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Risk factors affecting the clinical course of COVID-19 in patients with lymphoid malignancies in the Omicron subvariants era – a real-world analysis by the Polish Adult Lukemia Study Group

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Abstract

Introduction and Objective. Patients with lymphoid malignancies, were found to have a higher risk of SARS-CoV-2 infection and a severe course of COVID-19. Real-world data (RWD) is presented on the clinical course of COVID-19 in patients with lymphoid malignancies from the centres of the Polish Adult Leukemia Group (PALG).

Materials and Method. A retrospective analysis was carried between October 2023 – February 2024 of patients diagnosed with COVID-19.

Results. Antiviral treatment of COVID-19 was used in 72.9% of patients (51.8% nirmatrelvir+ritonavir, 9.4% remdesivir, 11.8% molnupiravir; the remaining patients were treated symptomatically. The hospitalization rate was 72.9%, but most patients presented with mild symptoms or asymptomatic COVID-19. Only 7.1% of patients required hospitalization in the Intensive Care Unit (ICU) and mechanical ventilation. The median hospitalization time was 10.0 days (IQR 15.0). A significant correlation was found between the length of hospitalization and the severity of COVID-19 course, assessed according to the AOTMiT scale, performance status according to the ECOG scale, number of previous COVID-19 episodes, use of antibiotic therapy, highest detected CRP and HCT ($p < 0.05$). On median, positive COVID-19 test result lasted 8.0 days (IQR 11.0), and the only risk factor for longer duration of COVID-19 test positivity was the absolute number and percentage of monocytes ($p<0.05$).

Conclusions. Analysis showed that the clinical course of COVID-19 was mild in the majority of patients. Regarding the changes in the clinical course of COVID-19 over time, further studies are necessary to isolate the risk factors risk of severe infection.

Key words

risk factors, treatment, COVID-19, SARS-CoV-2, haematological malignancies

INTRODUCTION

Severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) belongs to the coronavirus family (Coronaviridae), characterized by a very high mutation frequency in its genome [1]. During the COVID-19 pandemic, driven by subsequent variants, variable morbidity and mortality rates, as well as different clinical courses, were observed [2]. However, regardless of the stage of the COVID-19 pandemic, in most patients the infection was asymptomatic or presented a mild course in the form of a respiratory tract infection, with symptoms such as cough, sore throat, fever, impairment of smell or taste, dyspnea, weakness and musculoskeletal pain. In only a few patients the infection progresses to respiratory failure and multiorgan failure [3]. Long COVID, which is defined as symptoms and signs that develop during or after a SARS-CoV-2 infection, which are not explained by other diagnosis and continue for more than 12 weeks, was more frequently diagnosed in cases caused by an original virus strain infection than in cases of Alpha, Delta or Omicron variants [4].

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It has been proven that the clinical course of COVID-19 is influenced by the nature and type of the host immune response to infection, depending on the individual genetic predisposition of the patient and the viral load that the infected person received. Independent risk factors for infection and clinical course include age > 65 years, male gender, and comorbidities (diabetes, heart and kidney diseases, obesity, hypertension, chronic lung, liver, and neoplasms, especially haematological malignancies) [3]. Due to mutations in the viral genome, the widespread use of protective vaccinations against COVID-19, and the introduction of antiviral drugs, outcomes of COVID-19 patients have significantly improved, with most of them experiencing a mild and/or self-limiting infection [1].

Patients with neoplasms, regardless of the type, were characterized by a higher risk of SARS-CoV-2 infection as well as severe course of COVID-19 [5]. In patients with haematological malignancies, secondary immune disorders resulted both from the tumour itself and from the treatment used. In these patients, a decrease in the number of functional B cells, neutrophils, NK cells, CD4+ T cells and dendritic cells, an increased percentage of CD8+ cells and hypogammaglobulinemia, were found. Immune deficiencies occurred with varying frequency, depending on the histopathological diagnosis [3,6]. The highest risk of infection is associated with multiple myeloma and chronic lymphocytic leukemia with infectious complications accounting for up to 50% of the causes of early mortality in patients with these diagnoses [7]. The frequency and clinical course of infections are influenced not only by the diagnosis, but also by the anticancer treatment used [8]. Classical cytostatics, monoclonal antibodies, bi-specific antibodies, chimeric antigen receptor T-cell therapy (CART), and molecularly targeted drugs exert different degrees of immunosuppressive effect. The infection rate is high in patients after hematopoietic stem cell transplantation [3,7].

Even though the clinical course of COVID-19 is much milder nowadays, also in patients with lymphoid malignancies, some of them could still require hospitalization and anticancer treatment interruption. Therefore, further studies on the course of COVID-19 in patients with haematological malignancies in the era of new therapies, are needed.

