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High Mortality of COVID-19 Early after Allogeneic Stem Cell Transplantation: A Retrospective Multicenter Analysis on Behalf of the German Cooperative Transplant Study Group

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Recipients of allogeneic stem cell transplantation (alloSCT) are at high risk for contracting infectious diseases with high morbidity and mortality. Coronavirus disease 2019 (COVID-19) is a viral respiratory disease that can lead to severe pneumonia and acute respiratory distress syndrome, with a potentially fatal outcome. In this retrospective study conducted on behalf of the German Cooperative Transplant Study Group, we aimed to analyze risk factors, disease course, and outcomes of COVID-19 in patients who underwent alloSCT. AlloSCT recipients who became infected with SARS-CoV-2 at German and Austrian transplant centers between February 2020 and July 2021 were included. Classification of COVID-19 severity into mild, moderate-severe, or critical disease and division of the course of the pandemic into 4 phases were done according to the German Robert Koch Institute. The main endpoint was overall mortality at the end of follow-up. We further analyzed the need for treatment in an intensive care unit (ICU) and the severity of disease. Risk factors were evaluated using univariate and multivariate analyses, and survival analysis was performed using Kaplan-Meier method. The study cohort comprised 130 patients from 14 transplant centers, with a median age at diagnosis of COVID-19 of 59 years (range, 20 to 81 years) and a median interval between alloSCT and COVID-19 of 787 days (range, 19 to 8138 days). The most common underlying diseases were acute myeloid leukemia (45.4%) and lymphoma (10.8%). The majority of patients (84.9%) were infected in the later phases of the pandemic; 20.8% had moderate-severe disease, 12.3% had critical disease, and 19.2% were treated in an ICU. After a median follow-up of 127 days, overall mortality was 16.2%, 52.0% among patients treated in an ICU. Risk factors for mortality in multivariate analysis were active disease (odds ratio [OR], 4.46), infection with SARS-CoV-2 $\leq$365 days after alloSCT (OR, 5.60), age $>$60 years (OR, 5.39), and ongoing immunosuppression with cyclosporine (OR, 8.55). Risk factors for developing moderate-severe or critical disease were concurrent immunosuppression (OR, 4.06) and age $>$40 years (OR, 4.08). Patients after alloSCT exhibit a substantially

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increased mortality risk after COVID-19 infection compared with the normal population, without considerable improvement over the course of the pandemic. Risk factors include age, early infection post-alloSCT, and active immunosuppression. Further studies are needed to improve prevention and treatment in this high-risk patient group.

INTRODUCTION

Allogeneic stem cell transplantation (alloSCT) is an important therapeutic option for patients with various hemato-oncologic diseases and often offers the sole curative approach. However, alloSCT recipients are at high risk for contracting infectious diseases, including viral infections. In this highly immunocompromised patient group, infections are associated with pronounced morbidity and mortality and are the main cause of nonrelapse mortality after alloSCT [1]. These infections include, but are not limited to, respiratory tract infections with potential lethal disease courses [2-4].

In early 2020, Coronavirus disease 2019 (COVID-19), caused by the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged as a new viral disease and quickly spread around the world. In March 2020, the World Health Organization (WHO) declared COVID-19 a pandemic, and as of August 2021, more than 200 million people had been infected and almost 4.5 million people had died worldwide. Typical symptoms of the infection include cough, fever, sore throat, dyspnea, fatigue, muscle and body aches, and headache, as well as loss of taste and/or smell or gastrointestinal symptoms. Although some patients are asymptomatic or experience only a mild respiratory tract infection, COVID-19 can progress to severe pneumonia and acute respiratory distress syndrome (ARDS), with a potentially fatal outcome.

Within the general population, known risk factors for a severe course of the disease and mortality include, among others, older age, male sex, history of heart disease, hypertension, diabetes, autoimmune disease, asthma, chronic obstructive pulmonary disease, chronic kidney disease, and obesity [5–10]. Furthermore, both active cancer and a history of cancer are risk factors for a severe infection and SARS-CoV-2-related mortality [5,10-12]. In alloSCT recipients, a history of hemato-oncologic disease is combined with profound immunosuppression from both an incomplete immunologic reconstitution and immunosuppressive treatment required to prevent graft-versus-host disease (GVHD), leading to a combined humoral and cellular immunodeficiency.

While the mortality rate of COVID-19 in the German general population in October 2021 was is 2.2%, data on the outcome of immunocompromised patients and patients with underlying hemato-oncologic diseases remain inconsistent and limited [12-19]. In solid organ transplant recipients, some studies find no difference in survival [20], while others report a significantly increased mortality of more than 20 % in some cohorts [21–23]. Therefore, the aim of our study on behalf of the German Cooperative Transplant Study Group was to analyze the outcome of patients with SARS-CoV-2 infections after alloSCT and identify risk factors for a severe disease course and mortality.

METHODS

Patients and Definitions

The study cohort comprised 130 patients who became infected with SARS-CoV-2 between February 2020 and July 2021 and who had previously undergone a first or second alloSCT. In this multicenter study, patients from 14 German and Austrian transplant centers were included.

Patients had undergone alloSCT from either an unrelated or a related donor. In patients with 2 previous alloSCTs, data referring to the second alloSCT were included. COVID-19 had to be confirmed via PCR from nasopharyngeal swab, bronchoalveolar lavage, or liquid throat rinse or via antibody detection in peripheral blood. The type of antibody test was not recorded.

