Article

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Association of Red Blood Cell Transfusion Burden on Clinical Outcome After Allogeneic Hematopoietic Stem Cell Transplantation

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Background: Patients undergoing allogeneic hematopoietic stem cell transplantation (alloHSCT) frequently require red blood cell (RBC) transfusions. Immunomodulation by RBC transfusion is of great interest in the context of alloHSCT, as donor immune cells mediate tumor control, fight pathogens, but also cause graft-*versus*-host disease (GvHD), a potentially lethal complication of alloHSCT. Data linking RBC transfusion burden with relevant clinical outcome parameters after alloHSCT are scarce.
Methods: In this retrospective study, we examined the association between RBC transfusion burden and clinical outcomes in a cohort of 116 patients who underwent alloHSCT at a single transplant center. Therefore, we analyzed the impact of RBC transfusion burden on the following relevant outcomes after alloHSCT: overall survival, leukocyte engraftment, GvHD incidence, and infection rate.
Results: Reduced transfusion frequencies, both before ($p = 0.003$) and after ($p = 0.002$) alloHSCT, are associated with favorable survival rates 100 days after transplantation. In line, those patients showed an earlier leukocyte engraftment ($p < 0.001$). However, no significant association was found between the transfusion rate and the incidence of grade II–IV acute GvHD (aGvHD) ($p = 0.87$). Notably, it was not the frequency of pre-transplant RBC transfusions ($p = 0.05$), but rather an increased post-transplant transfusion rate ($p < 0.001$), that was significantly associated with a lower infection rate, particularly with infections within the first 21 days following alloHSCT ($p < 0.001$ for post-transplant transfusions).
Conclusion: In summary, our data support recent evidence that high RBC transfusion burden is associated with poor survival. GvHD incidence was not linked to RBC transfusion, but we were able to detect a negative association with infectious complications. Larger, multi-center trials are needed to confirm our findings, accompanied by molecular analysis of RBC–immune cell interactions.

Keywords: red blood cell transfusion; allogeneic stem cell transplantation; GvHD; infection; overall survival

Introduction

A high transfusion burden is associated with worse outcomes and poorer survival in critically ill patients [1]. Approaches in *patient blood management* aim to reduce the frequency of red blood cell (RBC) transfusions [2], and in critically ill patients, a more restrictive transfusion regimen is not inferior to a more liberal strategy [3]. Additionally, an increased infection rate after surgery is associated with RBC transfusion in a dose-dependent manner [4]. However, there exists some controversy, as other studies investigating a large cohort of patients requiring RBC transfusion for different medical indications, could not associate a restrictive or more liberal transfusion regimen with different outcomes regarding 30-day mortality [5,6]. Additionally, a more liberal transfusion regimen was not associated with an increased risk of infection in a meta-analysis including more than 21,000 patients [6]. Therefore, it remains unclear whether an increased transfusion rate merely identifies patients who are severely ill and have significant comorbidi-

ties or whether RBC transfusion itself influences survival or infection rates.

Improved screening procedures have minimized the risk of infectious complications of RBC transfusions. Nevertheless, noninfectious serious hazards have to be taken into account [7] as RBCs modulate immune cell function [8–11]. Moreover, transfusion-related immunomodulatory effects have been described due to the persistence of allogeneic mononuclear cells, white-blood-cell-derived soluble mediators, and soluble human leukocyte antigen (HLA) peptides circulating in allogeneic plasma [12,13]. Additionally, transfusion-induced iron overload may dampen T cell responses [14].

We have shown previously that transfusion burden influences the outcome of patients treated with immune checkpoint inhibitors [15]. In line, modulation of immune cell responses, especially T cell responses, is of high interest in the context of allogeneic hematopoietic stem cell transplantation (alloHSCT). AlloHSCT is a curative therapeutic option for hematological malignancies achieved by immunological tumor control by allogeneic immune cells. Novel approaches aim to identify whether a more restrictive transfusion regimen is associated with improved outcomes in patients with hematological malignancies and show noninferiority when investigating a cohort of patients undergoing allo- or autologous HSCT [16,17]. However, these studies also included patients undergoing autologous stem cell transplantation, where allogeneic immunological tumor control does not play a role.

Acute graft-versus-host disease (aGvHD) is characterized by inflammation of the gut, skin, or liver by activated alloreactive T cells, which are the effector cells of this life-threatening complication of alloHSCT [18]. Dampening T cell proliferation results in decreased rates of GvHD. On the other hand, T cells are the main effector cells fighting viral infections [19]. Given the clinical relevance of both infection control and GvHD development, the interplay between immune cells and transfused RBC units is of particular interest.

To investigate the concomitance of RBC transfusion in the peri-transplant setting, we retrospectively reviewed 116 patients undergoing alloHSCT and analyzed the association of pre-transplant and post-transplant RBC transfusion on mortality, engraftment, incidence of aGvHD, and infectious complications.

Methods

Patients

In this retrospective single-center study, patients >18 years undergoing their first allogeneic hematopoietic stem cell transplantation between October 2012 and February 2016 were included. Analysis of patients undergoing the second allogeneic hematopoietic stem cell transplantation was excluded. Follow-up was conducted until death or 100 days after the date of transplantation. We analyzed 116 patients transplanted for acute lymphatic leukemia (ALL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML), multiple myeloma (MM), myelodysplastic syndrome (MDS), non-Hodgkin lymphoma (NHL), chronic myelomonocytic leukemia (CMML), or myelofibrosis (MF) (Table 1). Hematopoietic cell transplantation–specific comorbidity index (HCT-CI) score and age-adjusted HCT-CI score were calculated as reported previously [20,21]. The European Society for Blood and Marrow Transplantation (EBMT) score was calculated according to Gratwohl *et al*. [22].

Medical records of all patients were reviewed to identify the date and number of RBC transfusions 30 days before and 100 days after transplantation. There was no restriction on the RBC transfusion rate, and patients received RBC concentrates upon clinical indication.

Leukocyte engraftment was defined as the first day with an absolute neutrophil count >500/µL and no further decline in the next two days [23].

