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Analysis of coinfections in patients with hematologic malignancies and COVID-19 by next-generation sequencing of bronchoalveolar lavage fluid

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Abstract

Background Coinfections in patients with coronavirus disease 2019 (COVID-19) affect patient prognosis. Patients with hematologic malignancies (HMs) are usually immunosuppressed and may be at high risk of coinfection, but few related data have been reported. Here, we conducted a retrospective study to explore coinfections in patients with HMs and COVID-19 by next-generation sequencing (NGS) of bronchoalveolar lavage fluid (BALF).

Methods The data of hospitalized patients with pneumonia who underwent NGS analysis of BALF were reviewed. COVID-19 patients with HMs were enrolled in the HM group, and those without HMs were enrolled in the non-HM group. The coinfections of the two groups identified by NGS were analyzed.

Results Fifteen patients were enrolled in the HM group, and 14 patients were enrolled in the non-HM group. The coinfection rates in the HM group and non-HM group were 80.0% and 85.7%, respectively. The percentage of coinfected bacteria in the HM group was significantly lower than that in the non-HM group (20.0% vs 71.4%, p = 0.005). The coinfection rates of fungi and viruses were 60.0% and 35.7%, respectively, in the HM group and 35.7% and 78.6%, respectively, in the non-HM group, with no significant differences. The most common coexisting pathogen in patients with HMs was *Pneumocystis jirovecii* (33.3%), and the most common coexisting pathogen in patients without HMs *was human gammaherpesvirus 4* (50%). Coinfection with herpesviruses occurred frequently in both groups.

Conclusions Our study showed that the majority of hospitalized patients with COVID-19 are likely to be co-infected with other pathogens. *Pneumocystis jiroveci* and herpesvirus are commonly coinfected pathogens in patients with HMs. Bacterial coinfection is rare in patients with HMs but is more common in patients without HMs.

Keywords COVID-19, Hematologic malignancy, Coinfection, Next-generation sequencing

Background

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in December 2019, and its impact on the world is still ongoing, affecting millions of people. SARS-CoV-2 is mainly transmitted by respiratory droplets. The main clinical symptoms include fever, cough, expectoration, fatigue, and dyspnea(1), which are sometimes difficult

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to distinguish from infections caused by other respiratory agents, such as bacteria, fungi, and other viruses. Viral infections cause a decrease in host immunity, which may lead to coinfection by other pathogens, and coinfections can significantly increase the mortality rate (2–4). Although most patients with COVID-19 develop mild illness with low coinfection rates, an increasing number of hospitalized patients are being diagnosed with coinfections, especially patients with severe illness(5–7).

Patients with hematologic malignancies (HMs) are usually in a state of severe immunosuppression due to bone marrow suppression, cytotoxic chemotherapy, glucocorticoids, and B-cell depletion therapy, resulting in a greater risk of severe COVID-19 and mortality(8). Despite concerns that these patients with COVID-19 may be at high risk of coinfection, few related data have been reported.

Next-generation sequencing (NGS) is a novel technique for providing rapid and objective pathogenic diagnosis that has been proven to be especially suitable for immunodeficient patients(9, 10). Moreover, the analysis of bronchoalveolar lavage fluid (BALF) by NGS is a very effective method for diagnosing pneumonia(11, 12). Therefore, we conducted a retrospective study to explore coinfections in HM patients with COVID-19 via NGS of BALF and compared the outcomes between patients with HMs and patients without HMs.

Methods

Patients

Patients (≥16 years) with pneumonia who underwent NGS analysis of BALF from January 2023 to October 2023 at Ningbo Medical Center Lihuili Hospital were reviewed. Patients with SARS-CoV-2-positive results according to NGS were enrolled in this study. We divided the enrolled patients into two groups: the HM group (patients with HMs) and the non-HM group (patients without HMs). Outcomes were compared between the two groups. Patients without HMs but with other hematologic diseases, such as aplastic anemias and autoimmune anemias, were excluded.

