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ORIGINAL ARTICLE

Platelet number and graft function predict intensive care survival in allogeneic stem cell transplantation patients

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Abstract

Despite significant advances in the treatment of complications requiring intensive care unit (ICU) admission, ICU mortality remains high for patients after allogeneic stem cell transplantation. We evaluated the role of thrombocytopenia and poor graft function in allogeneic stem cell recipients receiving ICU treatments along with established prognostic ICU markers in order to identify patients at risk for severe complications. At ICU admission, clinical and laboratory data of 108 allogeneic stem cell transplanted ICU patients were collected and retrospectively analyzed. Platelet counts (≤ 50,000/μl, $p < 0.0005$), hemoglobin levels (≤ 8.5 mg/dl, $p = 0.019$), and leukocyte count (≤ 1500/μl, $p = 0.025$) along with sepsis ($p = 0.002$) and acute myeloid leukemia ($p < 0.0005$) correlated significantly with survival. Multivariate analysis confirmed thrombocytopenia (hazard ratio (HR) 2.79 (1.58–4.92, 95% confidence interval (CI)) and anemia (HR 1.82, 1.06–3.11, 95% CI) as independent mortality risk factors. Predominant ICU diagnoses were acute respiratory failure (75%), acute kidney injury (47%), and septic shock (30%). Acute graft versus host disease was diagnosed in 42% of patients, and 47% required vasopressors. Low platelet (≤ 50,000/μl) and poor graft function are independent prognostic factors for impaired survival in critically ill stem cell transplanted patients. The underlying pathophysiology of poor graft function is not fully understood and currently under investigation. High-risk patients may be identified and ICU treatments stratified according to allogeneic stem cell patients' individual risk profiles. In contrast to previous studies involving medical or surgical ICU patients, the fraction of thrombocytopenic patients was larger and low platelets were a better differentiating factor in multivariate analysis than any other parameter.

Keywords Intensive care treatment · Allogeneic stem cell transplantation · Complications · Platelets · Thrombocytopenia · Anemia · Graft function

Introduction

Hematopoietic stem cell transplantation (HSCT) is associated with different complications such as infections, graft versus host disease (GVHD), and different organ failures, which may require intensive care. Deep and prolonged cytopenia occurs following conditioning and transplantation until hematopoietic cells recover [1], but may also persist in patients with poor

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graft function [2]. Due to high infection and mortality rates, HSCT patients were traditionally considered poorly suitable for intensive care treatment [3–5], but over the last years, critically ill patients with hematologic malignancies and other tumors did benefit from improved survival in intensive care units (ICU) [5–7]. Early ICU admission (< 10 days) resulted in significantly reduced mortality in patients after allogeneic transplantation [8], in neutropenic cancer patients [9], and also improved ICU outcome of hematologic patients with septic shock [10] or acute respiratory failure. The initiation of non-invasive ventilation resulted in decreased invasive ventilation rates in critically ill hematology patients [11].

