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FACTORS AFFECTING COVID-19 OUTCOMES IN PATIENTS WITH HEMATOLOGICAL MALIGNANCIES

Background. Patients with hematological malignancies (HM) are considered to have a high risk of developing severe and life-threatening infections including COVID-19 because of immune deficiency and immunosuppressive treatments. Although the COVID pandemic spread worldwide, morbidity and mortality data varied from country to country. A more accurate identification of risk factors would allow the improvement of the clinical management of HM patients. **Aim.** This study aimed to determine real-life data — the mortality rate, clinical outcomes, and risk factors affecting mortality in patients with HM and COVID-19 at the Riga East University Hospital (REUH) in Latvia. **Materials and Methods.** In this retrospective non-interventional cohort study, we included adult patients treated in REUH with ongoing HM and laboratory-confirmed COVID-19 observed between December 1st, 2020, and March 31st, 2023. All data were analyzed using descriptive statistics, binary logistic regression, univariable Cox regression model, and other methods. **Results.** We registered 156 patients with 11 different HMs. Multiple myeloma, non-Hodgkin lymphoma, and acute myeloid leukemia were the most common HM. COVID-19 mortality rate was 19.9% (31/156). Factors increasing the risk of death included the severity of COVID-19 ($p < 0.001$), the accession of bacterial infection ($p < 0.001$), longer hospital stay ($p = 0.037$), absolute neutrophil count (ANC) $\leq 0.5 \times 10^9/mm^3$ ($p = 0.014$), fever ($p = 0.039$), and acute myeloid leukemia ($p = 0.002$). We also confirmed that the mortality in the third pandemic wave was significantly lower than in the second wave ($p = 0.002$). Although vaccination seemed to be a risk-mitigating factor (58.8% [10/17] of those who died from COVID-19 were not vaccinated), no statistically important correlation was found ($p = 0.690$). **Conclusion.** This survey confirmed that the COVID-19 mortality rate was higher in patients with HM (19.9% [31/156]) than in the population. ANC, severity of COVID-19, accession of bacterial infection, hospital stay, fever, and acute myeloid leukemia were the factors that increased mortality in HM patients.

Keywords: COVID-19 mortality, COVID-19 risk factors, hematological malignancies.

In March 2020, the WHO declared a pandemic caused by SARS-CoV-2 virus [1]. The uncontrolled spread of the virus took more than 5 million lives within a year [2]. Elderly patients, patients with comorbidities, immunosuppression, and others were especially at risk. Patients with hematological malignancies (HM) are also at high risk due to immunosuppression caused by chemotherapy and the malignancy itself [3]. The data show that the highest COVID-19 mortality among oncological patients is registered specifically among patients with following HM — Hodgkin's lymphoma, non-Hodgkin's lymphoma, and multiple myeloma, compared to other cancers such as pancreatic, breast,

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prostate, lung, etc. [4]. Individuals with HM are at an increased risk of SARS-CoV-2 infection compared to the overall population, while the individuals with solid tumors are at a lower risk [5]. Patients with acute myeloid leukemia (AML) are at particularly high risk due to the aggressive therapy leading to immunosuppression. The studies show that delaying AML treatment during infection improves survival [6]. Unfortunately, treatment delay is often not possible due to the urgent need to start an active therapy. In high-risk myelodysplastic syndrome (MDS) patients, treatment with demethylating agents is also associated with a particularly high mortality rate [7].

This study aimed to analyze the COVID-19 mortality in HM patients and to delineate the risk factors affecting the outcome and survival of HM patients with COVID-19 infection to attract special attention to the patients at an increased risk.

Materials and Methods

This study included patients from the Riga East University Hospital (REUH) Hematology Clinic in Latvia who were treated due to their HM. During COVID-19 pandemic in Latvia, all the hospitalized patients were tested for SARS-CoV-2 before hospitalization and also during the hospital stay as part of COVID-19 screening. Patients were tested on the 3rd, 7th, and 10th day in the hospital. Then the tests were done every 7 days. We included patients who were infected during the hospital stay.

In this retrospective study, data were collected from patient records and the hospital electronic database. Inclusion criteria: hemato-oncological disease before COVID-19 infection that was active during the last year (diagnosed or treated), laboratory-confirmed SARS-Cov-2 infection in the period from December 1st, 2020, to March 31st, 2023, and patients older than 18 years.

In addition, two pandemic waves in Latvia were analyzed. The second wave from December 1st, 2020, to April 30th, 2021, and the third wave from September 1st, 2021, to May 31st, 2022 [8].

