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Early report on the severity of COVID-19 in hematologic patients infected with the SARS-CoV2 omicron variant

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Abstract

Introduction: Patients with hematologic disease are at high risk of morbidity and mortality from COVID-19 due to disease-inherent and therapy-related immunodeficiency. Whether infection with the SARS-CoV2 omicron variant leads to attenuated disease severity in these patients is currently unknown.

Methods: We assessed clinical and laboratory parameters in 61 patients with underlying hematologic conditions with a SARS-CoV2 omicron variant infection confirmed by nucleic acid amplification testing.

Results: Fifty patients reported symptoms of COVID-19, most commonly fatigue (37 patients, 60.66%) and cough (32 patients, 52.46%). 39.34% of patients reported fever. Dyspnea was reported by 10 patients and 7 patients (11.48%) required oxygen therapy. Anosmia and ageusia were relatively rare, occurring in less than 10% of patients. Severity of SARS-CoV2 infection could be assessed in 60 patients. Five cases of critical illness leading to ICU admission occurred during the observation period. Overall mortality was 9.84% in this patient cohort, with heterogeneous causes of death. The majority of omicron-infected hematologic patients experienced mild symptoms or remained asymptomatic.

Discussion: In this study, symptoms of COVID-19 tended to be milder than described for previous SARS-CoV2 variants. However, the extent to which attenuated severity of omicron-variant SARS-CoV2 infection is caused by altered viral pathogenicity or pre-existing host immunity cannot be inferred from our data and should be investigated in larger prospective studies.

KEYWORDS
COVID-19, hematologic diseases, omicron

1 | INTRODUCTION

The World Health Organization (WHO) declared coronavirus disease 19 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), as pandemic in March 2020. Morbidity and mortality of COVID-19 as well as effects of non-pharmaceutical interventions to prevent infection spread continue to have unprecedented impact on everyday life.

Although primarily presenting with respiratory symptoms in most cases, COVID-19 is now considered a multisystem disease affecting the nervous and the cardiovascular system as well as the gastrointestinal tract. Organ damage does not only arise from direct effects of SARS-CoV2 replication. A dysregulated host immune response is central to COVID-19 pathology and inflammatory symptoms such as hypercoagulability that are common especially in severe cases.[1,2] However, the course of the disease varies from asymptomatic courses to life-threatening pneumonia with respiratory failure. Overall infection fatality rates of COVID-19 in Germany have been estimated to range from 0.2% to 3.5%, with a large degree of variation over the course of the pandemic and between age groups.[3]

Due to disease-inherent severe immune deficiency and exposure to immunosuppressive treatments, patients with hematologic malignancy are at high risk for a severe course of COVID-19 with fatal outcomes.[4] Altogether, mortality has been described to range between 13.8% and 39%, corresponding to a tenfold increase when compared to the German general population.[3,5,6] Established risk factors for severe disease include comorbidities, type of the underlying disease, or laboratory parameters such as increased C-reactive protein (CRP) levels in this patient group.[4,7]

Whereas increased susceptibility to COVID-19-related morbidity and mortality is well documented in patients with hematologic malignancy, clinical course of SARS-CoV2 infection is less well studied in patients with nonmalignant hematologic disease. However, existing evidence suggests that patients with hemoglobinopathies such as sickle cell disease (SCD) or transfusion-dependent beta-Thalassemia (TDT) are at increased risk for death from COVID-19, probably in part owing to the extent of comorbidities present in this patient cohort already at a relatively young age.[8]

On a population level, vaccination against SARS-CoV2 has been recognized as a central tool to reduce COVID-19 morbidity and mortality. First-in-class messenger RNA (mRNA) vaccines have proven to be most effective in preventing SARS-CoV2 transmission.[9] Recent data suggests limited prevention of SARS-CoV2 infection but sustained protection from COVID-19-related hospitalization and death after completion of a multidose vaccination schedule.[10] However, patients with hematological malignancies respond poorly to vaccination against SARS-CoV2, especially when treated with antibodies directed against CD20 prior to vaccination.[11] Even after completing a schedule of three vaccination doses, a substantial proportion of these patients displayed a diminished antibody response.[12] Data on the clinical course of SARS-CoV2-infected patients with hematologic malignancies in the era of broadly available vaccines are scarce. Of note, a recent study indicates reduced COVID-19 severity in hematologic patients compared to pre-vaccination controls, but still reports a hospitalization rate of more than 60% and an early mortality rate of 12.4% with the majority of patients succumbing to symptoms of COVID-19.[13]