Pathological blood counts, such as, e.g., the relatively high incidence of thrombocytopenia (platelets < 50,000/μl in 10% of patients [12]), have been described in a number of retrospective studies involving critically ill medical ICU patients. In a prospective, surgical ICU study, thrombocytopenia (platelets < 100,000/μl in 35% of patients) correlated with significantly higher mortality, compared to non-thrombocytopenic patients (38% versus 20% $p = 0.02$) [13]. In this study, diagnosed sepsis and Acute Physiology and Chronic Health Evaluation (APACHE) II scores > 15 were independent risk factors for thrombocytopenia, but low platelets were not an independent mortality risk factor, whereas an APACHE II score > 19 was. Thrombocytopenia (< 150,000/μl) and poor survival were also associated in a large, prospective, medical ICU trial, but the same thrombocytopenic patients also had higher Simplified Acute Physiology Score (SAPS) and APACHE II scores at admission [14], which questioned the results. Unfortunately, these findings have been poorly applicable to HSCT patients. Only 10% of the patients had a hematologic malignancy, no patients with solid tumors were included, and cohorts were separated by a high nadir at 150,000 platelets. Sepsis was the most common reason for thrombocytopenia, which again was identified as independent mortality risk factor [14]. The occurrence of thrombocytopenia associated with a higher odds ratio (OR) (6.0; 95% confidence interval (CI) 3.0–12.0) than APACHE II or SAPS II scores (OR 4.2; 95% CI 1.8–10.2), which the authors explained by higher bleeding rates. In ICU studies involving allogeneic stem cell recipients, APACHE II score [15–17], vasopressor use [15, 16], high Sequential Organ Failure Assessment (SOFA) [18, 19], Hematopoietic Cell Transplantation-specific Comorbidity Index (HCT-CI) [20] scores, and GVHD [21] have been confirmed independent mortality risk factors in multivariate analysis. Still, the above-mentioned studies remained controversial on the relative impact of each prognostic factor. Laboratory findings, such as blood counts, were not analyzed and graft function was not regarded. Poor graft function after initial engraftment, defined as insufficient production of at least two hematopoietic lineages in allogeneic stem cell recipients, is associated with severe morbidity and mortality [2, 22], related to infections or hemorrhagic complications. It may involve all three lines of leucopoiesis, myelopoiesis, and megakaryopoiesis or be limited to two lines and can be treated with a CD34+ stem cell boost [23, 24]. In allogeneic stem cell recipients, low platelet levels have been described as independent risk factor for non-relapse mortality, but this collective did not involve ICU patients [25, 26]. Persistent thrombocytopenia associated with chronic- ($p = 0.03$) but also acute graft-versus-host disease (GVHD) [26].

Although cytopenias and poor graft function may have an important role in stem cell transplanted patient survival [27], their role in HSCT patients admitted to the ICU is presently unclear. In neutropenic ICU patients, both allogeneic stem cell transplantation and patient age > 70 years were associated with poor outcome [28]. In another study involving only HSCT patients, neutropenia was not a significant predictor of ICU survival ($p = 0.11$; OR 1.79, 95% CI 0.88–3.6), while again the APACHE II score was ($p = 0.001$; OR 1.07, 95% CI 1.03–1.11) [29]. In a large, retrospective study, blood count parameters were subject to univariate analysis and low platelets < 50,000/μl correlated with survival, but were not included in the ICU risk score calculation [30], while admission for respiratory failure and bilirubin were. In a large trial of 3782 ICU patients with neutropenia and respiratory failure, 20 allogeneic stem cell recipients were included [31], who had poor overall survival. While thrombocytopenia has been confirmed as mortality risk factor for a small fraction of medical ICU patients, data on patients with hematologic malignancies, especially those with allogeneic stem cell transplantation, is sparse. The aim of this retrospective analysis was to evaluate the role of cytopenias, especially thrombocytopenia, and graft function in allogeneic stem cell recipients requiring intensive care treatments.

Materials and methods

Patients

We retrospectively analyzed clinical and laboratory data of 108 consecutive intensive care patients (≥ 18 years of age), who received allogeneic stem cell transplantation at the Department of Bone Marrow Transplantation of the University Hospital of Essen, between November 2013 and August 2016. All consecutive ICU-admitted patients were screened and only HSCT patients were analyzed. One patient had three ICU admissions for different diagnoses during the observation period. The study was conducted in accordance with Good Clinical Practice Guidelines and the amended Declaration of Helsinki. The Institutional Ethical Review Board of the University Duisburg-Essen approved the protocol (board protocol no. 15–6446-BO).