Baseline data collection

The baseline characteristics of the patients at the time of hospitalization were collected, such as sex, age, smoking history, performance status (PS) according to the Eastern Cooperative Oncology Group (ECOG)(13), comorbidities (diabetes, pulmonary comorbidities and cardiac comorbidities), history of malignancy, previous treatments, laboratory parameters, radiological findings for interstitial pneumonia (IP) and severity of COVID-19. The necessary radiological findings of IP include diffuse pulmonary interstitial infiltration and other manifestations, such as traction bronchiectasis, bilateral reticular opacities, loss of lobe volume, and opacity in the lower lungs on computed tomography (CT) scans (14–16). Severe COVID-19 was defined as an SpO2 < 94% on room air, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) < 300 mmHg, a respiratory rate > 30 breaths/min, or > 50% lung infiltrates according to the National Institutes of Health (17).

BALF collection and NGS analysis

Senior respiratory physicians performed bronchoscopy and BAFL acquisition according to standard procedures(18). To avoid contamination, the initial 20 ml BAFL sample was discarded, and another 20 ml BALF sample was collected for NGS analysis.

NGS testing was performed at Matridx Biotechnology Co., Ltd. (Hangzhou, China). Total nucleic acid was extracted from 5 ml of BALF. DNA or RNA sequencing libraries were prepared by automatic nucleic acid extraction, reverse transcription (for RNA), enzymatic fragmentation, end repair, terminal adenylation and adaptor ligation (NGSmaster™ library preparation, Cat# MAR002, Matridx, Hangzhou, China). The concentrations of the libraries were quantified real-time polymerase chain reaction (KAPA). Libraries were pooled and subsequently sequenced on an Illumina NextSeq platform. Approximately 20 million 75 bp single-end reads were generated for each library. For each run, one negative control and one positive control (with the RNA fragment of the adenovirus) were included for quality control.

The sequencing data were first demultiplexed to obtain the sequence reads of each sample in fastq format. High-quality sequencing data were generated after removing short (< 35 bp) reads and low-quality and low-complexity reads. Then, the sequence reads of each sample were aligned to the human reference genome (GRCh38.p13) to eliminate human sequences. The remaining reads were aligned to a reference database (the NCBI nt database and GenBank) to identify microbial species.

Microbial reads identified from a library were reported if they met the following criteria: 1) the sequencing data passed quality control filters (library concentration > 50 pM, Q20 > 85%, Q30 > 80%) and 2) the species were different from the negative control (NC) of the same sequencing run or the ratio of RPM (sample) to RPM (NC) reached the cutoff that can discriminate true positives from contaminants and backgrounds (RPM (sample)/RPM (NC) ≥ 5).

Statistical analysis

Absolute and percentage frequencies were used for categorical variables, and differences between groups were analyzed by Fisher's exact test. Medians and ranges were

used for continuous variables, and differences between groups were analyzed by the Mann–Whitney test. Kaplan–Meier curves were generated to display survival after SARS-CoV-2 infection, and the log-rank test was used for comparison. Multivariate logistic regression was performed to assess the risk factors for severe COVID-19. Factors significant in the univariate logistic regression at the 0.10 level were included in the multivariate model. Forest plots were generated to present the outcomes of the multivariate analysis. The 95% confidence intervals (CIs) were used to estimate odds ratios (ORs). All tests were two-tailed, and P values ≤ 0.05 were considered statistically significant. All analyses were performed using the statistical software SPSS v. 25, and figures were drawn with GraphPad Prism 9.

Results

Patient characteristics

Between January 2023 and October 2023, 784 patients with pneumonia underwent NGS analysis of BALF, and 31 patients were SARS-CoV-2 positive. One patient with aplastic anemia and one patient with autoimmune anemia were excluded. Overall, 15 patients with HMs (14 patients with lymphoma and one patient with multiple myeloma) and 14 patients without HMs were enrolled in the study. The flowchart is shown in Fig. 1.

