQR	2-5	
Circumstances of ICU admission	451	44.6
Time between hospital and ICU admission < 24 hours*		
Median, days	4	
IQR, days	0-16	
Direct admission to the ICU	267	26
Neutropenia*	289	28.6
More than one request from the hematologist before admission	105	10.4
Reason for ICU admission		
Acute respiratory failure	632	62.5
Shock	428	42.3
Acute kidney injury	308	30.5
Coma	226	22.3
Chemotherapy in high-risk patients†	71	7.1

Abbreviations: BMT, bone marrow transplantation; HSCT, hematopoietic stem-cell transplantation; ICU, intensive care unit; IQR, interquartile range.
*These variables are associated with hospital mortality by univariate analysis (see Results).
†High risk for tumor lysis syndrome (bulky tumor, hyperleukocytic leukemia), arrhythmia, and bleeding.

Table 2. Hospital Mortality Associated With the Use of Life-Supporting Intervention Therapies in Five Predefined Subgroups

	Overall Cohort (N = 1,011)		Patients Age < 60 Years (n = 483)		Good Performance Status (n = 816)*		Partial or Complete Remission (n = 234)†		No Allogeneic BMT (n = 866)		Dysfunction of Zero or One Organ (n = 575)‡	
Life-Supporting Intervention	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Total patients who died	397	39.3	169	34.9	284	34.8	78	33.3	319	36.8	115	20.0
Chemotherapy in the ICU	244		133		208		NA		244		141	
Patients who died	93	38.1	40	30.1	73	35.1			93	38.1	27	19.1
Noninvasive mechanical ventilation	318		148		244		71		260		142	
Patients who died	147	46.2	62	41.0	104	42.6	27	38.0	116	44.6	38	26.8
Invasive mechanical ventilation	484		228		378		106		415		73	
Patients who died§	293	60.5	126	55.0	214	56.6	57	53.8	244	58.8	23	31.5
Vasoactive drugs	518		233		394		126		438		101	
Patients who died§	298	57.5	122	52.4	213	54.1	57	45.2	247	45.9	22	21.8
Renal replacement therapy	262		126		206		20		231		64	
Patients who died§	155	59.2	73	58.0	111	53.9	11	55.0	131	56.7	12	18.8

Abbreviations: BMT, bone marrow transplantation; ICU, intensive care unit.
*Good performance status was defined as neither bedridden nor completely disabled.
†BMT patients were all considered in partial or complete remission.
‡Requiring invasive mechanical ventilation, vasoactive drugs, or renal replacement therapy.
§These patients received only one of the three following life-supporting interventions: invasive mechanical ventilation, vasoactive drugs, and renal replacement therapy.

of patients had participated in studies of chemotherapy. Bone marrow or hematopoietic stem-cell transplantation (BMT/HSCT) was performed in 252 patients (24.9%); the transplantations were autologous in 107 patients and allogeneic in 145 patients. Neutropenia was present at ICU admission in 289 patients (28.6%) and developed in the ICU in 91 additional patients (9%).

Hospital mortality was 39.3%. Day-90 and 1-year mortality rates were 47.5% and 56.7%, respectively. By univariate analysis, variables associated with hospital mortality were age (18 to 50 years, 34%; 51 to 60 years, 35.3%; 61 to 70 years, 42.6%; and > 70 years, 45.8%; $P = .02$), poor performance status (57.4% *v* 34.9%; $P < .001$), Charlson comorbidity index (median, 5; IQR, 3 to 6; *v* median, 3; IQR, 1 to 4; $P = .0001$), remission of the malignancy (32.5% *v* 40.3%; $P = .02$), allogeneic BMT/HSCT (52.4% *v* 38.3%; $P = .0002$), and time from hospital to ICU admission less than 24 hours (33.9% *v* 43.7%; $P = .002$). There was no significant association between the rate of ICU refusal and hospital mortality.

Table 2 lists outcomes associated with the use of life-supporting interventions. The use of mechanical ventilation, vasoactive drugs, or RRT was associated with increased hospital mortality. Trends toward lower mortality rates were found in patients younger than 60 years, having a good performance status, or not having received allogeneic BMT/HSCT. However, mortality was significantly lower in patients who received no more than one life-supporting intervention. Figure 2 shows that hospital mortality increased with the number of days spent receiving both invasive mechanical ventilation and vasoactive drugs. Appendix Figure A1 (online-only) lists daily SOFA scores throughout the ICU stay indicating that the number of organ dysfunctions was significantly associated with mortality from day 1 onward. Importantly, neither time spent with any single life-supporting intervention nor time from ICU admission to initiation of a life-supporting intervention was associated with hospital mortality (Fig 3 and Appendix Figure A2). Table 3 lists the definite diagnoses and corresponding hospital mortality rates.

