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ARTICLE

Predictors of short-term and long-term mortality in critically ill patients admitted to the intensive care unit following allogeneic stem cell transplantation

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Abstract

Historically, the mortality of patients admitted to the ICU after allogeneic stem cell transplantation (alloSCT) is high. Advancements in transplantation procedures, infectious monitoring and supportive care may have improved the outcome. This study aimed to determine short-term and long-term mortality after ICU admission of patients after alloSCT and to identify prognostic clinical and transplantation-related determinants present at ICU admission for long-term outcome. A multicenter cohort study was performed to determine 30-day and 1-year mortality within 2 years following alloSCT. A total of 251 patients were included. The 30-day and 1-year mortality was 55% and 80%, respectively. Platelet count $<25 \times 10^9$/L (OR: 2.26, CI: 1.02–5.01) and serum bilirubin >19 μmol/L (OR: 2.47 CI: 1.08–5.65) at admission, other donor than a HLA-matched-related or HLA-matched-unrelated donor (OR: 4.59, CI: 1.49–14.1) and vasoactive medication within 24 h (OR: 2.35, CI: 1.28–4.31) were associated with increased 30-day mortality. Other donor than a HLA-matched-related or HLA-matched-unrelated donor (OR: 1.9, CI: 1.13–3.19), serum bilirubin >77 (OR: 2.05, CI: 1.28–3.30) and vasoactive medication within 24 h (OR: 1.65, CI: 1.12–2.43) were associated with increased 1-year mortality. Neutropenia was associated with decreased 30-day and 1-year mortality (OR: 0.29, CI: 0.14–0.59 and OR: 0.70, CI: 0.48–0.98). Myeloablative conditioning and T cell-depleted transplantation were not associated with increased mortality.

Introduction

Allogeneic stem cell transplantation (alloSCT) is a potential curative treatment for various malignant and non-malignant hematological diseases [1]. Without alloSCT, the prognosis

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of diseases such as acute myeloid leukemia is poor due to a high rate of relapse after chemotherapy. AlloSCT has been shown to reduce the risk of relapse in patients transplanted in their first complete remission to <20% [2]. Transplantation-related mortalit, however, is considerable and has been reported to be in the range of 15–50% [3]. Admission to the intensive care unit (ICU) is necessary in about 13% of the patients following alloSCT [4, 5]. Previous studies on the survival of alloSCT patients admitted to the ICU demonstrated a high ICU mortality ranging from 52 to 64% [5–8] and a 1-year mortality ranging from 72 to 85% [4, 5, 8, 9]. Recent advancements in transplantation procedures, prophylactic treatments, clinical infection monitoring, and supportive care may have led to a better prognosis of alloSCT patients admitted to the ICU [10]. For example, a study from 2013 reported improved ICU survival following reduced intensity-conditioning (RIC) alloSCT, a less intense regimen compared to conventional myeloablative conditioning (MAC) [11]. Although a trend towards improved ICU survival is demonstrated in The Netherlands [10], the exact short and long-term mortality of alloSCT patients admitted to the ICU in The Netherlands is unknown. An estimation of prognosis at the time that alloSCT patients are considered for ICU admission is difficult to ascertain. Most previously published studies reporting on the factors influencing ICU survival in post-alloSCT patients have focused on the relevant parameters present during the course of ICU admission. The aim of this study was to determine 30-day and 1-year mortality of alloSCT patients admitted to the ICU within 2 years following their alloSCT and to identify prognostic determinants present at admission to the ICU.

Methods

Patient selection

The study was executed in six University Hospitals in the Netherlands, with mixed surgical-medical ICUs. The study population consisted of all consecutive patients of 18 years or older admitted to one of these ICUs within 2 years following an alloSCT between 2003 and 2011, although not all 6 hospitals' data fully covered that time frame. Information collected routinely in electronic Patient Data Management Systems (PDMS) in the hospitals and the prospectively collected high quality data set on clinical and outcome parameters of the Dutch National Intensive Care Evaluation (NICE) [12] registry were used to analyze the survival of these patients and to investigate predictors of survival. Only first ICU admissions were included. Exclusion criteria were discharge alive from the ICU within 24 h of admission to avoid survival bias due to inclusion of non-critically ill patients.

