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COVID-19 in 96 Patients With Hematologic Disease: The First Single-center Experience From the Czech Republic

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Coronavirus disease 2019 (COVID-19) represents an important infectious complication in patients with hematologic diseases. Our study presents first single-center experience from the Czech Republic in 96 patients in whom COVID-19 was confirmed. The study results confirm the prognostic significance of age for achieving treatment response of hematologic disease as well as the severity and mortality of COVID-19 in hematology patients.

Background: Coronavirus disease 2019 (COVID-19) represents an important infectious complication associated with high mortality rates in patients with hematologic diseases. There have not been published any epidemiologic studies from Czech Republic so far. **Patients and Methods:** This study is the first analysis of patients with hematologic malignancies and bone marrow failure syndromes treated at single hematology center in the Czech Republic between March 1 and December 31, 2020, in whom COVID-19 infection was confirmed. **Results:** The sample comprised 96 patients aged 26 to 84 years (median, 66.0 years). At the time of their COVID-19 diagnosis, 75 patients (78.1%) were treated for hematologic diseases. Twenty-seven patients (28.1%) in the sample had complete remission (CR) of their hematologic disease. They were nonsignificantly more likely to have asymptomatic to moderate COVID-19 infection than those who failed to achieve CR (74.1% vs. 56.5%; $P = .06$). A more severe course of the infection was significantly correlated with older age ($P = .047$). Lung involvement was also statistically significantly associated with older age ($P = .045$). Over the study period, a total of 15 patients died. Age greater than 60 years was significantly associated with deaths from COVID-19 ($P = .036$), with failure to achieve CR having a statistically nonsignificant impact on mortality ($P = .22$). **Conclusion:** These results confirm the prognostic significance of age for achieving treatment response of hematologic disease as well as the severity and mortality of COVID-19 in hematology patients.

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Introduction

Coronavirus disease 2019 (COVID-19) infection is caused by a novel coronavirus named severe acute respiratory syndrome

coronavirus 2 (SARS-CoV-2). The virus, originally referred to as 2019-nCoV, was first identified in Wuhan, the capital city of Hubei province of China, at the end of 2019. Coronaviruses belong to Coronaviridae, which is a family of RNA viruses.¹ After its spread from Wuhan, the virus started a global pandemic that continues to date. Although the disease is predominantly manifested by fever and respiratory infection symptoms, its course may be quite variable, ranging from completely asymptomatic to acute respiratory failure. The theoretical and practical findings concerning the pathogenesis, clinical manifestations, therapy, and therapeutic options are becoming increasingly accurate, yet COVID-19 infection continues to have a major impact on health care systems and entire populations. Patients with hematologic malignancies and bone marrow failure syndromes constitute a very heterogeneous population with a generally high risk of infectious complications. Although the infection fatality rate for COVID-19 is approximately 1% in the general

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population, it may exceed 30% among patients with cancer.^{2,3} Published studies report significantly higher mortality associated with COVID-19 in patients with hematologic malignancies older than 60 years and those not achieving a complete remission (CR) of their disease.⁴⁻⁶ The groups most at risk are patients with acquired bone marrow failure and acute leukemia who were found to have higher infection fatality rates than those with lymphoproliferative disorders.^{4,7} In addition to the infection fatality rate, another important measure used to assess the impact of the COVID-19 pandemic on hematologic patients will be cancer fatality rate, reflecting delays in cancer treatment owing to infectious complications.

So far, no results from a large analysis of the epidemiology, clinical, and therapeutic aspects of COVID-19 infection in patients with hematologic malignancies and bone marrow failure syndromes conducted in the Czech Republic have been published. This article aims to present initial data from a 10-month experience at a single university hospital center for specialized hematology care operating its own COVID care unit during the pandemic caused by SARS-CoV-2.

Patients and Methods

The study is a retrospective descriptive analysis of patients with hematologic malignancies and bone marrow failure syndromes treated at the Department of Hemato-Oncology, Faculty of Medicine and Dentistry, Palacký University Olomouc and University Hospital Olomouc in 2020 in whom COVID-19 infection was confirmed. The sample comprised all patients cared for by the center who were tested positive for SARS-CoV-2 by real-time polymerase chain reaction (RT-PCR) tests of nasopharyngeal swabs between March 1 and December 31, 2020. Patients in whom SARS-CoV-2 was identified by other than the university hospital laboratory were only included if they were treated or observed for the above diseases at the center over the study period. As a rule, the first hospital stay for COVID-19 infection was included in the analysis. Between March 1 and December 31, 2020, a total of 4750 patients with hematologic diseases (including nonmalignant diseases) were examined or admitted for a stay at the center. Out of 102 SARS-CoV-2-positive patients, 96 had hematologic malignancies or bone marrow failure syndromes. The other 6 patients diagnosed with nonmalignant hematologic diseases were excluded from the study. None of the patients in the cohort underwent vaccination against COVID-19 before positive testing for SARS-CoV-2.