Patients admitted to the ICU within 1 day after hospital admission had SOFA scores on day 1 similar to those in patients admitted later but they also had lower incidences of life-supporting interventions (67.7% *v* 74.2%; $P = .04$). Patients admitted within 24 hours had shorter times since malignancy diagnosis (median, 153 days; IQR, 0 to 1,230 days; *v* median, 173.5 days; IQR, 20 to 812 days; $P = .04$) and were more likely to have good performance status (86.6% *v* 75.5%; $P < .001$). They were less likely to have their primary hematologists in the same hospital as the ICU (57.6% *v* 96.7%; $P < .001$), a history of allogeneic HSCT/BMT (11% *v* 17%; $P = .006$), neutropenia (19.6% *v* 35.8%; $P < .001$), and treatment with antifungal agents (27% *v* 47%; $P < .001$) or antiviral agents (36% *v* 48%; $P = .0002$) during the first 3

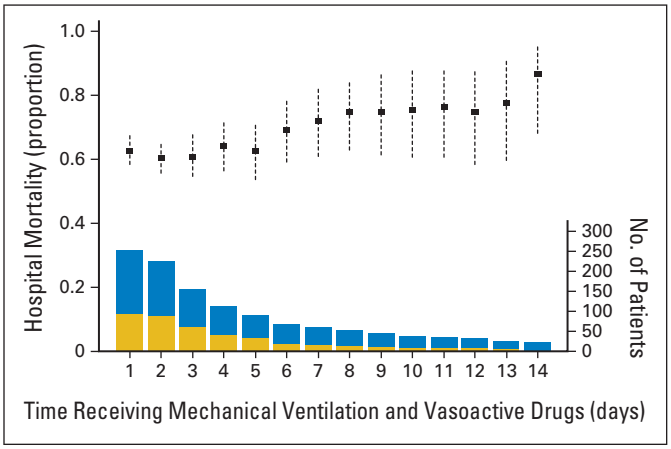

Fig 2. Daily assessment of the probability of hospital mortality according to the number of days spent receiving both invasive mechanical ventilation and vasoactive drugs. The *y*-axis on the left indicates hospital mortality rates with the corresponding curve (mean ± standard deviation) and the *y*-axis on the right indicates the number of patients, with corresponding bars showing the number of patients who survived (gold) and the number of patients who died (blue).

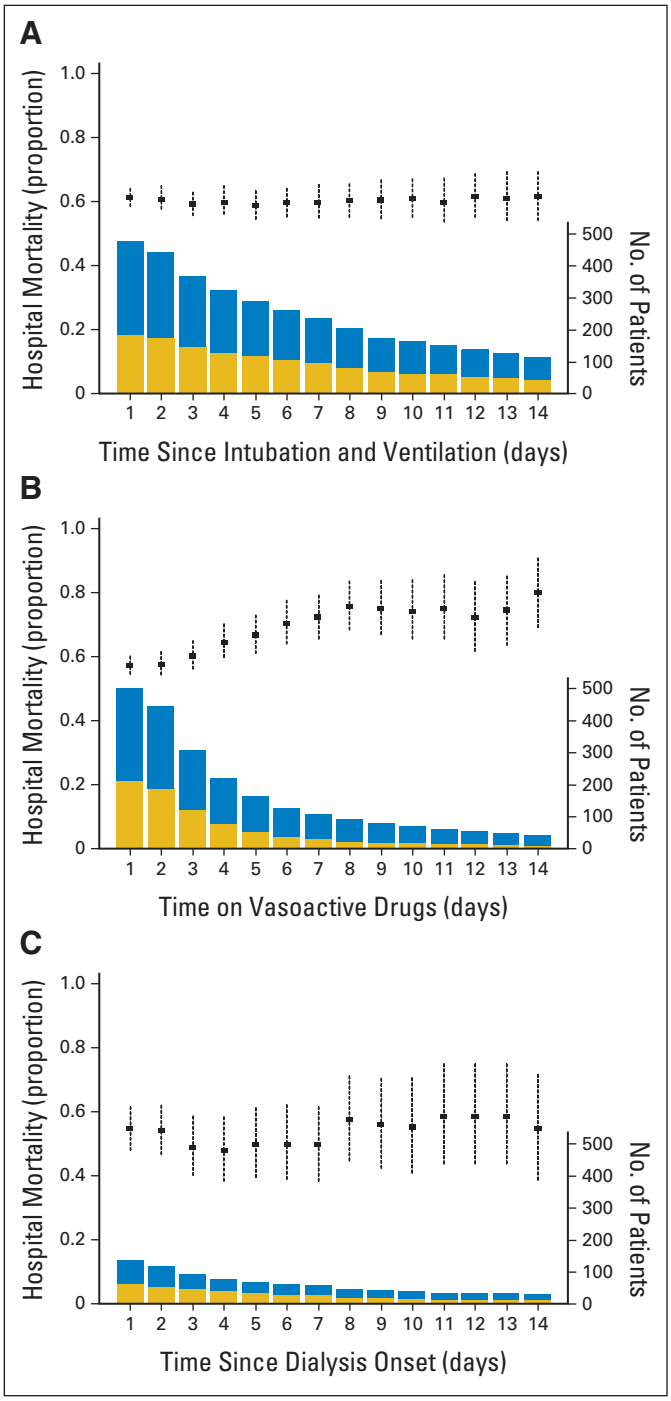

Fig 3. Daily assessment of the probability of hospital mortality according to the number of days spent receiving (A) invasive mechanical ventilation, (B) vasoactive drugs, or (C) renal replacement therapy. The *y*-axis on the left indicates hospital mortality rates with the corresponding curve (mean ± standard deviation) and the *y*-axis on the right indicates the number of patients with corresponding bars showing the number of patients who survived (gold) and the number of patients who died (blue).

days in the ICU. Obtaining ICU admission required more than one call to the ICU physician in only 5.9% of patients admitted within 24 hours compared with 18% of patients admitted later ($P < .001$).