Data collection and definitions

Apart from demographic parameters such as age and sex, we analyzed transplantation-related, clinical and laboratory parameters. Transplantation-related parameters included: hematologic diagnosis as the indication for alloSCT, type of pre-transplantation conditioning of the patient, type of donor, use of T-cell depletion (TCD), time from alloSCT to ICU admission, disease status on ICU admission, presence of graft versus host disease (GVHD) on ICU admission and use of systemic immune suppression on ICU admission. Clinical parameters included: Body Mass Index on ICU admission, presence of sepsis on ICU admission, Acute Physiology and Chronic Health Evaluation (APACHE) II [13], mechanical ventilation within 24 h after ICU admission, vasoactive medication within 24 h after ICU admission, and renal replacement therapy within 24 h after ICU admission. Laboratory parameters present on ICU admission included: neutropenia; duration of neutropenia; platelet count and serum bilirubin levels. The indication for alloSCT was classified as acute myeloid leukemia, acute lymphoid leukemia, chronic myeloid leukemia, chronic lymphoid leukemia, multiple myeloma, lymphoma and other, defined by any other indication for alloSCT. The type of conditioning was classified as MAC or RIC, defined by local protocols. The type of donor was classified as 'Human-Leucocyte-Antigen (HLA)-matched-related', 'HLA-matched-unrelated' or 'other donor than a HLA-matched-related or HLA-matched-unrelated donor' (i.e., haplo- identical, cord blood or mismatched donor). TCD was defined as any treatment to eliminate T cells from the stem cell graft. The primary treating clinician determined presence or absence of primary disease on admission to ICU. The presence of GVHD was defined as presence of symptoms diagnosed as GVHD by the primary treating clinician. Neutropenia was defined as neutrophil count of $<0.5 \times 10^9$/L. Sepsis on ICU admission was diagnosed according to Surviving Sepsis Campaign criteria [14, 15] by the attending physician.

Endpoints and outcome

Primary endpoints were 30-day and 1-year mortality. Secondary endpoint was to identify prognostic determinants present at admission to the ICU.

Statistical analysis

To determine potential prognostic factors for 30-day, univariable logistic regression analysis was used yielding odds ratio's (OR) with corresponding 95% confidence intervals (CI) and P-values for all potential factors. All variables that were significant ($P < 0.1$) in the univariable analysis and variables that were deemed clinically relevant such as age and gender were entered in a multivariable logistic regression model. To determine which combination of factors best predicted 30-day mortality, backward selection was applied with selection criterion of $P < 0.10$. To account for censored survival times, we applied Cox regression analyses to determine predictors of 1-year mortality. All variables that were significant ($P < 0.2$) in the univariable Cox regression analysis and variables that were deemed clinically relevant were entered in a multivariable Cox regression model. To determine which combination of factors best predicted 1-year mortality backward selection was applied with selection criterion of $P < 0.10$. To clarify their effect on mortality, significant scale variables were translated to clinical useful categories with equal percentiles based on scanned cases. The statistical analysis was conducted using the Statistical Package for the Social Sciences, release 23 (IBM SPSS).

Study approval and informed consent

The institutional review board of all participating hospitals approved the study protocol and statistical analysis plan, and waived the need for individual patient informed consent.

Results

Baseline characteristics and length of stay

A total of 251 patients admitted to the ICU after alloSCT were included. Baseline transplantation characteristics and clinical characteristics of patients at time of ICU admission are summarized in Table 1. In this cohort, 199/251 (79%) patients were treated with systemic immune suppression either for the prevention or treatment of GVHD. GVHD was present in 119/251 (47%) patients. More than half of the patients were transplanted with a T cell-depleted stem cell graft. The reason for ICU admission was respiratory failure in almost 50% of the patients. The median length of ICU stay and hospital stay after ICU admission was 6 days (range: 0–119 days) and 18 days (0–379 days), respectively.