GvHD was scored according to the local pathologist and clinical examination by physicians of the bone marrow transplant unit. Staging of acute GvHD according to Harris *et al*. [24] was performed.

The onset of infection was identified by clinical examination in combination with laboratory or diagnostic results (PCR for viral infection/reactivation, detection range for Epstein-Barr virus (EBV) >500 IU/mL and cytomegalovirus (CMV) >500 IU/mL, blood culture for bacterial and fungal infection, CT scan with typical signs for fungal or bacterial infection). A sole rise in C-reactive protein (CRP) was not classified as infection; either clinical correlation, clinical improvement upon antibiotic treatment, or the identification of a pathogen in combination with CRP elevation was mandatory. Patients received antibiotic prophylaxis with fluoroquinolone and antiviral prophylaxis with acyclovir. Moreover, every patient received prophylaxis for pneumocystis infection.

The study was approved by the local ethics committee of the University Hospital Bonn (2022-419). As a retrospective analysis was performed, no informed patient consent was mandatory according to the local ethics committee.

Statistical Analysis

SPSS version 27 (IBM, Armonk, NY, USA) and R version 4.1.2 (R Foundation for statistical computing, Vienna, Austria) were used to perform statistical analysis. Patient characteristics are presented as median (range) for continuous variables and counts and percentages for categorical variables.

A cause-specific Cox regression model with time-varying variables was used to account for the temporal changes in the absolute number of RBC concentrates and to investigate their association between the number of RBC concentrates and mortality, aGvHD, engraftment, and infection rate.

Table 1. Patient baseline characteristics.

		N	%			N	%
Sex	Female	57	49.1	Mismatch	MRD	28	24.1
	Male	59	50.9		MUD	63	54.3
					MMUD	17	14.7
Transplant indication							
	ALL	11	9.5		haplo	8	6.9
	AML	57	49.1	Conditioning intensity	NMA	8	6.9
	CML	1	0.9		RIC	97	83.6
	MM	3	2.6		MAC	11	9.5
	MDS	14	12.1	TBI	no	85	73.3
	NHL	18	15.5		yes	31	26.7
	MF	10	8.6	GvDH Prophylaxis	CsA/MTX	18	15.5
	CMML	2	1.7		CsA/MMF	77	66.4
Graft source	PBSC	107	92.2		Tac/MMF	12	10.3
	BM	9	7.8		Other	9	1.9

GvHD Prophylaxis: others: six patients received Sirolimus/MMF, two tacrolimus, MMF and cyclophosphamide, and one patient tacrolimus and MTX. ALL, acute lymphatic leukemia; AML, acute myeloid leukemia; BM, bone marrow; CML, chronic myeloid leukemia; MM, multiple myeloma; MDS, myelodysplastic syndrome; NHL, non-Hodgkin lymphoma; MF, myelofibrosis; CMML, chronic myelomonocytic leukemia; PBSC, peripheral blood stem cells; MRD, matched related donor; MUD, matched unrelated donor; MMUD, mismatch unrelated donor; haplo, haploident donor; NMA, non-myeloablative; RIC, reduced intesity conditioning; MAC, myeloablative conditioning; TBI, total body irradiation; GvHD, graft-versus-host disease; MMF, mycophenolate mofetil; MTX, methotrexate; CsA, cyclosporine A; Tac, tacrolimus.

The association between the number of RBC concentrates and response variables was analyzed by taking into account all RBC concentrates (i) post-alloHSCT, (ii) pre-alloHSCT, and (iii) pre-and post-alloHSCT.

Univariable and multivariable Cox regression models were conducted. Analyzing aGvHD incidence, the models were adjusted for known risk factors, age, unrelated donor, female donor for a male recipient, intensive conditioning regimen, or a conditioning regimen containing total body irradiation (TBI) [25–29].

Cox-regression models were adjusted for specific covariates depending on the outcome: for engraftment, adjustments included graft sources [30,31], recipient sex and age and general diagnosis [30]; for infection rate, adjustments included previous GvHD [32], leukocyte engraftment, TBI, intensive conditioning regimen [33] and the combination of a CMV-positive recipient with a CMV-negative donor [34].

For all analyses, hazard ratios (HR) with 95% confidence intervals (CIs) are shown. For example, an HR >1 implies that for every unit increase in the explanatory variable, there is a corresponding increase in the hazard of experiencing the event; an HR <1 implies a decrease in the hazard of experiencing the event. The association of transfusional burden and engraftment was analyzed by applying Tukey's multiple comparison test.

For illustrative purposes, extended Kaplan-Meier Plots for time-varying covariates are shown, stratified by patients receiving less than 5, 5 to 9, and 10 or more RBC units.

Table 2. Patient characteristics.

	Median	Min.	Max.
Age	58.0	18.0	73.0
Sorror score	4.0	1.0	14.0
EBMT score	4.0	1.0	7.0
Pre transplant RBC transfusion	2	0	22
Post transplant RBC transfusion	8	0	54
RBC transfusion until day 21	7	0	32
Leukocyte engraftment	14	0	22

EBMT, European Society for Blood and Marrow Transplantation; RBC, red blood cell.

Results

In this study, we included 116 patients undergoing their first alloHSCT. The median age was 58 years [range 18–73], and 49.1% were female. Median HCT-CI score was 4 [range 1–14], median EBMT score was 4 [range 1–7]. Most patients were transplanted for AML (49.1%), followed by NHL (15.5%) and MDS (12.1%). 92.2% of patients received peripheral blood stem cells, and 54.3% had a matched unrelated donor. Most patients received reduced intensity conditioning (83.6%). Post-transplant GvHD prophylaxis was mostly a combination of ciclosporin A and mycophenolate mofetil (66.4%). Within the first 100 days after transplantation, patients received a median of 8 red blood cell concentrates [range 0–54]. Additional patient characteristics are listed in Tables 1,2.

