Infection and Drug Resistance Dovepress

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The Differential Diagnostic Value of Chest Computed Tomography for the Identification of Pathogens Causing Pulmonary Infections in Patients with Hematological Malignancies

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Objective: The role of chest computed tomography (CT) in distinguishing the causative pathogens of pulmonary infections in patients with hematological malignancies (HM) is unclear. The aim of our study was to compare and assess the clinical characteristics, radiologic features and potential differential diagnostic value of CT in HM patients and other different immune statuses patients with pulmonary infections.

Methods: Patients were divided into immunocompetent (105 cases) and immunocompromised groups (99 cases) according to immune status. Immunocompromised patients included the HM group (63 cases) and the non-HM group (42 cases). The basic clinical data and CT findings were collected and statistically analyzed.

Results: Regarding the pathogen distribution, viral, *Pneumocystis jirovecii* and mixed infections were more common in the immunocompromised group than the immunocompetent ($p < 0.01$), but viral infections were more common in the HM group than in the non-HM group ($p=0.013$). Immunocompromised patients had more diverse CT findings and more serious lesions (mostly graded 2–4) than immunocompetent patients. The most common CT findings in HM patients were consolidation and ground-glass opacities (GGO), which were also found in the non-HM group. The overall diagnostic accuracy of CT was lower in immunocompromised patients than in immunocompetent patients (25.7% vs 50.5%, $p< 0.01$). CT had better diagnostic efficacy for fungi and *Pneumocystis jirovecii* in HM patients.

Conclusion: CT diagnosis is less efficient in distinguishing the causative pathogens of HM patients. However, CT can help distinguish fungal pneumonia and *Pneumocystis jirovecii* pneumonia in HM patients.

Clinical Relevance Statement: Our study might facilitate clinical decision-making in fungal pneumonia and *Pneumocystis jirovecii* pneumonia in HM patients.

Keywords: pneumonia, hematological malignancies, computed tomography, diagnostic value

Introduction

Patients diagnosed with hematological malignancies (HM) are usually susceptible to infections due to considerable immunosuppression mainly caused by chemotherapies.[1] It has been reported that approximately 17–50% of HM patients develop pulmonary infections during their treatment.[2,3] Severe and complicated pulmonary infections might increase overall mortality.[4] A prompt and accurate pathogenic diagnosis of pulmonary infections facilitates optimal antimicrobial therapy and thus decreases infection-related mortality.[5] Conventional microbiological tests such as blood culture, sputum culture, and other novel detection methods, including next-generation sequencing (NGS), have been extensively used for the diagnosis of pulmonary infections. However, these conventional tests have limitations in many aspects, such as long

Received: 17 April 2024
Accepted: 12 October 2024
Published: 21 October 2024

detection cycles, low sensitivity, and high costs.[6] Few studies have evaluated the use of noninvasive, rapid diagnostic tests to identify pathogens in HM patients with pulmonary infections.

Imaging plays a crucial role in the detection and management of patients with pneumonia.[7] Chest radiography has limited sensitivity and shows normal results in up to 10% of patients with pulmonary diseases.[8,9] Early chest computed tomography (CT) can be used to detect lesions missed by conventional chest radiography, which is used to identify pulmonary infections in immunocompetent patients.[10] However, patients with a compromised immune system suffer from a wide range of lung diseases and have diverse imaging features.[11] For instance, among patients affected by nontuberculous mycobacterial infection, large opacities and cavitation in pulmonary nodules are more frequent in immunocompromised than in immunocompetent patients.[12] Therefore, distinguishing different pathogens is often difficult due to nonspecific chest symptoms and radiologic findings in immunocompromised patients.[13] Some reports revealed that the differential diagnosis of pulmonary infections in immunocompromised patients could be partially established with early utilization of CT imaging.[14] However, the characteristic CT findings are different depending on the immune status.[15] A previous study revealed the presence of different radiological features in patients with *Pneumocystis jirovecii* pneumonia who did or did not have AIDS: widespread ground glass opacities in patients who did not have AIDS and cystic lesions in patients with AIDS.[16] Patients with HM often have various types of immunodeficiencies that differ from those observed in patients with other immunocompromised statuses, such as neutropenia with insufficient phagocytosis, abnormal T cells with cellular immune dysfunction or absent B cells with humoral immune dysfunction.[17] Few studies have shown the potential use of CT for the differential diagnosis of pulmonary infections in HM patients.[18,19] Therefore, further research is required to assess the value of CT imaging in the differential diagnosis of pulmonary infections in HM patients.

We collected the clinical data and CT images obtained from patients with pathogenically defined pulmonary infections from the Third Xiangya Hospital of Central South University from March 2019 to January 2022. We aimed to compare the clinical characteristics in patient groups and assess the potential application of CT in the differential diagnosis of infections with different pathogens in HM patients.