The obtained data were collected in an Excel table and later analyzed using "IBM SPSS statistics" program version 29.0.0.0 (241). All calculations were done with a confidence interval of 95%. The data were analyzed by descriptive statistics. The categorical variables were presented with frequencies and percentages and continuous variables — with median, interquartile range (IQR), and absolute range. A univariable Cox regression model was performed with variables suspected to play a role in the mortality of HM patients with COVID-19 (i.e. sex [reference male], age, HM type [reference multiple myeloma], COVID-19 infection [reference asymptomatic], arterial hypertension, chronic cardiomyopathy, liver disease, chronic pulmonary disease, diabetes mellitus, obesity, renal impairment, smoking history, COVID-19 symptoms (cough, fever, respiratory distress, lung damage, and rhinorrhea), the vaccination, an absolute neutrophil count (ANC) [reference $\geq 1 \times 10^9/mm^3$], an absolute lymphocyte count [reference $\geq 0.5 \times \times 10^9/mm^3$], last chemotherapy [reference > 3 months before COVID-19], pandemic waves [reference second wave (December 1st, 2020 — April 30th, 2021)], and superinfection [reference no superinfection]. The mortality was analyzed using Kaplan — Meier survival plots. A p-value ≤ 0.05 was considered statistically significant.

COVID-19 infection severity was assessed according to the criteria defined in [9]. A mild illness is characterized by the presence of the symptoms (e.g., fever, cough) but without evidence of a lower respiratory tract infection (e.g., shortness of breath, abnormal chest imaging). A moderate illness is characterized by the presence of a lower respiratory tract infection but with oxygen saturation measurements remaining at or above 94% on room air (at sea level). A severe or critical illness is characterized by the oxygen saturation of less than 94% on room air (at sea level), tachypnea, and/or lung infiltrates that affect more than 50% of the lung parenchyma on imaging. Respiratory failure, septic shock, and/or organ dysfunction indicate critical illness [9].

Results

Of 156 valid cases, 51.9% were men and 48.1% were women. The median age was 68 (Table1).

Among 11 HM that were registered, multiple myeloma (MM) was the most common, followed by non-Hodgkin lymphoma (NHL) and acute myeloid leukemia (AML) (Table 1).

We also analyzed the morbidity in different HMs, considering how many patients were treated at the hospital during the period from December

1st, 2020, to March 31st, 2023, and calculating how many got infected with COVID-19. The highest morbidity was observed among AML, MM, and acute lymphoid leukemia (ALL) (Table 1).

Table 1. **Demographic and clinical characteristics of enrolled patients with COVID-19 diagnosis**

Index	Number of patients	
	n	%
Sex		
Male	81	51.9
Female	75	48.1
Age (IQR) [range]	68 (58—75)	[20—85]
Comorbidities		
Arterial hypertension	75	48.1
Chronic cardiomyopathy	48	30.8
Smoking history	33	21.2
Obesity	23	14.7
Renal impairment	22	14.1
Chronic pulmonary disease	21	13.5
Diabetes mellitus	19	12.2
Liver disease	16	10.3
No possible risk factor identified	6	3.8
Baseline hematological malignancies with COVID-19 infection		
Multiple myeloma	45	28.8
Non-Hodgkin lymphoma	41	26.3
Acute myeloid leukemia	24	15.4
Chronic lymphoid leukemia	17	1.9
Hodgkin lymphoma	10	6.4
Myelofibrosis	8	5.1
Acute lymphoid leukemia	4	2.6
Chronic myeloid leukemia	3	1.9
Polycythemia vera	2	1.3
Myelodysplastic syndrome	1	0.6
Essential thrombocythemia	1	0.6
COVID-19 morbidity in hematological malignancies		
Acute myeloid leukemia	24/101	23.8
Multiple myeloma	45/211	21.3
Acute lymphoid leukemia	4/19	21
Hodgkin lymphoma	10/60	16.7
Myelofibrosis	8/51	15.7
Non-Hodgkin lymphoma	41/331	12.4
Chronic lymphoid leukemia	17/167	10.8
Chronic myeloid leukemia	3/40	7.5
Essential thrombocythemia	1/19	5.3
Polycythemia vera	2/47	4.3
Myelodysplastic syndrome	1/125	0.8

150 patients (96.2%) had at least one comorbidity with arterial hypertension and chronic cardiomyopathy being the most frequent. In addition, 21.2% of patients had a smoking history (Table 1).