Table 1 Patient baseline characteristics

($n = 108$)	n (%)
Age	55 (21–73)
Gender	
Male	63 (58)
Diagnosis	
Acute myeloid leukemia	40 (37)
Acute lymphoblastic leukemia	11 (10)
Myelodysplastic syndrome	11 (10)
Lymphomas	15 (15)
Chronic myelogenous leukemia	10 (9)
Chronic lymphocytic leukemia	8 (7)
Osteomyelofibrosis	2 (2)
Other hematologic malignancies	11 (10)
Disease relapse	24 (22)
Conditioning	
Myeloablative conditioning	81 (75)
Reduced intensity conditioning	27 (25)
Donor	
Sibling donor	21 (19)
Unrelated donor	87 (81)
HLA mismatch	23 (21)
Graft source	
Peripheral blood stem cells (PBSC)	100 (93)
Bone marrow	8 (7)
ATG as GVHD prophylaxis	74 (69)
Graft-versus host disease	
Acute GVHD, any grade	45 (42)
Acute GVHD, grade III/IV	25 (23)
Skin, stage 3/4	18 (17)
Intestinal, stage 3/4	12 (11)
Liver, stage 3/4	5 (5)
Chronic GVHD, any grade	30 (27)
Moderate/severe, chronic GVHD	46 (43)
Days from transplantation to ICU admission, median (95% CI)	89.5 (19–402)

HLA human leukocyte antigen, ATG anti-thymocyte globulin, GVHD graft versus host disease, CI confidence interval

Units of analysis

Data was retrospectively collected and analyzed. We evaluated clinical data, such as age, gender, diagnosis, allogeneic stem cell transplantation (including date, type of conditioning therapy, use of anti-thymocyte globulin (ATG), donor human leukocyte antigen (HLA) compatibility, graft source and death date (if applicable), or date of the last visit), and acute and chronic GVHD. GVHD was clinically graded as grade 0 to IV acute GVHD [32, 33] and as mild, moderate, or severe chronic GVHD [34, 35] according to the 2014 NIH guidelines. Poor graft function was diagnosed as previously described [27, 36]. In short, it required persistent cytopenia in at least two hematologic lineages due to insufficient production. We evaluated the severity of illness at ICU admission using different scores such as Simplified Acute Physiology Score II (SAPS II) [37, 38], Acute Physiology And Chronic Health Evaluation (APACHE) score [39], and Sequential Organ Failure Assessment (SOFA) score [40]. ICU admission diagnosis and laboratory parameters (creatinine, urea, hemoglobin, leukocyte count, platelets, and bilirubin- and C-reactive protein levels) were analyzed. Data on ICU measures such as vasopressors, non-invasive and invasive mechanical ventilation, extracorporeal life support (ECLS), acute kidney injury, renal replacement therapy, and different vasopressors were collected. Acute kidney injury and acute respiratory failure were diagnosed following established definitions [41, 42]. As response and follow-up parameters, ICU, hospital survival, and 6- and 12-month survival rates were assessed.

Statistical analysis

For statistical analysis, we used Statistical Package for the Social Sciences (SPSS 23.0; SPSS Inc., Chicago, IL) and MATLAB software (MathWorks Inc., Nantick, MA). Clinico-pathological parameters were compared using chi-squared tests. Overall survival was calculated from ICU admission until death from any cause in deceased patients. Surviving patients were censored at the time of last follow-up. Time from transplantation to ICU admission was dichotomized in periods of ≤ 30 days and > 30 days as previously described [43]. Survival estimates were calculated by the product-limit method and compared by the log-rank test. The degree of thrombocytopenia was categorized as platelets $\leq 50{,}000/\mu l$ or $> 50{,}000/\mu l$, the degree of anemia was divided into hemoglobin levels ≤ 8.5 mg/dl and > 8.5 mg/dl, and the degree of neutropenia was defined as white blood cell counts $\leq 1500/\mu l$ or $> 1500/\mu l$. Differences between strata were considered statistically significant with p values < 0.05. Univariate analysis was performed for the following parameters: age > 55, age > 60, gender, disease, graft source, conditioning regimen, aGVHD, cGVHD, ICU admission diagnosis, SAPS score, interval from transplantation to ICU admission < 30 days, catecholamine exposure, mechanical ventilation, renal replacement therapy, platelets $\leq 50{,}000/\mu l$, hemoglobin ≤ 8.5 mg/dl, and leukocytes $\leq 1500/\mu l$. The independent effect of thrombocytopenia, anemia, and neutropenia on mortality was evaluated using multivariate Cox-regression model with forward and backward selection of covariates and adjustment for confounding factors. The significance of multivariate models with respect to the univariate ones have been given with