Hospitalization and COVID-19 Treatment

SARS-CoV-2-positive patients were mostly cared for in the COVID care unit set up at the center as patient numbers reached their peak, that is, from October 1 to November 15, 2020 (phase 1), and from December 15, 2020 to 25 January 2021 (phase 2). Alternatively, they stayed in other COVID care units in either the university hospital or nearby hospitals cooperating with the center. All patients staying at the center were tested for the presence of SARS-CoV-2 by RT-PCR of nasopharyngeal swabs no longer than 72 hours before their admission. Patients requiring acute admission had to stay in quarantine rooms until their RT-PCR test results were obtained. Subsequently, they were moved to either a general medical unit or a COVID care unit at the center, in the university hospital,

or in a nearby hospital. The center had 20 and 12 monitored beds for intermediate care including high-flow oxygen therapy during phase 1 and phase 2, respectively. Critically ill patients requiring invasive mechanical ventilation were transferred to the university hospital's Department of Anesthesiology and Intensive Care Medicine. Patients staying in the center's COVID care unit were treated in accordance with the World Health Organization (WHO) guidance for clinical management of COVID-19.^{8,9} Depending on the severity of their condition, COVID-19 patients were treated with corticosteroids, remdesivir, convalescent plasma, inosine pranobex, and comprehensive supportive care including prophylactic anticoagulation with low molecular weight heparin. All hospitalized patients with lung involvement confirmed by imaging modalities (radiographs or high-resolution computed tomography scan) underwent initial antibiotic therapy targeting pathogens causing community pneumonia containing cefotaxime or piperacillin-tazobactam combined with clarithromycin, subsequently adjusted based on culture results or known colonization with multidrug-resistant bacteria. None of the patients with lung involvement were treated on an outpatient basis. Patients' hematologic diseases were treated and assessed in accordance with recommendations from the Czech Society of Hematology compliant with the global guidance.¹⁰

Clinical Findings and Laboratory Data Assessment

Patient data included demographics, hematologic disease at the time of COVID-19 diagnosis, cancer treatment, clinical pattern, and treatment of the infection. Additionally, laboratory findings were analyzed, namely, selected blood count parameters (absolute counts for leukocytes, lymphocytes, and neutrophils), acute phase reactants (C-reactive protein [CRP], presepsin, IL-6) and the presence of IgG antibodies at 1 month after diagnosis of the infection. Patients were assessed for comorbidities—chronic lung disease, diabetes mellitus (treated with oral antidiabetic drugs or insulin), heart diseases (hypertensive heart disease, cardiac failure, arrhythmia or valvular heart disease), liver, and kidney diseases. Finally, body mass index and smoking status were ascertained. Treatment for hematologic diseases in the last 3 months was classified into 3 following categories—chemotherapy alone or in combination with immunotherapy (eg, rituximab, obinutuzumab), oral inhibitors or targeted therapy (eg, tyrosine kinase inhibitors, ibrutinib, idelalisib, ruxolitinib), and category comprising other regimens and combinations (eg, cytoreductive therapy, growth factors, hypomethylating agents).

The imaging examinations (chest radiographs or high-resolution computed tomography scan of the lungs) were required for diagnosis of lung involvement in patients with high clinical suspicion. The severity of COVID-19 infection was classified according to the WHO recommendations.⁹ Mortality was analyzed with respect to COVID-19, age, and hematologic disease. Health care-associated infection was defined as developing COVID-19 on day 3 of the hospital stay or later after a negative SARS-CoV-2 test on admission. All patient data retrieved from available medical records were processed anonymously, in accordance with the hospital's regulations and Declaration of Helsinki. At the same time, 57 patients were also enrolled in the EPICOVIDEHA survey and 6 patients in

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the iCMLf—CML and COVID-19 Case Collection.^{11,12} The study was approved by the university and hospital's ethics committee.

Statistical Analysis

Data are expressed as percentages in case of categorical variables or as medians with minimum and maximum values in case of continuous variables. Categorical data were compared using Fisher's exact test in a contingency table; for continuous data, the Kruskal-Wallis test, a nonparametrical version of an analysis of variance, was used. Data were analyzed with MATLAB software. All tests were performed at a significance level set to 5%.