30-day mortality and determinants of 30-day mortality

The 30-day mortality was 55% (137/251). The survival over time is demonstrated in Fig. 1. Of the 114 patients surviving 30 days after ICU admission, 76 (67%) were alive at discharge from the hospital. Univariable logistic regression showed that platelet count APACHE II score, serum bilirubin, type of donor, neutropenia, mechanical ventilation, and vasoactive medication within 24 h after ICU admission had two-sided P-values <0.10 for 30-day mortality (Table 2). These variables and the variables age and sex

Table 1 Baseline and hematological characteristics

Baseline characteristics	$N = 251$
Female/male (%)	95/156 (37.8/62.2)
	Median (IQR)
Age at ICU admission in years	51 (40–59)
Time alloSCT to ICU admission (days)	93 (19–230)
Body mass index	23 (21–26)
APACHE II Score	22 (18–28)
Platelet count at admission ICU ($^a10^9$/L)	33 (19–59)
Serum bilirubin level at admission ICU (μmol/L)	39 (18–77)
	N (%)
Neutropenia at admission ICU	89 (35)
Sepsis at admission ICU	83 (32)
Mechanical ventilation within 24 h	167 (65)
Vasoactive medication within 24 h	122 (48)
Renal replacement within 24 h	42 (16)
Hematological characteristics (*n* (%))	
Active disease at admission ICU	46 (18)
GVHD at admission ICU	119 (47)
Use of immune suppression at admission ICU	199 (79)
Indication for alloSCT	
AML	92 (37)
ALL	24 (10)
CML	17 (7)
CLL	17 (7)
MM	32 (13)
Lymphoma	40 (16)
Other	29 (12)
Type of conditioning	
Myeloablative conditioning	127 (51)
Reduced intensity conditioning	124 (49)
Type of donor	
HLA-matched-related donor	132 (53)
HLA-matched-unrelated donor	91 (36)
Other donor[a]	28 (11)
T cell-depleted alloSCT	144 (57)

ICU intensive care unit, *alloSCT* allogeneic stem cell transplantation, *APACHE* Acute Physiology And Chronic Health Evaluation, *GVHD* graft versus host disease, *AML* acute myeloid leukemia, *ALL* acute lymphoid leukemia, *CML* chronic myeloid leukemia, *CLL* chronic lymphoid leukemia, *MM* multiple myeloma, *HLA* human leucocyte antigen

[a]Include haplo-identical donor, cord blood donor and major mismatched donor

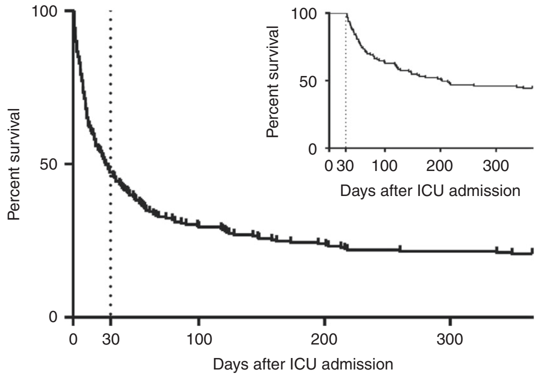

Fig. 1 Kaplan–Meier curve demonstrating survival over time after ICU admission of alloSCT patients. The 30-day mortality was 55% (137/251) and the 1-year mortality was 80% (201/251). The insert graphically represents the 25% added mortality between 30 days and 1 year

were used in the multivariable analysis. Multivariable logistic regression analysis demonstrated that a platelet count <25 × 10^9/L, serum bilirubin >19 µmol/L, use of an other donor than a HLA-matched-related or HLA-matched-unrelated donor and use of vasoactive medication within the first 24 h were associated with increased 30-day mortality. The presence of neutropenia was associated with a decreased 30-day mortality (Table 3).

1-year mortality and determinants of 1-year mortality

The 1-year mortality was 80% (201/251). The 25% added mortality between 30 days and 1 year is demonstrated in the insert of Fig. 1. Univariable Cox regression showed comparable two-sided *P*-values for 1-year mortality as for 30-day mortality with the exception of neutropenia (Table 4). However, since this parameter was significantly associated with 30-day mortality and deemed clinically relevant, neutropenia was included in the multivariable analysis as a relevant clinical parameter. In multivariable Cox regression analysis, serum bilirubin >77 µmol/L, use of an other donor than a HLA-matched-related or HLA-matched-unrelated donor and use of vasoactive medication within the first 24 h were associated with increased 1-year mortality. The presence of neutropenia was associated with a decreased 1-year mortality (Table 5).