The Polish Adult Leukemia Group (PALG) presents the results of a retrospective analysis of the clinical course of COVID-19 in patients with lymphoproliferative neoplasms, including clinical characteristics, therapeutic interventions, and outcomes in patients treated and not treated with nirmatrelvir + ritonavir (Paxlovid).

MATERIALS AND METHOD

Patients. In this retrospective analysis, the data of patients diagnosed with COVID-19 infection in Polish haematology departments were collected:

- 16 from the Department of Haematology and Bone Marrow Transplantation at the University of Medical Sciences in Poznań;
- 14 from Multi-Specialist Hospital in Gorzów Wielkopolski;
- 13 from Department of Haematooncology and Bone Marrow Transplantation at the Medical University in Lublin;
- 11 from Clinical Department of Haematology, Cell Therapies and Internal Diseases at Medical University in Wrocław;
- 10 from the Department of Haematology Institute of Haematology and Transfusion Medicine, Warsaw;
- 9 patients from the Department of Haematology National Medical Institute of the Ministry of Interior and Administration, Warsaw;
- 8 from the Department of Haematology and Bone Marrow Transplantation at the Medical University of Silesia in Katowice;
- 4 from the Department of Haematology, Oncology and Internal Medicine at the Medical University in Warsaw.

The inclusion criteria for the study were defined as SARS-CoV-2 infection confirmed by antigen or PCR test and diagnosis of chronic lymphocytic leukemia, multiple myeloma, non-Hodgkin lymphoma or Hodgkin lymphoma, using the criteria of International Workshop on Chronic Lymphocytic Leukemia (IWCLL)[9], International Myeloma Working Group (IMWG)[10] and World Health Organization (WHO)[11], respectively. Local guidelines included testing of all symptomatic patients upon admission to the Haematology unit or out-patient visits.

Key exclusion criteria were autoimmune diseases, primary immunodeficiencies, ongoing infections at the time of inclusion in the study, which were not related to COVID-19 (e.g. HIV infection), pregnancy, or diagnosis of a second neoplasm.

The study included both patients who were receiving antiviral treatment for COVID-19 and patients receiving only supportive care. Patients were retested for COVID-19 seven days after receiving a positive result. If symptoms resolved earlier, the patient was discharged, or if the infection persisted, testing was performed as clinically indicated.

Ethics statement. The study was performed in accordance with the ethical standards of the Declaration of Helsinki. Medical data were collected retrospectively using medical records and did not require approval from the Bioethics Committee.

Statistical analysis. Statistical analysis was performed using the Statistica 14.0 computer software (StatSoft, Poland). The Shapiro-Wilk test was used to assess the normality of the distribution of the numerical data. The obtained numerical data did not have a normal distribution. Further statistical analyses were conducted based on non-parametric tests. The Mann-Whitney U test was used to assess 2-category variables, and for more than 2-category variables, the Kruskall-Wallis test and Spearman's rank correlation test for studying dependencies between variables were used. The value of the correlation coefficient were presented as a measure of the association of variables. Differences were considered statistically significant with a p-value < 0.05.

RESULTS

Patients. Between October 2023 – February 2024, data of 85 patients from 8 Polish haematology centres were collected. The follow-up period was 90 days from the diagnosis of COVID-19. Median age of patients – 65 years (range: 20 – 94

Table 1. Clinical characteristics of patients with COVID-19 infection

Diagnosis	Parameter	Value
CLL	No. of patients	n=16 (18.8 %)
	Stage according to Rai's	Stage 0 (low risk): 35.7 % Stage I-II (intermediate risk): 28.6 % Stage III-IV (high risk): 35.7 %
	Stage according to Binet's	Stage A: 41.2 % Stage B: 11.8 % Stage C: 47.0 %
	Unfavourable cytogenetic prognostic factors	del17p: 11.1 % mutTP53: 5.5 % IgHV unmutated: 16.7%
	Past immunological complications	ITP: 0 % AIHA: 16.7%
	No. of previous lines of therapy	Md: 2 (range 0 – 8)
	Infectious complications in medical history	62.5 %
MM	No. of patients	n=33 (38.8 %)
	R-ISS stage	Stage I: 16.1 % Stage II: 38.7 % Stage III: 45.2 %
	Unfavourable cytogenetic prognostic factors	t(4;14): 21.7 % t(14;16): 0 % t(4;20): 0 % del17p: 0 % amp1q: 9.1 %
	Renal failure	42.4 %
	No. of previous lines of therapy	Md: 1 (range 1 – 8)
	Infectious complications in medical history	36.4 %
HL	No. of patients	n=2 (2.4 %)
	Lugano stage	Stage I: 0 % Stage II: 50 % Stage III: 50 % Stage IV: 0 %
	No. of previous lines of therapy	Md: 1.5 (range 1 – 2)
	Infectious complications in medical history	50 %
NHL	No. of patients	n = 29 (34.1 %)
	Lugano stage	Stage I: 10.7 % Stage II: 7.1 % Stage III: 21.4 % Stage IV: 60.7 %
	No. of previous lines of therapy	Md: 1 (range 0 – 8)
	Infectious complications in medical history	30.0 %
ALL	No. of patients	n = 5 (5.9 %)
	No. of previous lines of therapy	Md: 2 (range 1 – 3)
	Infectious complications in medical history	40 %

