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# Outcomes and Risk Factors in Patients with Hematologic Malignancies Following Late-Stage SARS-CoV-2 Infection

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**Purpose:** To investigate the outcomes and risk factors for patients with hematologic malignancies (HM) following late-stage SARS-CoV-2 infection.

**Background:** Patients with HM such as lymphoproliferative malignancies (including acute lymphoblastic leukemia and multiple myeloma) and myeloproliferative malignancies (including acute myeloid leukemia, myeloproliferative neoplasm, and myelodysplastic syndrome) are at increased risk of severe illness and high mortality from COVID-19. This study examines the impact of SARS-CoV-2 infection severity on HM prognosis during the late phase of COVID-19, using data from 203 patients at Shanxi Bethune Hospital.

**Methods:** This is a retrospective cohort study. Data was collected from hospitalized HM patients at a single center from December 1, 2023, to December 31, 2023. The primary outcome was overall survival (OS). Multivariable Cox regression was used to identify risk factors.

**Results:** This analysis includes data from 203 hospitalized patients with HM aged 36 to 67 years (median, 58 years). SARS-CoV-2 infection was observed in 42.86% (87/203) of the patients, among whom severe/critical cases accounted for 14.29% (29/203). Multivariable Cox regression shows active disease (hazard ratio [HR] 2.16, 95% confidence interval [CI] 1.00–4.64, p = 0.049), hematopoietic stem cell transplantation (HSCT) (HR 4.06, 95% CI 1.02–16.12, p = 0.047), and targeted therapy (HR 2.60, 95% CI 1.23–5.50, p = 0.012) were associated with a higher incidence of progression. In contrast, individuals whose platelets count $\geq 50\times10^9$/L at baseline (HR = 0.36, 95% CI 0.17–0.78, p = 0.009) and ferritin levels less than 500 μg/L (HR = 0.54, 95% CI 0.34–0.86, p = 0.010) were associated with a lower incidence of progression. Active status (HR 7.06, 95% CI 2.10–23.76, p = 0.002), HSCT (HR 7.17, 95% CI 1.10–46.63, p = 0.039), and severe/critical SARS-CoV-2 infection in HM patients (HR 11.98, 95% CI 2.57–55.82, p = 0.002) were associated with higher incidences of all cause of mortality. While a higher platelet level ($\geq 50\times10^9$/L) was linked to a lower mortality (HR 0.16, 95% CI 0.05–0.49, p = 0.002).

**Conclusion:** In the late stage of the COVID-19 pandemic, active disease status, recent HSCT, and severe/critical SARS-CoV-2 infection significantly increased the risks of disease progression and mortality in HM patients. Higher baseline platelet counts were associated with improved outcomes.

**Keywords:** late stage of COVID-19, hematologic malignancies, progression-free survival, overall survival

## Introduction

In March 2020, the WHO declared COVID-19, a disease caused by SARS-CoV-2, to be a global pandemic.[1] After three years of the COVID-19 pandemic, understanding the late-stage effects of SARS-CoV-2 infection on patients with hematologic malignancies (HM) can help guide clinical management.

In the early stages of SARS-CoV-2 infection, most studies suggest that patients with HM face an increased risk of developing severe cases of the illness, with mortality rates exceeding 30%.[2–4] Currently, we cannot predict which patients

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with HM are more likely to contract COVID-19. However, multivariate Cox regression analysis revealed that specific HM such as acute myeloid leukemia (AML), multiple myeloma (MM), and non-Hodgkin's lymphoma demonstrate a higher risk of mortality from COVID-19, with hazard ratios of 3.49, 2.48, and 2.19, respectively.[5–7] Anticancer treatments, essential for managing HM, can further complicate the course of COVID-19. Therapies such as anti-CD20 monoclonal antibody therapy, chimeric antigen receptor T-cell (CAR-T) therapy, and hematopoietic stem cell transplantation (HSCT) not only weaken the immune response but also extend the duration of viral shedding, potentially increasing the period of infectivity and the risk of severe COVID-19.[7]

However, after the onset of the 2/3 wave of SARS-CoV-2 infections, along with the understanding of the novel coronavirus and the publication of consensus statements regarding the management of HM in the context of COVID-19, as well as the early use of small molecule antiviral drugs, the postponement of chemotherapy, and appropriate adjustments in the dosage and frequency of treatment, these measures appear to have improved the prognosis of patients with HM to some extent.

To evaluate the impact of SARS-CoV-2 infection severity on the prognosis of HM during the late phase of COVID-19, a retrospective analysis was performed on clinical data from 203 patients with HM admitted to Shanxi Bethune Hospital during this period. The study aimed to explore the correlation between the severity of SARS-CoV-2 infection and the prognosis of hematologic neoplasms, providing clinical insights for the management of patients with both conditions.