Discussion

In this large Dutch cohort of alloSCT patients admitted to an ICU the 30-day mortality is 55% and 1-year mortality 80%. A platelet count <25*10^9/L, serum bilirubin >19 µmol/L, use of HLA-mismatched donor and use of vasoactive medication within the first 24 h were associated with an increased 30-day mortality and the presence of neutropenia was associated with a decreased 30-day mortality. Serum bilirubin >77 µmol/L, use of an HLA-mismatched donor and use of vasoactive medication within the first 24 h were associated with increased 1-year mortality. The presence of neutropenia is associated with a decreased 1-year mortality.

The observed 1-year mortality in our cohort is comparable to previous reported 1-year mortality rates [4, 5, 8, 9]. However, due to differences in reporting of baseline characteristics in the different studies, it is not possible to determine whether the patient cohorts are comparable.

Table 2 Univariable logistic regression analysis of parameters present on ICU admission for 30-day mortality

Parameter	30-day mortality		
	OR	95% CI	*P*
Platelet count at admission ICU			0.027
25–47 × 10^9/L vs. >47 × 10^9/L	1.49	0.80–2.78	0.21
<25 × 10^9/L vs. >47 × 10^9/L	2.33	1.26–4.30	<0.01
APACHE II Score			<0.01
APACHE II Score 19–22 vs. <19	1.23	0.61–2.51	0.56
APACHE II Score 23–28 vs. <19	1.00	0.51–1.97	0.99
APACHE II Score >28 vs. <19	3.43	1.59–7.44	<0.01
Serum bilirubin at admission ICU			<0.01
19–39 µmol/L vs. <19 µmol/L	2.04	0.98–4.24	0.06
40–77 µmol/L vs. <19 µmol/L	2.90	1.38–6.11	<0.01
>77 µmol/L vs. <19 µmol/L	5.45	2.45–12.1	<0.01
Type donor			0.05
MUD vs. MRD	1.55	0.90–2.66	0.12
Other donor vs. MRD	2.70	1.11–6.56	0.03
VA medication <24 h	3.02	1.78–5.10	<0.01
Neutropenia	0.60	0.36–1.02	0.06
MV <24 h	1.62	0.95–2.77	0.08
RRT <24 h	1.54	0.77–3.08	0.22
Female sex	0.87	0.52–1.45	0.59
BMI	1.02	0.97–1.08	0.44
Age	1.00	0.98–1.02	0.91
Time alloSCT to ICU	1.00	1.00–1.00	0.64
Active disease	1.01	0.52–1.94	0.98
Conditioning	0.88	0.54–1.45	0.62
T cell depletion	0.91	0.55–1.51	0.72
GVHD	1.3	0.79–2.17	0.29
Immune suppression	0.72	0.37–1.38	0.32
Sepsis	0.91	0.53–1.57	0.74

OR odds ratio, *CI* confidence interval, *APACHE* Acute Physiology And Chronic Health Evaluation, *MUD* matched-unrelated donor, *MRD* matched-related donor, *MV* mechanical ventilation, *VA* vasoactive medication, *RRT* renal replacement therapy, *alloSCT* allogeneic stem cell transplantation, *ICU* intensive care unit, *BMI* body mass index, *GVHD* graft versus host disease

Table 3 Multivariable logistic regression analysis of parameters present on ICU admission for 30-day mortality

Parameter	30-day mortality		
	OR	95% CI	*P*
Platelet count at admission ICU			0.04
25–47 × 10^9/L vs. >47 × 10^9/L	0.86	0.39–1.88	0.70
<25 × 10^9/L vs. >47 × 10^9/L	2.26	1.02–5.01	0.04
Serum bilirubin at admission ICU			<0.01
19–39 µmol/L vs. <19 µmol/L	2.47	1.08–5.65	0.03
40–77 µmol/L vs. <19 µmol/L	2.90	1.24–6.77	0.01
>77 µmol/L vs. <19 µmol/L	6.48	2.52–16.6	<0.01
Type donor			0.03
MUD vs. MRD	1.41	0.72–2.75	0.32
Other donor vs. MRD	4.59	1.49–14.12	<0.01
VA medication <24 h	2.35	1.28–4.31	<0.01
Neutropenia	0.29	0.14–0.59	<0.01