Table 2 Intensive care unit characteristics

Intensive care severity scores	Median (range)
SAPS II score	35 (8–67)
SOFA score	8 (1–21)
APACHE score	15 (2–39)
Intensive care unit admission diagnosis	*n* (%)
Acute respiratory failure	81 (75)
Acute kidney injury, all stages	51 (47)
Septic shock	32 (30)
Gastrointestinal complications[a]	32 (30)
Hepatic complications[a]	24 (22)
Cardiovascular complications[a]	22 (20)
Cutaneous complications[a]	21 (19)
Neurologic complications[a]	16 (15)
Pulmonary embolism	1 (1)
Creatinine at admission, mg/dl	0.85 (0.3–5.7)
C-reactive protein at admission, mg/dl	6.25 (0.5–42)
Catecholamines start within 24 h of ICU admission	
Norepinephrine	49 (45)
Dobutamine	9 (8)
Epinephrine	3 (3)
Kidney injury, at admission and during ICU	56 (52)
Renal replacement therapy	38 (35)
Ventilation	
Invasive mechanical ventilation	69 (64)
Noninvasive ventilation	16 (15)
Extracorporeal life support	12 (11)
Mortality rates	
Intensive care unit mortality	38 (35)
Hospital discharge mortality	73 (68)
6-month mortality	77 (71)
12-month mortality	81 (75)

SAPS II Simplified Acute Physiology score II, APACHE Acute Physiology and Chronic Health Evaluation, SOFA Sequential Organ Failure Assessment Score, ICU intensive care unit

[a] Gastrointestinal complications, intestinal bleeding, infarction; hepatic complications, acute liver failure; cardiovascular complications, acute heart failure, myocardial infarction; neurologic complications, cerebral bleeding, stroke, toxoplasmosis, JC virus—encephalitis; cutaneous complications, stage 3–4 skin GVHD, severe burn injuries

p^*, which is computed based on the cumulative chi-squared distribution function of the differences between the −2 times log-likelihood values of the univariate and multivariate models and the added number of degrees of freedom, as described in the SPSS manual and the MATLAB documentation. Covariates in the multivariate models were chosen such that the newly added risk factor improved the model by $p^* > 0.05$ with respect to the previous model. Multiple risk factors were considered as interaction terms (new risk factors).

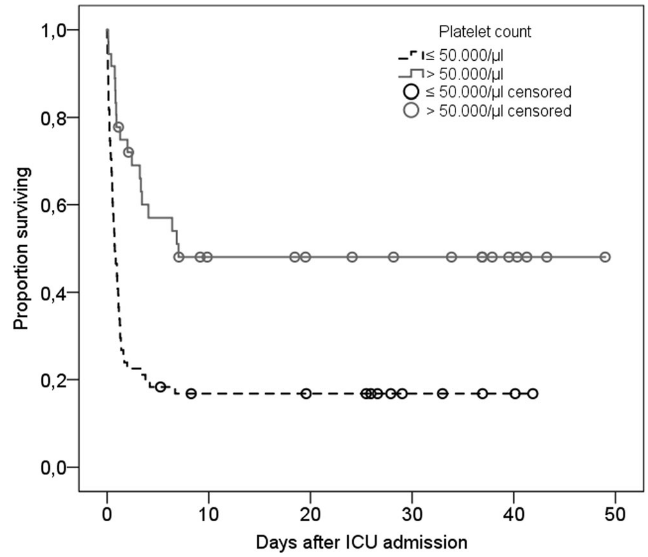

Fig. 1 Comparison of overall survival curves of patient cohorts according to platelet levels (≤ 50,000/µl versus > 50,000/µl)