# Methods

## Study Design

This research was conducted as a retrospective cohort study in a real-world setting. Data were collected from Shanxi Bethune Hospital between December 1, 2023, and December 31, 2023. Information gathered included patient demographics (age, sex), physical status scores, co-morbidities, type and status of HM, COVID-19 severity (categorized as mild, moderate, severe, or critical), laboratory parameters, and medication exposures (including palliative, chemotherapeutic, and targeted agents). The primary endpoint was overall survival (OS), with progression-free survival (PFS) as the secondary endpoint. Quality control measures included independent verification of data entries and reconciliation of any discrepancies in key clinical variables.

## Ethics

This study followed the ethnic and scientific principles of Helsinki's Declaration and regulation of Chinese law for Chinese Good Clinical Practice. A group of hematologists contacted all participants or their relatives to secure their consent. In cases where participants or their relatives could not be reached, the Ethics Committee of the Shanxi Bethune Hospital granted a waiver to obtain permission. The ethics committee of Shanxi Bethune Hospital approved this study. The consent and approval number is YXLL-2023-286.

## Participants

Individuals with diagnosed malignant hematologic conditions that satisfied the criteria for WHO-defined HM,[8–10] encompassing lymphoma, leukemia, myeloproliferative neoplasms, MM, and myelodysplastic syndromes, who were hospitalized in Shanxi Bethune Hospital from November 4, 2022, to July 5, 2023, were enrolled.

The inclusion criteria were:

1. Hospitalized patients;
2. Aged 12 years or older;
3. Diagnosed with HM;
4. Confirmed SARS-CoV-2 infection by PCR test (for infected participants).

The exclusion criteria were:

1. Patients with multiple primary cancer sites;
2. Patients whose initial HM diagnosis was established outside Shanxi Bethune Hospital and had limited follow-up data within the institution;
3. Patients with incomplete data, defined as missing essential variables such as diagnosis, treatment history, or outcome information;
4. Patients loss to follow-up;
5. Grouping of Participants.

Based on COVID-19 status and infection severity, participants were categorized into three groups: the non-infection group, the mild/moderate SARS-CoV-2 infection group, and the severe/critical SARS-CoV-2 infection group. Severity classifications followed the SARS-CoV-2 Infection Diagnosis and Treatment Protocol (Trial Version 10) by the People's Republic of China, where severe/critical cases included patients requiring ICU support or mechanical ventilation.[11] The non-infection group consisted of patients with negative COVID-19 PCR tests, irrespective of respiratory symptoms. A positive SARS-CoV-2 diagnosis required a positive RT-PCR test result, defined as ORF1ab/N RNA cycle threshold values ≤35.

## Treatment

Any patient who has received any form of therapy for the HM within the past 45 days was considered to be on active anticancer therapy, while HSCT treatment was defined as occurring within the past three months.

Treatment modalities can be classified into several categories, encompassing conventional chemotherapy, supportive care, targeted therapies, and HSCT. Within the scope of this research, targeted therapies included monoclonal antibodies, immunomodulatory medications, and molecular-targeted therapies. All subjects in the infection group received early treatment with nirmatrelvir/ritonavir (300mg/100mg × 5 days) as anti-SARS-CoV-2 therapy and oxygen supplementation or admission to an intensive care unit as needed. Conventional chemotherapy and targeted therapies, excluding Janus kinase two inhibitors, were postponed for patients infected with SARS-CoV-2. Standard treatment was initiated two weeks after the virus turned negative.

## Definitions

PFS was defined as the time from enrollment to observing disease progression, relapse, or death, whichever occurred first. OS was defined as the time from the date of COVID-19 diagnosis to the date of death from any cause or the end of follow-up.

HM patients are categorized by disease type into lymphoproliferative malignancies (including ALL and MM) and myeloproliferative malignancies (including AML, MPN, and MDS); by disease status, they are classified as follows: active disease refers to disease onset, refractory/resistant disease, or disease progression, while stable disease indicates that the disease is in the consolidation and maintenance phases.

## Statistical Analysis

Continuous variables were reported as either the mean accompanied by the standard deviation (SD) or the median with the interquartile range (IQR, Q1-Q3). The Student's *t*-test was employed for normally distributed data, while the Mann–Whitney test was used for abnormal distribution data. Categorical variables were presented as counts with corresponding percentages. The categorical variable analysis involved Pearson's chi-square test or Fisher's exact test.

For the primary endpoint, which was all cause of mortality, and the secondary endpoint, progression, multivariate Cox regression was employed. The models were adjusted for variables with a p-value no greater than 0.10 in univariate Cox regression. Additionally, variates with clinical significance related to the endpoints were adjusted for, irrespective of their specific p-values.

Sample size was calculated based on the primary endpoint of this study which was all cause of mortality. We hypothesized that the severity of SARS-CoV-2 infection is associated with a higher all cause of mortality rate, with a hazard ratio (HR) of 2.5 compared to non-infection with SARS-CoV-2. Referring to a 15% incidence rate of all cause

of mortality in the non-infection SARS-CoV-2 group and 30% across all subjects, we calculated a required sample size of 204. This determination was based on a Type I error (α) of 0.05 and a Type II error (β) of 0.05.