The baseline characteristics are shown in Table 1. The median ages of patients in the HM group and no-HM group were 63 and 67 years, respectively. Patients in the HM group had better PS (p = 0.014) and a lower incidence of comorbidities (p = 0.050) than those in the no-HM group. All the patients in the HM group received previous antitumor therapy, and 86.7% of them accepted anti-CD20 monoclonal antibody (mAB) therapy. Fourteen patients received systemic antineoplastic therapy within 6 months before COVID-19 infection, and 1 patient received the last antineoplastic therapy (CART) 11.6 months prior to COVID-19 infection. The median period between the last antineoplastic systemic therapy and COVID-19 infection was 2.8 months, with a range of 0.1–11.6 months. Among the 15 patients with HMs, 6 received prophylactic trimethoprim–sulfamethoxazole treatment. Two patients in the non-HM group had a history of lung cancer, and 1 of them had previously received PD-1 therapy. Half of the patients in the non-HM group presented with severe pneumonia, whereas 33.3% of the patients in the HM group presented severe pneumonia (p = 0.462). CT findings of IP were found in 18 of 29 patients at the infection of COVID-19. Of these patients, only 2 had prior CT evidence of IP, and at the time of COVID-19 infection, the IP have significantly worsened compared to before.

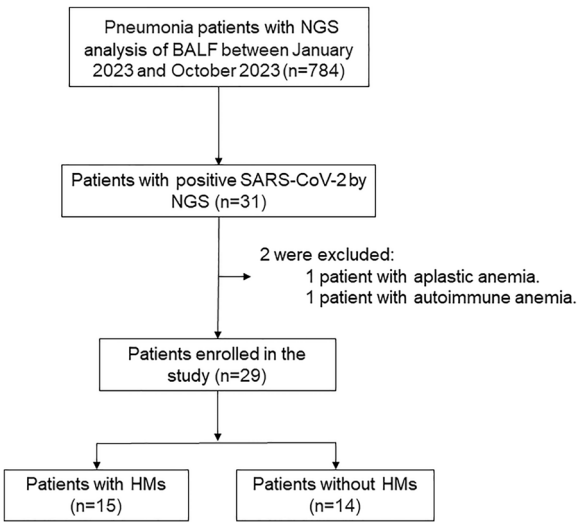

Fig. 1 Flowchart of patient selection in this study. NGS: next-generation sequencing; BALF: bronchoalveolar lavage fluid; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; HM: hematologic malignancy

Pathogens detected by NGS

A heatmap was drawn to show the pathogens and their abundance detected by NGS (Fig. 2). The most common coexisting pathogens in patients with HMs were *Pneumocystis jirovecii* (33.3%), *Candida albicans* (26.7%), *human alphaherpesvirus 1* (26.7%) and *human betaherpesvirus 5* (20.0%). The most common coexisting pathogens in patients without HMs were *human gammaherpesvirus 4* ((Epstein–Barr virus, 50%), *human alphaherpesvirus 1* (cytomegalovirus, 35.7%), *human betaherpesvirus 5 (21.4%), Candida albicans* (21.4%) and *Enterococcus faecalis* (21.4%). For the six HM patients with prophylactic trimethoprim–sulfamethoxazole treatment, no coinfection of *Pneumocystis jirovecii* was found. For those HM patients who did not receive prophylactic trimethoprim–sulfamethoxazole treatment, the coinfection rate of *Pneumocystis jirovecii* was as high as 55.6% (5/9). The sequence numbers of detected species-specific pathogens are shown by the color depth in the heatmap.

Comparison of coinfections in the HM and non-HM groups

The overall coinfection rates in the HM group and non-HM group were 80.0% and 85.7%, respectively, with no significant difference. The coinfection rate of bacteria in patients with HMs was significantly lower than that in patients without HMs (20.0% vs 71.4%, p = 0.005). The coinfection rates of fungi and viruses were 60.0% and 35.7%, respectively, in patients with HMs and 35.7% and 78.6%, respectively, in patients without HMs. There