Since its emergence in November 2021, the B.1.1.529 (omicron) variant has rapidly become the dominant SARS-CoV-2 variant globally with being the dominant variant in Germany since the first week of January 2022.[14] Clinical presentation of omicron strain infection varies considerably from other SARS-CoV2 variants, as lower respiratory tract infection appears to occur less frequent in patients infected with the omicron variant, resulting in a smaller proportion of severe COVID-19 cases.[15] To the extent of what is known so far, fewer patients with comorbidities are hospitalized when infected with the omicron variant and the rate of patients with respiratory failure is lower, overall resulting in a decreased mortality of COVID-19.[16] However, the omicron variant poses a considerable challenge to public health measures due to decreased susceptibility to neutralization by monoclonal antibody treatment or vaccination and accelerated transmission dynamics.[16,17]

Data on the clinical course of COVID-19 patients with hematologic diseases infected with the omicron variant are lacking. To assess disease characteristics in this highly vulnerable population, we evaluated clinical and laboratory findings in patients with suspected or confirmed omicron variant SARS-CoV2 infection treated for hematologic disease at our institution.

2 | METHODS

For this single-center, retrospective analysis we included all patients aged 18 years or above with a hematologic disease and SARS-CoV2 infection confirmed by a nucleic acid amplification test (NAAT). Tests were either performed at public test centers, by general practitioners, in outpatient emergency units, or inpatient or outpatient wards at our institution.

Due to the predominance of the omicron variant since the first calendar week of 2022 all patients with evidence of SARS-CoV2 since January 1, 2022, were included unless infection with a different SARS-CoV2 variant was confirmed via viral genome sequencing. Furthermore, patients with an infection before January 2022 were included when the omicron variant was detected by genome sequencing.

Patients were included in the analysis if they tested positive for SARS-CoV2 for the first time before March 1, 2022, and were followed up until May 2, 2022. Follow-up was performed either by telemedicine visits or phone when patients were isolated at home or by follow-up of the clinical course when they were hospitalized. Information on COVID-19 symptoms, vaccination status, and treatment at other institutions were assessed during follow-up and from electronic patient data whereas clinical and radiological data, hematologic disease status, laboratory findings, and data concerning COVID19-specific treatment at out institution were assessed in electronic health records. Disease severity was classified as asymptomatic, mild, moderate, severe, or critical based on clinical symptoms according to the National Institute of Health COVID-19 treatment guidelines.[18]

Data analysis and visualization was performed using GraphPad Prism. Spearman's rho was employed to determine the significance of correlation between variables.

The study was approved by the ethics committee of the university Duisburg-Essen, Essen, Germany and executed according to applicable regulations.

TABLE 1 Patient characteristics

All patients	**61 (100%)**
Female	20 (32.79%)
Median age	54 years (range 18–74 years)
Vaccination status	
Unvaccinated	8 (13.11%)
1 dose	3 (4.92%)
2 doses	25 (40.98%)
3 doses	21 (34.43%)
4 doses	2 (3.28%)
5 doses	1 (1.64%)
Unclear	1 (1.64%)
Administered vaccine doses	129 (100%)
mRNA vaccine	116 (89.92%)
Vector-based vaccine	7 (5.42%)
Unclear	6 (4.65%)
Median distance of vaccine administration to SARS-CoV2 infection	76 days (range 8–331 days)
Comorbidities	
Cardiovascular	19
Hypertension	17
Atrial fibrillation	3
Coronary artery disease	3
Pulmonary	9
Obstructive sleep apnea	4
Asthma	2
Sarcoidosis	1
Chronic obstructive pulmonary disease	3
Endocrine	10
Hyperthyroidism	1
Hypothyroidism	6
Hypopituitarism	3
Type III Diabetes	3
Type II Diabetes	1
Osteoporosis	2
Other malignancy (not on active treatment)	7
Breast cancer	1
Uveal melanoma	1
Diffuse large B-cell lymphoma	1
Acute lymphoblastic leukemia	1
Renal cell carcinoma	1
Testicular cancer (seminoma)	1
Multicentric Castleman's disease	1
Neurologic	4
Epilepsy	3
Stroke	2
Therapy-related	2
Active chronic graft-versus-host-disease	2
Infectious diseases	7
HIV	1
Tuberculosis	1
Prior SARS-CoV2 infection	5