ALL – acute lymphoblastic leukemia, CLL – chronic lymophocytic leukemia, NHL – non-Hodgkin lymphoma, HL – Hodgkin lymphoma, MM – multiple myeloma, Md – median, n - number of patients, R-ISS – revised international staging system

Table 2. Peripheral blood morphology parameters of patients with COVID-19 infection

Diagnosis	Value	
CLL	WBC (G/l)	Md: 86.1 (IQR 181.2)
	ANC (G/l)	Md: 4.1 (IQR 4.5)
	ALC (G/l)	Md: 75.2 (IQR 101.2)
	MON (G/l)	Md: 0.4 (IQR 2.1)
	Hgb (g/dl)	Md: 8.8 (IQR 2.5)
	PLT (G/l)	MD: 104.0 (IQR 61.0)
MM	WBC (G/l)	Md: 4.3 (IQR 2.7)
	ANC (G/l)	Md: 2.7 (IQR 3.2)
	ALC (G/l)	Md: 1.2 (IQR 1.1)
	MON (G/l)	Md: 0.4 (IQR 0.3)
	Hgb (g/dl)	Md: 9.1 (IQR 4.0)
	PLT (G/l)	Md: 142.5 (IQR 112.0)
HL	WBC (G/l)	Md 5.3 (IQR 5.9)
	ANC (G/l)	Md: 4.5 (IQR 6.1)
	ALC (G/l)	Md: 0.4 (IQR 0.01)
	MON (G/l)	Md: 0.3 (IQR 0.3)
	Hgb (g/dl)	Md: 9.8 (IQR 1.2)
	PLT (G/l)	MD: 126.5 (IQR 217.0)
NHL	WBC (G/l)	Md: 5.4 (IQR 5.8)
	ANC (G/l)	Md: 3.2 (IQR 4.5)
	ALC (G/l)	Md: 0.9 (IQR 1.1)
	MON (G/l)	Md: 0.4 (IQR 0.7)
	Hgb (g/dl)	Md: 10.4 (IQR 3.0)
	PLT (G/l)	Md: 173.5 (IQR 133.5)
ALL	WBC (G/l)	Md: 3.4 (IQR 1.4)
	ANC (G/l)	Md: 0.9 (IQR 0.6)
	ALC (G/l)	Md: 1.1 (IQR 0.1)
	MON (G/l)	Md: 0.2 (IQR 0.3)
	Hgb (g/dl)	Md: 7.0 (IQR 3.7)
	PLT (G/l)	MD: 55.0 (IQR 171.0)

ALL – acute lymphoblastic leukemia, CLL – chronic lymophocytic leukemia, NHL – non-Hodgkin lymphoma, HL – Hodgkin lymphoma, MM – multiple myeloma, Md – median, WBC – white blood cells, ANC – absolute neutrophil count, ALC – absolute lymphocyte count, MON – monocyte, Hgb – hemoglobin, PLT – platelet count, IQR - interquartile range

years). Women constituted 40.0 % of the study group, men – 60.0%. Baseline clinical and laboratory characteristics of the study group are presented in Tables 1–3.

The ECOG performance status at the time of COVID-19 diagnosis was assessed as 0 in 8.2%, 1 in 37.6%, 2 in 37.6 %, 3 in 8.2 %, and 4 in 8.2 % of patients. The study group was characterized by multi-morbidity – 40.4% of patients were diagnosed with 1 comorbidity, 16.8% with ≥ 2 comorbidity, and 42.7% of patients had no cardiovascular diseases, respiratory system diseases, diabetes, or renal failure. In the study group 15.2% of patients were diagnosed with heart failure, 48.5% with hypertension, 7.6% with coronary artery disease, 6.1% had a heart attack in the past, and 3.5% cardiac arrhythmias were observed. Carbohydrate metabolism disorders affected 13.6% of patients (including 9.9% treated for type 2 diabetes, 3.7% for type 1 diabetes, and 2.5% with diabetes complications). Renal failure, defined as abnormal creatinine and eGFR levels, was observed in 7.0% of patients. There were no haemodialysis patients in the study group. Bronchial asthma was diagnosed in 3.5% of patients, 21.3% were active smokers at the time of enrollment in the study, and 18.1% were obese.