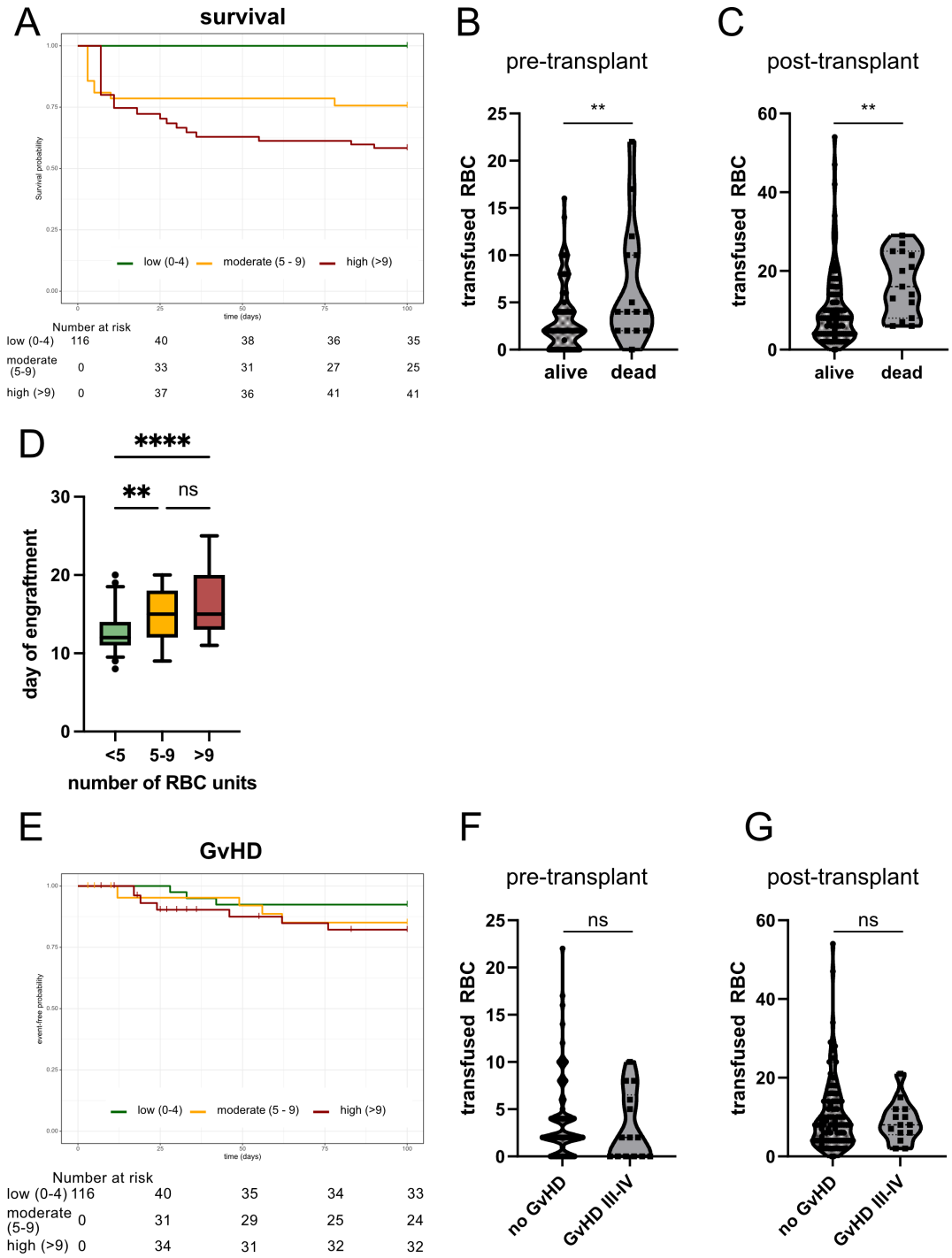

Fig. 1. The association of transfusion rate with overall survival, engraftment, and severe aGvHD. Extended Kaplan Meier plot for time-varying covariates depicting overall survival of our cohort (A). Violin plot showing cumulative number of transfused RBC units before (B) and after (C) alloHSCT, comparing those patients who survived or died within the first 100 days after alloHSCT. Bar chart depicting cumulative transfused RBC units after alloHSCT for patients receiving 0–4, 5–9, or more than 9. Only the 109 patients who experienced engraftment of neutrophil granulocytes were shown; 7 patients did not reach engraftment as they died before (D). The cumulative incidence of severe GvHD (12.5%) is shown in (E). Violin plot showing transfused RBC units of patients, who either developed GvHD (grade III–IV) compared with those who did not. The median number of transfused RBC units before alloHSCT for patients with or without GvHD is depicted in (F), respectively, (G) for post-alloHSCT transfusion rate. alloHSCT, allogeneic hematopoietic stem cell transplantation; GvHD, graft-versus-host disease; aGvHD, acute GvHD. **: $p < 0.01$; ****: $p < 0.0001$; ns: not significant.

Table 3. Survival analysis.

Variable	Beta (SE)	HR (95% CI)	*p*
Post-transplant transfusion rate			
RBC units	0.07 (0.02)	1.07 (1.03, 1.11)	<0.001
Adjusted association			
RBC units	0.06 (0.02)	1.06 (1.02, 1.10)	0.002
Age	0.03 (0.03)	1.03 (0.98, 1.09)	0.23
HCT-CI-score	0.14 (0.08)	1.15 (0.99, 1.35)	0.07
EBMT-score	0.21 (0.22)	1.23 (0.80, 1.91)	0.35
Pre-transplant transfusion rate			
RBC units	0.19 (0.05)	1.20 (1.09, 1.33)	<0.001
Adjusted association			
RBC units	0.16 (0.05)	1.17 (1.05, 1.30)	0.003
Age	0.02 (0.03)	1.02 (0.97, 1.08)	0.42
HCT-CI-score	0.08 (0.09)	1.09 (0.91, 1.30)	0.35
EBMT-score	0.26 (0.24)	1.30 (0.82, 2.06)	0.27
Overall transfusion rate			
RBC units	0.06 (0.01)	1.06 (1.03, 1.09)	<0.001
Adjusted association			
RBC units	0.05 (0.02)	1.06 (1.02, 1.09)	<0.001
Age	0.03 (0.03)	1.03 (0.97, 1.09)	0.30
HCT-CI-score	0.13 (0.08)	1.14 (0.97, 1.34)	0.10
EBMT-score	0.18 (0.23)	1.20 (0.77, 1.88)	0.42

HCT-CI, hematopoietic cell transplantation–specific comorbidity index; HR, hazard ratio; CI, confidence interval; SE, standard error.