36.5% of patients had an asymptomatic COVID-19 infection, 29.5% mild, and 14.1% severe, but 31 (19.9%) had a critical infection that ended with death in all cases (Table 2). Overall, 69.9% of pa-

Table 2. **Clinical features of COVID-19 in our patient cohort**

Index	Number of patients	
	n	%
COVID-19 infection		
Asymptomatic	57	36.5
Mild	46	29.5
Severe	22	14.1
Critical	31	19.9
COVID-19 test sample		
SARS-CoV-2 nasopharyngeal swab PCR	140	89.7
Saliva PCR	7	4.5
SARS-Cov-2 antigen express-test	9	5.8
Reason for COVID-19 test		
Pulmonary symptoms	53	34
Extrapulmonary symptoms	40	25.6
Screening	125	80.1
ANC at COVID-19 diagnosis		
$\leq 0.5 \times 10^9/mm^3$	16	10.3
$0.501—0.999 \times 10^9/mm^3$	2	1.3
$\geq 1 \times 10^9/mm^3$	138	88.4
ALC at COVID-19 diagnosis		
$\leq 0.2 \times 10^9/mm^3$	12	7.7
$0.201—0.499 \times 10^9/mm^3$	27	17.3
$\geq 0.5 \times 10^9/mm^3$	117	75
Stay during COVID-19		
Length of hospital stay, median	14 (IQR: 7—23; range: 2—168)	
Stay in COVID-19 unit, median	12 (IQR: 1—16; range: 3—60)	
Clinical outcome of COVID-19		
Death	31	19.9
Observation time, median	25 (IQR: 15—35; range: 7—48)	
Reason for death		
Attributable to COVID-19	17	10.9
Contributable by COVID-19	14	9
Attributable to HM	15	9.6
Death due to other reasons	5	3.2

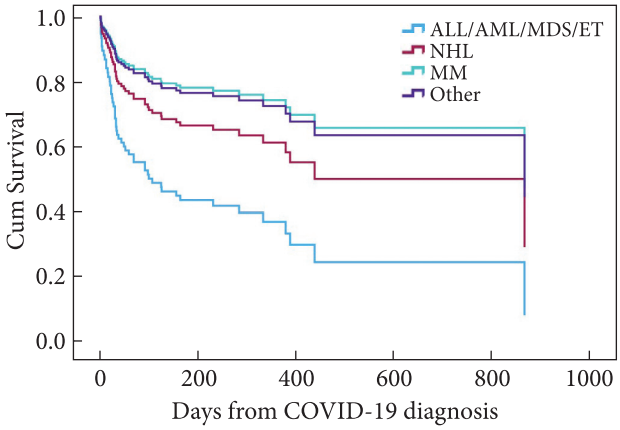

Fig. 1. Overall survival by the underlying disease

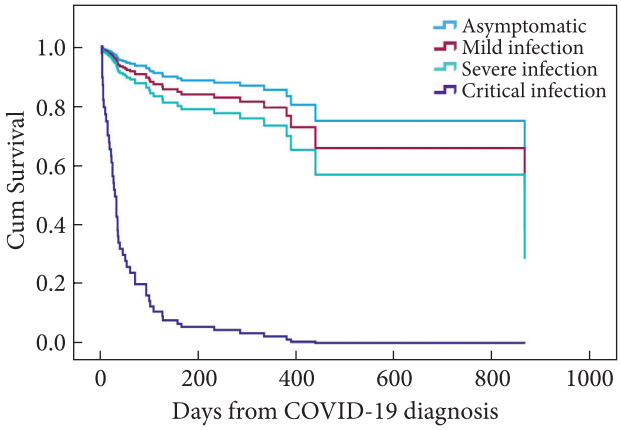

Fig. 2. Overall survival by COVID-19 severity

Table 3. **Overall and COVID-19-related mortality in different age groups**

Age	Survived n (%)	Died n (%)	Died from COVID-19 n(%)	Vaccinated % (n)	Died from COVID-19 and not vaccinated %(n)
20—29	4(80)	1(20)	1(20)	40 (2/5)	0 (0/1)
30—39	6(100)	0	0	66.7 (4/6)	0
40—49	7(63.6)	4(36.4)	2(18.2)	54.5 (6/11)	50 (1/2)
50—59	14(73.7)	5(26.3)	4(21.1)	63.2 (12/19)	25 (1/4)
60—69	27(62.8)	16(37.2)	8(18.6)	74.4 (32/43)	50 (4/8)
70—79	31(60.8)	20(39.2)	12(23.5)	68.6 (35/51)	50 (6/12)
80+	16(76.2)	5(23.8)	4(19.0)	85.7 (18/21)	25 (1/4)

Table 4. **Summary of received treatments for HM at the onset of COVID-19**

Last/ongoing treatment strategy before COVID-19	n	%
Targeted therapy*	12	7.7
Conventional chemotherapy	72	46.2
Immunochemotherapy	39	25.0
Hypomethylating agents	7	4.5
Immunotherapy only	1	0.6
Glucocorticoids only	25	16.0

Notes: *Targeted therapy: Ibrutinib, Ruxolitinib, Imatinib.