Table 1 Baseline characteristics of patients

Characteristics	Patients with HMs($n=15$)	Patients without HMs ($n=14$)	*P* value
Age, median (range), years	63 (43–77)	67 (17–88)	0.382
Sex			
Male	9 (60.0%)	9 (64.3%)	1.000
Female	6 (40.0%)	5 (35.7%)	
Smoking	2 (13.3%)	2 (14.3%)	1.000
ECOG PS score			0.014
≤ 2	14 (93.3%)	7 (50.0%)	
> 2	1 (6.7%)	7 (50.0%)	
Comorbidities[†]	2 (13.3%)	7 (50.0%)	0.050
Malignancy	15 (100%)	2 (14.3%)	< 0.001
Antitumor treatments	15 (100%)	1 (7.1%)	< 0.001
Anti-CD20 mABs	13 (86.7%)	/	/
CART	1 (6.7%)	/	/
Stem cell transplantation	1 (6.7%)	/	/
Period between last antineoplastic systemic therapy and COVID-19 infection, months	2.8 (0.1–11.6)	/	/
Prophylactic trimethoprim–sulfamethoxazole	6 (40%)	/	/
Neutrophil	2.6 (0.9–8.7)	8.0 (1.7–20.7)	0.055
Lymphocyte	0.8 (0.2–2.7)	1.1 (0.2–1.8)	0.759
High-sensitivity C-reactive protein	34.4 (5.6–106.9)	28.2 (0.5–346.0)	0.663
Albumin	37.5 (22.2–41.5)	32.2 (23.2–46.8)	0.077
Lactic dehydrogenase	271 (151–505)	184 (134–434)	0.169
Interstitial pneumonia	11 (73.3%)	7 (50.0%)	0.264
Severe COVID-19	5 (33.3%)	7 (50.0%)	0.462

[†] Comorbidities included diabetes, pulmonary comorbidities, and cardiac comorbidities. ECOG PS: eastern co-operative oncology group performance status; mAB: monoclonal antibody; CART: chimeric antigen receptor-T cell; COVID-19: coronavirus disease 2019; HM: hematologic malignancy

was no significant difference between the two groups (Fig. 3A).

We then listed the common coinfected pathogens between the two groups at the genus level (Fig. 3B, C, D). Only three patients had coinfections with bacteria in patients with HMs, namely, *Elizabethkingia, Escherichia*, and *Enterobacter,* at the genus level. The most commonly detected coinfections of bacterial genera in patients without HMs were *Enterococcus* (21.4%), *Escherichia* (14.3%), *Corynebacterium* (14.3%), and *Streptococcus* (14.3%). There was no significant difference in the coinfection rate of each bacterium at the genus level between the two groups. The largest proportion of fungal genera in patients without HMs was *Pneumocystis* (33.3%), which seems to be greater than the proportion in patients without HMs (7.1%), but the difference was not statistically significant. The other fungal genera coinfected with HMs at high rates were *Candida* (26.7%) and *Aspergillus* (6.7%), which were similar to the findings in patients without HMs.

Lymphocryptovirus was highly detected in patients without HMs, which was significantly greater than that in patients with HMs (50% vs 0.0%, p = 0.002). Other coinfected viral genera with high rates in the two groups were *simplex virus* (26.7% in the HM group vs 35.7% in the non-HM group, p = 0.700) and *cytomegalovirus* (20.0% in the HM group vs 21.4% in the non-HM group, p = 1.000).

The 90-day survivals of the two groups are shown in Fig. 4. The mortality rate was 13.3% (2/15) in the HM group and 28.6% (4/14) in the non-HM group, with no significant difference.

Treatments of patients

Supporting treatments and antimicrobial therapy are shown in Table 2. There were no significant differences in the supporting treatments (granulocyte colony-stimulating factor, intravenous immunoglobulin, steroids) received between the two groups. The majority of patients received corresponding antimicrobial treatment based on the results of BALF NGS. Seven patients did not receive antiviral treatment for COVID-19. Five patients were detected with human *alphaherpesvirus 1* or *human betaherpesvirus 5* but did not receive antiviral treatment, and two patients were detected with fungi but did not receive antifungal treatment.