Results

During the study period, a total of 96 SARS-CoV-2-positive patients with hematologic malignancies or bone marrow failure syndromes aged 26 to 84 years (median, 66.0 years) were identified. The sample comprised 56 females with a median age of 65.0 years (27-84 years) and 40 males with a median age of 67.7 years (26-84 years). Sixty-four patients (66.7%) were aged 60 and older. The prevalence of COVID-19 infection among patients examined at the center over the study period was 2.1% (102 cases out of 4750 patients). In as many as 23 patients (24.0%) in the sample, health care-associated COVID-19 infection could not be ruled out.

In the sample ($n = 96$), cardiac comorbidities were observed in 47 patients (49.0%), chronic lung diseases in 9 (9.4%), liver diseases in 3 (3.1%), and kidney diseases in 4 (4.2%). Twenty-one patients (21.9%) were treated for diabetes mellitus, with 15 taking oral antidiabetic drugs and 6 injecting themselves with insulin. At least 1 comorbidity was found in 54 patients (56.3%). Their median age was higher than that of 42 patients with no comorbidities (69.9 vs. 59.2 years). Fifteen patients (15.6%) smoked cigarettes when diagnosed with COVID-19. The body mass index ranged from 15.1 to 53.9 kg/m² (median, 25.1 kg/m²) in 90 patients for whom data were available.

Underlying Hematologic Disease

Lymphoproliferative disorders were present in 65 patients (67.7%), accounting for the largest subgroup of diagnoses in the sample. Of those, malignant lymphoma was most common (27/96 patients [28.1%]), followed by chronic lymphocytic leukemia (22/96 patients [22.9%]) and multiple myeloma (12/96 patients [12.5%]), with 2 patients suffering from both chronic lymphocytic leukemia and multiple myeloma, or Waldenstrom macroglobulinemia. Both patients observed for acute lymphoblastic leukemia had undergone allogeneic hematopoietic stem cell transplantation 3 or 6 years earlier. Myeloproliferative disorders were present in 29 patients (30.2%). The most frequent diagnosis was acute myeloid leukemia (12/96 patients [12.5%]), including 1 case of acute promyelocytic leukemia. Seven patients were treated for chronic myeloid leukemia and 4 for myelodysplastic syndrome. Two patients were observed for bone marrow failure syndromes, namely, aplastic anemia and paroxysmal nocturnal hemoglobinuria.

When diagnosed as SARS-CoV-2-positive by RT-PCR, 27 patients (28.1%) in the sample had CR of their hematologic disease, 12 (12.5%) had partial remission, and 2 (2.1%) had stable disease. In 33 patients (34.4%), hematologic disease was newly diagnosed

or their therapy had been initiated shortly beforehand, with no treatment response assessment yet. Relapse or progression after therapy was seen in 22 patients (22.9%). Patients who achieved CR were significantly younger than those who did not ($P = .0008$). At the time of their COVID-19 diagnosis, 75 patients (78.1%) were treated for hematologic diseases; in the remaining 21 patients (21.9%), their hematologic disease either did not require therapy or COVID-19 infection was diagnosed before its initiation. A detailed overview of hematologic diagnoses, treatment regimens, remission status, hospital stays, and severity of COVID-19 infection is provided in Table 1.

Laboratory Findings

In patients with available data, selected laboratory parameters were analyzed at the time of their COVID-19 diagnosis. The median absolute blood cell counts were as follows: leukocytes $5.23 \times 10^9/L$ (0.03-145.42), lymphocytes $0.91 \times 10^9/L$ (0.00-139.75) and neutrophils $3.4 \times 10^9/L$ (0.00-48.41). Further, the acute phase reactants CRP, presepsin, and IL-6 were analyzed. At the time of COVID-19 diagnosis, CRP levels ranged widely, from 0.2 to 299.5 mg/L (median, 31.9 mg/L). The median CRP level at diagnosis was higher in a subgroup of 15 patients who died of the infection than in those who were cured (76.7 mg/L vs. 22.6 mg/L). The median level of presepsin was 721 ng/L (318-2030 ng/L); IL-6 levels ranged from 0.21 to 1397 ng/L (median, 73.55 ng/L). In 22 patients with available serology test results, the presence of IgG antibodies after recovering from the infection was analyzed. Their antibody titers ranged from 3.8 to 165 AU/mL (median, 17.2 AU/mL). Sixteen of the 22 patients had B-cell lymphoproliferative disorders, with 4 of them receiving no cancer treatment in the previous 3 months. The results of selected laboratory tests performed at the time of COVID-19 diagnosis are shown in Table 2.