Survival

Overall survival after alloHSCT within the first 100 days was 87.1%. Transfusion of more RBC concentrates post alloHSCT was significantly associated with higher mortality risk ($p < 0.001$, HR 1.07 [1.03, 1.11]), which was also significant in a multivariate analysis containing patient age, HCT-CI, and EBMT score ($p = 0.002$, HR 1.06 [1.02, 1.10]. Reduced frequency of RBC transfusion before alloHSCT was associated with longer survival time in an univariate analysis ($p < 0.001$, HR 1.20 [1.09, 1.33] and in an adjusted regression model ($p = 0.003$, HR 1.17 [1.05, 1.30]). In line, combining transfusion of RBC units pre- and post-alloHSCT was significantly associated with shorter survival time ($p < 0.001$, HR 1.06 [1.03, 1.09]) and in an adjusted model ($p < 0.001$, HR 1.06 [1.02, 1.09]) (Table 3 and Fig. 1A–C).

Leukocyte Engraftment

Patients reached leukocyte engraftment median at day 14 [range 0–22]. A total of 7 patients died before engraftment of leukocytes. The cumulative number of transfused red blood cell concentrates after alloHSCT was significantly higher in patients presenting with later leukocyte engraftment ($p < 0.001$, HR 0.78 [0.74, 0.82]). In an adjusted analysis, including known risk factors (age, graft source, transplantation for myelodysplastic syndrome), the association of RBC transfusion was more pronounced ($p < 0.001$, HR 0.77 [0.72, 0.82]). Also, the number of pre-transplant transfused RBC concentrates was significantly associated with later engraftment ($p < 0.001$, HR 0.89 [0.84, 0.94]), but in an analysis adjusted for the above-mentioned risk factors, the effect was smaller ($p = 0.01$, HR 0.92 [0.86, 0.98]). Combining transfused RBC concentrates pre- and post-transplantation, we detected a significant association between transfused RBC concentrates and the time to engraftment in univariable ($p < 0.001$, HR 0.87 [0.83, 0.90]) and multivariate analysis ($p < 0.001$, HR 0.87 [0.83, 0.90]). Comparing different cohorts, median day of engraftment was significantly earlier (day 12.8) for patients transfused with less than 5 RBC concentrates, compared to the cohort receiving 5–9 RBC untis (median 14.94 days to engraftment, $p = 0.0092$ in Tukey's multiple comparision test) or equal or more than 10 RBC units (median 16.52 days to engraftment, $p < 0.0001$ in Tukey's multiple comparision test) (Table 4 and Fig. 1D).

GvHD Incidence

Thirty-eight patients were found to have developed aGvHD of any grade. 60.5% affected the skin, 18.4% the gut, 7.9% skin and gut, and 10.5% the liver. GvHD (grade II–IV), staged according to Harris *et al.* [24], was diagnosed in 21.6%, and severe GvHD (grade III–IV) affected 11.2% of patients. No association between the incidence of GvHD (grade II–IV) and the number of transfused RBC concentrates after alloHSCT ($p = 0.60$, HR 0.98 [0.92, 1.05] and $p = 0.63$, HR 0.98 [0.91, 1.06] in a multivariate analy-

Table 4. Analysis of engraftment.

Variable	Beta (SE)	HR (95% CI)	*p*
Post-transplant transfusion rate			
RBC units	–0.25 (0.03)	0.78 (0.74, 0.82)	<0.001
Adjusted association			
RBC units	–0.26 (0.03)	0.77 (0.72, 0.82)	<0.001
Diagnosis	–0.39 (0.37)	0.68 (0.33, 1.41)	0.30
Graft source	–1.25 (0.41)	0.29 (0.13, 0.63)	0.002
Age	0.02 (0.01)	1.02 (1.00, 1.04)	0.02
Sex			
Female (ref)	–	–	–
Male	–0.62 (0.20)	0.54 (0.36, 0.80)	0.002
Pre-transplant transfusion rate			
RBC units	–0.12 (0.03)	0.89 (0.84, 0.94)	<0.001
Adjusted association			
RBC units	–0.08 (0.03)	0.92 (0.86, 0.98)	0.01
Diagnosis	–1.24 (0.39)	0.29 (0.13, 0.62)	0.001
Graft source	–0.65 (0.38)	0.52 (0.25, 1.09)	0.08
Age	0.03 (0.01)	1.03 (1.01, 1.05)	<0.001
Sex			
Female (ref)	–	–	–
Male	–0.70 (0.21)	0.50 (0.33, 0.75)	0.001
Overall transfusion rate			
RBC units	–0.14 (0.02)	0.87 (0.83, 0.90)	<0.001
Adjusted association			
RBC units	–0.14 (0.02)	0.87 (0.83, 0.90)	<0.001
Diagnosis	–0.20 (0.39)	0.82 (0.38, 1.74)	0.60
Graft source	–0.93 (0.38)	0.39 (0.19, 0.83)	0.01
Age	0.03 (0.01)	1.03 (1.01, 1.04)	0.002
Sex			
Female (ref)	–	–	–
Male	–0.62 (0.20)	0.54 (0.36, 0.80)	0.002

sis) and before alloHSCT (p = 0.95, HR 1.00 [0.90, 1.12], and p = 0.95, HR 1.00 [0.88, 1.13] in multivariate analysis, or overall transfusion rate (p = 0.69, HR 0.99 [0.94, 1.04] and p = 0.68, HR = 0.99 [0.93, 1.05]) was found (data not shown). For high-grade GvHD (grade III–IV), there was again no significant association with the number of RBC concentrates transfused before transplant (p = 0.93, HR 0.99 [0.84, 1.17], p = 0.94, HR 0.99 [0.83, 1.18] for multivariate analysis), after transplant (p = 0.88, HR 1.01 [0.94, 1.08], p = 0.81, HR 1.01 [0.93, 1.09] for multivariate analysis) or in a combined analysis (p = 0.93, HR 1.00 [0.95, 1.06], p = 0.87, HR 1.01 [0.94, 1.08] for multivariate analysis) (Table 5 and Fig. 1E–G).