The median time from diagnosis of haematologic malignancy to the diagnosis of COVID-19) was 11 months (IQR 45.0). Most patients (77.1%) were receiving anticancer treatment at the time of COVID-19 diagnosis and the median number of previously used treatment lines was 2 (range: 0

Table 3. Laboratory characteristics of patients with COVID-19 infection

Parametr	Diagnosis	Value
Creatinine (mg/dl)	CLL	Md: 0.9 (IQR 0.3)
	MM	Md: 1.0 (IQR 0.5)
	HL	Md: 0.9 (IQR 0.4)
	NHL	Md: 0.8 (IQR 0.4)
	ALL	Md: 0.6 (IQR 0.1)
CRP (mg/l)	CLL	Md: 73.0 (IQR 108.0)
	MM	Md: 90.5 (IQR 98.1)
	HL	Md: 56.7 (IQR 69.5)
	NHL	Md: 24.0 (IQR 93.9)
	ALL	Md: 26.0 (IQR 135.9)
IL-6 (ng/ml)	CLL	Md: 58.8 (IQR 112.3)
	MM	Md: 19.5 (IQR 20.3)
	HL	
	NHL	Md: 2.7 (IQR 46.3)
	ALL	Md: 11.9 (IQR 18.4)

ALL – acute lymphoblastic leukemia, CLL – chronic lymophocytic leukemia, NHL – non-Hodgkin lymphoma, HL – Hodgkin lymphoma, MM – multiple myeloma, Md – median, CRP – C-reactive protein, IL-6 – interleukin 6, IQR - interquartile range

– 8). In the group of CLL patients, 35.7% (n=5) were treated with Bruton tyrosine kinase inhibitor (BTKi) and 64.3% (n=9) with BCL-2 inhibitor (wenetoclax) combined with monoclonal antibody (rituximab). In the group of MM patients, 40.4% (n=19) were treated with proteasome inhibitor-based protocols, 31.9% (n=15) with immunomodulatory drugs, 21.3% (n=10) with anti-CD38 monoclonal antibody and 6.4% (n=3) with other protocols. All the protocols used in MM patients included glicocortycosteroids. One patient with HL COVID-19 infection was diagnosed during autologous stem cell transplantation (ASCT) procedure. In the group of NHL patients who required treatment, 82.4% (n=17) received various protocols of immunochemiotherapy, 5.9% (n=1) monotherapy with rituximab, 5.9% (n=1) monotherapy with mosenutusumab, 5.9% (n=1) chimeric antigen receptors T cell therapy (CAR-T). All patients with ALL were undergoing induction therapy: 60% (n=3) were receiving treatment based on ALL-7 PALG protocol, 20% (n=1) was treated with dasatynib, and 20% (n=1) with methotrexate combined with cytarabine.

Infectious complications before diagnosis of COVID-19. Infectious complications grade ≥ 2 before the diagnosis of COVID-19 were found in 40.0% of patients: 34.1% of bacterial etiology, 18.9% of viral etiology and 1.2% of fungal etiology. As many as 79.5% of patients had not previously suffered from COVID-19, 20.5% had a SARS-CoV-2 infection in the past. Most patients (80.9%) were vaccinated against COVID-19 (1 dose of the vaccine was received by 1.2%, 2 doses by 20%, 3 doses by 41.2%, 4 or more doses by 8.3 % of patients). Class G immunoglobulin levels were assessed in 22.4% of patients, and hypogammaglobulinemia was found in 52.6% of them (all patients were diagnosed with CLL or MM).

COVID-19 treatment. Antiviral treatment was used in 72.9% of patients, including nirmatrelvir+ritonavir (Paxlovid) in 51.8% of cases, remdesivir in 9.4% and molnupiravir in 11.8% cases. A total of 18.8% of patients received glucocorticosteroids, 24.7% required oxygen therapy, and 7.1% required mechanical ventilation. Antibiotic therapy was used in 35.3% of patients depending on clinical indications, in accordance with local practice.

Clinical course of COVID-19. The hospitalization rate at the moment of diagnosis of COVID-19 was 72.9%, although some patients had been admitted to the hospital for a medical reason other than COVID-19 (e.g. continuation of haematological treatment), and diagnosed with SARS-CoV-2 infection during hospitalization when they became symptomatic. Most patients presented with mild symptoms or asymptomatic COVID-19 disease (56.5% – grade 1, 31.8% – grade 2, 7.1% grade 3, 4.7% grade 4 according to the COVID-19 severity scale by the Agency for Health Technology Assessment and Tariff System). Only 7.1% of patients required hospitalization in the Intensive Care Unit (ICU).