By multivariate analyses (Fig 4; Table 4), 10 variables were independently associated with hospital mortality. Mortality was lower in patients with complete or partial remission of the malignancy and in those patients admitted to the ICU within 24 hours after hospital admission. Other factors were associated with higher mortality: poor performance status (bedridden or completely disabled), higher Charlson comorbidity index, allogeneic BMT/HSCT, SOFA score on ICU admission, ICU admission after cardiac arrest or for acute respiratory failure, organ infiltration by the malignancy, and invasive aspergillosis. No significant center effect on mortality was found.

On day 90, 69.2% of the survivors who were eligible for telephone interviews (Appendix Fig A3) completed the short form 36 questionnaire. Among survivors, no differences could be found between patients responding to telephone interviews and those who could not be reached. Twenty per cent of patients perceived their physical and mental health as altered, with no significant differences compared to age- and gender-matched cancer patients who were not admitted to the ICU. After 6 months, the hematologists reported that all but seven ICU survivors were continuing their cancer treatment, that ICU admission did not influence therapeutic intensity in 80% of ICU survivors, and that 80% of ICU survivors were in complete or partial remission.

DISCUSSION

This work is the first large, prospective multicenter study of ICU and post-ICU outcomes in patients with hematologic malignancies only. In addition to mortality data, quality-of-life data were obtained after 3 months, and treatment intensity and disease status were assessed after 6 months. The 39.3% hospital mortality rate is encouraging, particularly as most patients had at least two organ dysfunctions, and up to 75% required mechanical ventilation, vasoactive drugs, or RRT. Other encouraging findings are the continued use of intensive cancer treatments after ICU discharge, the good quality of life in ICU survivors after 3 months, and the 80% disease-control rate after 6 months. Thus, ICU admission prolonged survival with good quality of life. ICU admission within 24 hours of hospital admission was identified as a variable significantly associated with better survival and possibly amenable to modification.

Previous studies included far fewer patients,[20,33,34] mixed patients with solid cancers and hematologic malignancies,[20,33,34] focused on specific complications,[21,23,25] and studied only ICU or hospital mortality without obtaining quality-of-life data. Consequently, their results are difficult to compare with ours. The 1,011 hematology patients in our study were consecutive patients who probably reflect the overall population of patients with hematologic malignancies and a need for ICU admission. Our hospital mortality rate is lower than in previous recent studies.[20,33,34] Older age is a known risk factor in hematology patients,[13] particularly those with critical illnesses,[43] and the comorbidity burden and performance status are also well-established prognostic factors.[13] Also in agreement with previous publications is our finding of higher mortality in bedridden patients[20,22,33,43] and in allogeneic BMT or HSCT recipients.[24,44-46] However, substantial survival rates can be achieved in select allogeneic BMT/HSCT recipients without uncontrolled graft-versus-host disease,[47] in whom mechanical ventilation is no longer futile.[24,44,48] Worse organ dysfunction scores, cardiac arrest, and invasive pulmonary aspergillosis were associated with hospital mortality in our cohort and in previous studies.[20,23,33,43,49,50] The independent impact of acute respiratory failure on mortality indicates a need for developing better

Table 3. Univariable Analysis of Impact of Each Diagnosis on Hospital Mortality

Diagnosis	Patient Cases		Mortality		Odds Ratio	95% CI	*P*
	No.	%	No.	%			
Sepsis							< .001
Septic shock	259	25.6	120	46.5	1		
Multiple organ failure	26	2.6	22	84.6	6.32	2.12 to 18.87	
No sepsis	377	37.3	133	35.4	0.63	0.46 to 0.87	
Severe sepsis	349	34.5	120	34.5	0.61	0.44 to 0.84	
Gram-positive infections	85	8.6	28	32.9	0.74	0.46 to 1.19	.24
Gram-negative infections	192	19.1	79	41.1	1.11	0.8 to 1.52	.56
Pneumonia	367	36.3	171	46.7	1.64	1.26 to 2.13	.00002
Invasive pulmonary aspergillosis	69	6.8	42	60.9	2.48	1.56 to 4.26	.0001
Urinary tract infection	46	4.5	18	39.1	1	0.54 to 1.83	1
Colitis and typhlitis	106	10.5	36	34.3	0.79	0.52 to 1.21	.29
Catheter-related infections	29	2.9	7	24.1	0.48	0.21 to 1.15	.12
Acute respiratory failure	632	62.5	273	43.2	1.46	1.13 to 1.49	.004
Acute kidney injury	204	20.2	83	40.7	1.08	0.79 to 1.48	.63
Cardiac events	138	13.6	57	41.3	1.11	0.77 to 1.60	.63
Cardiac pulmonary edema	56	5.5	15	26.8	0.55	0.3 to 1.01	.06
Admission after cardiac arrest	30	3.0	23	76.7	5.35	2.27 to 13.6	.0005
Organ infiltration by the malignancy	132	13.1	61	46.2	1.39	1.00 to 2.02	.05
Leukemic pulmonary infiltrates	38	3.8	20	52.6	1.48	1.04 to 3.10	.02
Hemophagocytic lymphohistiocytosis	21	2.1	14	66.7	3.18	1.27 to 7.96	.01
Tumor lysis syndrome	97	9.6	40	41.2	1.10	0.72 to 1.68	.66
Severe bleeding	50	4.9	18	36.0	0.87	0.48 to 1.57	.66
Severe metabolic disturbances	40	4.0	5	12.5	0.21	0.08 to 0.55	.0002
Coma	27	2.7	9	33.3	0.77	0.34 to 1.73	.69
Acute liver dysfunction	17	1.7	14	82.4	7.47	2.13 to 26.17	.0005
Admission to the ICU for safer chemotherapy initiation*	71	7.1	16	22.5	0.43	0.24 to 0.76	.002
Severe chemotherapy-related toxicity	37	3.7	12	32.4	0.74	0.37 to 1.48	.49