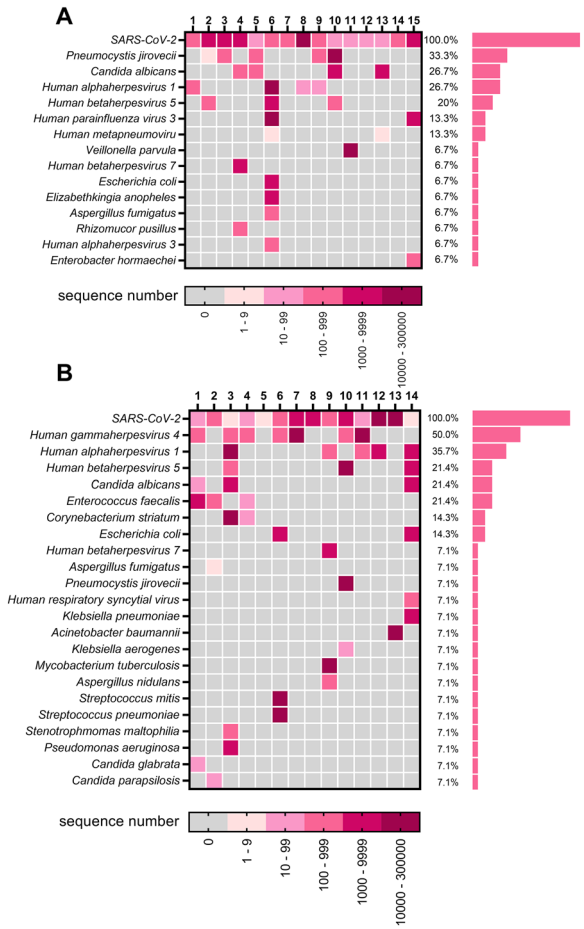

Fig. 2 Heatmap of the pathogens and their sequence numbers detected by next-generation sequencing in patients with hematologic malignancies (**A**) and patients without hematologic malignancies (**B**). SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

Risk factors for severe COVID-19

Baseline characteristics (including age, sex, smoking, performance status, comorbidities, patients with HMs or not, neutrophil, lymphocyte, high-sensitivity C-reactive protein, albumin, lactic dehydrogenase, interstitial pneumonia), coinfections detected by NGS, and treatment factors (including use of granulocyte colony-stimulating factor, intravenous immunoglobulin, steroids, antiviral therapies for COVID-19) were first analysis by univariate logistic regression. Only four factors (coinfection with bacteria, patients with HMs, performance status and IP) were significantly associated with severe disease in the univariate analysis at the 0.10 level and were included in the multivariate logistic regression analyses. The results are shown in Fig. 5. Coinfection with bacteria was an independent risk factor for severe disease (OR 19.61, 95% CI 1.32–292.05; $p=0.031$). No other factors were found to be associated with severe disease, probably because of the small sample size.

Discussion

Although COVID-19 has been effectively controlled, it can still cause severe pneumonia and death, especially in immunocompromised patients and elderly patients. Respiratory virus infections can increase susceptibility to secondary bacterial or fungal infections, and coinfections can have an adverse effect on prognosis(6, 7, 19, 20). Previous studies reported that the probability of COVID-19 coinfection was 8–14.5%(5, 6, 21). In a study of all hospitals or outpatient patients with malignancies, the incidence of coinfections was 16.6%(22). In another study of patients with malignancies or who underwent organ transplantation in the intensive care unit, the incidence of coinfections was 27%, whereas it was as high as 46.7% in patients with HMs(23). However, the main microbiological detection methods used in previous studies were traditional methods, and their sensitivity remains to be evaluated. To the best of our knowledge, this is the first study to describe coinfections in HM patients with SARS-CoV-2-caused pneumonia by detecting the BALF of patients using the highly sensitive NGS method.