Table 5. **Time when therapy was received**

Last time when therapy was received	n	%
In the last month	93	59.6
In the last 3 months	28	17.9
Treatment ended > 3 months ago	10	6.4

Table 6. **HM as a mortality predictor**

HM	*P*	HR	95% CI
ALL/AML/MDS/ET	—	—	—
NHL	0.046	0.491	0.244—0.988
MM	0.002	0.297	0.136—0.647
Other	0.006	0.322	0.144—0.720

Table 7. **Overall mortality predictors in COVID-19 HM patients**

Factor	*P*	HR	95% CI
Male	—	—	—
Female	0.066	1.696	0.965—2.980
Age	0.334	1.012	0.988—1.037
Hematological malignancy			
Multiple myeloma	—	—	—
Acute lymphoid leukemia	0.207	2.665	0.582—12.208

Table 7. (ending)

Factor	*P*	HR	95% CI
Chronic lymphoid leukemia	0.506	1.441	0.492—4.225
Acute myeloid leukemia	0.002	3.582	1.588—8.082
Chronic myeloid leukemia	0.057	7.773	0.942—64.151
Myelodysplastic syndrome	0.831	1.284	0.130—12.679
Hodgkin lymphoma	0.393	0.408	0.052—3.200
Non-Hodgkin lymphoma	2.43	1.627	0.718—3.685
Ph-negative myeloproliferative neoplasms*	0.698	1.292	0.354—4.710
Comorbidities			
Chronic cardiomyopathy	0.959	1.018	0.518—2.000
Arterial hypertension	0.521	1.224	0.661—2.265
Liver disease	0.121	1.995	0.834—4.770
Chronic pulmonary disease	0.506	1.289	0.610—2.723
Diabetes mellitus	0.611	1.267	0.509—3.150
Obesity	0.544	1.280	0.577—2.840
Renal impairment	0.031	2.295	1.081—4.875
Smoking history	0.971	0.986	0.458—2.125
Alcohol consumption	0.696	0.817	0.297—2.250
No risk factors	0.311	0.359	0.049—2.604
Symptoms			
Cough	0.379	0.601	0.193—1.869
Fever	0.039	2.954	1.057—8.260
Respiratory distress	0.088	2.569	0.868—7.601
Lung damage	0.443	1.547	0.507—4.721
Rhinorrhea	0.262	0.642	0.296—1.392
ANC, cells/mm^3			
$\geq 1 \times 10^9$/mm^3	—	—	—
$0.501—0.999 \times 10^9$/mm^3	0.065	2.840	0.937—8.611
$\leq 0.5 \times 10^9$/mm^3	0.014	16.491	1.773—153.406
ALC, cells/mm^3			
$\geq 0.5 \times 10^9$/mm^3	0.046	0.491	0.244—0.988
$0.201—0.499 \times 10^9$/mm^3	0.046	0.491	0.244—0.988
$\leq 0.2 \times 10^9$/mm^3	0.046	0.491	0.244—0.988
Last chemotherapy			
>3 months before COVID-19	—	—	—
In the last 3 months	0.874	0.906	0.269—3.051
In the last month	0.517	1.544	0.415—5.739
COVID-19 severity			
Asymptomatic	—	—	—
Mild infection	0.485	1.453	0.509—4.151
Severe infection	0.252	1.959	0.621—6.183
Critical infection	<0.001	23.859	10.002—56.916
Vaccination	0.690	1.127	0.627—2.025
Pandemic waves			
Second wave (December 1st 2020-April 30th 2021)	—	—	—
Third wave (September 1st 2021-May 31st 2022)	0.002	0.298	0.139—0.638
June 1st 2022-end of the research	0.027	0.445	0.217—0.911
Superinfection			
No	—	—	—
Bacterial	0.001	3.897	1.711—8.877
Viral	0.140	2.931	0.703—12.216
Fungal	0.199	2.565	0.609—10.804
Unknown	0.101	5.343	0.721—39.597

Notes: * Ph-negative myeloproliferative neoplasms: polycythemia vera (PV), ET, and primary myelofibrosis (PMF).

tients received a COVID-19 vaccine, and 30.1% were not vaccinated.