Clinical Course of COVID-19

According to the WHO definition of severity, COVID-19 infection was classified as asymptomatic in 15 patients (15.6%), mild in 30 (31.2%), moderate in 14 (14.6%), severe in 20 (20.8%), and critical in 7 patients (7.3%). In the remaining 10 patients, severity could not be determined from the available information. Patients in CR were nonsignificantly more likely to have asymptomatic to moderate COVID-19 infection than those who failed to achieve CR (74.1% vs. 56.5%; $P = .06$). A similar trend, that is a higher proportion of milder cases of COVID-19, was observed in those less than 60 years of age (71.9% vs. 56.3%; $P = .47$). A more severe course of the infection was significantly correlated with older age ($P = .047$).

Lung diseases, confirmed by imaging modalities, were found in 43 patients (44.8%). There were no signs of lung involvement in 38 patients (39.6%); for 15 patients, data on lung involvement were unavailable. The results point to nonsignificantly higher rates of lung diseases among patients without CR (49.3% vs. 33.3%; $P = .32$) and those more than 60 years of age (50.0% vs. 34.4%; $P = .1$). In the sample, lung involvement was significantly associated with older age ($P = .045$).

As part of their specific COVID-19 therapy, 17 patients (17.7%) received remdesivir; convalescent plasma and corticosteroids were administered to 18 (18.8%) and 35 (36.5%) patients, respectively.

Table 1 Overview of Hematologic Diagnoses, Treatment Regimens, Remission Status, Hospital Stays, and Severity of Coronavirus Disease-19 Infection in the Sample

Diagnosis	No. of Patients	Chemotherapy ± Immunotherapy/Oral Inhibitors and Targeted Therapy/Other Regimens and Combinations/No Treatment	Complete Remission (%)	Inpatient Treatment (%)	Severe to Critical/Asymptomatic to Moderate Course of COVID-19/Not Detected
Lymphoproliferative disorders	65	27 / 17 / 3 / 18	12 (18.5)	51 (78.5)	19 / 38 / 8
Chronic lymphocytic leukemia	20	4 / 8 / 0 / 8	4	17	8 / 8 / 4
Multiple myeloma	11	1 / 7 / 3 / 0	4	5	3 / 7 / 1
Diffuse large B-cell lymphoma	8	7 / 0 / 0 / 1	0	8	1 / 5 / 2
Follicular lymphoma	6	5 / 0 / 0 / 1	1	4	2 / 4 / 0
Hodgkin lymphoma	3	2 / 0 / 0 / 1	0	2	1 / 2 / 0
B-cell non-Hodgkin lymphoma, NOS	3	2 / 0 / 0 / 1	0	3	1 / 2 / 0
Mantle cell lymphoma	2	1 / 0 / 0 / 1	1	2	0 / 2 / 0
T-cell non-Hodgkin lymphoma	2	1 / 0 / 0 / 1	0	2	0 / 2 / 0
Burkitt lymphoma	2	2 / 0 / 0 / 0	0	2	1 / 1 / 0
Hairy cell leukemia	2	0 / 0 / 0 / 2	0	1	0 / 1 / 1
Acute lymphoblastic leukemia	2	1 / 1 / 0 / 0	2	1	0 / 2 / 0
Marginal zone lymphoma	1	0 / 0 / 0 / 1	0	1	0 / 1 / 0
Waldenstrom macroglobulinemia	1	1 / 0 / 0 / 0	0	1	1 / 0 / 0
CLL + MM	1	0 / 1 / 0 / 0	0	1	0 / 1 / 0
CLL + WM	1	0 / 0 / 0 / 1	0	1	1 / 0 / 0
Myeloproliferative disorders	29	7 / 7 / 13 / 2	14 (48.3)	18 (62.1)	8 / 19 / 2
Acute myeloid leukemia	12	7 / 0 / 4 / 1	7	11	6 / 6 / 0
Chronic myeloid leukemia	7	0 / 7 / 0 / 0	7	1	0 / 6 / 1
Myelodysplastic syndrome	4	0 / 0 / 3 / 1	0	3	1 / 3 / 0
Polycythemia vera	2	0 / 0 / 2 / 0	0	1	1 / 1 / 0
Primary thrombocythemia	2	0 / 0 / 2 / 0	0	1	0 / 1 / 1
Primary myelofibrosis	1	0 / 0 / 1 / 0	0	0	0 / 1 / 0
Chronic myelomonocytic leukemia	1	0 / 0 / 1 / 0	0	1	0 / 1 / 0
Bone marrow failure syndromes	2	0 / 0 / 1 / 1	1 (50.0)	0 (0)	0 / 2 / 0
Aplastic anemia	1	0 / 0 / 0 / 1	0	0	0 / 1 / 0
Paroxysmal nocturnal hemoglobinuria	1	0 / 0 / 1 / 0	1	0	0 / 1 / 0

Abbreviations: CLL = chronic lymphocytic leukemia; MM = multiple myeloma; WM = Waldenstrom macroglobulinemia; NOS = not otherwise specified.