Our study showed that the coinfection rates of patients with HMs and those without HMs were 80.0% and 85.7%, respectively, which were significantly greater than those previously reported. The NGS method we used in this study was highly more sensitive than traditional microbiological detection methods used in previous studies, which may account for the greater rate of coinfection in our study. *Pneumocystis jirovecii* was the most common coinfected pathogen, with a coinfection rate of 33.3%. And for those HM patients who did not receive prophylactic trimethoprim–sulfamethoxazole treatment, the coinfection rate of *Pneumocystis jirovecii* was as high as 55.6% (5/9). No coinfection of *Pneumocystis jirovecii* was found in patients with prophylactic trimethoprim–sulfamethoxazole treatment. *Pneumocystis jirovecii* is a common opportunistic infection pathogen in immunocompromised patients. *Pneumocystis jiroveci* pneumonia may also present as diffuse pulmonary interstitial infiltration(24–26), which is sometimes difficult to distinguish from SARS-CoV-2 pneumonia. The traditional detection methods for *Pneumocystis jiroveci* infection have poor sensitivity, but NGS has been proven to be an effective method for detecting this disease(27–30) (9). In our previous study of lymphoma patients with chemotherapy-related IP, *Pneumocystis jirovecii* was detected in the BALF of 12 of 15 patients by NGS(29). In this study, all the patients with HMs had previously received chemotherapy, and 13 of 15 (86.7%) patients had received anti-CD20

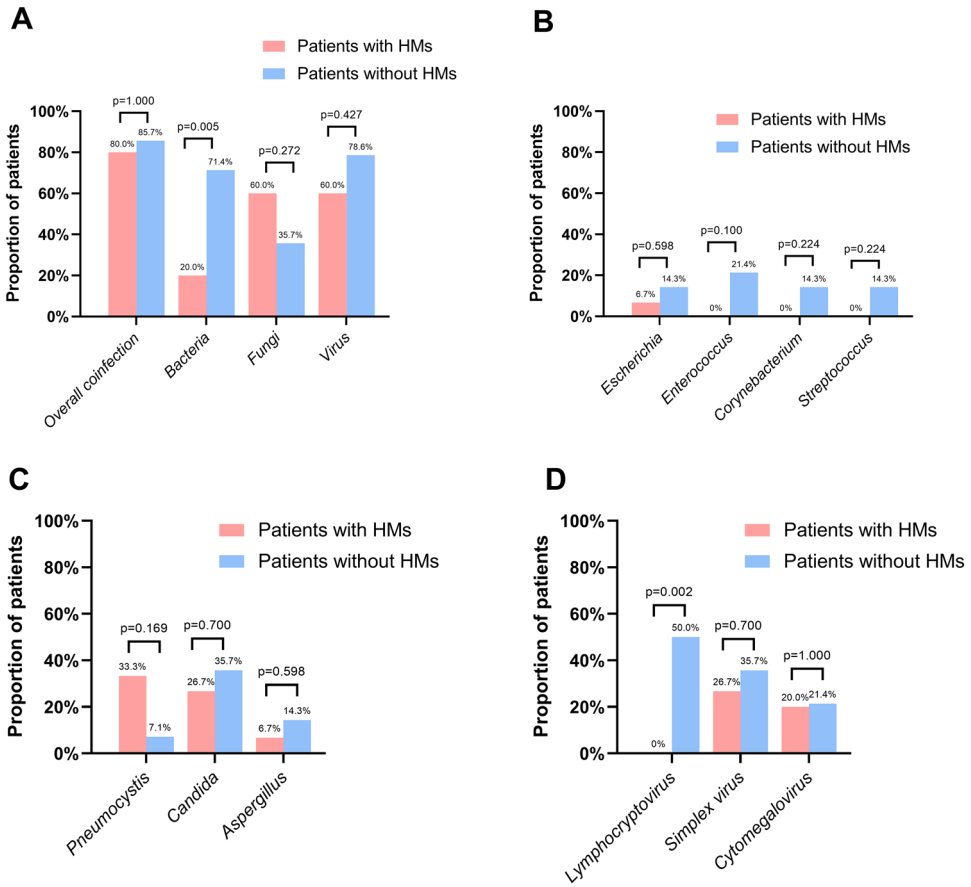

Fig. 3 Comparison of coexisting pathogens between the HM and non-HM groups. **A** Overall coinfection, bacterial coinfection, fungal coinfection, and viral coinfection in the two groups. **B** Coinfection of bacteria in the two groups at the genus level. **C** Coinfection of fungus in the two groups at the genus level. **D** Coinfection of viruses in the two groups at the genus level. HM: hematologic malignancy