The results were expressed as adjusted hazard ratios (HRs) with 95% confidence intervals (95% CIs). All hypothesis tests were two-sided, and statistical significance was defined as a p-value below 0.05. Stata SE 13, R (version 3.6.1, http://cran.r-project.org/), and EmpowerStat 2.0 (www.empowerstats.com) were applied for the data analysis.

## Results

Data from 283 individuals were screened. After excluding the data from 80 participants, 203 individuals with HM were enrolled. Among them, 116 were classified into the non-infection group, 58 into the mild/moderate infection group, and 29 into the severe/critical infection group (Figure 1).

### The Basic Information of All Participants

Table 1 provides a comprehensive overview of the demographic and clinical characteristics of hospitalized patients with HM across three groups: non-infection, mild/moderate infection, and severe/critical infection.

The diagnosis of HM reveals a significant association with infection severity ($p = 0.039$). A higher percentage of patients with lymphoproliferative malignancies are found in the severe/critical infection group, whereas myeloproliferative malignancies are more common in the non-infection group.

Tumor status significantly correlates with infection severity ($p = 0.040$), with active disease being more common in the severe/critical infection group.

Palliative care is more frequently administered as infection severity increases, with a significant difference ($p < 0.001$). The use of chemotherapy and hematopoietic stem cell transplantation decreases with increasing infection severity, with chemotherapy showing a significant difference ($p < 0.001$). The use of targeted therapy and the presence of autoimmune deficiency, rheumatic diseases, and liver disease do not show significant associations with infection severity (other information is listed in the Supplementary Document).