(Continues)

TABLE 1 (Continued)

Laboratory findings			
Parameter	**Mean**	**Median**	**Range**
Pre-diagnosis WBC count ($\times 10^9$/L)	6.90	5.83	0.02–25.05
Pre-diagnosis lymphocyte count ($\times 10^9$/L)	1.46	0.87	0.0–10.58
Post-diagnosis CRP level (mg/dl)	2.57	0.50	0–20.4

TABLE 2 Hematologic disease characteristics

All patients	61 (100%)
Malignant disease	45 (73.77%)
Myeloproliferative	7 (11.48%)
AML	6 (9.83%)
CML	1 (1.64%)
Lymphoproliferative	37 (60.66%)
Multiple myeloma	8 (13.11%)
Aggressive B-NHL	7 (11.48%)
Low-grade B-NHL (excluding CLL)	7 (11.48%)
CLL (including CLL with Richter's transformation)	4 (6.55%)
T-NHL	3 (4.92%)
Hodgkin's lymphoma	3 (4.92%)
Acute lymphoblastic leukemia or lymphoblastic lymphoma	3 (4.92%)
Mantle cell lymphoma	2 (3.27%)
Unclassifiable	1 (1.64%)
Acute biphenotypic leukemia	1 (1.64%)
Allogeneic stem cell transplant recipients	6 (9.83%)
Nonmalignant disease	16 (26.23%)
Sickle cell disease	6 (9.83%)
β Thalassemia	5 (8.2%)
Transfusion-dependent	4 (6.56%)
Non-transfusion-dependent	1 (1.64%)
AL amyloidosis	3 (4.92%)
Hereditary hemolytic anemia	1 (1.64%)
Autoimmune hemolytic anemia	1 (1.64%)

3 | RESULTS

A total of 61 patients was diagnosed with SARS-CoV2 infection during the observation period, of whom 20 (32.79%) were female (Table 1). Five patients reported previous infection with SARS-CoV2.

TABLE 3 Modalities of treatment

Malignant disease	45 (100% of subgroup)
Lines of treatment	
Untreated	2 (4.44%)
First line	31 (68.89%)
Second line	7 (15.56%)
More than two lines	5 (11.11%)
Patients on active treatment during the 6 months prior to infection	37 (82.2%)
Immunochemotherapy	9 (20%)
Conventional chemotherapy	8 (17.78%)
Combination therapy for multiple myeloma	6 (13.33%)
Targeted therapy	5 (11.11%)
Immunosuppression after allogeneic HSCT	4 (8.89%)
Monoclonal antibody monotherapy	3 (6.67%)
Immunomodulatory drug monotherapy	1 (2.22%)
Hypomethylating agent	1 (2.22%)
Exposure to B cell-directed agents during the 6 months prior to infection[a]	18 (40%)
Remission status	
Complete remission	17 (37.78%)
Partial remission	15 (33.33%)
Stable disease	1 (2.22%)
Refractory disease	2 (4.44%)
Relapsed disease (confirmed or suspected)	3 (6.67%)
Before first staging after therapy initiation	5 (11.11%)
Before therapy initiation (watch and wait)	2 (4.44%)
Controlled disease	32 (71.11%)
Active disease	13 (28.89%)
Nonmalignant disease	**16 (100% of subgroup)**
Regular red blood cell transfusion	6 (37.5%)
Systemic treatment	8 (50%)
No therapy	4 (25%)
Exposure to B cell-directed agents during the 6 months prior to infection[a]	3 (18.75%)

[a]B cell-directed agents included BTK inhibitors and antibodies directed against B cell or plasma cell antigens.