OR odds ratio, *CI* confidence interval, *VA* vasoactive medication, *MUD* matched-unrelated donor, *MRD* matched-related donor

Nevertheless, the observed 1-year mortality of alloSCT patients admitted to an ICU is still high despite advancements in transplantation procedures, prophylactic treatments, clinical infection monitoring and supportive care. We choose to report 30-day and 1-year mortality as short-term and long-term mortality and not to report ICU or hospital mortality to avoid bias due to local differences in ICU and hospital discharge policy of patients. However, it would be very informative to know whether patients alive at 30 days after ICU admission die due to withdrawal of supportive therapy after 30 days or due to new complications that might have occurred after discharge from the hospital. In our database, 76 of the 114 (67%) patients alive at 30 days after ICU admission were alive at discharge from the hospital.

Platelet count can be a parameter of severity-of-illness and may therefore be associated with increased mortality. Although low platelet count may reflect low bone marrow capacity after alloSCT, the effect on mortality in critically ill alloSCT patients is contradicted by the observation that neutropenia in our study is associated with a decreased risk for 30-day mortality and 1 year mortality. The association of elevated serum bilirubin level with increased 30-day and 1-year mortality of alloSCT patients admitted to the ICU has also been demonstrated in previous studies [8, 16] Increased serum bilirubin presumably represents liver insufficiency which can be caused by drug toxicity, GVHD, veno-occlusive disease, or sepsis-induced multi-organ failure. The association with increased 30-day and 1-year mortality and the need for vasoactive medication has also been demonstrated in previous studies [7, 9, 16] and can be considered a parameter determining the severity-of-illness.

Table 4 Univariable Cox regression analysis of parameters present on ICU admission for 1-year mortality

Parameter	1-year mortality		
	OR	95% CI	*P*
Platelet count at admission ICU			0.02
25–47 × 10^9/L vs. >47 × 10^9/L	1.50	1.04–2.14	0.03
<25 × 10^9/L vs. >47 × 10^9/L	1.86	1.32–2.62	<0.01
APACHE II Score			<0.01
APACHE II Score 19–22 vs. <19	1.31	0.87–1.96	0.19
APACHE II Score 23–28 vs. <19	1.23	0.84–1.81	0.29
APACHE II Score >28 vs. <19	2.03	1.37–3.02	<0.01
Serum bilirubin at admission ICU			<0.01
19–39 µmol/L vs. <19 µmol/L	1.20	0.79–1.81	0.40
40–77 µmol/L vs. <19 µmol/L	1.41	0.94–2.13	0.10
>77 µmol/L vs. <19 µmol/L	2.18	1.46–3.25	<0.01
Type donor			0.02
MUD vs. MRD	1.18	0.88–1.60	0.27
Other donor vs. MRD	1.83	1.19–2.83	<0.01
MV <24 h	1.29	0.95–1.76	0.10
VA medication <24 h	1.85	1.39–2.46	<0.01
Neutropenia	0.87	0.65–1.17	0.36
RRT <24 h	1.27	0.88–1.84	0.20
Female sex	1.07	0.81–1.42	0.65
BMI	1.01	0.97–1.04	0.67
Age	1.00	0.99–1.01	0.86
Time alloSCT to ICU	1.00	1.00–1.00	0.24
Active disease	1.12	0.78–1.62	0.52
Conditioning	1.01	0.76–1.33	0.97
T cell depletion	1.07	0.80–1.42	0.65
GVHD	1.05	0.79–1.38	0.76
Immune suppression	0.85	0.59–1.21	0.37
Sepsis	0.97	0.72–1.32	0.85

OR odds ratio, *CI* confidence interval, *APACHE* Acute Physiology And Chronic Health Evaluation, *MUD* matched-unrelated donor, *MRD* matched-related donor, *MV* mechanical ventilation, VA vasoactive medication, *RRT* renal replacement therapy, *alloSCT* allogeneic stem cell transplantation, *ICU* intensive care unit, *BMI* body mass index, *GVHD* graft versus host disease