For most of the patients (89.7%), the SARS-Cov-2 virus was detected with the nasopharyngeal swab polymerase chain reaction (PCR). In 80.1% of cases, it was done as a screening (Table 2). At the onset of COVID-19, 10.3% of patients had ANC below $0.5 \times 10^9/mm^3$ and 7.7% had ALC below $0.2 \times 10^9/mm^3$ (Table 2). The median length of the hospital stay was 14 days (Table 2).

Of all registered (n = 156) patients, 51 died. In 17 cases, the death was attributable to COVID-19, but 15 died because of HM. In 14, the reason for death was a combination of both COVID-19 and progressing HM (Table 2).

Patients aged 70—79 years not only had the highest overall mortality rate 20/51 (39.2%) but also the highest COVID-19 mortality rate. Of all 20 death cases, 12 (60%) were attributable or contributable to COVID-19 (Table 3).

All the patients had active HM, and all received treatment. The most frequent treatments were conventional chemotherapy (46.2%) and immunochemotherapy (25%), which is also proportional to the most frequent HM, namely, MM and NHL. 16% of patients did not receive any specific therapy, only glucocorticoids (Table 4). The time when patients received any specific treatment before their last admission to the clinic was also determined (Table 5). Those who received only glucocorticoids were not included in Table 5. 59.6% had the treatment in the last month before COVID-19 infection, 17.9% had the treatment in the last 3 months, whereas 6.4% received the treatment in more than 3 months before infection (Table 5).

Mortality in AML/ALL/MDS/ET (essential thrombocythemia) was significantly higher when compared to mortality in other HM ($p = 0.006$), MM ($p = 0.002$), and NHL ($p = 0.046$) (Fig. 1).

The mortality rate observed in patients with critical infection was 100% (31/31). It was significantly higher than in asymptomatic patients (12.3%, 7/57) ($p < 0.001$). The mortality in patients with mild infection (7/46, 15.2%, $p = 0.485$) and severe infection (6/22, 27.3%, $p = 0.252$) was not vastly different from patients with asymptomatic infection (Fig. 2).

In the univariable Cox regression analysis, multiple factors negatively influenced mortality: renal impairment, fever, ANC $\leq 0.5 \times 10^9/mm^3$, critical COVID-19 infection, and bacterial superinfection. Among HMs, AML was associated with a significantly higher mortality rate compared to MM.

Comparing the two studied pandemic waves, there was a significant difference in survival. In the third wave, patients had a 70.2% lower mortality risk (15/57, 26.3%) than in the second wave (13/18, 72.2%) (Table 7). It is also important that in the second wave, all 13 patients who died were not vaccinated. In the third wave, only 3 who died were not vaccinated.

Discussion

The data obtained in this study show that the COVID-19 mortality rate among HM patients is higher than in the general population. The overall mortality rate of COVID-19 in the world varies from 0.1%—4.9 % according to currently available data [10].

The data obtained in the study show that COVID-19 mortality is also affected by the age of the patients. The highest COVID-19 mortality was observed in the age group of 70—79 years, but mortality also remains high in the younger patients, aged 50—59. Although age was found to be a risk factor in other studies [7], it was not a statistically significant risk factor in this study ($p = 0.334$).

The patients with AML had the highest mortality rate among all HM patients, and AML was found to be one of the risk factors in the univariable Cox regression model. These data are in agreement with literature data [7].

In previous studies of HM patients, it was found that COVID-19 vaccines are less effective in such patients compared to the general population because of the suppression of normal B-cell expansion. In addition, some treatments have a B-cell-depleting activity, which, in turn, may impair the immune response to vaccination [11]. This is probably the reason why the vaccination in our study was not found as a risk-reducing factor ($p = 0.690$).

The mortality among HM patients was shown to be significantly higher than in the general population implying that HM requires particularly careful infection monitoring and care. The data show that the majority of patients were tested not because of symptoms but only as part of the screening and developed symptoms later on. Some of these patients were sent home without symptoms after a positive screening result, but the symptoms developed later

on, and the patients were re-hospitalized in critical condition. It is possible that the regular screening and monitoring of patients would allow earlier initiation of treatment for COVID-19 and the use of preventive medications that would reduce the severity of the infection.