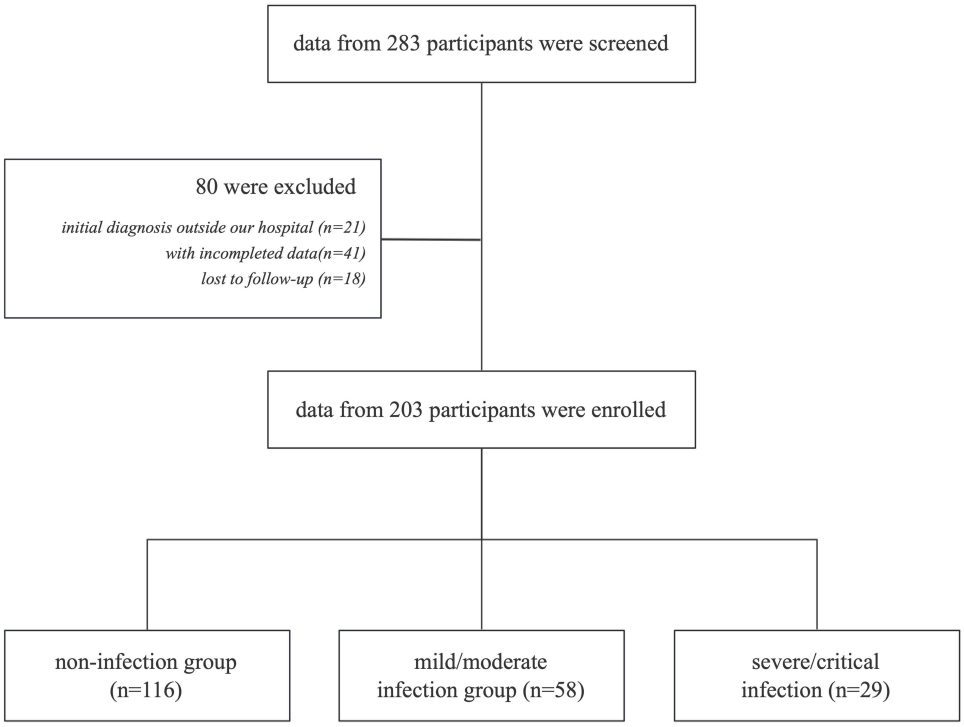


**Figure 1** The diagram flow of the data enrollment.

**Table 1** The Demographic and Clinical Characteristics of the Hospitalized Patients with Hematologic Malignancies

| | | Non-Infection (n=116) | Mild/Moderate Infection (n=58) | Severe/Critical Infection (n=29) | Statistics | p-value |
|---|---|---|---|---|---|---|
| Sex | Male | 63 (54.31%) | 29 (50.00%) | 18 (62.07%) | $\chi^2$=1.14 | 0.567 |
| Age | | | | | z=2.20 | 0.028 |
| | Mean±SD | 51.43±18.63 | 50.12±17.83 | 62.03±14.30 | | |
| | Median (q1-q3) | 56 (36.00–67.00) | 53 (33.00–64.50) | 65 (58.00–69.00) | | |
| | Min-Max | 14.00–90.00 | 13.00–81.00 | 24.00–83.00 | | |
| Diagnose of hematologic malignance | | | | | $\chi^2$=6.48 | 0.039 |
| | Lymphoproliferative malignancies | 37 (31.90%) | 26 (44.83%) | 16 (55.17%) | | |
| | Myeloproliferative malignancies | 79 (68.10%) | 32 (55.17%) | 13 (44.83%) | | |
| ECOG | Below 2 | 64 (55.17%) | 28 (48.28%) | 0 (0.00%) | Fisher | <0.001 |
| Tumor status | | | | | $\chi^2$=6.42 | 0.040 |
| | Stable disease | 62 (53.45%) | 26 (44.83%) | 8 (27.59%) | | |
| | Active disease | 54 (46.55%) | 32 (55.17%) | 21 (72.41%) | | |
| Vaccination | | 74 (63.79%) | 11 (18.97%) | 3 (10.34%) | Fisher | <0.001 |
| Palliative care | | 29 (25.00%) | 30 (51.72%) | 23 (79.31%) | $\chi^2$=32.75 | <0.001 |
| Chemotherapy | | 67 (57.76%) | 20 (34.48%) | 2 (6.90%) | Fisher | <0.001 |
| Hematopoietic stem cell transplantation | | 13 (11.21%) | 8 (13.79%) | 0 (0.00%) | Fisher | 0.096 |
| Targeted therapy | | 33 (28.45%) | 16 (27.59%) | 11 (37.93%) | $\chi^2$=1.15 | 0.562 |

**Abbreviations**: ECOG, Eastern Cooperative Oncology Group Score; Q1, the 1st quartile; Q3, the 3rd quartile; SD, standard deviation.

## Laboratory Test

Table 2 presents the laboratory test results for patients with HM across the non-infection, mild/moderate infection, and severe/critical infection groups.

Lymphocyte count is significantly different among the groups, with a p-value of 0.025.

Hemoglobin levels also show significant differences across the groups, with a p-value of 0.002. This finding indicates that patients with severe/critical infections are likely to experience more pronounced anemia (detailed information is listed in Table 1 and Table 2).

## The Analysis of the Primary Endpoint

Table 3 presents the results of the univariate and multivariate Cox regression analyses for all-cause mortality in patients with HM. The all-cause mortality rates in the three groups were 10.34% in the non-infection group, 5.17% in the mild/moderate infection group, and 41.38% in the severe/critical infection group (stable 1 in the Appendix). The 5-year OS rate was 83.00% in the non-infection group, 95.24% in the mild/moderate infection group, and 49.52% in the severe/critical infection group (stable 2 in the Appendix and Figure 2).

**Table 2** Laboratory Test for Hematologic Malignancies Patients

| | | Non-Infection (n=116) | Mild/Moderate Infection (n=58) | Severe/Critical Infection (n=29) | Statistics | p-value |
|---|---|---|---|---|---|---|
| White blood cell ($\times10^9$/L) | | | | | z=0.33 | 0.740 |
| | Mean±SD | 11.85±28.59 | 10.83±27.14 | 31.25±79.20 | | |
| | Median (q1-q3) | 4.65 (3.18–6.60) | 3.75 (2.20–6.55) | 6.30 (3.20–26.50) | | |
| | Min-Max | 0.30–210.30 | 0.10–140.70 | 1.00–422.30 | | |
| Lymphocytes counts ($\times10^9$/L) | | | | | z=−2.24 | 0.025 |
| | Mean±SD | 3.18±16.69 | 1.46±2.27 | 7.90±17.79 | | |
| | Median (q1-q3) | 1.19 (0.80–1.80) | 0.81 (0.45–1.49) | 0.84 (0.57–2.90) | | |
| | Min-Max | 0.27–180.44 | 0.05–14.17 | 0.09–63.32 | | |
| Platelets counts ($\times10^9$/L) | | | | | z=−0.48 | 0.629 |
| | Mean±SD | 177.26±189.60 | 148.50±146.74 | 198.14±244.82 | | |
| | Median (q1-q3) | 145.50 (88.00–210.00) | 116.50 (42.25–204.50) | 130.00 (78.00–244.00) | | |
| | Min-Max | 2.60–1410.00 | 5.00–839.00 | 23.00–1337.00 | | |
| Hemoglobin (g/L) | | | | | z=−3.09 | 0.002 |
| | Mean±SD | 106.21±33.79 | 93.92±31.28 | 91.50±41.51 | | |
| | Median (q1-q3) | 108 (83.50–132.00) | 96 (73.50–121.00) | 87 (71.00–107.00) | | |
| | Min-Max | 28.00–183.00 | 9.21–149.00 | 9.36–244.00 | | |

**Abbreviations**: Q1, the 1st quartile; Q3, the 3rd quartile; SD, standard deviation;

## Univariate Analysis on All-Cause Mortality

In the univariate analysis, the following variables have p-values less than 0.05. ECOG performance status is significantly associated with an increased risk of all-cause mortality, with an HR of 1.44 (95% CI: 1.03 to 2.00). Active disease shows a strong association with increased all-cause mortality, with an HR of 6.08 (95% CI: 2.08 to 17.80). Severe or critical infection is associated with a higher risk of mortality, with an HR of 2.49 (95% CI: 1.06 to 5.84). Platelet count is significantly associated with a reduced risk of mortality, with an HR of 0.26 (95% CI: 0.12 to 0.57). Hemoglobin levels show a significant association with reduced mortality risk, with an HR of 0.39 (95% CI: 0.15 to 0.97). D-dimer levels of 500 mg/L or higher are associated with increased mortality risk, with an HR of 3.18 (95% CI: 1.42 to 7.15). Lactate dehydrogenase levels of 256 U/L or higher are linked to increased mortality, with an HR of 5.13 (95% CI: 1.91 to 13.84).