Results

Patient characteristics

Patient baseline characteristics are detailed in Table 1. A total of 192 consecutive ICU-admitted patients were screened between 2013 and 2016. For analysis, 108 patients (median age 55 years (range (21–73)), who had received prior allogeneic stem cell transplantation, were included for analysis. Most common malignancies were acute myeloid leukemia (37%), followed by lymphomas (15%). Myeloablative conditioning regimens were used in 75% of patients. The preferred graft source were peripheral blood stem cells (93%), and cells came predominantly from matched unrelated donors (81%), with HLA-mismatch in 21% of patients. Acute GVHD was diagnosed in 42%, grade III–IV GVHD in 23% and chronic GVHD in 27% of patients. Clinically relevant cytomegalovirus (CMV) reactivation was detected in 15% of patients. Poor graft function as previously defined [36] with cytopenias in at least two of three cell lines was diagnosed in 51% of patients. The majority of patients (55.1%) had platelets < 30,000/µl, 51.4% had a hemoglobin value < 10 mg/dl, and 32.7% had neutrophils < 1000/µl.

Intensive care unit admission

Patients were admitted to the ICU at a median of 89.5 days (95% CI 19–402) after allogeneic stem cell transplantation. The majority of patients (80%) was admitted after day 30 of transplantation, i.e., after engraftment. The interval from HSCT to ICU admission did not correlate with survival. Leading reasons for ICU referral were acute respiratory failure (75%), acute kidney injury (47%), septic shock (30%), and

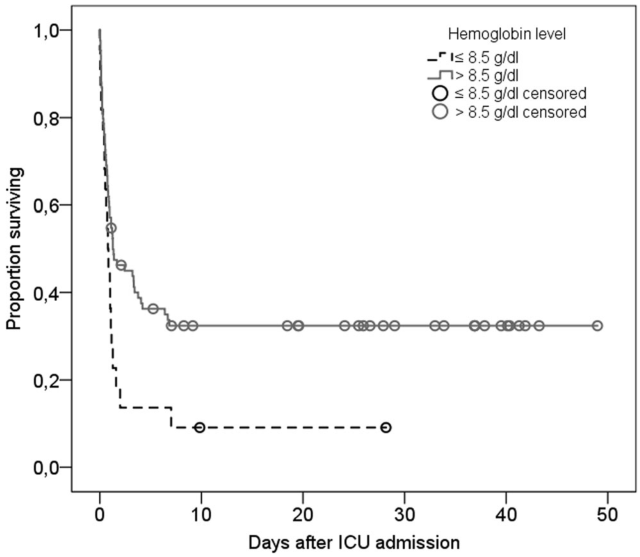

Fig. 2 Comparison of overall survival curves of patient cohorts according to hemoglobin levels (≤ 8.5 g/dl versus > 8.5 g/dl)

gastrointestinal complications (30%). Table 2 summarizes clinical and interventional ICU data. Median SAPS II score was 35 (range 8–67). Invasive and non-invasive mechanical ventilation were necessary in 64% and 15% of patients, respectively. The total number of patients with mechanical ventilation exceeded the number of patients admitted for respiratory failure, because ventilation was initiated secondary to, e.g., initial sepsis. Mechanical ventilation did not significantly correlate with reduced survival. Extracorporeal life support using veno-venous extracorporeal membrane oxygenation (vvECMO) was performed in 11% of patients. Vasopressor therapy within the first 24 h after ICU admission was necessary in 45% of patients. Vasopressor therapy and sepsis diagnosis both correlated significantly with survival. Continuous renal replacement therapy was necessary in 35% of patients and also correlated with survival.

Survival analysis

Global ICU, hospital, and 6- and 12-month mortality rates were 35%, 68%, 71%, and 75%, respectively. The majority of patients (81%) with platelets < 50,000/μl died within the first 10 days after ICU referral. The leading causes of death were lung-related, followed by septic shock and relapse (Supplement Table S1). Patients with platelets > 50,000/μl had a significantly higher survival rate (45%; $p < 0.0005$) (Fig. 1). Severely anemic patients (Hb ≤ 8.5 mg/dl) also had a significantly impaired survival rate with a mortality rate of 90% at 10 days after ICU admission compared to 35% in the group with a higher hemoglobin > 8.5 mg/dl ($p = 0.019$) (Fig. 2).