The median hospitalization time time was 10.0 days (days (IQR 15.0). Six patients required hospitalization in the ICU, and the average hospitalization time in the ICU was 8.0 days (IQR 5.0). On the 60th day after COVID-19 diagnosis, 4.7% of patients still required hospitalization.

The ECOG performance status was assessed on the 30th and 60th day from the diagnosis of COVID-19 (Tab. 4).

Table 4. ECOG assessment on the 30th and 60th day from the diagnosis of COVID-19

ECOG	0	1	2	3	4	5	No data
On day 30 after the diagnosis of COVID-19 (n; % of patients)	8; 9.4%	33; 38.8%	26; 30.6%	3; 3.5%	1; 1.2%	5; 5.9%	9; 10.6%
On day 60 the diagnosis of COVID-19 (% of patients)	9; 10.6%	38; 44.7%	18; 21.2%	1; 1.2%	1; 1.2%	6; 7.1%	12; 14.1%

ECOG – Eastern Cooperative Oncology Group Performance Status Scale

During the 90-day follow-up, a total of 14.1% of patients died (including 1 patient with disease progression, 1 with gastrointestinal bleeding, 1 with ischemic stroke, and 2 with infectious complications of bacterial etiology. In the remaining cases, the cause of death was multifactorial. By the 30th day of follow-up, 5.9% of patients had died, the remaining deaths were recorded between 30 and 90 days after the diagnosis of COVID-19 infection.

Thromboembolic complications were diagnosed in a total of 7.0% during the 90-day follow-up (superficial vein thrombosis – 4.7% of cases, pulmonary embolism – 1.2%, ischemic stroke – 1.2%). Throughout the entire follow-up, cardiac complications were found in 8.4% (including 3.6% of patients with cardiac arrhythmias and 2.4% with exacerbation of heart failure). On the 30th day of observation, thrombocytopenia was found in 11.8% of patients, which persisted until the 60th day of observation in 1.2% of the studied patients; the etiology of thrombocytopenia was complex in all cases, but an immunological component could not be excluded. No cases of autoimmune haemolytic anaemia were recorded.

Factors affecting the length of hospitalization. No correlation was found between the length of hospitalization and gender, type of haematological cancer (Tab. 5), anticancer treatment, previously diagnosed infectious complications, vaccinations against COVID-19, obesity, respiratory diseases,

Table 5. Assessment of the impact of hematological diagnosis on the course of COVID-19

Parameter	Diagnosis	Value	p
Hospitalization (n; % of patients with analyzed HM)	CLL	12; 75.0%	R=0.047; p>0.05
	MM	25; 75.8%	
	HL	2; 100%	
	NHL	20; 69.0%	
	ALL	3; 60.0%	
Hospitalization in ICU (n; % of patients with analyzed HM)	CLL	0; 0%	R=-0.012; p>0.05
	MM	4; 12.1%	
	HL	0; 0%	
	NHL	2; 6.9%	
	ALL	0; 0%	
Length of hospitalization (days)	CLL	Md: 12.0 (IQR 10.0)	R=0.015; p>0.05
	MM	Md: 8.0 (IQR 9.0)	
	HL	Md: 28.5 (IQR 11.0)	
	NHL	Md: 7.0 (IQR 9.0)	
	ALL	Md: 51 (IQR 32.0)	
Duration of a positive COVID-19 test (days)	CLL	Md: 7.0 (IQR 0.0)	R=0.246; p>0.05
	MM	Md: 7.5 (IQR 9.0)	
	HL	Md: 21.0 (IQR 0.0)	
	NHL	Md: 8.0 (IQR 11.0)	
	ALL	Md: 9.0 (IQR 0.0)	

ICU - Intensive Care Unit, p - p-value, HM - hematological malignancies, ALL – acute lymphoblastic leukemia, CLL – chronic lymophocytic leukemia, NHL – non-Hodgkin lymphoma, HL – Hodgkin lymphoma, MM – multiple myeloma, Md – median, n - number of patients, IQR - interquartile range

cardiovascular diseases, diabetes, or smoking (p>0.05). A statistically significant correlation was found, however, between the length of hospitalization and the severity of the COVID-19 course, assessed according to the AOTMiT scale, performance status according to the ECOG scale, the number of previous COVID-19 infections, use of antibiotic therapy, and the highest detected CRP and HCT (p < 0.05). Neither were any differences found in the length of hospitalization and the treatment method, between the groups of patients receiving individual antiviral drugs (remdesivir, molnupiravir and paxlovid) and patients not receiving antiviral treatment. The use of mechanical ventilation or oxygen therapy did not affect the duration of hospitalization (p>0.05) (Tab. 6).