In patients with an unknown exact date of COVID-19 diagnosis, the 15th of the corresponding month was used for calculation if the month of diagnosis was known. If the month of diagnosis could not be determined, patients were completely excluded from the analysis of time-related variables. For calculation of the median age at diagnosis of our cohort, January 1, 2021, served as the date of diagnosis in these patients.

The severity of COVID-19 was classified according to the recommendation of the German Robert Koch Institute (Table 1) [24]. To facilitate classification and due to missing data on radiologic pulmonary patterns and oxygen saturation, the categories moderate disease and severe disease were combined into a single category, moderate-severe disease. In brief, the classification critical disease was applied to patients with ARDS or signs of hyperinflammation, such as sepsis or multiple organ failure; moderate-severe disease to patients with pneumonia; and mild disease to all other patients.

We did not ask whether patients had been retested at the end of treatment or about the resolution of symptoms. There was no differentiation between different causes of death; therefore, COVID-19-related deaths and deaths from other causes were not analyzed separately.

For the comparison between the phases of the pandemic, we refer to the division of the pandemic course in Germany into 4 phases by Schilling et al. [25]: phase 0, calendar week 5/2020 to 09/2020; phase 1, calendar week 10/2020 to 20/2020; phase 2, calendar week 21/2020 to 39/2020; and phase 3, calendar week 40/2020 to 08/2021 [25]. Infections with SARS-CoV-2 after calendar week 08/2021 were included in phase 3, and because of the small number of patients in phases 0 and 2, phases 0 and 1 as well as phases 2 and 3 were combined for comparison.

Data Collection

In this multicenter study, all data were collected retrospectively by the transplant centers for all alloSCT recipients diagnosed with COVID-19 during the given time period. In April 2020, centers were asked to document all patients who had already been infected, as well as all applicable patients consecutively from that time forward. Sources for data were local inpatient and outpatient documentation.

Table 1
Clinical Classification of COVID-19 (adapted from Feldt et al. [24])

Classification		Definition	Symptoms
Mild disease		No pneumonia	
Moderate-severe disease	Moderate disease	Pneumonia	No symptoms of severe pneumonia
	Severe disease	Severe pneumonia	Fever and bilateral lung infiltrates and either a respiratory rate >30/min, severe dyspnea, or SpO_2 <90%-94% at room air
Critical disease		ARDS	
		Hyperinflammation	Clinical signs of sepsis or septic shock with multiple organ failure

Data analysis was performed centrally at our center. Varying numbers for different parameters resulted from missing data that could not be obtained from the participating centers. In cases of missing data, the items were classified as unknown.

All patients had consented to treatment according to local standards. During all stages of collection and analysis, data were pseudonymized. All patients consented to the collection and analysis of their data. All analyses were in accordance with the Declaration of Helsinki. The study was approved by the local Ethics Committee of the Martin Luther University Halle (Saale) (registry no. 2021-079).

Statistical Analysis

All statistical analyses were conducted using SPSS version 25 (IBM, Armonk, NY). To describe the characteristics of COVID-19 and its treatment, descriptive statistics based on the available data were used, expressed as absolute and percentage frequencies for categorical variables and median and range for continuous variables.

To identify potential risk factors, unifactorial analyses of associations of parameters with mortality and disease severity were performed using cross-tabulation with the chi square test. A P value of $<.05$ was considered significant. Multivariate analysis was performed with a binary logistic regression model with stepwise backward likelihood inclusion for parameters showing an association in univariate analysis and relevant cofactors as stated. Results are presented as odds ratio (OR) with 95% confidence interval (CI). If values of 0 precluded calculation of the OR, an estimated OR was calculated by adding 0.5 to each cell of the 2×2 table. Survival analysis was performed using the Kaplan-Meier method with log-rank testing.

RESULTS

Patient Characteristics

General patient characteristics are summarized in Table 2. One hundred thirty patients from 14 transplant centers in Germany and Austria were included in the study. The median age at diagnosis of COVID-19 was 59 years (range, 20 to 81 years), and the median age at alloSCT was 55 years (range, 15 to 74 years). The median time from alloSCT to diagnosis of COVID-19 was 787 days (range, 19 to 8138 days). Four patients had undergone 2 alloSCTs.

The 4 dominant underlying diseases were acute myeloid leukemia (45.4%), Hodgkin and non-Hodgkin lymphoma (10.8%), acute lymphoblastic leukemia (10.0%), and myelodysplastic syndrome (9.2%). In total, 85.4% were in complete remission at the time of COVID-19 diagnosis, and 12.3% had active disease. Acute GVHD was present in 13 patients (10.0%) at the time of SARS-CoV-2 detection, and chronic GVHD was present in 55 patients (42.3%). Sixty-one patients (46.9%) required systemic immunosuppressive treatment, as either prophylaxis for or treatment of GVHD.

COVID-19 Characteristics

Characteristics of COVID-19 in the study cohort are summarized in Table 3. Infection with SARS-CoV-2 was detected via nasopharyngeal swab PCR test in 84.6% of the patients, via PCR from liquid throat rinse in 3.1%, and via antibody detection in peripheral blood in 1.5% (data missing for 10.8%). The 2 patients diagnosed by antibody detection only were diagnosed before the availability of the vaccination, were previously symptomatic, and had close contact to patients with COVID-19.