Infection Rate and Viral Reactivation

Infection and/or viral reactivation were diagnosed in 77.6% of patients. Among them, 52.2% developed a viral infection or CMV/ EBV/herpes simplex virus (HSV) reactivation (median 31 days after transplantation, with 51% CMV (24 patients), 16.3% EBV (9 patients), 18.4% herpes virus (4 patients) reactivations, and 14.3% other viral infections). Non-viral infections occurred earlier (median after 5 days), and 72.2% of these infections were classified as fever of unknown origin, while 19% had proven bacterial infection and 8.9% had proven fungal infection.

In our study, higher post-transplantation transfusion rates were associated with reduced occurrence of any infection ($p < 0.001$, HR 0.86 [0.80, 0.92]), which was consistent in a multivariate analysis adjusted for known risk factors to develop an infection ($p < 0.001$, HR 0.85 [0.80, 0.91]). These are patients with previous GvHD (1), patients who either received total body irradiation (2) or myeloablative conditioning (3), patients with later leukocyte engraftment (4), and a combination of CMV-positive recipients with CMV-negative donors (5).

The number of transfused RBC concentrates before transplant, in contrast, was not associated with the incidence of infection (p = 0.21, HR 1.03 [0.98, 1.08] and p = 0.31, HR 1.03 [0.97, 1.09] for multivariate analysis).

If both pre- and post-transplant RBC transfusions were considered cumulatively, a lower overall transfusion burden

Table 5. Analysis of Graft-versus-Host disease.

Variable	Beta (SE)	HR (95% CI)	*p*
Post-transplant transfusion rate			
RBC units	0.01 (0.04)	1.01 (0.94, 1.08)	0.88
Adjusted association			
RBC units	0.01 (0.04)	1.01 (0.93, 1.09)	0.81
Age	–0.00 (0.02)	1.00 (0.95, 1.05)	0.90
Sex match			
Low risk (ref)	–	–	
High risk	–0.24 (0.80)	0.78 (0.16, 3.77)	0.76
Donor type	0.33 (0.68)	1.39 (0.37, 5.22)	0.63
TBI			
No (ref)	–	–	
Yes	0.74 (0.57)	2.10 (0.69, 6.42)	0.19
Conditioning intensity	0.19 (0.89)	1.21 (0.21, 6.94)	0.83
Pre-transplant transfusion rate			
RBC units	–0.01 (0.08)	0.99 (0.84, 1.17)	0.93
Adjusted association			
RBC units	–0.01 (0.09)	0.99 (0.83, 1.18)	0.94
Age	–0.00 (0.02)	1.00 (0.95, 1.05)	0.88
Sex match			
Low risk (ref)	–	–	
High risk	–0.21 (0.81)	0.81 (0.17, 3.95)	0.79
Donor type	0.35 (0.68)	1.42 (0.38, 5.32)	0.61
TBI			
No (ref)	–	–	
Yes	0.73 (0.57)	2.08 (0.68, 6.33)	0.20
Conditioning intensity	0.17 (0.92)	1.18 (0.19, 7.18)	0.86
Overall transfusion rate			
RBC units	0.00 (0.03)	1.00 (0.95, 1.06)	0.93
Adjusted association			
RBC units	0.01 (0.03)	1.01 (0.94, 1.08)	0.87
Age	–0.00 (0.02)	1.00 (0.95, 1.05)	0.90
Sex match			
Low risk (ref)	–	–	
High risk	–0.24 (0.81)	0.78 (0.16, 3.82)	0.76
Donor type	0.33 (0.68)	1.39 (0.37, 5.26)	0.62
TBI			
No (ref)	–	–	
Yes	0.74 (0.57)	2.09 (0.69, 6.37)	0.19
Conditioning intensity	0.20 (0.90)	1.23 (0.21, 7.11)	0.86

was associated with a higher risk of infection ($p = 0.005$, HR 0.95 [0.92, 0.99] and $p = 0.002$, HR 0.94 [0.91, 0.98] for multivariate analysis) (Table 6 and Fig. 2A–C).

Analyzing only viral infections and reactivations, an increased transfusion rate after alloHSCT was associated with a lower incidence of viral infections in a multivariate analysis ($p = 0.04$, HR 0.95 [0.90, 1.00]), but not in univariate analysis ($p = 0.30$, HR = 0.98 [0.93, 1.02]). The pre-transplant number of RBC concentrates did not affect the viral infection rate ($p = 0.54$, HR 0.97 [0.89, 1.06]; $p = 0.27$, HR 0.95 [0.87, 1.04] for multivariate analysis). However, combined analysis of peri-transplant RBC transfusion showed a significant association regarding viral infection in a multivariate analysis, but not in univariate analysis ($p = 0.29$ in univariate analysis and $p = 0.04$, HR 0.96 [0.93, 1.00] in multivariate analysis) (Table 7 and Fig. 2D–F).

As the majority of RBC concentrates (67.4%, n = 884) were transfused and most infections (92.2% of all infection events) occurred within the first 21 days following alloHSCT, we performed a more detailed analysis of this time period and identified an association between post-alloHSCT RBC transfusions and infection incidence in both univariate and multivariate analyses ($p < 0.001$, HR 0.86 [0.79, 0.93]; ($p < 0.001$, HR 0.83 [0.76, 0.90]. Regarding pre-transplant and peri-transplant (day-30 to day+21) transfusion of RBC concentrates, results were different. As pre-transplant RBC transfusion does not show significant association of RBC transfusion and early infections in univariate

Table 6. Analysis of infectious complications.