Factors affecting the duration of a positive COVID-19 test. Median positive COVID-19 test time lasted 8.0 days (IQR 15.0). There was no relationship between the duration of a positive test and gender, age, diagnosis of haematological cancer (Tab. 5), anticancer treatment, previously diagnosed infectious complications, previous vaccinations against COVID-19, previous SARS-CoV-2 infection, obesity, respiratory diseases, cardiovascular diseases, diabetes, cigarette smoking, severity of COVID-19 assessed according to the AOTMiT scale (Tab. 7), performance status assessed according to the ECOG scale, or treatment method (p>0.05). However, a significant correlation (p<0.05) was found between the absolute number and percentage of monocytes in whole blood count and the duration of a positive COVID-19 test. In patients with a higher monocyte count, a faster negative COVID-19 test was observed (Fig. 1).

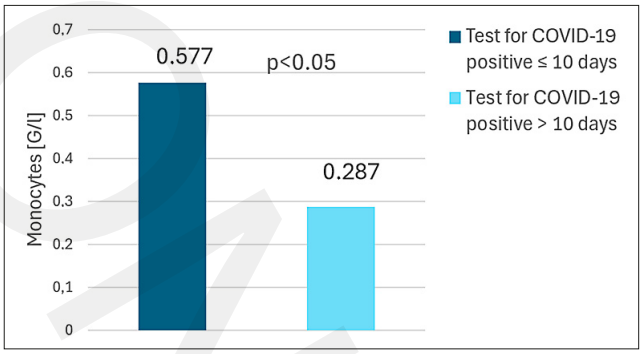

Figure 1. Assessment of the relationship between the duration of a positive test for COVID-19 and the number of monocytes in peripheral blood morphology

DISCUSSION

The study presents a group of patients with lymphoproliferative neoplasms infected by SARS-CoV-2 in the Omicron era, and who experiencing COVID-19. Most of the patients presented with mild symptoms or asymptomatic COVID-19 disease; however, the hospitalization rate was 72.9%, and the median hospitalization time was 10.0 days. The high rate of hospitalization could be due to local regulations, such as the possibility of using antiviral treatment only in the hospital, and the need for supportive treatment. Also, some patients had been admitted to hospital to continue haematological treatment and subsequently diagnosed with SARS-CoV-2 infection during the hospitalization, after chemotherapy administration. The higher rate of hospitalization in patients with haematological malignancies than in the general population could also be associated with a higher estimated risk of complications in this group. Only 7.1% of patients in the study group required hospitalization in the Intensive Care Unit (ICU). At the beginning of the COVID-19 pandemic, the clinical course of the infection was severe in most patients with chronic lymphocytic leukemia (CLL), the 30-day mortality was 31%-50% in patients requiring hospitalization [12]. Similar conclusions were drawn from the ERIC study that showed a mortality rate of 32.5% in patients with CLL requiring hospitalization [13]. Later studies indicated that in the subsequent phases of the pandemic, mortality in this group of patients, similarly to the general population, decreased [14]. Nieman et al. [15] reported a 30-day OS rate of 77% in patients with CLL, with a 30-day fatality rate of <2 % [15].

After 2022, the number of reports published in PubMed regarding the course of COVID-19 in patients with HM decreased significantly. In January 2024, the results of a large study conducted from 27 February 2020 – 1 October 2022 in a group of patients with haematological malignancies were published [16]. Martínez-López J. et al. [16] showed that the diagnosis of CLL was associated with a higher risk of a severe course and higher mortality, compared to other haematological malignancies. Multimorbidity and advanced age also worsened the prognosis. In patients who received at least 1 dose of the COVID-19 vaccine, the risk of fewer cases with a severe course of infection was noted. At the same time, the researchers confirmed that infection with the Omicron BA.1/BA.2 and BA.4/BA.5 variants were associated with a better prognosis. The rate of hospitalization in the