Table 2 Results of Selected Laboratory Tests Performed at the Time of Severe Acute Respiratory Disease Coronavirus 2 Detection by Polymerase Chain Reaction

Parameter/Unit (No. of Analyzed Samples)	Minimum Value	Maximum Value	Median	Mean
Leukocyte count/10 ⁹ /L (n = 61)	0.03	145.42	5.23	12.29
Lymphocyte count/10 ⁹ /L (n = 59)	0.00	139.75	0.91	6.75
Neutrophil count/10 ⁹ /L (n = 59)	0.00	48.41	3.40	4.82
C-reactive protein, mg/L (n = 60)	0.2	299.5	31.9	54.9
Presepsin, ng/L (n = 9)	318	2030	721	863
IL-6, ng/L (n = 18)	0.21	1397.00	73.55	218.88

Five patients (5.2%) were given inosin pranobex. The other patients either did not receive this therapy or such information could not be obtained from their medical records.

Hospitalization

Sixty-nine patients (71.9%) receiving treatment were admitted to a hospital, with 55 cases spending at least some time in COVID care

units in the university hospital, mostly the center’s unit. Fourteen patients were admitted to COVID care units in nearby hospitals. Their details, however, were unavailable, so only data from patients staying in the university hospital were analyzed. As of the end of the study period (December 31, 2020), 8 patients were still hospitalized. The median length of hospital stay of 47 patients was 14 days (2–67 days). Hospitalization was significantly more frequently required

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Table 3 Prognostic Significance of Disease Status and Age for the Course of COVID-19 Infection in Patients With Hematologic Diseases

Parameter	Disease status		P value	Age at diagnosis of the infection		P value
	CR	Non-CR		<60	≥60	
No. of patients	27	69	–	32	64	–
Median age	54.9	67.8	.0008	48.0	69.9	–
CR	–	–	–	15 (46.9%)	12 (18.6%)	.007
Non-CR	–	–	–	17 (53.1%)	52 (81.3%)	–
COVID-19 severity						.047
Asymptomatic to moderate course	20 (74.1%)	39 (56.5%)	.06	23 (71.9%)	36 (56.3%)	.47
Severe to critical course	4 (14.8%)	23 (33.3%)	–	8 (25.0%)	19 (29.7%)	–
Not known	3 (11.1%)	7 (10.1%)	–	1 (3.1%)	9 (14.0%)	–
Lung involvement						.0045
Yes	9 (33.3%)	34 (49.3%)	.32	11 (34.4%)	32 (50.0%)	.1
No	12 (44.4%)	26 (37.7%)	–	17 (53.1%)	21 (32.8%)	–
Not known	6 (22.2%)	9 (13.0%)	–	4 (12.5%)	11 (17.2%)	–
Hospital stay/death						
Hospital stay	15 (55.6%)	54 (78.3%)	.04	21 (65.6%)	48 (75.0%)	.47
Death	2 (7.4%)	13 (18.8%)	.22	1 (3.1%)	14 (21.9%)	.036

COVID-19 = coronavirus disease 2019; CR = complete remission; Non-CR = complete remission not achieved.

by patients without CR (78.3% vs. 55.6%; $P = .04$). By contrast, age had no significant impact on the need for hospital admission ($P = .47$). As a part of their oxygen therapy, 7 patients required invasive mechanical ventilation; in one of them, this therapy needed to be combined with extracorporeal membrane oxygenation. High-flow oxygen therapy was delivered to 6 patients. In 18 patients, the use of a nasal cannula or oxygen mask was sufficient. As many as 23 of the 55 patients (41.8%), mostly those with asymptomatic to mild COVID-19 infection, required no oxygen therapy. For 1 patient, data on oxygen therapy were unavailable in the medical records. Nine critically ill patients had to be cared for at the university hospital's department of intensive care medicine.