Variable	Beta (SE)	HR (95% CI)	*p*
Post-transplant transfusion rate			
RBC units	–0.16 (0.04)	0.86 (0.80, 0.92)	<0.001
Adjusted association			
RBC units	–0.16 (0.03)	0.85 (0.80, 0.91)	<0.001
TBI			
No (ref)	–	–	
Yes	–0.17 (0.27)	0.84 (0.50, 1.43)	0.53
Conditionig intesity	1.15 (0.37)	3.15 (1.52, 6.52)	0.002
High risk CMV constellation	0.43 (0.30)	1.54 (0.85, 2.79)	0.15
Leukocyte engraftment	–4.68 (0.47)	0.01 (0.00, 0.02)	<0.001
GvHD (grade II–IV)	–0.02 (0.47)	0.98 (0.39, 2.44)	0.96
Pre-transplant transfusion rate			
RBC units	0.03 (0.02)	1.03 (0.98, 1.08)	0.21
Adjusted association			
RBC units	0.03 (0.03)	1.03 (0.97, 1.09)	0.31
TBI			
No (ref)	–	–	
Yes	–0.09 (0.27)	0.92 (0.54, 1.54)	0.74
Conditionig intesity	1.22 (0.37)	3.39 (1.63, 7.04)	0.001
High risk CMV constellation	–0.54 (0.30)	0.58 (0.32, 1.05)	0.07
Leukocyte engraftment	–4.24 (0.38)	0.01 (0.01, 0.03)	<0.001
GvHD (grade II–IV)	–0.08 (0.48)	0.92 (0.36, 2.38)	0.87
Overall transfusion rate			
RBC units	–0.05 (0.02)	0.95 (0.92, 0.99)	0.005
Adjusted association			
RBC units	–0.06 (0.02)	0.94 (0.91, 0.98)	0.002
TBI			
No (ref)	–	–	–
Yes	–0.08 (0.27)	0.92 (0.54, 1.56)	0.76
Conditionig intesity	0.98 (0.37)	2.67 (1.29, 5.54)	0.008
High risk CMV constellation	0.01 (0.31)	1.01 (0.55, 1.88)	0.96
Leukocyte engraftment	–4.47 (0.42)	0.01 (0.01, 0.03)	<0.001
GvHD (grade II–IV)	0.24 (0.47)	1.27 (0.50, 3.22)	0.61

CMV, cytomegalovirus.

($p = 0.52$, HR 1.02 [0.97, 1.07]) or multivariate analysis ($p = 0.05$, HR 1.06 [1.00, 1.12], a combined analysis of transfusion in the peri-alloHSCT period until day 21 showed only significant association in univariate analysis ($p = 0.04$, HR 0.96 [0.92, 1.00]) but not in multivariate analysis ($p = 0.12$, HR 0.96 [0.92, 1.01]) (Table 8 and Fig. 2G–I).

Discussion

Thrombocytopenia and anemia have been identified as independent risk factors for mortality in patients admitted to the intensive care unit after alloHSCT [35]. Further, reduced hemoglobin levels before transplant have been identified as an independent risk factor for (a) higher transfusion burden peri-alloHSCT and (b) increased 6-month mortality after alloHSCT [36]. These results are consistent with the observation that a higher transfusion burden correlates with poorer overall survival post-alloHSCT [37,38]. This finding is corroborated by the significant association between elevated pre-transplant ferritin levels—an indicator of a high transfusion burden—and reduced overall survival [39]. Mechanistically, excessive iron overload may contribute in part to poor outcomes as well [40], but there is a lack of studies providing mechanistic insight into the relationship between iron overload caused by extensive transfusion and poor survival. While our findings corroborate that reduced frequencies, both pre- and post-transplantation transfused RBC units are associated with improved survival, the question of causality remains unresolved. It is unclear whether patients requiring more transfusions are more severely ill, or if the high transfusion rate itself adversely affects patient outcomes. Notably, in multivariate analysis, a higher HCT-CI or EBMT score, reflecting the comorbidities of these patients, did not show a significant association

Table 7. Analysis of viral infections.

Variable	Beta (SE)	HR (95% CI)	*p*
Post-transplant transfusion rate			
RBC units	–0.02 (0.02)	0.98 (0.93, 1.02)	0.30
Adjusted association			
RBC units	–0.05 (0.03)	0.95 (0.90, 1.00)	0.04
TBI			
No (ref)	–	–	
Yes	–0.71 (0.39)	0.49 (0.23, 1.05)	0.07
Conditionig intesity	0.43 (0.50)	1.54 (0.58, 4.09)	0.39
High risk CMV constellation	0.80 (0.41)	2.23 (1.01, 4.95)	0.05
Leukocyte engraftment	–2.89 (0.50)	0.06 (0.02, 0.15)	<0.001
GvHD (grade II–IV)	0.74 (0.33)	2.09 (1.09, 4.00)	0.03
Pre-transplant transfusion rate			
RBC units	–0.03 (0.04)	0.97 (0.89, 1.06)	0.54
Adjusted association			
RBC units	–0.05 (0.04)	0.95 (0.87, 1.04)	0.27
TBI			
No (ref)	–	–	
Yes	–0.73 (0.39)	0.48 (0.23, 1.03)	0.06
Conditionig intesity	0.32 (0.51)	1.38 (0.51, 3.73)	0.53
High risk CMV constellation	0.46 (0.39)	1.58 (0.74, 3.38)	0.23
Leukocyte engraftment	–2.78 (0.49)	0.06 (0.02, 0.16)	<0.001
GvHD (grade II–IV)	0.76 (0.33)	2.14 (1.12, 4.08)	0.02
Overall transfusion rate			
RBC units	–0.02 (0.02)	0.98 (0.95, 1.02)	0.29
Adjusted association			
RBC units	–0.04 (0.02)	0.96 (0.93, 1.00)	0.04
TBI			
No (ref)	–	–	
Yes	–0.70 (0.39)	0.50 (0.23, 1.06)	0.07
Conditionig intesity	0.34 (0.50)	1.40 (0.53, 3.74)	0.50
High risk CMV constellation	0.71 (0.39)	2.03 (0.93, 4.39)	0.07
Leukocyte engraftment	–2.93 (0.51)	0.05 (0.02, 0.14)	<0.001
GvHD (grade II–IV)	0.77 (0.33)	2.16 (1.12, 4.13)	0.02

with overall mortality. This suggests that transfusion burden may represent an independent risk factor for poor outcome after alloHSCT, irrespective of baseline comorbidities. Nevertheless, there is a systematic bias in this analysis as patients with severe complications after alloHSCT, such as sepsis or severe intestinal GvHD, are both more likely to require transfusions and more likely not to survive.