The p-values of the following variables are greater than 0.05, including age over 50 years, the diagnosis of myeloproliferative versus lymphoproliferative malignancies, palliative care, chemotherapy, hematopoietic stem cell transplantation, targeted therapy, mild or moderate infection, white blood cell count, lymphocyte count, fibrinogen, serum albumin, ferritin, interleukin-6, calcitoninogen.

## Multivariate Analysis on All-Cause Mortality

In the multivariate analysis, the following variables have p-values less than 0.05. ECOG performance status shows a significant inverse association with mortality risk after adjustment, with an HR of 0.58 (95% CI: 0.35 to 0.96),

**Table 3** Univariable and Multivariable Cox Analysis of PFS and OS

| | | PFS | | | | OS | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Univariate | | Multivariate | | Univariate | | Multivariate | |
| | | HR (95% CI) | p-value | HR (95% CI) | p-value | HR (95% CI) | p-value | HR (95% CI) | p-value |
| Age | Above 50 | 1.00 (0.52, 1.92) | 0.995 | | | 1.74 (0.69, 4.39) | 0.240 | | |
| ECOG | | 1.15 (0.89, 1.48) | 0.285 | | | 1.44 (1.03, 2.00) | 0.032 | 0.58 (0.35,0.96) | 0.036 |
| Diagnose | MM vs LM | 0.84 (0.46, 1.52) | 0.555 | | | 1.10 (0.50, 2.43) | 0.814 | | |
| Active disease | | 2.99 (1.53, 5.84) | 0.001 | 2.16 (1.00, 4.64) | 0.049 | 6.08 (2.08, 17.80) | 0.001 | 7.06 (2.10, 23.76) | 0.002 |
| Palliative care | | 1.00 (0.55, 1.82) | 0.992 | | | 1.32 (0.61, 2.88) | 0.480 | | |
| Chemotherapy | | 0.82 (0.43, 1.56) | 0.548 | | | 0.76 (0.33, 1.76) | 0.520 | | |
| HSCT | | 0.79 (0.28, 2.24) | 0.659 | 4.06 (1.02, 16.12) | 0.047 | 0.64 (0.15, 2.75) | 0.550 | 7.17 (1.10, 46.63) | 0.039 |
| Targeted therapy | | 1.73 (0.95, 3.14) | 0.072 | 2.60 (1.23, 5.50) | 0.012 | 1.24 (0.56, 2.73) | 0.602 | 1.83 (0.65, 5.16) | 0.249 |
| Infection classification (non-infection as ref.) | Mild/ moderate | 1.10 (0.53, 2.31) | 0.792 | 1.46 (0.64, 3.34) | 0.371 | 0.49 (0.14, 1.73) | 0.266 | 0.62 (0.16, 2.43) | 0.492 |
| | Severe/critical | 1.50 (0.72, 3.14) | 0.281 | 2.75 (0.87, 8.69) | 0.084 | 2.49 (1.06, 5.84) | 0.036 | 11.98 (2.57, 55.82) | 0.002 |
| White blood cell count | ≥2 $\times 10^9$/L | 0.55 (0.24, 1.27) | 0.162 | | | 1.50 (0.35, 6.40) | 0.587 | | |
| Lymphocytes count | ≥$10^9$/L | 0.68 (0.37, 1.24) | 0.211 | | | 0.57 (0.26, 1.26) | 0.167 | | |
| Platelets count | ≥50$\times 10^9$ L | 0.40 (0.21, 0.74) | 0.004 | 0.36 (0.17, 0.78) | 0.009 | 0.26 (0.12, 0.57) | 0.001 | 0.16 (0.05, 0.49) | 0.002 |
| Hemoglobin | ≥60 g/L | 0.52 (0.24, 1.14) | 0.101 | | | 0.39 (0.15, 0.97) | 0.043 | 0.74 (0.22, 2.47) | 0.620 |
| D-dimer (<500 mg/L as ref) | ≥500 | 1.87 (0.98, 3.54) | 0.057 | 0.94 (0.52, 1.72) | 0.850 | 3.18 (1.42, 7.15) | 0.005 | 1.88 (0.91, 3.90) | 0.089 |
| | Unknown | 0.31 (0.04, 2.33) | 0.258 | | | 1.53 (0.34, 6.92) | 0.580 | | |
| Lactate dehydrogenase (<256 U/L as ref.) | ≥256 | 1.78 (0.96, 3.31) | 0.066 | 0.97 (0.50, 1.86) | 0.917 | 5.13 (1.91, 13.84) | 0.001 | 2.45 (0.99, 6.02) | 0.051 |
| | Unknown | 0.82 (0.11, 6.18) | 0.848 | | | 5.24 (1.01, 27.20) | 0.048 | | |
| Serum albumin (<30 g/L as ref.) | ≥30 | 0.38 (0.17, 0.83) | 0.016 | 0.55 (0.24, 1.25) | 0.153 | 0.38 (0.14, 1.02) | 0.054 | 0.66 (0.22, 1.97) | 0.461 |
| | Unknown | 0.29 (0.03, 2.35) | 0.244 | | | 0.44 (0.05,3.89) | 0.461 | | |