Vaccination status was heterogenous among patients. Eight patients (13.11%) were unvaccinated. Three patients (4.92%) had received one vaccination dose. Twenty-five patients (40.98%) were vaccinated twice, 21 patients (34.43%) received three, two patients (3.27%) received four, and one patient (1.64%) had received 5 vaccination doses. Vaccination status could not be evaluated in one patient. In total, 129 vaccine doses were administered to our patient cohort, with mRNA-vaccines being largely dominant (116 doses, 89.92%). Median time from administration of the last vaccination dose to NAAT confirmation of SARS-CoV2 infection was 76 days (range 8–331 days).

The majority of patients with hematologic malignancy was followed for lymphoproliferative disease ($n = 37$, 60.65% of all patients). In this group, B cell neoplasia was largely predominant. In total, seven patients (11.48%) were followed for myeloproliferative disease, the majority having received treatment for acute myeloid leukemia (AML, $n = 6$) and one patient with chronic myelogenous leukemia (CML). One patient was in follow-up after treatment of acute biphenotypic leukemia according to an ALL protocol. The cohort included six patients who were recipient of an allogeneic stem cell transplantation between 49 and 1213 days prior to SARS-CoV2 infection (median 697 days). Four patients received systemic immunosuppression at the time of infection, and two had signs of active chronic graft versus host disease (GvHD). All hematologic disease characteristics are shown in Table 2.

The large majority of patients ($n = 37$, 82.22%) had received systemic treatment during the 6 months prior to confirmation of SARS-CoV2 infection. Of note, 40% of the patients had been exposed to B cell-targeted agents during this period, indicating impaired humoral immunity to viral infections and reduced vaccination efficacy.[11] Thirty-two out of the 45 patients with hematologic malignancies had controlled disease activity, defined as confirmation of an at least partial remission as defined by relevant consensus criteria for the respective disease. Patients who had not received any therapy for their malignant disease were considered to have active disease. Additional information regarding treatment and remission status of patients with hematologic malignancy is displayed in Table 3.

Nonmalignant hematologic disease was present in 26.23% of patients (n = 16), the majority of whom were suffering from hemoglobinopathy (β Thalassemia: 5 patients, SCD: 6 patients). One patient presented with congenital hemolytic anemia, one had been diagnosed with acquired autoimmune hemolytic anemia (AIHA), and three were treated for light chain amyloidosis. All three patients with amyloidosis had been exposed to Daratumumab, a CD138-directed monoclonal antibody, during the last 6 months.

Comorbidities in our patient cohort included cardiovascular comorbidities in 19 patients, endocrine or metabolic conditions in 11 patients, pulmonary disease in nine patients, and neurologic disease in four patients. One patient had been treated for Tuberculosis and one patient was HIV positive. Five patients had previously been treated for malignant disease, including two patients who received treatment for blood cancers prior to being diagnosed with their current hematologic main diagnosis. Both were in complete remission at the time of assessment. One patient was diagnosed with renal cell carcinoma treated by total unilateral nephrectomy during the observation period. One patient diagnosed with HHV8-associated Castleman's disease had not yet received any treatment for this condition. No association was found to be present between the number of comorbidities and severity of COVID-19 ($r = .08033$, $p = .5418$, Spearman's correlation).

To characterize clinical course of SARS-CoV2 infection in our patient cohort, we assessed common symptoms of COVID-19 during patient follow-up and from electronical health records.

TABLE 4 Characteristics of SARS-CoV2 omicron variant infection in hematologic patients