Mortality

Over the study period (ie, until December 31, 2020), a total of 15 patients died. The median age of the deceased patients was 72 years (58–84 years). Only 2 patients achieved CR of their hematologic disease; three patients had partial remission, and one had stable disease. Four patients had newly diagnosed or untreated diseases; 5 patients progressed or relapsed. Lymphoproliferative disorders were seen in 9 patients (including 6 patients with chronic lymphocytic leukemia) and myeloproliferative disorders in 6 patients (4 acute myeloid leukemia cases including 1 acute promyelocytic leukemia case). Age greater than 60 years was significantly associated with deaths from COVID-19 ($P = .036$), with failure to achieve CR having a statistically nonsignificant impact on mortality ($P = .22$). Table 3 shows the prognostic significance of achieved CR and age for selected studied parameters of COVID-19 affliction and therapy.

Discussion

The authors present their own experiences with treating patients with hematologic diseases and COVID-19 infection obtained in a

single center for specialized hematology care in the Czech Republic in 2020. In a study by Girmenia et al,¹³ the prevalence of COVID-19 among patients with hematologic diseases (including nonmalignancies) was 0.24%, as compared with only 0.12% in the general population ($P = .14$). Other studies reported prevalence rates of 0.17% to 0.9%, depending on the type of hematologic malignancy.^{14–16} A Turkish population-based study identified 740 patients (0.39%) with hematologic malignancies among 188,897 individuals who tested positive for SARS-CoV-2.¹⁷ The prevalence rate of 2.1% found in the present study may be skewed by overall lower rates of follow-up check-ups, nonacute examinations, and consultations owing to health care restructuring. Because most of the nonacute hematologic treatment was postponed during the COVID-19 pandemic, the number of patients examined or admitted for a hospital stay decreased from 5825 to 4750 (81.5%) in comparison with the same study period in 2019. By contrast, patients with malignancies (96/102 [94.1%]) sought our care more frequently, one of the reasons being infectious complications.

In studies of adult patients with hematologic malignancies, the median age ranges from 50 to 76 years of age, reflecting both the generally higher prevalence of malignancies at older age and the more severe course of COVID-19.^{4–6,17} A similar trend was seen in our study, with a median age of 66 years and high proportions of patients who did not achieve remission of their hematologic disease (69/96 [71.9%]) or those undergoing cancer treatment (75/96 [78.1%]).

Lymphoproliferative disorders account for 55% to 91% malignancies in studies.^{5–7,17} The high proportions may be explained by the higher immunosuppressant potential of therapies (including frequently used monoclonal antibodies) for these conditions as compared with chronic myeloproliferative disorders typically associated with a less complicated course and lower mortality rates.^{7,17}

The present study found lymphoproliferative disorders in as many as 67.7% of cases and a generally milder course of COVID-19 was observed in patients with selected myeloproliferative disorders. Out of 7 patients with chronic myeloid leukemia, 6 (85.7%) had an asymptomatic to moderate course and only 1 required hospital admission. Thus, it may be assumed that there may have been more patients with asymptomatic or minimally symptomatic infection. These patients recovered from COVID-19 without needing specialized hospital care and therefore were not identified.

In the present study, younger age was significantly associated with achieving CR of hematologic malignancies and a nonsignificantly more frequent less severe course of COVID-19 or less frequent lung involvement. Similar results were reported by other authors.^{5,7} The observed trends suggest that age is an important prognostic factor affecting other studied parameters as well, namely, achieving CR of hematologic disease, the prevalence of comorbidities, and mortality. Younger patients may undergo more intense therapy, thus being more likely to achieve CR. It may be assumed that patients in CR with immune reconstitution are generally more likely to overcome infectious complications than those with active disease requiring cancer therapy with immunosuppressant potential. In contrast, some studies suggest a protective potential of immune system modulation resulting from cancer therapy.^{18,19}

The most important blood count change observed at the time of COVID-19 diagnosis was lymphocytopenia, with a median count of $0.91 \times 10^9/L$. Similar findings were published earlier.²⁰ Apart from leukopenia, no other blood count changes seen in the present study were significantly different from those found in other infections. Deng et al²¹ reported significantly higher CRP levels on admission in patients with a fatal course of COVID-19 than in those who recovered (109.25 vs. 3.22 mg/L; $P < .001$), with the former having significantly more frequent complications such as kidney failure, acute respiratory distress syndrome, shock, or disseminated intravascular coagulation. The prognostic significance of CRP was also confirmed by Sahu et al²² in a meta-analysis including 2745 patients with COVID-19. Our results showed associations of increased CRP levels at the time of COVID-19 diagnosis and maximum CRP levels during the hospital stay with patient deaths owing to the infection.