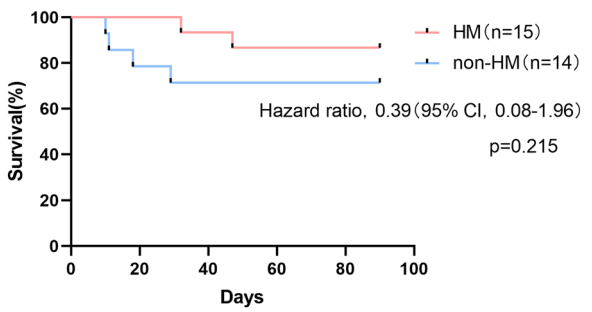

Fig. 4 90 day survival in the HM and non-HM groups. HM: hematologic malignancy

mAbs, which may have resulted in severe immunodeficiency and increased susceptibility to *Pneumocystis jirovecii*. These data suggest that we need to be highly vigilant about the coinfection of *Pneumocystis jirovecii* in HM patients without prophylactic trimethoprim–sulfamethoxazole treatment. The prophylactic trimethoprim–sulfamethoxazole treatment can effectively reduce the coinfection of *Pneumocystis jirovecii* in HM patients with COVID-19.

Previous studies have reported that the probability of bacterial coinfection in patients with COVID-19 is approximately 8–15%, while the incidence is relatively high in critically ill patients (approximately 20–30%)(5, 6, 31). Our study showed that the probability of bacterial coinfection in patients with HMs was significantly lower than that in patients without HMs. This may be related to the differences in baseline characteristics between the two groups. Patients in the non-HM group had worse performance status and more comorbidities. Moreover, half of the patients in the non-HM group had severe diseases. This selection bias may be due to the differences between hematologists and respiratory physicians in deciding which patients to perform bronchoscopy and NGS. For COVID-19 patients without HMs, respiratory physicians may suggest bronchoscopy for more critically ill patients. Multivariate analysis in our study also showed that bacterial coinfection was associated with severe disease. Notably, according to

Table 2 Treatments of patients

Treatments	Patients with HMs ($n=15$)	Patients without HMs ($n=14$)	*P* value
Granulocyte colony-stimulating factor	4 (26.7%)	0 (0%)	0.100
Intravenous immunoglobulin	8 (53.3%)	5 (35.7%)	0.462
Steroids	11 (73.3%)	9 (64.3%)	0.700
Antibiotics	15 (100%)	14 (100%)	/
Antifungals	8 (53.3%)	3 (21.4%)	0.128
Antivirals (Except for anti-COVID-19)	4 (26.7%)	2 (14.3%)	0.651
Antiviral therapies for COVID-19	13 (86.7%)	9 (64.3%)	0.215

COVID-19: coronavirus disease 2019; HM: hematologic malignancy

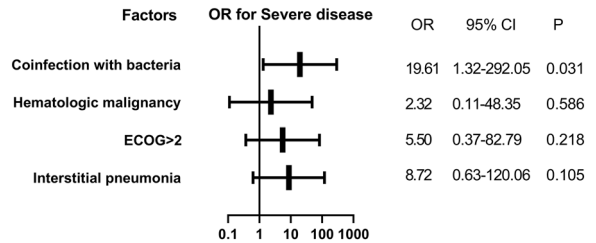

Fig. 5 Risk factors for severe COVID-19. ECOG: Eastern Co-operative Oncology Group; OR: odds ratio; CI: confidence interval

previous reports, the majority of hospitalized COVID-19 patients received antibiotics, despite the low incidence of bacterial coinfection(6, 32). The overuse of antibiotics can increase the risk of multidrug-resistant infections and lead to poor prognosis(33). Therefore, we should carefully evaluate the use of antibiotics in HM patients with mild COVID-19.