(*Continued*)



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**Table 3** (Continued).

| | | PFS | | | | OS | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Univariate | | Multivariate | | Univariate | | Multivariate | |
| | | HR (95% CI) | p-value | HR (95% CI) | p-value | HR (95% CI) | p-value | HR (95% CI) | p-value |
| Ferritin (<500 g/L as ref.) | ≥500 | 1.22 (0.53, 2.81) | 0.636 | 0.54 (0.34, 0.86) | 0.010 | 1.83 (0.64, 5.18) | 0.258 | | |
| | Unknow | 0.51 (0.25, 1.05) | 0.066 | | | 0.54 (0.20, 1.47) | 0.227 | | |
| Interleukin-6 (<80 pg/mL as ref.) | ≥80 | 1.67 (0.55, 5.10) | 0.366 | 1.59 (0.95, 2.67) | 0.077 | 2.36 (0.61, 9.14) | 0.215 | 1.78 (0.88, 3.59) | 0.107 |
| | Unknown | 1.30 (0.67, 2.53) | 0.431 | | | 1.43 (0.58, 3.51) | 0.434 | | |
| Calcitoninogen (<0.5 ng/mL as ref.) | ≥0.5 | 1.30 (0.51, 3.31) | 0.585 | | | 0.55 (0.12, 2.46) | 0.436 | 0.95 (0.58, 1.54) | 0.827 |
| | Unknown | 0.74 (0.39, 1.44) | 0.379 | | | 0.48 (0.21, 1.08) | 0.077 | | |
| Fibrinogen (<1.5 g/L as ref.) | ≥1.5 | 0.38 (0.11, 1.23) | 0.107 | | | 0.34 (0.08, 1.46) | 0.145 | | |
| | Unknown | 0.48 (0.10, 2.43) | 0.377 | | | 0.47 (0.06, 3.48) | 0.463 | | |

**Abbreviations**: ECOG, Eastern Cooperative Oncology Group Score; ref, reference; HSCT, Hematopoietic stem cell transplantation; LM, lymphoproliferative malignancies; MM, myeloproliferative malignancies; OS, Overall Survival; PFS, Progression-free Survival.