Methods and Materials

Study Design and Patient Population

In this retrospective, single-center cohort study, data on pulmonary infection patients with identified pathogens were collected from electronic medical records in our hospital from March 2019 to January 2022. The study was conducted in accordance with the Declaration of Helsinki, International Conference on Harmonization/Good Clinical Practice and nationally mandated ethical requirements. The study protocol and informed consent document were reviewed and approved by the Ethics Committee of the Central South University. Written informed consent has been obtained from the patients and their anonymous information will be published in this article.

Figure 1 depicts the process of patient selection. Patients who met the following criteria were enrolled.[20] (1) aged ≤ 65 years, (2) positive NGS results center obtained from bronchoalveolar lavage fluid or pulmonary biopsy, and (3) available CT scans of the lungs. Patients with diabetes or infections with pathogens that could not be clearly identified were excluded. Using these inclusion/exclusion criteria, 204 patients were included for analysis and categorized into three groups: the HM group, the non-HM immunocompromised group, and the immunocompetent group. For every enrolled patient, we recorded demographic data; the presence of underlying diseases and immune status; clinical symptoms and signs; the results of laboratory tests, including microbiological testing and NGS; antibiotic treatment; and patient outcomes. Immunocompromise was defined according to a previous article as follows:[15] primary immune deficiency diseases; active malignancy, excluding patients with localized skin cancers or early-stage cancers; receival of cancer chemotherapy; human immunodeficiency virus (HIV) infection with a CD4 T-lymphocyte count < 200 cells/mL or percentage < 14%; solid organ transplantation; hematopoietic stem cell transplantation; receival of corticosteroid therapy with a dose ≥ 20 mg prednisone or equivalent daily for ≥ 14 d or a cumulative dose > 600 mg of prednisone; receival of biological immune modulators; receival of disease-modifying antirheumatic drugs or other immunosuppressive drugs.