Symptoms of COVID-19			
Symptom	**Yes (%)**	**No**	**Unclear**
Fatigue	37 (60.66%)	20	4
Cough	32 (52.46%)	23	6
Fever	24 (39.34%)	34	3
Headaches	16 (26.23%)	37	8
Arthralgia	12 (19.67%)	41	8
Anosmia/ageusia	5 (8.2%)	48	8
Dyspnea	10 (16.39%)	50	1
Requirement of oxygen therapy	7 (11.48%)	53	1
Hospitalization			
Hospitalizations during observation period			24 (39.34%)
For symptoms or treatment of hematologic disease			17 (27.87%)
For symptoms of COVID-19			6 (9.84%)
Unrelated to hematologic disease or COVID-19			1 (1.64%)
ICU admissions			5 (8.2%)
Discharged from ICU alive			1 (1.64%)
Radiographic assessment			
Chest imaging performed			16 (26.23%)
Positive for lower respiratory disase			8 (13.11%)
Negative for lower respiratory disease			8 (13.11%)
Chest imaging not performed			44 (72.13%)
No information available			1 (1.64%)
Severity of COVID-19			
Asymptomatic			10 (16.39%)
Mild			37 (60.66%)
Moderate			5 (8.2%)
Severe			3 (4.92%)
Critical illness			5 (8.2%)
Not evaluable			1 (1.64%)
Deaths during observation period			**6 (9.83%)**
Respiratory failure			2
Progressive disease			2
Sepsis			1
Liver failure			1
SARS-CoV2-specific treatment			
Sotrovimab			17 (27.87%)
Molnupiravir			4 (6.56%)
Dexamethasone			3 (4.92%)
Remdesivir			1 (1.64%)
Casirivimab/Imdevimab			1 (1.64%)
None			37 (60.66%)
No information available			1 (1.64%)
Duration of infection			
Negative PCR available after infection			41 (67.21%)
No negative PCR available and tested positive for SARS-CoV2 during the last 30 days of the observation period			4 (6.56%)
No follow-up data available			16 (26.23%)
Median duration until negative PCR test			32 days (range 3–87 days)

Ten patients (16.39%) showed no symptoms attributable to COVID-19. The most common clinical finding in symptomatic patients was fatigue, reported by 37 patients (60.66%), followed by cough, occurring in 32 patients (52.46%). Twenty-four patients (39.34%) displayed fever during SARS-CoV2 infection. Headaches were reported by 16 patients (26.23%) and arthralgia was found in 12 patients (19.67%). Anosmia and ageusia, symptoms present in a large fraction of patients during infection with previous SARS-CoV2 variants,[19] was relatively rare, affecting less than 10% of our patient cohort. Dyspnea was seen in 10 patients (16.39%), with 7 patients requiring oxygen therapy. Five patients showed respiratory failure, all of which were admitted to an intensive care unit (ICU). Chest imaging was performed in 16 patients (26.1%), eight of whom (13.11% of all patients) exhibited signs of lower respiratory disease in the form of atypical pulmonal infiltrates.

Severity of COVID-19 according to the NIH COVID19 treatment guidelines could be evaluated in all but one patient based on the available clinical and radiographic data (Table 4). Ten patients (16.39%) showed no symptoms of SARS-CoV2 infection during the observation period. Thirty-seven patients (60.6%) exhibited a mild course of disease and five patients (8.2%) showed moderate disease. Three patients presented with severe disease, and five cases (8.2%) of critical illness occurred in our patient cohort. In one case, severity of infection could not be evaluated based on the available clinical information. However, the patient was not hospitalized and showed no symptoms of respiratory disease during follow-up visits.

Twenty-four out of the 61 patients (39.34%) were hospitalized during the observation period. In total, the majority of hospitalizations occurred due to symptoms or for scheduled treatment of the underlying hematologic condition. One hospitalization was unrelated to hematologic disease or SARS-CoV2 infections. Six patients were hospitalized for symptoms of COVID-19. Of these patients, three were admitted to an ICU, together with two other patients that were initially hospitalized due to their hematologic condition. All ICU admissions occurred due to respiratory symptoms.

COVID-19 specific treatment was administered to 23 patients in total: 17 patients were treated with Sotrovimab (27.87%), four patients received Molnupiravir (6.56%), and in three patients Dexamethasone was administered (4.92%). One patient each (1.64%) was treated with Remdesivir or Casirivimab/Imdevimab, respectively. Sotrovimab is widely used in patients at increased risk for a severe course of COVID-19 and has demonstrated efficacy in this cohort in randomized trials.[20,21] In our patient cohort, no critical illness and/or ICU admission occurred after