The use of an other donor than a HLA-matched-related or HLA-matched-unrelated donor, namely a haplo-identical, cord blood, or mismatched donor is associated with increased 30-day and 1-year mortality. Selecting a fully matched donor for allogeneic stem cell transplantation is based on the general concept that a direct association exists between the number of donor-recipient HLA mismatches and mortality [17]. The association of an increased ICU mortality with the use of an other donor than a HLA-matched donor confirms this general concept. However the use of an other donor than a HLA-matched donor is in general a last resort strategy and without its use the patient

Table 5 Multivariable Cox regression analysis of parameters present on ICU admission for 1-year mortality

Parameter	1-year mortality		
	OR	95% CI	*P*
Serum bilirubin at admission ICU			0.02
19–39 µmol/L vs. <19 µmol/L	1.28	0.81–2.02	0.29
40–77 µmol/L vs. <19 µmol/L	1.31	0.81–2.12	0.27
>77 µmol/L vs. <19 µmol/L	2.05	1.28–3.30	< 0.01
Type donor			0.04
MUD vs. MRD	0.99	0.70–1.39	0.93
Other donor vs. MRD	1.90	1.13–3.19	0.02
VA medication <24 h	1.65	1.12–2.43	0.01
Neutropenia	0.70	0.48–0.98	0.04

OR odds ratio, *CI* confidence interval, *MUD* matched-unrelated donor, *MRD* matched-related donor, *VA* vasoactive medication

cannot be transplanted and the hematological malignancy cannot be further treated.

Surprisingly, the presence of neutropenia is significantly associated with a decreased risk for 30-day mortality and 1 year mortality. One can hypothesize that neutropenia is potentially reversible and the patient can therefore improve and recover from infections upon repopulation of neutrophil granulocytes whereas the non-neutropenic patients are not able to benefit from this potentially reversible factor. Our findings are in line with recent studies reporting on mortality of neutropenic patients admitted to the ICU. These studies failed to demonstrate an association of neutropenia with increased mortality [18–20].

In contrast with a study by Townsend that demonstrated a superior ICU survival following reduced intensity-conditioning (RIC) alloSCT [11], in our study RIC is not associated with decreased mortality compared to MAC. In the Townsend study, the ICU mortality following MAC regimen was considerably higher compared to our present study (i.e., ICU mortality MAC patients Townsend 73% vs. 53% in our study, data not shown), explaining the different findings in both studies. The beneficial effect of RIC on ICU survival can be obscured by confounding factors negatively influencing mortality and not accounted for in our analysis. For example, although in our study not a prognostic factor, the median age of RIC patients at ICU admission was significantly higher compared to MAC patients, 56 vs. 42 years (data not shown).

To date, no comparison of ICU mortality between T cell depleted (TCD) and non-TCD is known in literature. In our large cohort more than half of the transplantations were T cell depleted. In this unique analysis no difference in mortality was present in TCD alloSCT compared to non-TCD alloSCT.

There are several limitations to our study. First, we performed a partially retrospective, albeit nationwide study and information bias and incompleteness of the data might have played a role. Information on patient selection before ICU admission is therefore lacking. Heterogeneity, for example in case mix or in delivered care might have been introduced just because of this multicenter study design. Any differences in case mix between institutions, for example severity of illness at ICU admission, we hoped to have corrected for in the multivariable analysis. Furthermore, we corrected for remaining differences between institutions, with a random effect model. The sample size and the retrospective design of our study preclude analysis of whether a combination of the predicting factors could identify groups with a particularly poor prognosis. Such an analysis of our data would need the introduction of a great number of interaction terms with the risk for multiple testing.

Second, our study is limited due to the inability to diagnose disease relapse and GVHD in our database. The presence of active disease and the presence of GVHD were determined by the primary treating clinician and not by clinical guidelines, potentially leading to errors in diagnosis. Due to the retrospective design of our study, we were unable to correct this shortcoming.

The 30-day mortality and 1-year mortality in alloSCT patients needing ICU admission within 2 years of transplantation is high with donor type, platelet count, serum bilirubin, use of vasoactive medication and neutropenia predicting outcome. These clinical factors carry the potential to add to better risk stratification of critically ill alloSCT patients and selective intensified supportive care.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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