Abbreviation: ICU, intensive care unit.
*ICU admission for safer chemotherapy initiation was restricted to patients with high tumoral burden (hyperleukocytic leukemia or bulky lymphoma) who were at high risk for leukostasis, tumor lysis syndrome, or compression from bulk tumors.

management strategies.[25] Recent advances in the understanding of organ infiltration by leukemia and lymphoma cells may help to improve survival.[27,51] Recent studies that report improved outcomes in critically ill hematology patients[18,19,21,34] have led to broader ICU admission policies, the main selection criteria being good performance status and availability of potentially life-prolonging treatments.[14,15,30] Consent should be obtained from the patient, after a discussion of the disease status and range of treatment options.[52]

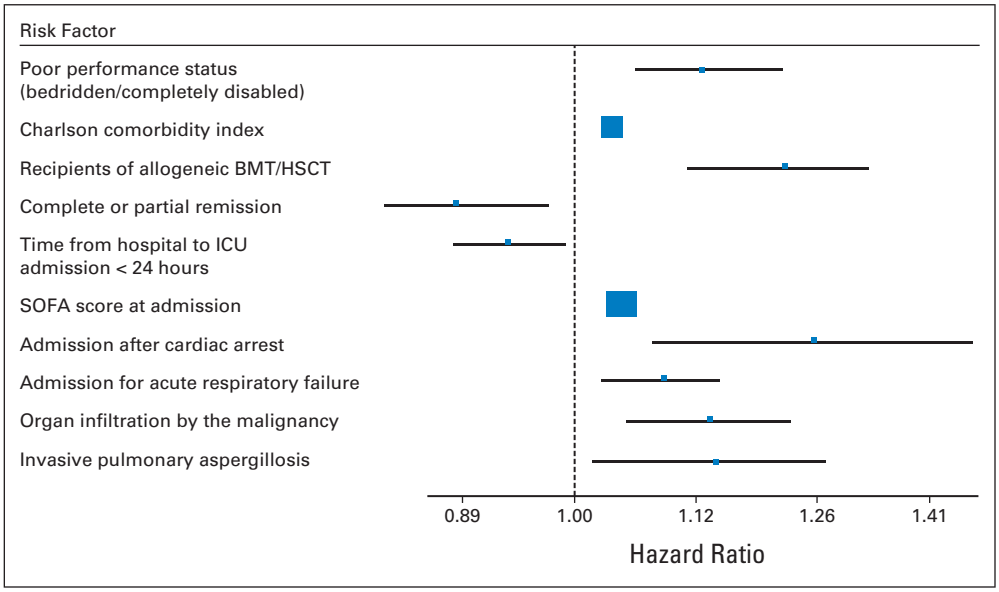

Fig 4. Multivariable analysis: effects on hospital mortality of covariates identified by multivariate logistic regression. Results are presented with and without imputation on the missing data from the Sepsis-Related Organ Failure Assessment (SOFA) score. Goodness-of-fit (Le Cessie-van Houwelingen test) is more than 0.28 for both models. BMT/HSCT, bone marrow transplantation/hematopoietic stem-cell transplantation; ICU, intensive care unit.

Table 4. Multivariate Logistic Regression: Variables Independently Associated With Hospital Mortality

Covariate	Model Without Imputation			Model With Imputation		
	Odds Ratio	95% CI	*P*	Odds Ratio	95% CI	*P*
Poor performance status (bedridden/completely disabled)	1.58	1.06 to 2.34	.02	1.13	1.06 to 1.21	.0005
Charlson comorbidity index	1.13/point	1.06 to 1.21	.0004	1.02	1.01 to 1.03	.0006
Recipients of allogeneic BMT/HSCT	2.18	1.33 to 3.57	.002	1.20	1.10 to 1.31	< .001
Complete or partial remission	0.63	0.42 to 0.95	.02	0.890	0.84 to 0.96	.002
Time from hospital to ICU admission < 24 hours	0.7	0.51 to 0.96	.02	0.94	0.89 to 0.99	.02
SOFA score at admission	1.21/point	1.16 to 1.27	< .001	1.04	1.03 to 1.05	< .001
Admission after cardiac arrest	2.63	1.00 to 6.97	.05	1.25	1.06 to 1.47	.008
Admission for acute respiratory failure	1.34	0.94 to 1.90	.09	1.08	1.01 to 1.15	.01
Organ infiltration by the malignancy	1.894	1.23 to 3.07	.004	1.14	1.05 to 1.24	.002
Invasive pulmonary aspergillosis	1.97	1.03 to 3.76	.03	1.14	1.01 to 1.28	.02

NOTE. Results are presented with and without imputation on the missing data from the SOFA score. Goodness-of-fit test results (Le Cessie-van Houwelingen test) > 0.28 for both models.
Abbreviations: BMT, bone marrow transplantation; HSCT, hematopoietic stem-cell transplantation; ICU, intensive care unit; SOFA, Sepsis-Related Organ Failure Assessment.