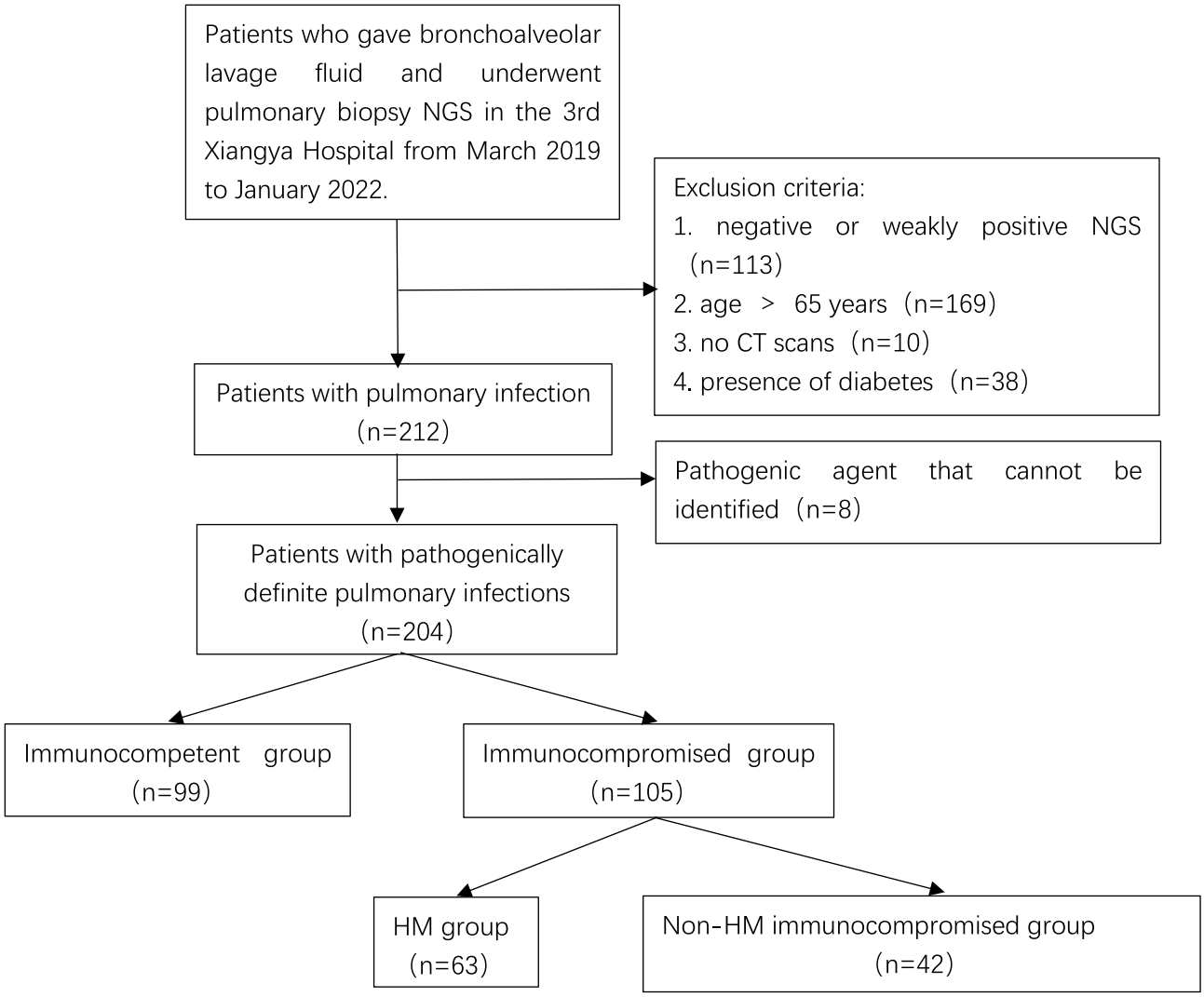

Figure 1 Flowchart of case selection.

Clinical Composite Diagnosis as the Reference Standard

Two intensivists with expertise in the management of infection in HM patients (CQ and TYS) independently reviewed the medical records of all the patients, including clinical presentations, laboratory tests, imaging, microbiological tests (including conventional microbiological tests and NGS), and treatment responses to confirm the diagnosis. Any disagreement between the two intensivists was resolved by in-depth discussion, and a third senior intensivist (LX) was consulted if consensus could not be reached.

CT Examination and Image Analysis

The CT scans were acquired by using the following systems: 1) Philips Brilliance: tube voltage, 120 kVp; tube current, 240 mAs; rotation time, 0.5 s; matrix, 512 × 512; beam collimation, 64×0.625 mm; field of view, 350×350 mm; and slice thickness, 5 mm; 2) GE Revolution: tube voltage, 120 kVp; tube current, 135–240 mAs with automated dose modulation; rotation time, 0.5 s; matrix, 512 × 512; beam collimation, 80×0.625 mm; field of view, 330×330 mm; and slice thickness, 5 mm; 3) Siemens SOMATOM Definition AS+: tube voltage, 120 kVp; tube current, 225 mAs; rotation time, 0.5 s; matrix, 512 × 512; beam collimation, 32×1.2 mm; field of view, 350×350 mm; and slice thickness, 7 mm. The CT scans were obtained at suspended end-inspiratory effort while patients were in the supine position. Two radiologists reviewed all CT images independently (YDD and YZM, with 5 and 8 years of experience in chest imaging, respectively). When

there was a discrepancy between the two radiologists, a third experienced radiologist (LQ, with 20 years of experience in chest imaging) was consulted. The evaluating radiologists were not provided with (or had access to) clinical information. The imaging features that were analyzed include (a) airspace consolidation; (b) GGO; (c) crazy-paving pattern; (d) mosaic pattern (mosaic perfusion); (e) nodules; (f) CT-halo sign; (g) tree-in-bud pattern; (h) bronchial wall thickening; (i) interlobular septal (ILS) thickening; (j) hilar or mediastinal lymph node (LN) enlargement; and (k) pleural effusion. For the CT findings (a), (b), (e), and the overall lesion, the extent of the lesions within the entire lung field was graded subjectively on a five-point scale (0 =0%, 1 = 1–25%, 2 = 26–50%, 3 = 51–75%, and 4 = 76–100%).

Statistical Analysis

Statistical analysis of the data was performed using SPSS software (version 20.0, IBM). Results with P values < 0.05 were considered significant, and all tests were 2-tailed. Categorical variables were compared using the X2 test or Fisher's exact test, while continuous variables were compared with the t test or the nonparametric Mann–Whitney test. Diagnostic performance was evaluated using sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), and 2×2 contingency tables were generated to determine sensitivity, specificity, PPV and NPV. Cohen's kappa was used to measure the concordance between the clinical composite and CT diagnostic criteria.

Results

Comparison of Patient Characteristics and Pathogen Distribution in the Three Groups

A total of 204 patients, including 63 hM patients, 42 non-HM immunocompromised patients and 99 immunocompetent patients, were retrospectively included. The baseline characteristics of the patients and the distribution of pathogens in the patients are shown in Table 1. We have shown more information about the most common specific pathogens in the different pathogen groups in Supplementary Tables 1−1 and 1−2 to review.