Additionally, other confounding factors—such as the severity of the underlying disease, pre-transplant response, and comorbidities beyond those captured by the HCT-CI and EBMT scores—may also contribute to transplant outcomes and transfusion dependency.

Consistent with our results, a higher transfusion frequency has been linked with delayed engraftment previously [41]. Again, it remains uncertain whether high transfusion rates are a surrogate parameter for delayed hematological engraftment or whether increased RBC transfusion itself delays the engraftment.

No significant association was observed between transfusion burden and the incidence of acute GvHD in our dataset, while Hosoba *et al*. [42] showed an association between the transfusion of more than five RBC units between day-7 and day +27 after alloHSCT and high-grade GvHD. Similarly, increased pre-transplant ferritin levels in MDS patients correlated with a higher probability of developing severe aGVHD [38], and in patients with aplastic anemia, receiving more than 32 RBC units was associated with a higher incidence of GvHD, potentially due to severe iron overload [43]. However, our study analyzed a more heterogeneous group of patients and not only those with an extremely high transfusion rate, like patients with MDS or aplastic anemia. Therefore, transfusion frequencies as high as those reported in these studies, were not reached in our cohort. In conclusion, current evidence regarding a potential association between RBC transfusion and GvHD incidence remains inconsistent. Larger, multicenter trials in-

Table 8. Analysis of infectious complications within the first 21 days.

Variable	Beta (SE)	HR (95% CI)	*p*
Post-transplant transfusion rate			
RBC units	–0.16 (0.04)	0.86 (0.79, 0.93)	<0.001
Adjusted association			
RBC units	–0.19 (0.04)	0.83 (0.76, 0.90)	<0.001
TBI			
No (ref)	–	–	
Yes	–0.14 (0.28)	0.87 (0.51, 1.49)	0.61
Conditionig intesity	1.21 (0.37)	3.35 (1.61, 6.97)	0.001
High risk CMV constellation	0.47 (0.31)	1.60 (0.87, 2.93)	0.13
Leukocyte engraftment	–2.72 (0.50)	0.07 (0.02, 0.17)	<0.001
GvHD (grade II–IV)	–0.49 (0.60)	0.62 (0.19, 1.98)	0.41
Pre-transplant transfusion rate			
RBC units	0.02 (0.03)	1.02 (0.97, 1.07)	0.52
Adjusted association			
RBC units	0.06 (0.03)	1.06 (1.00, 1.12)	0.05
TBI			
No (ref)	–	–	
Yes	–0.07 (0.27)	0.93 (0.55, 1.58)	0.80
Conditionig intesity	1.37 (0.37)	3.94 (1.89, 8.21)	<0.001
High risk CMV constellation	–0.13 (0.30)	0.88 (0.49, 1.58)	0.66
Leukocyte engraftment	–2.53 (0.46)	0.08 (0.03, 0.19)	<0.001
GvHD (grade II–IV)	–0.68 (0.60)	0.51 (0.16, 1.66)	0.26
Overall transfusion rate			
RBC units	–0.04 (0.02)	0.96 (0.92, 1.00)	0.04
Adjusted association			
RBC units	–0.04 (0.02)	0.96 (0.92, 1.01)	0.12
TBI			
No (ref)	–	–	
Yes	–0.07 (0.27)	0.93 (0.55, 1.60)	0.80
Conditionig intesity	1.10 (0.37)	3.02 (1.45, 6.28)	0.003
High risk CMV constellation	0.05 (0.31)	1.05 (0.57, 1.93)	0.88
Leukocyte engraftment	–2.52 (0.46)	0.08 (0.03, 0.20)	<0.001
GvHD (grade II–IV)	–0.34 (0.60)	0.71 (0.22, 2.32)	0.58

cluding patients with diverse hematological malignancies are required to clarify this relationship.

Beyond the context of alloHSCT, high transfusion burden is associated with postoperative infections [44–47], although this effect may not be dose-dependent [48]. Infectious complications, including viral reactivations, are a major concern during the course of alloHSCT [49]. In contrast to previous studies, our study revealed a negative association between post-alloHSCT transfused RBC units and infection rates, irrespective of pre-transplant transfusion burden, representing a novel and unexpected observation.

However, when the analysis was restricted to viral infections and reactivations—comprising 14.3% primary infections and 85.7% reactivations (HSV, CMV, and EBV)—the observed effect was less pronounced. Notably, most infectious events (92.2%) occurred within the first 21 days after alloHSCT, and we were able to confirm the negative association between RBC units transfused after alloHSCT and the onset of infectious complications. The pre-transplant transfusion rate showed no influence on infection incidence, indicating a possible short-term protective effect of transfused RBCs. This phenomenon may be explained as RBCs have been shown to directly interfere with immune cells [8,10,50–52] and might directly regulate lung injury by binding mitochondrial DNA via toll-like receptor 9 (TLR9) [53]. However, our data is limited as we performed a retrospective analysis and did not investigate causal relationships. Therefore, the mechanism between RBC transfusion and the incidence of infectious complications should be the focus of further studies. Next, our data may be biased as all of our patients received antibiotic prophylaxis, which is no longer standard in every transplantation center. Additionally, we investigated a period prior to the approval of letermovir, which dramatically reduced CMV reactivation after alloHSCT [54]. Finally, the standard for GvHD prophylaxis has evolved with the introduction of post-transplantation cyclophosphamide, supported by promising novel data [55], which in turn may increase infection rates after alloHSCT [56].