In our cohort, we collected daily information on organ dysfunctions. Severity of organ dysfunctions is known to be a major prognostic factor.[19,20,30,33,53] However, our study contributes three new findings. First, use of a single life-supporting intervention was associated with good survival. For instance, among patients receiving mechanical ventilation but no vasoactive drugs or RRT, 67.6% were alive at hospital discharge (Table 2); this proportion was 77.5% for vasoactive drugs only and 81.3% for RRT only. Second, the time from ICU admission to initiation of life-supporting interventions did not influence survival. Third, longer time on life-supporting interventions was not associated with worse survival. These last two findings indicate that current practices regarding patient selection for starting and continuing life-supporting interventions are appropriate.

Our finding that a shorter time from hospital to ICU admission was independently associated with better survival offers some hope that prompt ICU admission might improve survival. It suggests that immediate ICU admission of hematology patients with incipient organ dysfunction may be appropriate. In previous studies, early ICU management of acute respiratory failure decreased the rates of intubation[25] and septic shock[21] as well as improved outcomes of patients at high risk for tumor lysis syndrome and acute respiratory failure.[51,54] However, the effect of early ICU admission on mortality is difficult to interpret. Patients admitted early had similar SOFA scores to those admitted later on; consequently, their earlier admission might reflect a more acute disease process compared with patients admitted later. It is striking however that a smaller proportion of early-admitted patients required more than one call to the intensivist (5.9% *v* 18% in patients admitted later), suggesting that late ICU admission may be due in some cases to reluctance to admit hematology patients, with later-admitted patients being initially considered too sick to benefit from intensive care. Studies conducted jointly by intensivists and hematologists are needed to evaluate criteria for early ICU admission in terms of their ability to improve survival. Until they become available, our finding of better outcomes after earlier ICU admission supports a broad ICU admission policy with a trial of full-code therapy. Intermediate-care units located contiguous to the ICU could also be used for those patients at high risk for rapid deterioration. Rapid response teams should also be evaluated in this very specific patient population.[55]

This study has several limitations. First, all the study centers had hematologists and intensivists available around the clock, a situation not encountered in all hospitals. Second, the study was performed in France and Belgium and may not be relevant to other countries. However, in this study and a previous study by our group,[25] the results were within the ranges reported in other European countries,[16] North America,[17,24,45] and Brazil.[23,33] Third, 9.6% of the patients were lost to follow-up during the 1-year study period, and the day-90 telephone interview was conducted in 69% of eligible patients. Finally, in this multicenter study, no rigid criteria have been used to make the decision to send patients to ICUs across the different participating centers. However, ICU refusal rate was not significantly different across centers and was not associated with mortality. Moreover, there was no center effect on hospital mortality.

In summary, the 39.3% hospital mortality rate in our study supports the usefulness of ICU admission of select critically ill patients with hematologic malignancies. The good cancer control and good-to-excellent HRQOL in ICU survivors constitute further evidence that ICU resources are being used to good effect in this population. The better survival in patients admitted more rapidly to the ICU invites studies evaluating the effects on outcomes of earlier ICU admission.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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Provision of study materials or patients: All authors
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REFERENCES

1. Jones DS, Podolsky SH, Greene JA: The burden of disease and the changing task of medicine. N Engl J Med 366:2333-2338, 2012

2. Ferlay J, Shin HR, Bray F, et al: Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 127:2893-2917, 2010

3. Castaigne S, Pautas C, Terré C, et al: Effect of gemtuzumab ozogamicin on survival of adult patients with de-novo acute myeloid leukaemia (ALFA-0701): A randomised, open-label, phase 3 study. Lancet 379:1508-1516, 2012

4. Raab MS, Podar K, Breitkreutz I, et al: Multiple myeloma. Lancet 374:324-339, 2009

5. Récher C, Coiffier B, Haioun C, et al: Intensified chemotherapy with ACVBP plus rituximab versus standard CHOP plus rituximab for the treatment of diffuse large B-cell lymphoma (LNH03-2B): An open-label randomised phase 3 trial. Lancet 378: 1858-1867, 2011

6. Kantarjian H, Shah NP, Hochhaus A, et al: Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med 362:2260-2270, 2010

7. Vogelzang NJ, Benowitz SI, Adams S, et al: Clinical cancer advances 2011: Annual Report on Progress Against Cancer from the American Society of Clinical Oncology. J Clin Oncol 30:88-109, 2012

8. Verdecchia A, Francisci S, Brenner H, et al: Recent cancer survival in Europe: A 2000-2002 period analysis of EUROCARE-4 data. Lancet Oncol 8:784-796, 2007

9. Vento S, Cainelli F, Temesgen Z: Lung infections after cancer chemotherapy. Lancet Oncol 9:982-992, 2008

10. Altena R, Perik PJ, van Veldhuisen DJ, et al: Cardiovascular toxicity caused by cancer treatment: Strategies for early detection. Lancet Oncol 10:391-399, 2009