Table 6. Factors affecting hospitalization timeC

Factor that could potentially affect the duration of hospitalization	Median hospitalization time (days)					p
Gender	Female			Male		R=-0.009; p>0.05
	10.5			10.0		
Age	< 75 years			≥ 75 years		R=0.024; p>0.05
	10.0			11.0		
Diagnosis	CLL	MM	NHL	HL	ALL	R=0.014; p>0.05
	12.0	8.0	7.0	28.5	51.0	
Ongoing haematological treatment	Yes			No		R=-0.015; p>0.05
	10.0			9.0		
Infectious complications before COVID-19 diagnosis	Present			Absent		R=-0.222; p>0.05
	12.0			7.0		
Vaccinations against COVID-19	Vaccinated			Not vaccinated		R=0.035; p>0.05
	10.0			10.5		
Infection with SARS-CoV-2 virus	First			Consecutive		R=-0.243; p<0.05
	11.0			8.0		
Diabetes	Present			Absent		R=0.186; p>0.05
	8.0			12.0		
Cardiovascular diseases	Present			Absent		R=-0.182; p>0.05
	11.0			8.0		
Respiratory diseases	Present			Absent		R=0.065; p>0.05
	12.5			10.0		
Obesity	Present			Absent		R=-0.146; p>0.05
	10.0			10.0		
Smoking	Smoking			Non-smoking		R=0.058; p>0.05
	9.0			10.5		
Performance status assessed on the ECOG scale at the time of COVID-19 diagnosis	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	R=0.344; p<0.05
	11.0	5.0	11.0	12.0	18.0	
COVID-19 severity according to AOTMiT	Grade 1	Grade 2	Grade 3		Grade 4	R=0.335; p<0.05
	6.5	12.0	15.0		23.5	
Antiviral treatment	Nirmatrelvir+ritonavir	remdesivir	molnupiravir		No antiviral treatment	R=-0.071; p>0.05
	8.0	13.0	8.0		11.0	
Mechanical ventilation	Applied			Not applied		R=-0.125; p>0.05
	15.5			10.0		
Antibiotic therapy	Applied			Not applied		R=-0.288; p<0.05
	12.5			8.0		
Oxygen therapy	Applied			Not applied		R=-0.214; p>0.05
	12.0			8.0		
Glucocorticosteroids	Applied			Not applied		R=-0.172; p>0.05
	11.0			8.5		
Haematocrit	<35%			≥35%		R=0.408; p<0.05
	6.0			12.0		

p - p-value

pre-Omicron and Omicron period was 75.3% vs. 35.7%, respectively, the rate of hospitalization in intensive care admission was 30.0% vs. 14.7%, the overall mortality rate was 31.9% vs. 9.9 %, and in the case of hospitalized patients the mortality rate was 41.3% vs. 22.0% [16]. In Poland, since 2022, COVID-19 is caused by the omicron variant. At the time when the current study was conducted, an XBB.1.5-like subvariant was most frequently detected [17], for which the hospitalization rate was 1.6%, and the median hospitalization time – 5.2 days [18].

In patients with ALL, a worse clinical course of COVID-19 was demonstrated compared to the general population. In the study by Passamonti et al., acute myeloid leukemia (AML) and ALL were the two most common causes of death in a group of adult patients [19]. On the other hand, Cai J. et al., in the study conducted in ALL patients, showed that infection with the Omicron sub-variant of COVID-19 caused mild illness in children, even when they were receiving chemotherapy [20].

Mitra et al.[21] characterized the risk factors for severe

Table 7. Agency for Health Technology Assessment and Tariff System (AOTMiT) COVID-19 severity classification.SGrade

	Description	Form of the disease	Characteristic
1	Asymptomatic or mildly symptomatic		Without symptoms or mild upper respiratory symptoms (fever, cough without dyspnea), which may sometimes be accompanied by headache, myalgia, nausea, vomiting, diarrhea, SpO2 >94%, stable clinical condition
2	Symptomatic without signs of respiratory failure	Moderate	Exhaustion, asthenia, fever >38°C, cough and dyspnea, clinical and radiological evidence of lung involvement, without clinical or laboratory evidence of respiratory failure (SpO2 >90 and <94%)
3	Severe pneumonia with respiratory failure/pre-ARDS	Severe	Clinical and laboratory evidence of deterioration in respiratory function and gas exchange (dyspnea, increased respiratory rate >30/min, SpO2 <90%), acute respiratory symptoms without ARDS, septic shock, multi-organ failure, or impaired consciousness
4	ARDS/multi-organ failure	critical	Patient with respiratory failure and impairment of other vital functions: ARDS, sepsis/septic shock, multi-organ failure

COVID-19 and all-cause mortality in patients with multiple myeloma using the NCATS National COVID Cohort Collaborative (N3C) database (data collected until 16 May 2022). Mortality during 30 days of COVID-19 hospitalization was 4.47%. The risk of severe infection was increased by lung disease, renal failure, dexamethasone (a proteasome inhibitor), immunomodulatory drugs, and a high Charlson comorbidity index. The protective effect of vaccination against COVID-19 was also confirmed [21]. Similar conclusions are drawn from the current study – a relationship was shown between the length of hospitalization and the severity of the course of COVID-19, ECOG, the number of previous COVID-19 infections, the highest detected concentration of CRP and lower haematocrit level. However, there was no effect of age, gender, diagnosis of haematological cancer, anticancer treatment, previously diagnosed infectious complications, vaccinations against COVID-19, obesity, respiratory diseases, cardiovascular diseases, diabetes, smoking, or method of treatment on the length of hospitalization. Mortality rate in the study group by the 30th day of follow-up was 5.9%, and by the 90th day of follow-up – 14.1%. The study group was too small and the observation time too short to reliably estimate the overall survival (OS). The ERIC group showed that age and number of comorbidities did not affect the OS in patients with CLL. Interestingly, patients on recent or ongoing treatment compared to untreated patients were characterized by milder COVID-19. Bruton's tyrosine kinase inhibitor (BTKi) therapy was also associated with a lower hospitalization rate [13]. Literature data confirm that higher haematocrit values and lower CRP concentrations correlate with a better course of COVID-19 [22–24]. Interestingly, in in the current study, the use of anti-COVID-19 therapies did not shortened the duration of hospitalization. This is likely due to the fact that most patients received antiviral treatment when clinical symptoms appeared, which translated into lower treatment effectiveness.