Transmission occurred within the family and home environment for 42.3% of patients, within medical institutions for 6.2%, and within the work environment for 0.8%; in 50.8%, the route of transmission remained unclear. For the patient who had 2 episodes of COVID-19, only the first episode was included. The majority of patients (84.9%) were infected during phase 3 of the pandemic. Main symptoms included fever (40.8%), cough (43.1%), dyspnea (22.3%), and fatigue (22.3%); 30.8% developed pneumonia. Of the 130 patients, 25 (19.2%) required treatment in an intensive care unit (ICU), 25 (19.2%) required mechanical ventilation, and 2 (1.5%) received extracorporeal membrane oxygenation. Eighty-four patients (64.6 %) had mild disease, 27 (20.8%) had moderate-severe disease, and 16 (12.3%) had critical disease.

A wide range of different specific treatment options was used. Overall, 29 patients (22.3%) received specific treatment, mainly corticosteroids (19; 14.6%), convalescent plasma (17; 13.1%), remdesivir (17; 13.1%), and/or bamlanivimab (6; 4.6%).

Table 2
Patient Characteristics

Characteristic	Value
Number of patients	130
Sex, n (%)	
Female	44 (33.8)
Male	86 (66.2)
Age at SARS-CoV-2, yr, median (range)	59 (20-81)
Age at SARS-CoV-2, n (%)	
≤40 yr	24 (18.5)
41-60 yr	46 (35.4)
>60 yr	60 (46.2)
Age at alloSCT, yr, median (range)	55 (15-74)
Underlying disease, n (%)	
AML	59 (45.4)
ALL	13 (10.0)
MDS	12 (9.2)
MPN	7 (5.4)
Multiple myeloma	4 (3.1)
Lymphoma	14 (10.8)
CLL	5 (3.8)
CML	9 (6.9)
Aplastic anemia	3 (2.3)
Other	4 (3.1)
Disease status, n (%)	
CR	111 (85.4)
Not in remission, requiring treatment	4 (3.1)
Not in remission, not requiring treatment or treatment unclear	12 (9.2)
Unknown	3 (2.3)
GVHD present at diagnosis of COVID-19, n (%)	
Yes	66 (50.8)
Acute GVHD	13 (10.0)
Chronic GVHD	55 (42.3)
No	64 (49.2)
Systemic immunosuppression at diagnosis of COVID-19, n (%)	
Yes	61 (46.9)
Steroids	33 (25.4)
Mycophenolate mofetil/mycophenolate sodium	10 (7.7)
Cyclosporine	19 (14.6)
Tacrolimus	16 (12.3)
Everolimus	6 (4.6)
Vedolizumab	1 (0.8)
Itacitinib	1 (0.8)
Ruxolitinib	14 (10.8)
ECP	3 (2.3)
Other	3 (2.3)
No	66 (50.8)
Unknown	3 (2.3)

AML indicates acute myeloid leukemia; ALL, acute lymphoblastic leukemia; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; CLL, chronic lymphoblastic leukemia; CML, chronic myeloid leukemia; CR, complete remission; ECP, extracorporeal photopheresis,

Table 3
COVID-19 Characteristics

Characteristics	Value
Time from alloSCT to SARS-CoV-2 detection, d, median (range)	787 (19-8138)
Time from alloSCT to SARS-CoV-2 detection, n (%)	
≤100 d	7 (5.4)
≤365 d	32 (24.6)
Phase of the pandemic, n (%)	
Phase 0	1 (0.8)
Phase 1	13 (10.9)
Phase 2	4 (3.4)
Phase 3	101 (84.9)
Method of SARS-CoV-2 detection, n (%)	
Nasopharyngeal swab PCR	110 (84.6)
Liquid throat rinse PCR	4 (3.1)
Antibody detection in the peripheral blood	2 (1.5)
Unknown	14 (10.8)
Severity of COVID-19, n (%)	
Mild disease	84 (64.6)
Moderate-severe disease	27 (20.8)
Critical disease	16 (12.3)
Unknown	3 (2.3)
Clinical presentation of COVID-19, n (%)	
Symptoms, overall	114 (87.7)
Fever	53 (40.8)
Cough	56 (43.1)
Sore throat	7 (5.4)
Melalgia	7 (5.4)
Dyspnea	29 (22.3)
Gastrointestinal symptoms	13 (10.0)
Fatigue, weakness	29 (22.3)
Change in taste and/or smell	8 (6.2)
Complications of COVID-19, n (%)	
Pneumonia	40 (30.8)
ARDS	12 (9.2)
Treatment, n (%)	
ICU admission	25 (19.2)
Mechanical ventilation	25 (19.2)
High-flow oxygen	1 (0.8)
Noninvasive ventilation	6 (4.6)
Invasive ventilation	14 (10.8)
ECMO	2 (1.5)
Specific drug therapy	
Yes	29 (22.3)
Steroids	19 (14.6)
Remdesivir	17 (13.1)
Bamlanivimab	6 (4.6)
Casirivimab/Imdevimab	2 (1.5)
Tocilizumab	3 (2.3)
Baricitinib	2 (1.5)
Camostat	1 (0.8)
Convalescent plasma	17 (13.1)
Outcomes	
Completely recovered, n (%)	88 (67.7)
Ongoing, n (%)	17 (13.1)
Unknown, n (%)	4 (3.1)
Deceased, n (%)	21 (16.2)
Time from diagnosis to death, d, median (range)	32 (4-98)
I CU mortality, n (%)	13 (52)

ECMO, extracorporeal membrane oxygenation.