In a study of 41 patients with hematologic malignancies by Infante et al,⁶ nosocomial transmission of SARS-CoV-2 was confirmed in 5 patients (15%) and seemed likely in 25 patients who had attended the hospital in the previous 14 days. Moreover, Elkrief et al^{23,24} showed that patients with health care-associated COVID-19 infection had a significantly worse prognosis. Therefore, the authors recommend fewer visits to the hospital by patients optimally responding to treatment to decrease the risk of nosocomial transmission. This recommendation is one possible way of preventing the spread of COVID-19 infection among high-risk patients. This finding is consistent with the fact that, in the present study, health care-associated infection could not be ruled out in 23 patients (24.0%). Because we could not exclude nosocomial spreading from health care workers or patients admitted in the incubation period, all admitted patients had been tested for the presence of SARS-CoV-2 by RT-PCR no longer than 24 hours before hospitalization followed by second test between days 5 and 7 of hospitalization since January 2021. Moreover, all health care workers underwent

COVID-19 vaccination or were at least once weekly screened with rapid COVID-19 antigen test. The patients in greatest risk of COVID-19 infection were vaccinated, as well. No more cases of nosocomial transmission of SARS-CoV-2 had been observed since the adoption of these strategies (at the time of writing preparation [April 2021]).

In a meta-analysis of 34 studies including 3240 adult patients with hematologic malignancies, systemic cancer therapy only nonsignificantly increased the risk of death from COVID-19, as compared with untreated patients (relative risk, 1.17; $P = .37$). This finding may be explained by therapy-induced anergy of the immune system with an attenuated overall inflammatory response of the organism. Therefore, the authors suggest that urgent cancer therapy should not be withheld despite the risk of COVID-19 infection.⁴ Another important fact to be considered when planning cancer therapy is that, compared with the general population, hematologic patients remain SARS-CoV-2-positive on PCR for a longer time.^{6,23,24} In all cases, the risk of hematologic disease progression owing to delayed cancer therapy in patients who tested positive for COVID-19 should be considered individually.

The study limitations are its retrospective design, recommendations changing over time, and heterogeneous practices and experiences of health care personnel in various COVID care units and hospitals where the patients were treated. Assessment of the statistical significance of the observed trends is limited by the small total number of patients in the sample and only partial availability of the retrospectively analyzed parameters.

Conclusion

This study is the first to report on patients with hematologic malignancies and bone marrow failure syndromes with COVID-19 infection treated in the Czech Republic (at the time of writing [April 2021]). COVID-19 is an important infectious complication associated with high mortality rates in patients with hematologic diseases. Its course is generally more severe, with higher mortality rates in elderly patients and those with uncontrolled malignancies. Further research is necessary to increase therapeutic effectiveness and to prevent this infectious complication in the entire population, not only in hematology patients. The current situation points to the need for national registries cooperating with hematology care centers to perform prospective surveillance, allowing a more accurate assessment of the epidemiologic analysis and treatment outcomes in patients with hematologic disease in the Czech Republic and worldwide. This is the only approach to improving treatment outcomes and reducing COVID-19 infection mortality.

Clinical practice points

- Coronavirus disease 2019 (COVID-19) represents an emergent infectious complication associated with high mortality rates in patients with hematologic diseases.
- High nosocomial spread of COVID-19 was observed in hematology patients. Fewer hospital visits should be recommended for patients optimally responding to treatment to reduce the risk of nosocomial transmission.
- Vaccination against COVID-19 should be considered in high-risk patients with hematologic diseases and all health care workers.

COVID-19 in 96 patients with hematologic disease

Unvaccinated personnel should be regularly screened for the presence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by rapid antigen test.

- Testing patients for the presence of SARS-CoV-2 by real-time polymerase chain reaction no longer than 24 hours before hospitalization with second test between days 5 and 7 of hospitalization may identify patients in incubation period and prevent nosocomial spread of COVID-19.
- The observed trends suggest that age is an important prognostic factor affecting achieving complete remission of hematologic disease, prevalence of comorbidities and mortality of COVID-19 infection.
- Our results point to nonsignificantly higher rates of lung involvement owing to COVID-19 among patients without complete remission and those more than 60 years of age.
- Hematologic patients remain SARS-CoV-2-positive on polymerase chain reaction for a longer time. The risk of hematologic disease progression owing to delayed cancer therapy in patients positively tested for COVID-19 should be individually considered and urgent cancer therapy should not be withheld despite the risk of COVID-19 infection.

Disclosure

The authors have stated that they have no conflicts of interest.