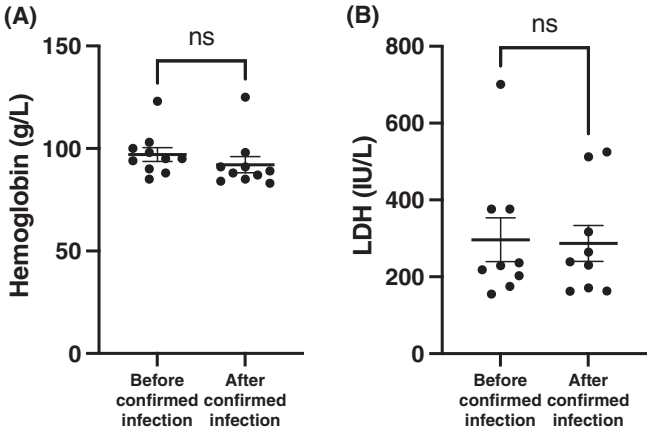

FIGURE 1 Hemoglobin and LDH levels in patients with hereditary hemolytic anemia. Hemoglobin (panel A, $n = 10$) and lactate dehydrogenase (LDH, panel B, $n = 9$) levels in patients with hemolytic disease before and after testing positive for SARS-CoV2 are displays. Bars are mean and SEM, each data point represents an individual measurement. Significance was determined using Wilcoxon's matched-pairs signed rank test. ns, not significant

Sotrovimab administration. Patients generally reported excellent tolerance to SARS-CoV2-specific medication.

Overall mortality in our cohort during the observation period was 9.83% (6 out of 61 patients). Causes of death were progressive malignant disease and respiratory failure in two patients, respectively, and sepsis and liver failure in one patient each.

One patient who died due to respiratory failure had received computed tomography of the chest 3 days prior to rapid respiratory deterioration and 4 days prior to death. Chest imaging displayed no evidence of lower respiratory infection but revealed large intrathoracic masses suspected to represent relapsed AML in the form of myeloid sarcoma, concomitant with bilateral pleural effusion (Supplementary Figure 1). As no other images were obtained at a later time point and no autopsy was performed at the deceased's family's request, it could not be determined whether respiratory failure occurred as a consequence of rapidly progressing COVID-19 or was unrelated to SARS-CoV2 infection.

Prior studies have aimed at establishing laboratory parameters predictive of severe disease course and adverse outcome in COVID-19. Among other risk factors, these studies have established low baseline lymphocyte count and high levels of C-reactive protein (CRP) after diagnosis, particularly a level of more than 20 mg/dl, as risk factors for severe disease.[6,22] To determine whether this association would be present in our patient cohort, we assessed total white blood cell (WBC) and lymphocyte count in peripheral blood at the last follow-up prior to SARS-CoV2 NAAT detection as well as CRP serum levels after confirmation of infection in our patient cohort. Neither WBC ($r = .1501$, $p = .2566$, Spearman's correlation) nor lymphocyte count ($r = -.06195$, $p = .6471$, Spearman's correlation), nor CRP after diagnosis ($r = .2412$, $p = .095$, Spearman's correlation) showed a significant association with COVID-19 severity in our patient cohort.

Furthermore, as most studies establishing risk factors for severe COVID-19 were performed in the pre-vaccination era, we investigated whether vaccination status would be predictive for the clinical course of SARS-CoV2 infection in our cohort. However, no signification correlation could be demonstrated between number of vaccines received prior to infection and COVID-19 severity ($r = -.04362$, $p = .7497$, Spearman's correlation).

In patients with inborn hemolytic anemia such as SCD or Thalassemia, viral infection is a well-described trigger for acute hemolysis.[23] Our patient cohort comprised 12 patients with hereditary hemolytic anemia. In this cohort, we observed no decrease in blood Hemoglobin levels before and after SARS-CoV2 infection (Figure 1). Likewise, Lactated dehydrogenase (LDH) levels as a surrogate parameter for hemolysis were not elevated after SARS-CoV2 infection. No red blood cell transfusions were administered outside the respective patients' regular transfusion interval during the observation period. Thromboembolism, a major complication of hemolysis, was not reported.

4 | DISCUSSION

In this study, we assessed symptom load and disease severity of infection with the SARS-CoV2 omicron variant in hematologic patients treated at our tertiary care university hospital.