11. Morgan C, Tillett T, Braybrooke J, et al: Management of uncommon chemotherapy-induced emergencies. Lancet Oncol 12:806-814, 2011

12. Bergeron A, Réa D, Levy V, et al: Lung abnormalities after dasatinib treatment for chronic myeloid leukemia: A case series. Am J Respir Crit Care Med 176:814-818, 2007

13. Estey E: Acute myeloid leukemia and myelodysplastic syndromes in older patients. J Clin Oncol 25:1908-1915, 2007

14. Azoulay E, Afessa B: The intensive care support of patients with malignancy: Do everything that can be done. Intensive Care Med 32:3-5, 2006

15. Azoulay E, Soares M, Darmon M, et al: Intensive care of the cancer patient: Recent achievements and remaining challenges. Ann Intensive Care 1:5, 2011

16. Schellongowski P, Staudinger T, Kundi M, et al: Prognostic factors for intensive care unit admission, intensive care outcome, and post-intensive care survival in patients with de novo acute myeloid leukemia: A single center experience. Haematologica 96:231-237, 2011

17. Khassawneh BY, White P Jr, Anaissie EJ, et al: Outcome from mechanical ventilation after autologous peripheral blood stem cell transplantation. Chest 121:185-188, 2002

18. Peigne V, Rusinová K, Karlin L, et al: Continued survival gains in recent years among critically ill myeloma patients. Intensive Care Med 35:512-518, 2009

19. Pène F, Percheron S, Lemiale V, et al: Temporal changes in management and outcome of septic shock in patients with malignancies in the intensive care unit. Crit Care Med 36:690-696, 2008

20. 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 31:104-112, 2003

21. Legrand M, Max A, Peigne V, et al: Survival in neutropenic patients with severe sepsis or septic shock. Crit Care Med 40:43-49, 2012

22. Azoulay E, Thiery G, Chevret S, et al: The prognosis of acute respiratory failure in critically ill cancer patients. Medicine (Baltimore) 83:360-370, 2004

23. Soares M, Salluh JI, Carvalho MS, et al: Prognosis of critically ill patients with cancer and acute renal dysfunction. J Clin Oncol 24:4003-4010, 2006

24. Groeger JS, Lemeshow S, Price K, et al: Multicenter outcome study of cancer patients admitted to the intensive care unit: A probability of mortality model. J Clin Oncol 16:761-770, 1998

25. Azoulay E, Mokart D, Lambert J, et al: Diagnostic strategy for hematology and oncology patients with acute respiratory failure: Randomized controlled trial. Am J Respir Crit Care Med 182: 1038-1046, 2010

26. Hilbert G, Gruson D, Vargas F, et al: Noninvasive ventilation in immunosuppressed patients with pulmonary infiltrates, fever, and acute respiratory failure. N Engl J Med 344:481-487, 2001

27. Coiffier B, Altman A, Pui CH, et al: Guidelines for the management of pediatric and adult tumor lysis syndrome: An evidence-based review. J Clin Oncol 26:2767-2778, 2008

28. Wilson FP, Berns JS: Onco-nephrology: Tumor lysis syndrome. Clin J Am Soc Nephrol 7:1730-1739, 2012

29. Freifeld AG, Bow EJ, Sepkowitz KA, et al: Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis 52:e56-e93, 2011

30. Lecuyer L, Chevret S, Thiery G, et al: The ICU trial: A new admission policy for cancer patients requiring mechanical ventilation. Crit Care Med 35: 808-814, 2007

31. 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 23:4406-4413, 2005

32. Lengliné E, Raffoux E, Lemiale V, et al: Intensive care unit management of patients with newly diagnosed acute myeloid leukemia with no organ failure. Leuk Lymphoma 53:1352-1359, 2012

33. Soares M, Salluh JI, Spector N, et al: Characteristics and outcomes of cancer patients requiring mechanical ventilatory support for > 24 hrs. Crit Care Med 33:520-526, 2005

34. Azoulay E, Alberti C, Bornstain C, et al: Improved survival in cancer patients requiring mechanical ventilatory support: Impact of noninvasive mechanical ventilatory support. Crit Care Med 29: 519-525, 2001

35. Azoulay E, Pochard F, Kentish-Barnes N, et al: Risk of post-traumatic stress symptoms in family members of intensive care unit patients. Am J Respir Crit Care Med 171:987-994, 2005

36. Herridge MS, Cheung AM, Tansey CM, et al: One-year outcomes in survivors of the acute respiratory distress syndrome. N Engl J Med 348:683-693, 2003

37. Boini S, Briancon S, Guillemin F, et al: Impact of cancer occurrence on health-related quality of life: A longitudinal pre-post assessment. Health Qual Life Outcomes 2:4, 2004

38. Vincent JL, Moreno R, Takala J, et al: The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure: On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med 22:707-710, 1996

39. Charlson ME, Pompei P, Ales KL, et al: A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chronic Dis 40:373-383, 1987

40. De Pauw B, Walsh TJ, Donnelly JP, et al: Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis 46:1813-1821, 2008

41. Azur MJ, Stuart EA, Frangakis C, et al: Multiple imputation by chained equations: What is it and how does it work? Int J Methods Psychiatr Res 20:40-49, 2011