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References

1. Gorbalenya AE, Baker SC, Baric RS, et al. The species severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. *Nat Microbiol.* 2020;5:536–544.
2. Shilpa P, Rausch CR, Jain N, et al. Treating leukemia in the time of COVID-19. *Acta Haematol.* 2021;144:132–145.
3. Williams M, Mi E, Le Calvez K, et al. Estimating the risk of death from COVID-19 in adult cancer patients. *Clin Oncol (R Coll Radiol).* 2021;33:e172–e179.
4. Vijenthira A, Gong IY, Fox TA, et al. Outcomes of patients with hematologic malignancies and COVID-19: a systematic review and meta-analysis of 3377 patients. *Blood.* 2020;136:2881–2892.
5. Borah P, Mirgh S, Sharma KS, et al. Effect of age, comorbidity and remission status on outcome of COVID-19 in patients with hematological malignancies. *Blood Cells Mol Dis.* 2020;87.
6. Infante MS, Marín IG, Muñoz-Novas C, et al. COVID-19 in patients with hematological malignancies: a retrospective case series. *Int J Lab Hematol.* 2020;42:e256–e259.
7. García-Suárez J, Cruz J, Cedillo Á, et al. Impact of hematologic malignancy and type of cancer therapy on COVID-19 severity and mortality: lessons from a large population-based registry study. *J Hematol Oncol.* 2020;13:133.
8. Coronavirus disease 2019 (COVID-19): Management in hospitalized adults. Uptodate.com. Available at: <https://www.uptodate.com/contents/coronavirus-disease-2019-covid-19-management-in-hospitalized-adults>; 2021. Accessed January 21, 2021.
9. Clinical management of COVID-19. Who.int. <https://www.who.int/publications/i/item/clinical-management-of-covid-19>; 2021. Accessed January 21, 2021.
10. Doubek M, Mayer J, eds. *Léčebné Postupy v Hematologii [in Czech]*. Brno: Tribuna EU; 2020.
11. Epidemiology of covid-19 infection in patients with hematological malignancies: A European Haematology Association survey. Seifem.org. <https://seifem.org/wp-content/uploads/2020/11/1-EPICOVIDEHA-synopsis-LIVIO-PAGANO.pdf>; 2021. Accessed February 12, 2021.
12. iCMLF - COVID-19 case collection and case discussion. CML-foundation.org. <https://www.cml-foundation.org/covid-19-hub/1462-the-international-cml-foundation-and-covid-19-covid-19-case-collection-2.html>; 2021. Accessed February 12, 2021.
13. Girmenia C, Gentile G, Micozzi A, et al. COVID-19 in patients with hematologic disorders undergoing therapy: perspective of a large referral hematology center in Rome. *Acta Haematol.* 2020;143:574–582.
14. Foà R, Bonifacio M, Chiaretti S, et al. Ph+ acute lymphoblastic leukaemia in Italy during the Covid-19 pandemic: a Campus ALL study. *Br J Haematol.* 2020;190:e3–e5.
15. Breccia M, Abruzzese E, Bocchia M, et al. Campus CML working group. Chronic myeloid leukemia management at the time of the COVID-19 pandemic in Italy. A campus CML survey. *Leukemia.* 2020;34:2260–2261.
16. Li W, Wang D, Guo J, et al. COVID-19 in persons with chronic myeloid leukaemia. *Leukemia.* 2020;34:1799–1804.
17. Yigenoglu TN, Ata N, Altuntas F, et al. The outcome of COVID-19 in patients with hematological malignancy. *J Med Virol.* 2021;93:1099–1104.
18. Treon SP, Castillo JJ, Skarbnik AP, et al. The BTK inhibitor ibrutinib may protect against pulmonary injury in COVID-19-infected patients. *Blood.* 2020;135:1912–1915.
19. Derosa L, Melenotte C, Griscelli F, et al. The immuno-oncological challenge of COVID-19. *Nature Cancer.* 2020;1:946–964.
20. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet.* 2020;395:507–513.
21. Deng Y, Liu W, Liu K, et al. Clinical characteristics of fatal and recovered cases of coronavirus disease 2019 in Wuhan, China: a retrospective study. *Chin Med J (Engl).* 2020;133:1261–1267.
22. Sahu BR, Kampa RK, Padhi A, et al. C-reactive protein: a promising biomarker for poor prognosis in COVID-19 infection. *Clin Chim Acta.* 2020;509:91–94.
23. Elkrief A, Desilets A, Papneja N, et al. High mortality among hospital-acquired COVID-19 infection in patients with cancer: a multicentre observational cohort study. *Eur J Cancer.* 2020;139:181–187.
24. Shah V, Ko Ko T, Zuckerman M, et al. Poor outcome and prolonged persistence of SARS-CoV-2 RNA in COVID-19 patients with haematological malignancies: King's College Hospital experience. *Br J Haematol.* 2020;190:e268–e288.