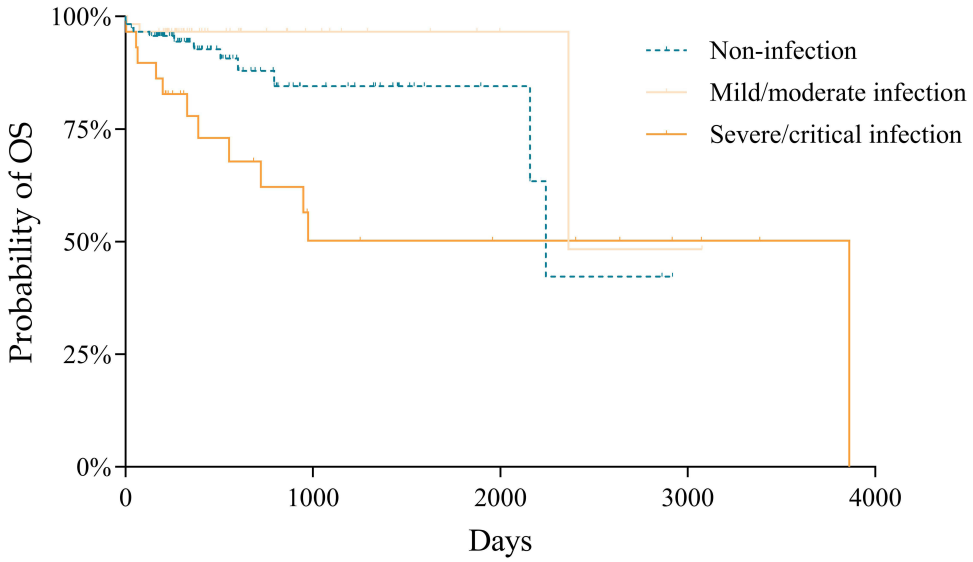


**Figure 2** The probability of overall survival.

indicating that better performance status may protect against mortality. Active disease remains significantly associated with increased all-cause mortality, with an HR of 7.06 (95% CI: 2.10 to 23.76). Severe or critical infection shows a strong association with increased mortality risk after adjustment, with an HR of 11.98 (95% CI: 2.57 to 55.82). Platelet count is significantly associated with a reduced risk of mortality, with an HR of 0.16 (95% CI: 0.05 to 0.49). Hematopoietic stem cell transplantation shows a significant increase in mortality risk after adjustment, with an HR of 7.17 (95% CI: 1.10 to 46.63). Lactate dehydrogenase levels of 256 U/L or higher remain significantly associated with increased mortality, with an HR of 5.13 (95% CI: 1.91 to 13.84).

## The Analysis of the Secondary Endpoint

Table 3 presents the results of the univariate and multivariate Cox regression analyses for progression-free survival in patients with HM. The progression rates in the three groups were 17.24% in the non-infection group, 18.97% in the mild/moderate infection group, and 48.28% in the severe/critical infection group (stable 1 in the Appendix). The 5-year PFS rate was 54.12% in the non-infection group, 56.59% in the mild/moderate infection group, and 41.18% in the severe/critical infection group (stable 3 in the Appendix and Figure 3).

### Multivariate Analysis on Progression-Free Survival

In the multivariate analysis, variables with p-values less than 0.05 include active disease, which remains significantly associated with a higher risk of progression, with an HR of 2.16 (95% CI: 1.00 to 4.64). Hematopoietic stem cell transplantation also shows a significant association with an increased risk of progression after adjustment, with an HR of 4.06 (95% CI: 1.02 to 16.12). Targeted therapy is significantly linked to a higher risk of progression, with an HR of 2.60 (95% CI: 1.23 to 5.50), indicating that patients receiving this treatment face an elevated risk of disease progression. Platelet count continues to be significantly associated with a lower risk of progression, with an HR of 0.36 (95% CI: 0.17 to 0.78), suggesting that higher platelet counts offer protection against disease progression.

### Multivariate Analysis on Progression-Free Survival

In the multivariate analysis, variables with p-values less than 0.05 include active disease, which remains significantly associated with a higher risk of progression, with an HR of 2.16 (95% CI: 1.00 to 4.64). Hematopoietic stem cell transplantation also shows a significant association with an increased risk of progression after adjustment, with an HR of 4.06 (95% CI: 1.02 to 16.12). Targeted therapy is significantly linked to a higher risk of progression, with an HR of 2.60 (95% CI: 1.23 to 5.50), indicating that patients receiving this treatment face an elevated risk of disease progression.

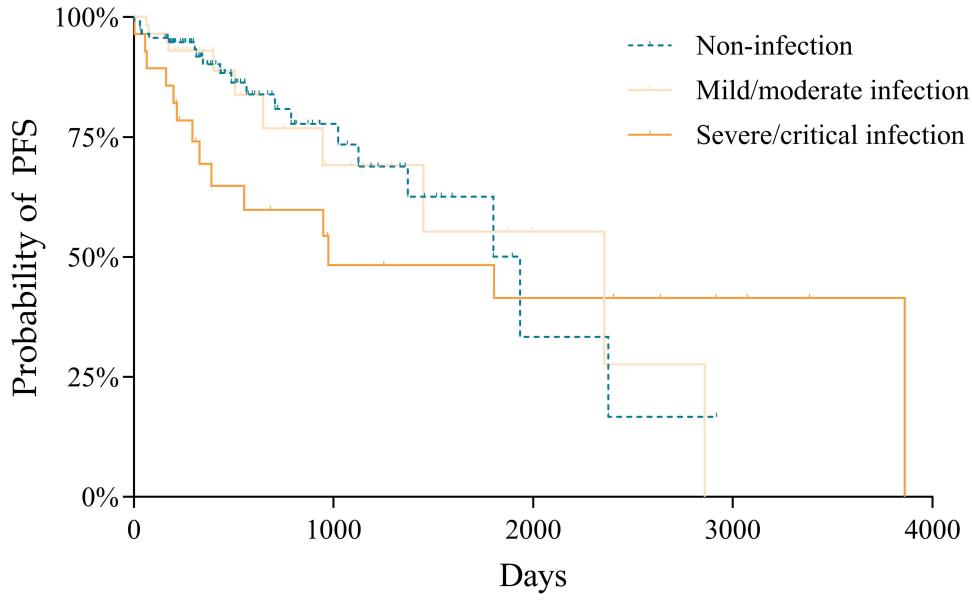


**Figure 3** The probability of progression-free survival.

Platelet count continues to be significantly associated with a lower risk of progression, with an HR of 0.36 (95% CI: 0.17 to 0.78), suggesting that higher platelet counts offer protection against disease progression.