Venous thromboembolism (VTE) is a well-established complication of COVID-19, and this risk increases in patients with haematological malignancies, [25,26]. Cook et al. [25] found that thrombotic complications occurred in about 8.0% of patients with haematological malignancies, a percentage that was significantly higher than in the general population (3.6%) [25]. In the current study, thromboembolic complications were diagnosed in a total of 7.0% during the 90-day follow-up, with serious thromboembolic complications noted in two patients (pulmonary embolism and ischemic stroke), supporting the results of Cook et al. [25].

SARS-CoV-2 infection is also associated with an increased incidence of cardiovascular complications. In some patients, clinical symptoms of heart failure may not occur, and cardiac arrhythmias may be asymptomatic. However, in some patients, symptomatic heart disease or symptomatic cardiac arrhythmias develop [27,28]. In the group of patients with lymphoproliferative disorders in the current, study, cardiac complications were found in 8.4%, cases of cardiac arrhythmias – 3.6%, and exacerbation of heart failure – in 2.4 %.

The syndrome of persistent COVID-19 in patients with lymphoid malignancies is a significant clinical problem [29–31]. Yasuda et al. [31] described the case of a patient with follicular lymphoma (FL) treated with rituximab, in whom symptoms of infection persisted for 10 months and a positive RT-PCR test result lasted for 46 days [31.] Duléry et al. [32] showed that positive tests in patients with haematological malignancies are detected up to 143 days [32], while studies conducted by Lee et al. [33] confirm that positive RT-PCR tests are detected ≥30 days after infection in 13.9% [33]. Risk factors include impaired humoral immunity and active chemotherapy [29–31]. In the current study, the average positive COVID-19 test result lasted 10.0 days. At the same time, no statistically significant relationship was demonstrated between the duration of a positive test and gender, type of lymphoid malignancy, treatment, previously diagnosed infectious complications, previous vaccinations against COVID-19, previous SARS-CoV-2 infection, obesity, comorbidities, cigarette smoking, severity of COVID-19 assessed according to the AOTMiT scale, or clinical condition. However, the study demonstrated that the number of monocytes is statistically significantly lower in patients with a positive repeat test for COVID-19 lasting > 10 days. This is confirmed by literature data, which indicate the participation of monocytes in COVID-19, and their reduced percentage, was found in convalescents [34].

Limitations of the study. First, due to the retrospective character of the study it was not possible to obtain all the information needed to ascertain the exact reason for the hospitalization of every patient at the time of COVID-19 diagnosis. Secondly, the study group was relatively small and heterogenous, which means that the obtained results should be interpreted with caution. Third, there was no age-matched control group for direct comparison of clinical course of COVID-19; therefore, a comparison was made between the available data and the general population. However, it should be noted that currently the analysis of COVID-19 incidence in haematological patients is more difficult than at the beginning of pandemic, since most patients perform the COVID-19 test at home. If the course of the infection is mild, they do not inform the haematologist about the result or treat the infection as a common viral infection, and the test for SARS-CoV-2 infection is not routinely performed. Therefore, symptomatic patients who require hospitalization and the use of antiviral and supportive treatment are tested more often. Hence, conducting large, reliable population

studies is currently difficult. The data obtained concern patients undergoing treatment for lymphoid malignancies, or symptomatic patients, i.e. patients from the highest risk groups for severe COVID-19. There are no recommendations regarding postponing chemotherapy/targeted therapy in patients with only the SARS-CoV-2 positive Omicron variant not presenting with any symptoms/presenting with mild symptoms.

The present approach to COVID-19 prevention has also changed. Hospital epidemiologists do not close entire hospital wards upon diagnosis of infection, and patients with a positive test are isolated.

SUMMARY

Numerous reports refer to the clinical course and complications of COVID-19 in patients with haematologic malignancies (HM) [16]; however, taking into account the change in the clinical picture over time and the introduction of new drugs and treatment regimens for the treatment of lymphoid malignancies, and limitations on the use of antiviral drugs used in the treatment of SARS-CoV-2 infection, further studies are necessary to identify the group of patients who should be hospitalized and receive antiviral and supportive treatment.

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