Univariate survival analysis is detailed in Table 3 and showed a significant correlation between survival and female gender, acute myeloid leukemia, myeloablative conditioning, PBMCs as graft source, SAPS score at admission, septic shock as ICU admission diagnosis, catecholamine use, renal replacement therapy, and leukopenia.

In multivariate Cox-regression analysis (Table 4), hemoglobin levels ≤ 8.5 mg/dl and platelets ≤ 50,000/μl both significantly correlated with survival (hazard ratio (HR) 1.82 (95% CI 1.06–3.11) and HR 2.79 (95% CI 1.58–4.92)) and were independent predictors for reduced overall survival in critically ill allogeneic stem cell recipients. Several significant risk factors of the univariate analysis turned out to be insignificant confounding factors, most likely as consequence of a linear dependency of cofactors. White blood cell count was not confirmed as independent factor by multivariate analysis (HR 1.09 (95% CI 0.65–1.81)). In combined multivariate analysis models (Table 4) adjusting for platelets together with other significant factors from univariate analysis, low platelets were confirmed as stronger predictors than gender, acute myeloid leukemia, SAPS score, and hemoglobin levels.

Discussion

Our results indicate that platelet number and sustained graft function correlate with ICU survival in critically ill patients after allogeneic stem cell transplantation. While previous studies established the association of platelet number and survival in general medical or surgical ICU patients, we report data from a large collective of consecutive, ICU-admitted, allogeneic stem cell transplanted patients and discuss pathophysiological mechanisms, involving graft function.

Pathophysiological explanations for thrombocytopenia in ICU patients are various including sepsis as the most common cause. The association of sepsis with thrombocytopenia correlated with poor outcome for surgical ICU patients [13]. A more recent, large medical ICU study confirmed this association in sepsis patients and suggested an association of thrombocytopenia with dysregulated host response in critically ill sepsis patients [44]. Septic patients with thrombocytopenia (< 50,000/μl) had a higher 30-day mortality (HR 2.00 (95% CI 1.32–3.05)), but patients with hematologic malignancies were excluded and the proportion of patients with platelets < 50,000/μl was low with only 6.6%. The result from our multivariate analysis (HR 2.79 (95% CI 1.58–4.92)) compared well and showed one of the first studies in an ICU population with hematologic malignancies. Patients in our study had a lower survival rate at day 30 (18% versus 45%) than in the medical ICU study, which might be explained by their allogeneic stem cell transplantation diagnosis. Previous ICU studies involving critically ill stem cell transplanted patients did not simultaneously analyze graft function. The reported ICU, hospital, and 6-month mortality rates were high with 61%, 75%,