In addition, the study proved that the mortality in the third pandemic wave decreased significantly. This could be explained not only by the change and mutation of the SARS-Cov-2 variant [12] but also by improved patient management. Remdesivir (prodrug of an adenosine nucleotide analog [13]) was administered to the infected patients in the second wave by the council decision, but in the third wave, many patients received Molnupovir (nucleoside analog [14]) therapy, including patients who were asymptomatic at baseline. However, to draw such conclusions, it is necessary to expand the research.

Renal failure, fever, ANC below $0.5 \times 10^9/mm^3$, and bacterial superinfection were found as significant risk factors for HM patients with COVID-19 infection.

Research limitations. It is not possible to comment on the incidence of COVID-19 in different HM groups as only patients who were treated at the hospital at the time of diagnosis of the infection were registered.

A major shortcoming of the study is the fact that patients who got ill at home were not registered. There is no data on the course of infection in these patients. Only those who came to the hospital and were registered in the hospital database were included in the survey. Furthermore, the study was conducted in one clinic, and the studied group of patients was relatively small.

It would be purposeful to increase the group of patients by including other Latvian hospitals in order to be able to comment on the course of the infection in Latvia.

Also, vaccination is one of the unknown factors in HM patients. It would be reasonable to target the response of HM patients to the COVID-19 vaccine (at what titer antibodies are produced and how long they remain in the blood).

Considering that MM patients had one of the highest morbidity rates but the best overall survival, it would be worth extending the study by expanding this particular group.

Conflict of interest

The authors declare that they have no conflict of interest concerning this research, whether financial, personal, authorship, or otherwise, that could affect the research and its results presented in this paper.

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Data availability

Data will be made available on reasonable request.

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ФАКТОРИ, ЩО ВПЛИВАЮТЬ НА СМЕРТНІСТЬ ВІД КОВІД-19 У ХВОРИХ НА ОНКОГЕМАТОЛОГІЧНІ ЗАХВОРЮВАННЯ

Стан питання. Онкогематологічні хворі мають високий ризик розвитку тяжких та загрожуючих життю інфекцій, таких як КОВІД-19, через імунну недостатність та імуносупресивне лікування. Хоча пандемія КОВІД-19 має всесвітній характер, показники захворюваності та смертності варіюють у різних країнах. Уточнення факторів ризику дозволить поліпшити лікування онкогематологічних хворих. **Мета**. Визначити реальні показники смертності та фактори ризику, що впливають на неї у хворих на онкогематологічну патологію із супутнім КОВІД за даними Ризького університетського госпіталю. **Матеріали та методи**. До ретроспективного неінвазивного когортного дослідження були залучені дорослі хворі, які проходили лікування онкогематологічних захворювань з лабораторно підтвердженим КОВІД-19 впродовж грудня 2022 р. — березня 2023 р. Дані аналізували методами дескриптивної статистики, а також із застосуванням бінарної логістичної регресії та однофакторної регресійної моделі Кокса. **Результати**. Усього було залучено дані щодо 156 хворих з 11 різними онкогематологічними захворюваннями. Найчастіше це були множинна мієлома, неходжкінська лімфома та гострий мієлоїдний лейкоз. Смертність від КОВІД склала 19,9% (31/156). Серед факторів, що підвищують ризик смерті, були тяжкість КОВІД ($p < 0,001$), набута бактеріальна інфекція ($p < 0,001$), тривале перебування в госпіталі ($p = 0,037$), абсолютний вміст нейтрофілів $\leq 0,5 \times 10^9$/мм^3 ($p = 0,014$), лихоманка ($p = 0,039$) та гострий мієлоїдний лейкоз як основне захворювання ($p = 0,002$). Смертність у третю хвилю пандемії була нижчою, ніж у другу хвилю ($p = 0,002$). Хоча вакцинація була фактором, що знижував ризик (58,8% [10/17] померлих від КОВІД не були вакциновані), статистично вірогідної кореляції не виявлено ($p = 0,690$). **Висновки**. Смертність онкогематологічних хворих від КОВІД (19.9% [31/156]) була вищою порівняно з популяційними показниками. Тяжкість КОВІД, набута бактеріальна інфекція, тривалість перебування в госпіталі, абсолютний вміст нейтрофілів, лихоманка та гострий мієлоїдний лейкоз як основне захворювання ідентифіковані як фактори, що підвищують ризик смерті від КОВІД серед онкогематологічних хворих.

Ключові слова: смертність від КОВІД-19, фактори ризику, онкогематологічні хворі.