We did not inquire vaccination status, but given the study period, it is very unlikely that any vaccinated patients were included in the study.

Outcome and Mortality

The median follow-up after confirmation of SARS-CoV-2 infection was 127 days (range, 1 to 504 days). Four patients (3.1%) were lost to follow-up after diagnosis of COVID-19, and 17 patients (13.1%) did not have complete resolution of clinical symptoms at last follow-up. Overall mortality was 7.7% (10 patients) at day +30 after detection of SARS-CoV-2 and 16.2% (21 patients) at the end of follow-up, with a median time from diagnosis to death of 32 days. The Kaplan-Meier analysis for overall survival after diagnosis of COVID-19 of all patients is shown in Figure 1A.

Mortality at the end of follow-up among the severity groups was 2.4 %, 25.9 % and 68.8 % for patients with mild, moderate-severe and critical disease, respectively. Overall survival according to severity group is shown in Figure 1B, indicating a significant difference in survival times both between mild and moderate-severe disease (489.6 days versus 220.1 days;
$P < .001$) as well as moderate-severe and critical disease (220 days versus 172.9 days; $P < .001$).

Of the 25 patients requiring treatment in an ICU, 13 died (52.0%). The difference in survival times compared with patients without ICU treatment was significant (470.5 days with ICU versus 254.9 days without ICU; $P < .001$; Figure 1C).

Given the wide range of different treatment modalities and drugs used and the ensuing small number of patients in each group, we did not analyze the impact of different treatments on outcomes.

Risk Factors for Mortality

Potential risk factors for mortality were evaluated by univariate and multivariate analyses; the results are summarized in Table 4 and Table 5. In univariate analyses, the following risk factors for all-cause mortality were identified: lymphoma as underlying disease (OR, 3.47), infection within the first 2 phases of the pandemic (phase 0 + 1; OR, 3.61), active hemato-oncologic disease (OR, 4.04), ongoing immunosuppression with cyclosporine (OR, 7.94), infection with SARS-CoV-2 ≤100 days (OR, 4.50) and ≤365 days after alloSCT (OR, 5.17), moderate-severe COVID-19 (OR, 14.35), critical COVID-19 (OR, 90.20), pneumonia (OR, 23.73), ARDS (OR, 16.15), ICU treatment (OR, 13.14), mechanical ventilation (OR, 13.14), extracorporeal membrane oxygenation (OR 26.52, estimated), age >60 years (OR 1.33, age ≤40 as the reference group). Patients aged >40 years also had an increased risk for mortality (OR, 12.32, estimated; $P = .017$, data not shown), while the age group 41 to 60 years alone did not show an increased mortality risk compared with patients age ≤40 years.

Interestingly, compared with the whole cohort, patients with acute GVHD had an elevated risk of mortality (OR, 3.95; $P = .021$, data not shown). However, compared with patients without GVHD, excluding patients with chronic GVHD, acute GVHD did not remain a significant risk factor.

In the multivariate analysis, we included all parameters for which univariate analysis yielded significant differences and that where independent of the disease itself; therefore, severity group, pneumonia, ARDS, and treatment modalities were not included. Active hemato-oncologic disease (OR, 4.46), infection with SARS-CoV-2 at ≤365 days after alloSCT (OR, 5.60), age >60 years (OR, 5.39), and immunosuppression with cyclosporine (OR, 8.55) remained significant. When included