Table 3 Univariate Cox-regression analysis of overall survival

	HR	95% CI	*P*
Hematologic			
Platelets < 50.000/µl	2.88	(1.69–4.92)	< 0.0005
Hemoglobin < 8.5 mg/dl	1.88	(1.11–3.17)	0.019
Leukocytes < 1500/µl	1.76	(1.09–2.84)	0.025
Creatinine[a]	0.74	(0.54–1.03)	0.078
CRP[a]	1.02	(1.01–1.04)	0.036
Platelets < 50.000/µl and hemoglobin < 8.5 mg/dl	3.10	(1.75–5.47)	< 0.0005
Demographic			
Age > 60	0.84	(0.52–1.35)	0.465
Age > 55	1.12	(0.72–1.74)	0.621
Gender (female)	1.82	(1.17–2.84)	0.008
Disease			
Acute myeloid leukemia	2.22	(1.43–3.45)	< 0.0005
Lymphomas	1.08	(0.52–2.22)	0.844
Graft source (PBMC versus bone marrow)	4.82	(1.18–19.7)	0.028
Disease relapse	1.11	(0.65–1.88)	0.715
Reduced intensity versus myeloablative conditioning	1.88	(0.96–2.62)	0.074
Time from transplantation to ICU admission (> 30 days)	0.88	(0.49–1.56)	0.646
SAPS score at admission (> 34.5)	1.71	(1.03–2.85)	0.039
SAPS score[a]	1.04	(1.01–1.07)	0.009
Graft versus host disease			
Acute GVHD versus no GVHD	1.54	(0.82–2.86)	0.177
Chronic GVHD versus no GVHD	1.60	(0.90–2.84)	0.111
ICU admission diagnosis			
Septic shock	2.07	(1.30–3.29)	0.002
Respiratory failure	1.10	(0.66–1.84)	0.663
Cardiovascular complication	1.30	(0.75–2.26)	0.343
Sepsis admission	1.43	(1.14–1.82)	0.002
Catecholamines within 24 h of ICU admission	2.53	(1.61–3.97)	< 0.0005
Mechanical ventilation	1.60	(0.88–0.90)	0.123
Renal replacement therapy	2.82	(1.32–3.41)	0.002
Cytomegalovirus reactivation	2.79	(1.63–4.76)	0.161

HR hazard ratio, 95% CI 95% confidence interval, *p* significant as *p* value

[a] One unit increase in SAPS corresponds to a 4% increase in the hazard rate

and 80% [45], despite low GVHD rates (63% of patients without any GVHD) and the median SOFA score was 10 (range 6–16). Patients in our cohort had a comparable SOFA score and lower 6- and 12-month mortality rates of 71% and 75%, respectively. General medical and ICU progress might explain the observed survival difference as patients in the above-mentioned study had been observed > 10 years ago. In our study, the main reason for ICU admission was respiratory failure in 75% of patients compared to 63% in a large, American HSCT patient ICU cohort [30]. Another ICU study including 70 patients after allogeneic transplantation showed 6- and 12- month mortality rates of 74% and 83.6%, respectively [46]. The observed mortality difference might be explained by the lower SAPS II score in our population (35 versus 48), lower acute GVHD rates (42% versus 100%) extent of catecholamine support, mechanical ventilation, and renal replacement therapy. In our study, thrombocytopenia (< 50,000/µl), anemia (< 8.5 mg/dl), neutropenia, sepsis, and renal replacement therapy all associated with poor outcome, but in contrast to other published studies [13], thrombocytopenia and anemia were confirmed independent risk factors in multivariate analysis. As thrombocytopenia is common among hematological patients, the incidence of low platelets (< 50,000/µl) was also higher with 66% in our study compared to published medical ICU studies with 10% [12] or 6.6% [44].

Table 4 Multivariate Cox-regression analysis of overall survival analysis

Multivariate analysis	$p*^{a}$	HR	95% CI	p
Hematologic parameters	0.011			
Platelets < 50.000/µl		2.79	(1.58–4.92)	< 0.0005
Hemoglobin < 8.5 mg/dl		1.82	(1.06–3.11)	0.030
Leukocytes < 1500/µl		1.09	(0.65–1.81)	0.747
Platelets and hemoglobin	0.032			
Platelets < 50.000/µl		2.87	(1.68–4.91)	< 0.0005
Hemoglobin < 8.5 mg/dl		1.84	(1.08–3.13)	0.025
Platelets and leukocytes	0.531			
Platelets < 50.000/µl		2.72	(1.54–4.80)	0.001
Leukocytes < 1500/µl		1.18	(0.71–1.95)	0.529
Platelets and acute myeloid leukemia	0.006			
Platelets < 50.000/µl		2.54	(1.47–4.37)	0.001
Acute myeloid leukemia		1.92	(1.20–3.03)	0.006
Platelets and SAPS	< 0.0005			
Platelets < 50.000/µl		2.34	(1.27–4.34)	0.007
SAPS[b]		1.02	(1.00–1.04)	0.053
Platelets and gender	0.037			
Platelets < 50.000/µl		2.68	(1.56–4.60)	< 0.0005
Gender (female)		1.63	(1.03–2.58)	0.036
Platelets and sepsis admission	0.021			
Platelets < 50.000/µl		2.70	(1.58–4.64)	< 0.0005
Sepsis admission		1.79	(1.11–2.89)	0.017
Hematologic and sepsis admission	0.047			
Platelets < 50.000/µl		2.67	(1.55–4.60)	< 0.0005
Hemoglobin < 8.5 mg/dl		1.77	(1.03–3.02)	0.038
Sepsis admission		1.74	(1.07–2.82)	0.025
Hematologic model with interaction terms	0.012			
Platelets < 50.000/µl		2.48	(1.42–4.33)	0.001
Platelets < 50.000/µl and hemoglobin < 8.5 mg/dl		2.21	(1.23–3.98)	0.008