The variables with p-values greater than 0.05 include age, ECOG performance status, the diagnosis of myeloproliferative versus lymphoproliferative malignancies, palliative care, chemotherapy, mild or moderate infection, severe or critical infection, white blood cell count, neutrophil count, lymphocyte count, hemoglobin levels, D-dimer, lactate dehydrogenase, serum albumin, ferritin, interleukin-6, calcitoninogen, fibrinogen.

## Discussion

During the COVID-19 pandemic, patients with HM are potentially at high risk due to their frailty, immunosuppressive therapy, frequent hospitalizations, and increased risk of mortality.[3,12–14] Results from the Italian Hematologic Cancer Registry indicate a mortality rate of 20.5% in our entire cohort, with 67% of patients experiencing mild COVID-19. Mortality rates were approximately 8%, 16%, and 65% in patients with mild, moderate, and severe COVID-19, respectively.[15]

While various guidelines and recommendations have been established to manage COVID-19 risk in HM patients,[3,16] these strategies continue to evolve. Our study addressed a specific gap by examining the outcomes and risk factors of HM patients during the late phase of the COVID-19 pandemic, providing new insights into mortality and progression risks under the heightened awareness and improved prevention measures of this period.

In our cohort of 87 HM patients with COVID-19, the mortality rate was significantly higher in those with severe/critical infection (41.38%) compared to those with mild/moderate infection (5.17%). This result is consistent with previous findings yet highlights that severe COVID-19 infection remains a critical risk factor for mortality, even as the pandemic has progressed. This observation emphasizes that, despite increased awareness and preventative efforts, severe COVID-19 remains a significant risk factor for adverse outcomes in HM patients, whereas infection severity did not significantly correlate with disease progression in this cohort.

In our study of 203 patients with HM, divided into lymphoproliferative and myeloproliferative categories, we did not find a significant association between specific HM types and COVID-19 severity or mortality. This contrasts with earlier research suggesting that certain HM types, such as AML, lymphoma, and multiple myeloma, may be linked to higher COVID-19 mortality.[3,17] Our findings indicate that in the later stage of the pandemic, factors such as active disease status and recent hematopoietic stem cell transplantation (HSCT) are more likely to be predictive of COVID-19 outcomes in HM patients than HM subtype alone.

The study also highlights the impact of active disease status and recent HSCT on outcomes. Patients with active HM had significantly higher mortality, supporting findings from prior studies[18–25] that linked disease activity with poor COVID-19 prognosis. Recent HSCT recipients also exhibited worse outcomes, which may be due to immune system vulnerability during the recovery phase post-transplant. This reinforces the need for heightened monitoring and potentially enhanced protective measures for this subgroup during COVID-19 infection.

An important finding of our study is the association between higher baseline platelet counts (≥50 × 10^9/L) and improved survival outcomes. Platelets play a crucial role in immune response, clotting, and inflammation modulation, all of which can impact COVID-19 severity.[26,27] Our results suggest that maintaining stable platelet counts could be beneficial for HM patients with COVID-19, potentially serving as a marker of disease resilience. This finding may guide clinical practice by encouraging regular platelet monitoring in HM patients as part of infection management and as a potential focus for supportive therapy. Future studies could explore whether targeted interventions aimed at stabilizing platelet counts can further reduce mortality risk.

Although prior studies have suggested that recent chemotherapy is associated with poor outcomes in cancer patients with COVID-19, there is limited specific research on how treatments for HM affect COVID-19 outcomes. Small-sample data indicate that chemotherapy-related hematologic toxicities, alterations in the T-cell compartment, and immunosuppressive effects may influence short-term mortality.[28] Conversely, recent literature suggests that hormone therapy, targeted therapy, and immune checkpoint inhibitors do not significantly worsen COVID-19 outcomes.[29] However, our study found that prior targeted therapy was associated with increased disease progression risk in HM patients with COVID-19, potentially due to immune response alterations. This highlights the need for clinicians to carefully consider the timing and risks of targeted therapies in HM patients with COVID-19, balancing the benefits of cancer control with the potential impact on infection outcomes. Further research is needed to establish definitive evidence in this area.

## Conclusions

In conclusion, this study underscores the ongoing risks faced by HM patients with COVID-19, particularly those with active disease, recent HSCT, or low baseline platelet counts. Our findings highlight the need for an integrated approach to care that addresses both HM management and COVID-19 prevention. By focusing on personalized monitoring and treatment strategies, clinicians may improve survival outcomes in this vulnerable population.

## Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author (R.Z.) on reasonable request.

## Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki and other relevant ethical guidelines and regulations. Ethical approval (Reference Number: YXLL-2023-286) was obtained from the Ethical Review Committee of Shanxi Bethune Hospital. The Institutional Review Board (IRB) of Shanxi Bethune Hospital determined that informed consent was not required for the use of retrospective data, provided that all personal identifiers were removed from the dataset. This waiver of informed consent was granted due to the study's retrospective nature and the use of de-identified data. All methods and procedures in this study were carried out in compliance with the approved protocol and relevant ethical standards.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

All authors declare no competing interests.

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