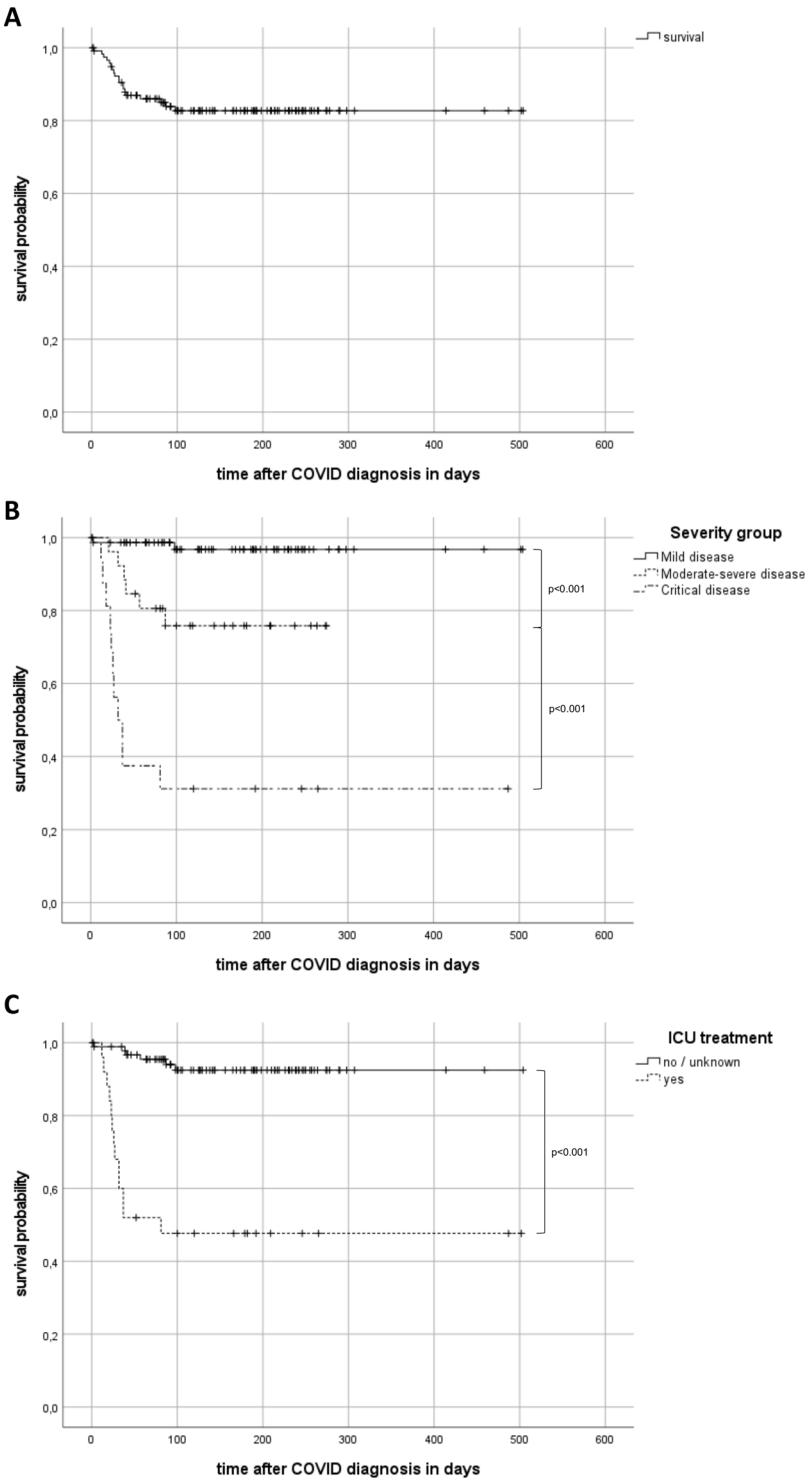

Figure 1. Survival after diagnosis of COVID-19. (A) Overall survival of the entire cohort after diagnosis of COVID-19. (B) Overall survival according to COVID-19 severity group. (C) Overall survival according to treatment in an ICU. Significance of the difference in survival times was calculated using the log-rank test.

in the analysis, neither acute GVHD nor age >40 years remained a significant risk factor for mortality.

Kaplan-Meier analyses comparing survival according to age groups, time after alloSCT, cyclosporine use, and remission status of the underlying disease are shown in Figure 2.

There were significant differences in survival time between the age groups ≤40 years and >60 years (P= .030), but not between the age groups ≤40 years and 41 to 60 years or the age groups 41 to 60 years and >60 years (Figure 2A). Patients diagnosed with COVID-19 at ≤1 year after alloSCT had a significantly reduced survival time compared with those patients diagnosed at >1 year after alloSCT (P< .001; Figure 2B). Medication with cyclosporine at the time of COVID-19 diagnosis also led to a significantly reduced survival time after alloSCT (P< .001; Figure 2C). The difference in survival times between patients with complete remission of

Table 4
Univariate Analysis of Risk Factors for Mortality, Severity of COVID-19 (Moderate-Severe and Critical Disease), and ICU Admission