Lower respiratory disease is a major global health burden and among the leading causes of death worldwide.[24] Infection with respiratory viruses contributes to a significant fraction of respiratory disease mortality; however, outcomes are largely different between immunocompetent and immunocompromised individuals.[25] Due to severe immunodeficiency, patients with hematologic disease are particularly susceptible to critical illness due to respiratory virus infection.[26]

Blood cancer patients are among the most vulnerable individuals during the COVID-19 pandemic. Before the introduction of systematic vaccination against SARS-CoV2, infection was fatal in about 18% of patients with hematologic malignancy, and ICU mortality exceeded 60% in this group.[4] Widespread vaccination has impacted COVID-19 morbidity and mortality. Although SARS-CoV2 vaccination efficacy has been extensively studied in hematologic patients, these studies have almost exclusively focused on the quantification of post-vaccination antibody response.[11,12,27,28] Contrastingly, little is known about the clinical course of SARS-CoV2 infection in vaccinated patients with hematologic malignancy. Early data reporting on the course of disease this group indicate attenuation of SARS-CoV2 infection severity, but morbidity and mortality of COVID-19 remain considerably elevated as compared to the general population.[13] While infection with the SARS-CoV2 omicron variant is associated with favorable outcomes compared to previous virus variants,[15] its impact on outcomes of patients with hematologic disease is unclear. To our knowledge, this is the first case series describing the severity of omicron variant infection in hematologic patients, both in the inpatient and outpatient setting. Additionally, this work contributes to the

currently limited comprehension of COVID-19 disease course in vaccinated patients with blood disorders.

Although limited by the small sample size, our data indicate mild disease course among infected patients. Throughout the observation period, 10 out of 61 individuals with evaluable COVID-19 severity remained asymptomatic. Data from the pre-vaccination, pre-omicron era suggest a similar percentage of asymptomatic SARS-CoV2 infected individuals with hematologic malignancies.[4] However, in this study, representing the largest clinical data assembly on COVID-19 in hematologic patients, over 60% of patients presented with severe or critical illness, translating into a mortality rate of over 30% with about two thirds of death directly attributable to COVID-19.[4] Contrastingly, we report mild or moderate disease in the majority of patients (41 out of 61 patients, 67.21%). Only one case with mild disease was hospitalized due to COVID-19, while the majority could be followed as outpatients throughout the observation period unless their hematologic condition required otherwise.

Overall mortality in our patient cohort was 9.83% (6 patients out of 61). We estimate that three out of six deaths in our cohort are direct consequences of SARS-CoV2 infection, including the patient with rapid-onset respiratory deterioration mentioned above; however, these estimations are uncertain as no autopsies were performed on fatalities in this cohort.

As mentioned before, mortality exceeded 30% in SARS-CoV2-infected patients with hematologic malignancies before the introduction of systematic vaccination.[4] Limited data are available on outcomes in the vaccination era. However, a recently published study reports a mortality of 12.4% after 30 days, with about two third of deaths directly attributable to COVID-19.[13] In this study, data cutoff was end of August 2021, before the emergence of the SARS-CoV2 omicron variant. While 28% of deaths in the reported cohort were attributed to the SARS-CoV2 alpha variant, no viral sequence analysis was performed in the remaining fatalities.

Prior to the emergence and rapid spread of the SARS-CoV2 omicron variant, the SARS-CoV2 delta variant was dominant in most European countries. Compared to the delta variant, omicron-infected patients tend to report less severe symptoms, including relatively few instances of anosmia and ageusia as recapitulated in our cohort.[29] While community-based transmission of the omicron variant is greatly exacerbated compared to previous SARS-CoV2 variants and has led to unprecedented incidence of SARS-CoV2 infection worldwide, disease severity and mortality appear to be reduced.[16,29] Clinical data on the outcome of delta-variant hematologic patients are scarce, although there is evidence suggesting impaired delta variant neutralization by available vaccines in chronic lymphocytic leukemia patients.[30] The lack of comprehensive data on variant-based outcome in hematologic patients complicates comparison of omicron-infected patients with previous waves, but we are optimistic that larger registries will expand our knowledge in this study.