42. Hosmer DW, Hosmer T, Le Cessie S, et al: A comparison of goodness-of-fit tests for the logistic regression model. Stat Med 16:965-980, 1997

43. Soares M, Carvalho MS, Salluh JI, et al: Effect of age on survival of critically ill patients with cancer. Crit Care Med 34:715-721, 2006

44. Rubenfeld GD, Crawford SW: Withdrawing life support from mechanically ventilated recipients of bone marrow transplants: A case for evidence-based guidelines. Ann Intern Med 125:625-633, 1996

45. Price KJ, Thall PF, Kish SK, et al: Prognostic indicators for blood and marrow transplant patients admitted to an intensive care unit. Am J Respir Crit Care Med 158:876-884, 1998

46. Pène F, Aubron C, Azoulay E, et al: Outcome of critically ill allogeneic hematopoietic stem-cell transplantation recipients: A reappraisal of indications for organ failure supports. J Clin Oncol 24:643-649, 2006

47. Gooley TA, Chien JW, Pergam SA, et al: Reduced mortality after allogeneic hematopoietic-cell transplantation. N Engl J Med 363:2091-2101, 2010

48. Groeger JS, White P Jr, Nierman DM, et al: Outcome for cancer patients requiring mechanical ventilation. J Clin Oncol 17:991-997, 1999

49. Burghi G, Lemiale V, Seguin A, et al: Outcomes of mechanically ventilated hematology patients with invasive pulmonary aspergillosis. Intensive Care Med 37:1605-1612, 2011

50. Reisfield GM, Wallace SK, Munsell MF, et al: Survival in cancer patients undergoing in-hospital cardiopulmonary resuscitation: A meta-analysis. Resuscitation 71:152-160, 2006

51. Azoulay É, Canet E, Raffoux E, et al: Dexamethasone in patients with acute lung injury from acute monocytic leukaemia. Eur Respir J 39:648-653, 2012

52. Wright AA, Keating NL, Balboni TA, et al: Place of death: Correlations with quality of life of patients with cancer and predictors of bereaved caregivers' mental health. J Clin Oncol 28:4457-4464, 2010

53. Darmon M, Thiery G, Ciroldi M, et al: Intensive care in patients with newly diagnosed malignancies and a need for cancer chemotherapy. Crit Care Med 33:2488-2493, 2005

54. Azoulay E, Fieux F, Moreau D, et al: Acute monocytic leukemia presenting as acute respiratory failure. Am J Respir Crit Care Med 167:1329-1333, 2003

55. Jones DA, DeVita MA, Bellomo R: Rapid-response teams. N Engl J Med 365:139-146, 2011

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Appendix

The following institutions participated in this study: Medical Intensive Care Unit (ICU), Saint-Louis Teaching Hospital, Paris, France; Medical ICU, Paoli Calmette Institute, Marseille, France; Medical ICU, Cochin Teaching Hospital, Paris, France; Medical ICU, Angers Teaching Hospital, Angers, France; Medical ICU, Pitié-Salpêtrière Teaching Hospital, Paris, France; Medical ICU, Avicenne Teaching Hospital, Bobigny, France; Medical ICU, Roubaix Hospital, Roubaix, France; Medical ICU, Mignot Hospital, Versailles, France; Medical ICU, Hôtel-Dieu Teaching Hospital, Paris, France; Medical ICU, La Roche sur Yon Hospital, La Roche sur Yon, France; Medical ICU, Nancy Teaching Hospital, Nancy, France; Medical ICU, Brest Teaching Hospital, Brest, France; Medical ICU, Jules Bordet Institute, Brussels, Belgium; Medical ICU, Ghent University Hospital, Ghent, Belgium; Medical ICU, Grenoble Teaching Hospital, Centre Hospitalier Universitaire de Grenoble, Grenoble, France; Medical ICU, Lille Teaching Hospital, Lille, France; Medical ICU, Saint-Etienne Teaching Hospital, Saint-Etienne, France.

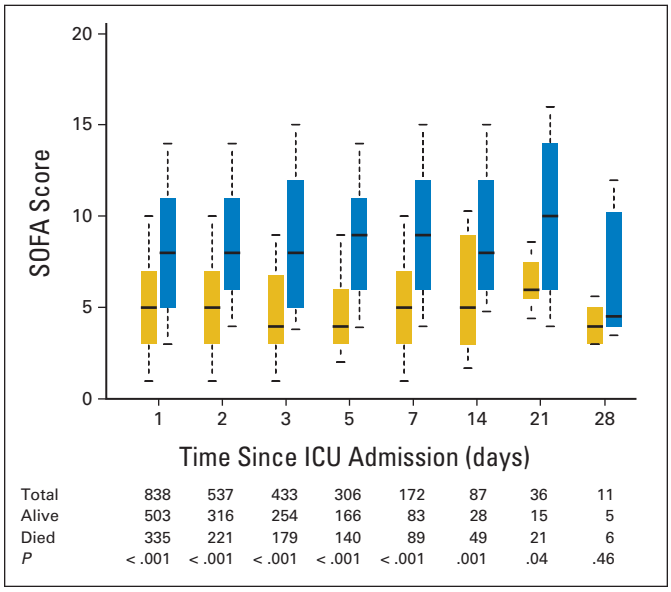

Fig A1. Sepsis-Related Organ Failure Assessment (SOFA) score throughout the intensive care unit (ICU) stay in hospital survivors and nonsurvivors. $P < .001$ for all tests except on day 28 ($P = .26$).