Variables	Mortality		Moderate-Severe and Critical Disease		ICU Admission	
	OR (95 % CI)	*P*	OR (95 % CI)	*P*	OR (95 % CI)	*P*
Sex						
Male	1.03 (0.38-2.77)	.957	0.80 (0.37-1.73)	.568	1.11 (0.44-2.82)	.828
Age at SARS-CoV-2						
≤40 yr	Ref		Ref		Ref	
41-60 yr	1.15 (1.03-1.29)	.064	3.33 (0.85-13.02)	.073	10.82 (est)	.090
>60 yr	1.33 (1.15-1.54)	.007*	4.90 (1.31-18.33)	.012*	19.71 (est)	.004*
Phase of the pandemic						
Phase 0 + 1	3.61 (1.06-12.35)	.032*	2.78 (0.90-8.66)	.069	4.83 (1.51-15.48)	.005*
Phase 2 + 3	Ref		Ref		Ref	
Underlying disease						
AML	0.70 (0.27-1.82)	.464	0.83 (0.40-1.75)	.624	0.50 (0.20-1.26)	.135
ALL	0.82 (0.75-0.89)	.095	0.32 (0.07-1.53)	.137	0.13 (est)	.064
MDS	2.97 (.81-10.96)	.090	2.11 (0.64-6.98)	.214	5.21 (1.52-17.89)	.005*
MPN	2.76 (.47-16.16)	.242	2.03 (0.39-10.49)	.392	2.2 (0.38-12.72)	.369
Multiple myeloma	0.83 (0.77-0.90)	.373	0.65 (0.57-0.74)	.146	0.44 (est)	.322
Lymphoma	3.47 (1.03-11.69)	.035*	2.53 (0.79-8.06)	.108	2.67 (0.81-8.81)	.098
CLL	0.83 (0.77-0.90)	.317	3.08 (0.49-19.14)	.208	0.36 (0.73-0.87)	.266
CML	0.63 (0.08-5.33)	.670	0.54 (0.11-2.70)	.444	1.22 (0.24-6.25)	.813
Aplastic anemia	0.84 (est.)	.442	0.98 (0.09-11.08)	.984	0.57 (est)	.393
Disease status						
CR	Ref		Ref		Ref	
Active disease	4.04 (1.36-11.99)	.008*	2.21 (0.80-6.05)	.118	0.76 (0.20-2.84)	.680
GVHD present at diagnosis of COVID-19						
GVHD, overall	1.08 (0.42-2.75)	.872	2.90 (1.34-6.27)	.006 *	2.43 (0.96-6.12)	.055
Acute GVHD (compared to no GVHD)	3.38 (0.92-12.45)	.058	4.90 (1.31-18.33)	.011 *	4.38 (1.15-16.72)	.023*
Chronic GVHD (compared to no GVHD)	0.66 (0.22-1.95)	.452	2.48 (1.11-5.57)	.025 *	1.95 (0.73-5.20)	.175
Immunosuppression at diagnosis of COVID-19	1.78 (0.67-4.69)	.243	3.95 (1.80-8.67)	.000 *	3.53 (1.35-9.19)	.007*
Steroids	0.94 (0.31-2.83)	.913	4.75 (2.05-11.02)	.000 *	2.86 (1.14-7.17)	.022*
Mycophenolate mofetil/mycophenolate sodium	2.52 (0.59-10.72)	.197	3.24 (0.86-12.19)	.069	3.05 (.80-11.76)	.092
Cyclosporine	7.94 (2.65-23.73)	.000*	1.96 (0.73-5.26)	.177	2.92 (1.01-8.42)	.041*
Time from alloSCT to SARS-CoV-2 detection						
≤ 100 d	4.50 (0.92-22.02)	.045*	1.40 (0.30-6.59)	.666	3.07 (0.64-14.72)	.144
≤ 365 d	5.17 (1.85-14.49)	<.001*	2.35 (1.02-5.39)	.042 *	2.73 (1.08-6.90)	.030*
Severity of COVID-19						
Mild disease	Ref		–		–	
Moderate-severe disease	14.35 (2.77-74.40)	.000*	–	–	–	–
Critical disease	90.20 (15.57-522.42)	.000*	–	–	–	–
Complications of COVID-19						
Pneumonia	23.73 (6.41-87.82)	.000*	–	–	–	–
ARDS	16.15 (4.27-61.16)	.000*	–	–	–	–
ICU admission	13.14 (4.53-38.13)	.000*	–	–	–	–
Treatment						
Mechanical ventilation	13.14 (4.53-38.13)	.000*	–	–	–	–
ECMO	26.52 (est)	.000*	–	–	–	–

Est, estimated.
* Significant risk factors using the chi-square test.

their underlying disease and those with active disease was not significant (*P* = .136; Figure 2D). Acute GVHD was also a risk factor significantly reducing survival times compared with those patients with no GVHD or chronic GVHD (*P*= .013; data not shown).

Risk Factors for Disease Severity

Potential risk factors for severity of COVID-19 as well as ICU admission were also evaluated using univariate and multivariate analyses and are summarized in Table 4 and Table 5. Risk factors for developing moderate-severe or critical disease in our cohort were GVHD at the time of diagnosis of COVID-19 (all GVHD [OR, 2.90], acute GVHD [OR, 4.90], and chronic GVHD [OR, 2.48]), ongoing immunosuppression (OR, 3.95), immunosuppression with steroids (OR, 4.75), infection with SARS-CoV-2 ≤365 days after alloSCT (OR, 2.35), and both age >40 years (OR, 4.17; *P*= .020, data not shown) and age >60 years (OR, 4.90), whereas the age group 41 to 60 years alone did not show an increased risk.

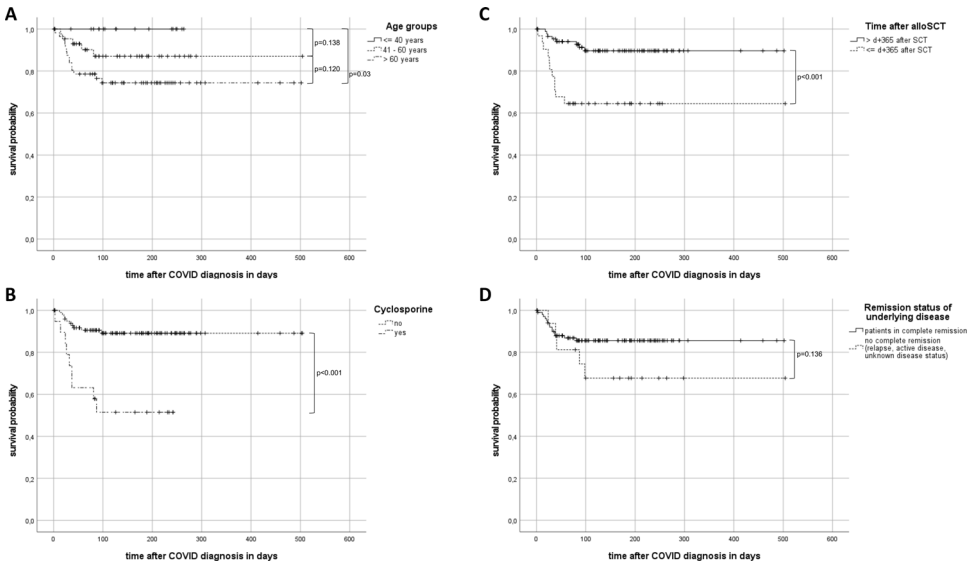

Figure 2. Survival after diagnosis of COVID-19 according to risk group. (A) Overall survival according to age group. (B) Overall survival according to time between alloSCT and diagnosis of COVID-19. (C) Overall survival according to treatment with cyclosporine. (D) Overall survival according to remission status of the underlying disease. Significance of the difference in survival times was calculated using the log-rank test.