Interestingly, vaccination status was unable to predict disease severity. The fact that vaccination greatly reduces risk of severe COVID-19 in the general population[10] and is effective in cancer patients[31] makes it plausible that our study underestimates the effect of vaccine-based immunization due to small sample size. Furthermore, a large fraction of patients in this cohort was exposed to B cell-directed agents, potentially impairing humoral immunity against viral infection.[11] It should be noted that all fatalities in our patient cohort were either unvaccinated (one patient) or had been exposed to B cell-directed therapy in the period prior to infection (five patients).

Patients with nonmalignant hematologic disease exhibit increased susceptibility to mortality from COVID-19.[8] The high prevalence of cardiovascular and pulmonary comorbidities in this group as well as the possibility of life-threatening complications of infection, such as hemolysis or acute chest syndrome in SCD as well as thromboembolic events, warrant treatment of these patients as high-risk individuals. Fortunately, symptoms were mostly mild in this subgroup. In patients with hereditary hemolytic anemia, we did not observe significant hemolysis based on laboratory parameters, and no complications potentially related to hemolysis occurred. However, one patient with acquired AIHA succumbed to acute liver failure following high grade liver cirrhosis, amounting to a mortality of 6.25% in patients with nonmalignant blood disease.

During the course of the pandemic, SARS-CoV2 specific treatment options reducing the risk of hospitalization and death from COVID-19 have emerged. Molnupiravir[32] and Sotrovimab[20] have been approved for outpatient treatment of at-risk individuals with a confirmed SARS-CoV2 infection, including patients infected with the omicron variant. In 17 patients treated with Sotrovimab and 4 patients treated with Molnupiravir (including one patient who received both medications), only one case of severe COVID-19 and no ICU admissions occurred. Given the excellent tolerance of both drugs, we do find these results encouraging in spite of the small sample size insufficient for in-depth analysis of therapy efficacy. In our opinion, virus-specific treatments are in urgent need of further evaluation in hematologic patients with a SARS-CoV2 infection.

Altogether, our data suggest reduced morbidity and mortality in hematologic patients infected with the omicron variant of SARS-CoV2 as compared to prior waves of the COVID-19 pandemic. Our data are unable to determine whether virus-intrinsic properties or host factors such as immunity from previous (undetected) SARS-CoV2 infection or vaccination determine trajectories of omicron variant infections in patients with blood disorders. Thus, larger prospective studies in this high-risk collective are urgently needed.

AUTHOR CONTRIBUTIONS

Fabian Ullrich and Julia von Tresckow assessed and analyzed the patient data and wrote the manuscript. Christine Hanoun, Amin T. Turki, Ferras Alashkar, and Tobias Liebregts provided clinical information on patients. Katharina Breuckmann provided radiographic images. Hans Christian Reinhardt and Bastian von Tresckow supervised the study. All authors approved the final form of the manuscript.

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CONFLICT OF INTEREST

Fabian Ullrich: reports travel support from AbbVie and Kite/Gilead.

Christine Hanoun: has nothing to disclose.

Amin T. Turki: reports consultancy for CSL Behring and Maat Pharma.

Tobias Liebregts: has nothing to disclose.

Katharina Breuckmann: has nothing to disclose.

Ferras Alashkar: has nothing to disclose.

Hans-Christian Reinhardt: has nothing to disclose.

Bastian von Tresckow: is an advisor or consultant for Allogene, BMS/Celgene, Cerus, Incyte, Miltenyi, Novartis, Pentixafarm, Roche, Amgen, Pfizer, Takeda, Merck Sharp & Dohme, and Gilead Kite; has received honoraria from AstraZeneca, Novartis, Roche Pharma AG, Takeda, and Merck Sharp & Dohme; reports research funding from Novartis (Inst), Merck Sharp & Dohme (Inst), and Takeda (Inst); and reports travel support from AbbVie, AstraZeneca, Kite-Gilead, Merck Sharp & Dohme, Takeda, and Novartis.

Julia von Tresckow: is an advisor or consultant for AbbVie, AstraZeneca, Janssen-Cilag and Roche, has received honoraria from AbbVie, AstraZeneca, Janssen-Cilag and Roche, reports research funding from Janssen-Cilag and Roche, and reports travel support from AbbVie, AstraZeneca, Janssen-Cilag and Roche.

DATA AVAILABILITY STATEMENT

Data and other artifacts supporting the results in the paper will not be archived it in a public repository due to data protection reasons.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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