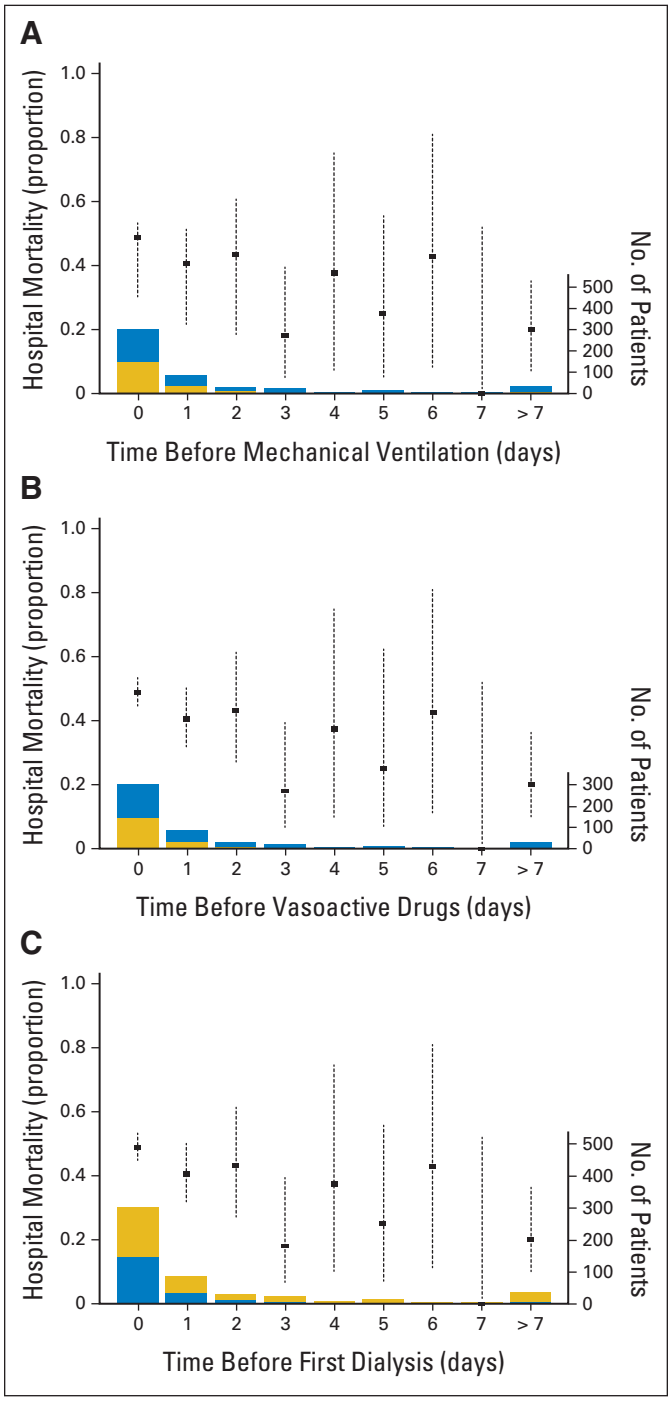

Fig A2. Daily assessment of the probability of hospital mortality according to time from intensive care unit admission to initiation of (A) invasive mechanical ventilation, (B) vasoactive drugs, or (C) renal replacement therapy. The *y*-axis on the left indicates hospital mortality rates with the corresponding curve (mean ± standard deviation) and the *y*-axis on the right indicates the number of patients with corresponding bars showing the number of patients who survived (gold) and the number of patients who died (blue).

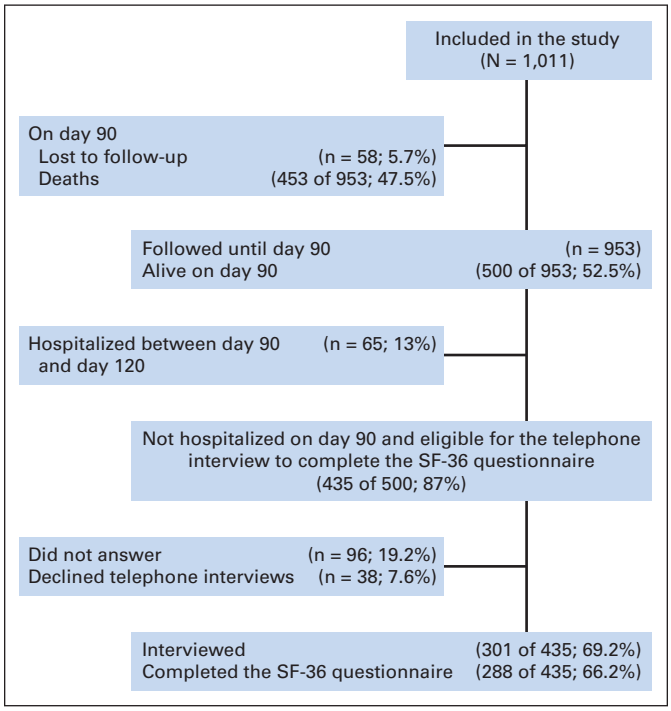

Fig A3. Day-90 follow-up and reasons for not assessing health-related quality of life. SF36, short-form 36 questionnaire.