To avoid multicollinearity, immunosuppression with steroids, GVHD overall, and age >40 years were excluded from the multivariate analysis. Immunosuppression (OR, 4.06) and age >60 years (OR, 2.38) remained significant. In a model including the age group >40 years instead of >60 years, age >40 years also remained a significant risk factor for developing moderate-severe or critical disease (OR, 4.08).

Considering the requirement of ICU admission, risk factors were MDS as underlying disease (OR 5.21), infection within the first 2 phases of the pandemic (phase 0 + 1; OR 8.04), acute GVHD (OR, 4.38), ongoing immunosuppression (OR, 3.53), immunosuppression with steroids (OR, 2.86) or cyclosporine (OR, 2.92), infection with SARS-CoV-2 ≤365 days after alloSCT (OR, 2.73) and both age >40 years (OR, 15.33, estimated; P = .008; data not shown) and age >60 years (OR, 19.71; estimated). Interestingly, of the patients with active disease, only 3 patients (15.8%) were transferred to an ICU.

To avoid multicollinearity in multivariate analysis, ongoing immunosuppression was included, whereas immunosuppression with steroids and/or with cyclosporine alone were excluded. In this model, MDS as underlying disease (OR, 4.98), ongoing immunosuppression (OR, 3.92), and infection within the first 2 phases (OR, 5.24) were significant risk factors for ICU admission.

DISCUSSION

Here we report the results of an observational multicenter retrospective study of COVID-19 in alloSCT recipients. Overall mortality among this high-risk cohort was 16.2% at the end of follow-up, and the median time from diagnosis to death was 32 days. Significant risk factors for mortality in multivariate analysis were infection with SARS-CoV-2 ≤365 days after alloSCT, age >60 years, active disease, and immunosuppression with cyclosporine at the time of COVID-19 diagnosis. To our knowledge, this is the first analysis of patients after alloSCT who contracted COVID-19 in the so-called second and third waves of the pandemic.

The majority of patients in our cohort had myeloid malignancies as their underlying disease, followed by Hodgkin and non-Hodgkin lymphoma, which is comparable to the overall patient population undergoing alloSCT in Europe [26]. The median age of 55 years at the time of alloSCT in our cohort was

Table 5
Multivariate Analysis of Risk Factors for Mortality, Severity of COVID-19 (Moderate-Severe and Critical Disease), and ICU Admission

Variables	Mortality		Moderate-Severe and Critical Disease		ICU Admission	
	OR (95 % CI)	*P*	OR (95 % CI)	*P*	OR (95 % CI)	*P*
Age at SARS-CoV-2						
>40 yr			4.08 (1.05-15.77)	.042		
>60 yr	5.39 (1.46-19.92)	.011	2.379 (1.05-5.38)	.037		
Underlying disease						
MDS					4.98 (1.22-20.35)	.025
Disease status						
Active disease	4.46 (1.00-19.84)	.049				
Immunosuppression at diagnosis of COVID-19			4.06 (1.76-9.36)	.001	3.92 (1.33-11.57)	.013
Cyclosporine	8.55 (2.24-32.63)	.002				
Time from alloSCT to SARS-CoV-2 detection						
≤365 d	5.6 (1.63-19.21)	.006				
Phase of the pandemic						
Phase 0 + 1					5.24 (1.35-20.34)	.017

only slightly above the median age of patients undergoing alloSCT in Germany in 2020 [27]. The median age at the time of infection with SARS-CoV-2 was 59 years. Comparisons of our cohort with other studies or the general age distribution of patients with COVID-19 are hindered by the rapid changes in the epidemiologic distribution of COVID-19 over the course of the pandemic. During the first wave of COVID-19 in Germany (until October 2020), the median age of patients diagnosed with COVID-19 in the general population was 50 years, slightly younger than our cohort [28].

The mortality of 16.2% in our cohort is clearly higher than that in the general German population [29], underscoring the very high risk of infection-related mortality in alloSCT recipients and corresponding to the high mortality of these patients after infection with other respiratory viruses [30,31]. This high mortality rate is also comparable to that of solid organ transplant recipients who contract COVID-19 and are on chronic immunosuppressant medication [32–34]. Mortality rates in other observational studies of SCT recipients with COVID-19 range between 18% and 35% [15,17-19,35-37]. The 2 largest cohorts of patients with COVID-19 after alloSCT have been reported on behalf of the European Society for Blood and Marrow Transplantation (EBMT) and the Center for International Blood and Marrow Transplant Research (CIBMTR). Both showed a considerably higher mortality rate compared to our study, at 28.6% and 22%, respectively [17,18]. Similar to our study, both studies referred to all-cause mortality and thus had comparable endpoints.