HR hazard ratio, 95% CI 95% confidence interval, p significant as p value

[a] $p*$ is the significance of the multivariate model to univariate model with only platelet category

[b] One-unit increase in SAPS corresponds to a 2% increase in the hazard rate

The exact pathophysiology of low platelet counts in critically ill patients is not fully understood and their role in innate immunity and sepsis is under investigation. High platelet transfusion rates associated with increased mortality and a need for ICU measures in transplanted patients [47]. On the other hand, a comparison of restrictive with non-restrictive transfusion practice showed a survival benefit in the intensively transfused cohort [48]. Inflammatory signal molecules, endothelial markers such as soluble ICAM1 or fractalkine, along with interleukin 10 and complement system pathway genes were significantly upregulated in sepsis patients with very low platelets, while leukocyte mobility genes were downregulated [44]. Preclinical findings from murine models suggested that platelets might limit bacterial growth through the activation of toll-like-receptor 4 in the presence of neutrophils [49], influenced immune cell migration through P-selectin expression [50], and inhibited macrophage function through a cyclooxygenase1-dependent pathway [51]. In non-ICU patients with prolonged, isolated thrombocytopenia after HSCT bone marrow examinations revealed megakaryocyte abnormalities including a significant shift toward immature cells (left shift) [52]. Their bone-marrow microenvironment was altered. Th1, Tc1, and Th17 cells were upregulated [53] and endothelial progenitor cells were significantly reduced [54].

Our study has a number of limitations due to its retrospective character and its single specialized cancer center ICU data basis. Neutrophil counts were not available for all 108 patients. The higher prevalence of thrombocytopenia might explain the confirmation of low platelets as independent risk factor in multivariate analysis. Prospective ICU studies are warranted for critically ill patients after allogeneic stem cell transplantation in order to validate the recently discussed simple and readily available outcome predictors for clinical decision-making.

Conclusion

In summary, our data show that low platelets as well as impaired graft function with low hemoglobin levels were independent prognostic factors for decreased survival in critically ill patients, who had received allogeneic stem cell transplantation. This is one of the first ICU studies analyzing graft function in HSCT patients. In contrast to previous studies involving medical ICU patients, the fraction of thrombocytopenic patients was larger and low platelets were a better differentiating factor in multivariate analysis than any other parameter.

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Authors' contributions TL, WL, and ATT designed the study. EB, WL, and ATT performed the statistical analysis. CS and WL performed the data collection. PW, MM, and FA participated in the data acquisition and analysis. ATT and TL wrote the manuscript. WL, DWB, and CS contributed to the writing of the manuscript. All authors read and approved the final manuscript.

Compliance with ethical standards

The study was conducted in accordance with Good Clinical Practice Guidelines and the amended 1964 Declaration of Helsinki. The Institutional Ethical Review Board of the University Duisburg-Essen approved the protocol (board protocol no. 15–6446-BO).

Conflict of interest ATT has received lecture fees from Jazz Pharmaceuticals and travel subsidies from Neovii Biotech outside the submitted work. The other authors declare that they have no conflict of interest.

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