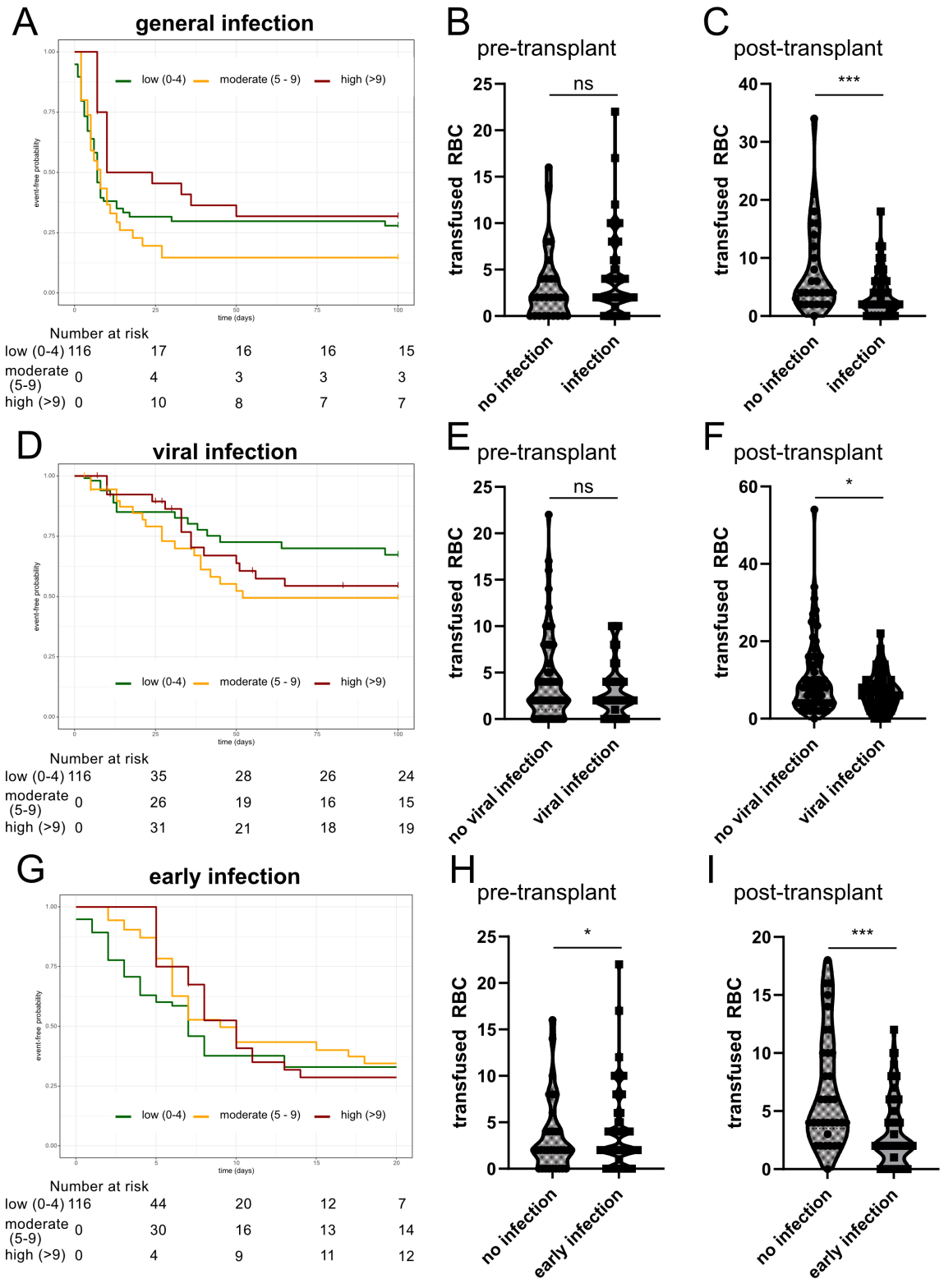

Fig. 2. Higher transfusion burden is associated with reduced infection rate. Extended Kaplan-Meier plot for time-varying covariates showing general infection rate (A), viral infections (D), or early infections within the first 21 days (G) after alloHSCT in patients receiving less than 5, 5 to 9, or more than 9 RBC units. The number of transfused RBC units before alloHSCT is depicted in violin plots for general infection rate (B), viral infections (E), or early infections (H). Post-transplantation transfusion rate in patients analyzed for general (C), viral (F), and early (I) infectious complications are shown separately. ns: $p > 0.05$; *: $p < 0.05$; ***: $p < 0.001$.

Conclusion

In summary, this study shows a significant negative correlation between red blood cell transfusion burden and overall survival, which is in line with earlier findings. Moreover, we further established an association between a higher number of RBC transfusions and delayed neutrophil recovery. Although the small number of patients diagnosed with GvHD limits the statistical power of this anlysis, no significant impact of transfused RBC transfusions on the incidence of aGvHD was observed. Significantly, a higher post-alloHSCT RBC transfusion rate was associated with a lower infection rate. Larger, multi-center studies are warranted to validate these findings. Additionally, mechanistic insights into how RBC transfusions affect immune cell effector functions following alloHSCT analyses investigating the interaction between donor immune cells and allogeneic RBCs in the early post-alloHSCT period.

Availability of Data and Materials

Data are available upon reasonable request from the corresponding author.

Author Contributions

Conceptualization, AH, PB, and DW; methodology, AH, SS and CK; software, LW and SS; validation, CK, SS and LW; formal analysis, CK, LW and SS; investigation, KM, TAWH, CK and SS; resources, AH, and PB; data curation, SS and CK; writing—original draft preparation, SS; writing—review and editing, AH, DW, PB, TAWH, KM, CK and LW; visualization, LW and SS; supervision, AH; project administration, AH; funding acquisition, AH and SS. All authors have been involved in revising it critically for important intellectual content. All authors have read and agreed to the published version of the manuscript. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics Approval and Consent to Participate

The study was conducted in accordance with the Declaration of Helsinki and approved by the local ethics committee of the University Hospital Bonn (2022-419). As a retrospective analysis was performed, no informed patient consent was mandatory according to the local ethics committee.

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Conflict of Interest

The authors declare no conflict of interest.

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