One reason for the lower mortality rate may be the temporal distribution in our study, with <12% of the infections in phases 0 and 1 of the pandemic. In our cohort, mortality was significantly higher in these first 2 phases in univariate analysis. This difference may be influenced by the unequal distribution of patients in our cohort resulting from inclusion of a large number of patients from an outbreak within a single center in the first phase. A similar observation was reported in a large study of patients with hematologic malignancies on behalf of the European Hematology Association (EHA), with a significantly decreased mortality rate between the first COVID-19 wave (March to May 2020) and the second COVID-19 wave (October to December 2020) (40.7% versus 24.8%) [16]. In contrast, several studies of hospitalized COVID-19 patients have shown divergent results, with equal, lower, and increased in-hospital mortality in the later phases of the pandemic reported [38-40]. Comparing treatment modalities is hindered by the variety of treatments used, but only 6.1% of the patients in our cohort received specific monoclonal antibodies that were not available in the first phases. Therefore, new therapeutic options do not seem to have contributed to the better outcomes, although this remains speculative.

Interestingly, despite the high mortality rate of alloSCT recipients with COVID-19 compared with the general population, mortality in our cohort was lower than in various studies of patients with hematologic malignancies who did not undergo transplantation [12-15]. This finding is consistent with studies comparing mortality after SARS-CoV-2 infection in transplantation recipients and nonrecipients with hematologic malignancies [16,37]. In both studies, the worse outcome of non-SCT patients was attributed to the different composition of the cohorts; the patients without SCT were older, had been both diagnosed with and treated for their malignancy more recently before SARS-CoV-2 infection, and had higher rates of uncontrolled hematologic disease and/or comorbidities. This contrasts the usual prerequisites for undergoing alloSCT and thus may explain the higher mortality in non-SCT patients.

In our cohort, significant risk factors for mortality in multivariate analysis were age >60 years, infection with SARS-CoV-2 ≤365 days after alloSCT, active disease, and/or immunosuppression with cyclosporine at the time of COVID-19 diagnosis. The higher mortality rate in elderly patients is consistent with the outcome in the general population, with several studies identifying older age as an independent risk factor for COVID-19 mortality [41,42]. In univariate analysis of our cohort, even patients age >40 years were at higher risk for mortality and had a significantly increased risk for developing moderate-severe or critical disease. This underscores the vulnerability of this patient group and may lead to greater caution for intermediate-aged patients in the clinical practice.

An increased risk of mortality in patients who contracted SARS-CoV-2 early after alloSCT was observed in other studies [18,19] but not in the EBMT cohort [17]. This finding is of particular importance, because in these patients a sufficient response to vaccination and thus adequate protection cannot be expected [43]. Patients early after alloSCT regularly receive immunosuppressive medication for GVHD prophylaxis. Interestingly, only medication with cyclosporine represented a risk factor, whereas ongoing immunosuppression with any other medication did not. Cyclosporine's inhibition of the calcineurin pathway has been discussed as a treatment option for COVID-19 [44,45], and some data suggest that immunosuppressive treatment may reduce the COVID-19-related overreaction of the immune system [46]. However, most studies have identified immunosuppression as an independent predictor of mortality [42,47]. Most studies of alloSCT recipients have found an impact of immunodeficiency on mortality and/or severity. Ljungman et al. [17] found a high immunodeficiency index (including absolute neutrophil and lymphocyte counts, among other criteria) to predict higher mortality. A low lymphocyte count (<0.3 Gpt/L) was a risk factor in the CIBMTR cohort, and concurrent immunosuppression predicted disease severity in the cohort of Mushtaq et al. [18,35]. Two studies identified neutropenia as a risk factor for disease severity or mortality [36,37].

Active disease at the time of COVID-19 diagnosis was an independent risk factor for mortality in our study. This finding also was reported by Piñana et al. [37] in their non-SCT-specific cohort, and underlying malignancy has been identified as a risk factor for severe COVID-19 and mortality in other studies [42,48]. Taken together, our findings show that the risk factors for mortality in our cohort are similar to those reported in previous studies on COVID-19 after alloSCT including mostly patients from the first phase of the pandemic.

Our study has several limitations. Because data were collected retrospectively, some information, especially on time of diagnosis, clinical characteristics of the infection, and treatment modalities, was not complete for all patients and could not be acquired in hindsight. The study also might be further limited by a potential recall bias prior to starting consecutive patient accrual in April 2020.

Owing to the study's multicenter design and the lack of guidelines in the early phase of the pandemic, treatment modalities differed greatly both among centers and across time periods during the pandemic. Therefore, the study does not allow for conclusions regarding the effect of different therapies on the outcomes of COVID-19 in alloSCT recipients. Moreover, unfortunately, we did not have any laboratory data and had only limited data on both comorbidities and

transplantation modalities. Therefore, some risk factors might not have been recognized.

In addition, as has been done by health authorities for the general population and other studies on COVID-19 after alloSCT, we chose all-cause mortality as our endpoint [49]. This was based on the rationale that mortality in this patient cohort is often multifactorial. In particular, COVID-19 may trigger GVHD or prevent intensive treatment for relapse. Therefore, a precise distinction between COVID-19-related and COVID-19-independent mortality was considered prone to bias and not performed in our study.

As a final point, there is an overlap between the study period until July 2021 and the availability of COVID-19 vaccines, which became available in January 2021 and widely accessible in spring 2021. Because the study was initiated in April 2020, vaccination status was not obtained. Thus, inclusion of patients who became infected after vaccination is very unlikely, but the possibility cannot be excluded.

Despite these limitations, our study confirms the significantly increased mortality risk of patients after alloSCT. Mortality in our cohort was several-fold higher than that of the normal population; patients early post-alloSCT, older patients, and those receiving immunosuppression were particularly at risk. Further studies are needed to identify the best treatment and vaccination options for this vulnerable patient group.

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