The incidence of viral coinfection reported in previous literature was 2.1%(22), which was significantly lower than that in our study. This may be due to the poor sensitivity of traditional virus detection methods. In our study, coinfection with herpesviruses occurred frequently in the two groups. Previous studies showed that herpesviruses, such as Epstein–Barr virus and cytomegalovirus, are common in critically ill patients, patients with hematologic disorders, and patients treated with immunosuppressive agents(34–37). Moreover, the reactivation of herpesviruses is associated with the severity and length of COVID-19 symptoms(38, 39). Gold et al. suggested that long COVID-19 symptoms may not be a direct result of the SARS-CoV-2 virus but may be the result of COVID-19-induced Epstein–Barr virus reactivation(40). Furthermore, anti-herpesvirus therapy with ganciclovir may reduce the risk of death in patients with severe COVID-19(41). Therefore, coinfection with herpesviruses may affect the prognosis of patients with COVID-19. The high detection rate of herpesviruses in our study suggested that we need to pay attention to coinfections caused by these viruses and provide effective treatment.

At present, NGS technology is commonly used in clinical practice with low risk, and its results are quickly available, within 24 h, which can provide rapid and accurate guidance to clinical physicians to reduce hospitalization time and adverse outcomes of infection. Therefore, for patients with COVID-19 pneumonia, especially for those with a long course of SARS-CoV-2 pneumonia or severe disease, NGS testing of BALF may be considered.

In our study, 18 of 29 patients had a CT manifestation of IP, and in univariate analysis, the presence of IP was associated with severe disease. Previous study showed that multifocal IP is the most common cause of intensive care units' admission and death during COVID-19 infection(42). Intense cytokine storm leads to interstitial inflammatory infiltration in the lungs, followed by expanded alveolar damage(43, 44). Recently, the renin–angiotensin–aldosterone system was reported to play an important role in COVID-19 pathogenesis(45–47). The downregulation of angiotensin-converting enzyme-2 leads to an increase in angiotensin II, resulting in increased vascular permeability, pulmonary edema, and apoptosis of bronchoalveolar epithelial cells(45–47). Therefore, this can lead to lung injury and fibrosis. These studies provide new targets for the treatment of COVID-19 pneumonia.

There are several limitations of our study. First, this was a single-center study, and the results only represent coinfections around our center. Prophylactic anti-microbial treatment such as trimethoprim–sulfamethoxazole or valaciclovir may affect the outcomes of coinfections. As practices are diverse and centers follow their own prophylactic anti-microbial treatment recommendation, the common coinfections in different centers may differ. Second, because this was a retrospective study, the baseline characteristics of patients in the HM group and non-HM group were not completely compared. Patients in the non-HM group had worse performance status and more comorbidities and seemed to have more severe disease. This selection

bias may be due to the differences between hematologists and respiratory physicians in deciding which patients to perform bronchoscopy and NGS. Third, we were unable to clarify whether identifying coinfections through NGS test of BALF can improve the prognosis of patients. To make the above conclusion, it may be necessary to include patients with COVID-19 who have not undergone BALF NGS test as controls. Finally, the small sample size may be the greatest limitation of the study, resulting in no significant differences in the comparison of some outcomes between the two groups. In particular, small sample size for multivariate analysis may lead to bias. We look forward to larger and better matched cohort study in the future.

Conclusions

Our study showed that the majority of hospitalized patients with COVID-19 are likely to be co-infected with other pathogens. *Pneumocystis jiroveci* and herpesvirus are commonly coinfected pathogens in patients with HMs. Bacterial coinfection is rare in patients with HMs but is more common in patients without HMs.

Abbreviations

BALF	Bronchoalveolar lavage fluid
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CT	Computed tomography
ECOG	EASTERN cooperative oncology group
HM	Hematologic malignancy
IP	Interstitial pneumonia
mAB	Monoclonal antibody
NC	Negative control
NGS	Next-generation sequencing)
OR	Odds ratio
PS	Performance status
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2

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Author contributions

D.J.conceived the study; W.S. and Q.Y. analyzed data and wrote the paper; J.L. revised the paper; Q.C., HD, L.L., J.T., Y.S., B.C., Y.T. collected data; All authors reviewed the manuscript.

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Availability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethical Review Committee of Ningbo Medical Center Lihuili Hospital (approval No. YJZ2023SL2). The procedures used in this study adhere to the tenets of the Declaration of Helsinki. Informed consent was obtained from all subjects and/or their legal guardian(s).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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