The median age (47 years old) of HM patients was significantly younger than that of the other two groups (56 years and 53 years). Cardiovascular disease was more common in the immunocompetent group (p=0.02), and hepatitis was more common in the HM group (p=0.039). The most frequent clinical symptom in the HM patients was fever (76.2%), which was significantly more prevalent than in the immunocompetent group (p=0.022) and the non-HM immunocompromised group (p=0.001). Immunocompromised and non-HM immunocompromised patients were more likely to have pulmonary symptoms (p<0.05). Laboratory results showed that the HM group had lower neutrophil counts (p=0.000), lymphocyte counts (p=0.017), and globulin titers and a higher incidence of neutropenia (p=0.000). The non-HM immunocompromised group had a lower lymphocyte count (p=0.000) and a higher incidence of neutropenia (p=0.000).

Regarding the distribution of pathogens in the three groups, viral, *Pneumocystis jirovecii*, and mixed infections were more frequent in the immunocompromised group than in the immunocompetent group (p<0.05). Among the immunocompromised groups, the pathogens in the HM and non-HM groups were similar, but more viral infections (p=0.09) and fewer bacterial infections (p=0.016) were found in the HM group.

Comparison of CT Findings in Immunocompetent and Immunocompromised Patients with or without HM

The results of the comparisons of CT scan abnormalities between the immunocompetent and immunocompromised groups are summarized in Table 2. The immunocompromised group showed more diverse findings and tended to have a larger extent of pulmonary involvement than the immunocompetent group. The common CT findings in the immunocompromised group were consolidation (59%), GGO (49.5%), nodules (34.3%), interlobular septal thickening (24.8%), and CT-halo sign (21.0%). In the immunocompetent group, the frequent findings were consolidation (77.6%), GGO (37.4%), and nodules (47.5%). The frequency of the CT halo sign was significantly higher and the level of consolidation was significantly lower in the immunocompromised group than in the immunocompetent group. In terms of lesion severity, higher CT severity scores[2–4] were found in the immunocompromised group.

The results of the comparisons of CT scan abnormalities between the HM and non-HM groups are summarized in Supplementary Table 2. Our study suggests that the CT findings in HM patients were generally similar to those in non-

Table 1 Demographic and Baseline Characteristics of Patients

	HM group (n=63)	non-HM group (n=42)	Immunocompetent group (n=99)	p^a	p^b	p^c
Age, mean (range), years	47 (33.5~56.75)	56 (46.5~62.0)	53 (42~59)	0.004	0.158	0.001
Sex, male, n (%)	38 (60.3)	27 (64.3)	65 (65.7)	0.491	0.876	0.682
Comorbidity, n (%)						
Cardiovascular disease	9 (14.3)	7 (16.7)	30 (30.3)	0.020	0.092	0.739
Pulmonary disease	13 (20.6)	10 (23.8)	31 (31.3)	0.136	0.370	0.700
Hepatitis	12 (19.0)	6 (14.3)	8 (8.1)	0.039	0.413	0.526
Digestive diseases	13 (20.6)	9 (21.4)	14 (14.1)	0.280	0.284	0.922
Symptoms (n (%))						
Fever	48 (76.2)	18 (42.9)	58 (58.6)	0.022	0.087	0.001
Cough	34 (54.0)	29 (69.0)	76 (76.8)	0.002	0.336	0.122
Chest pain	2 (3.2)	2 (4.8)	15 (15.2)	0.015	0.083	1.000
Shortness of breath	7 (11.1)	13 (31.0)	26 (26.3)	0.020	0.569	0.011
Hemoptysis	1 (1.6)	2 (4.8)	17 (17.2)	0.002	0.048	0.720
Abnormal breath sounds	22 (34.9)	34 (81.0)	81 (81.8)	0.000	0.904	0.000
Laboratory findings						
Neutrophil count×10^9/L	2.81 (1.48~4.92)	6.77 (3.85–9.22)	5.59 (3.67~8.99)	0.000	0.537	0.000
Lymphocyte count, 10^9/L	0.69 (0.443~1.485)	0.85 (0.55–1.07)	1.16 (0.765~1.615)	0.017	0.000	0.977
Globulin, g/L	25.80 (22.45~32.075)	29.3 (24.1–34.0)	28.7 (24.85~32.25)	0.056	0.882	0.015
Neutropenia, n (%)	19 (30.6)	4 (9.5)	0	0.000	0.000	0.011
Antibiotic (n (%))						
Antibiotics before CT, n (%)	36 (57.1)	11 (26.2)	53 (53.5)	0.653	0.003	0.002
Pathogenic agent (n (%))						
Bacteria	30 (47.6)	30 (71.4)	60 (60.6)	0.105	0.221	0.016
Virus	16 (25.4)	5 (11.9)	2 (2.0)	0.000	0.013	0.090
Fungi	18 (28.6)	10 (23.8)	17 (17.2)	0.086	0.360	0.589
Tuberculosis	7 (11.1)	6 (14.3)	16 (16.2)	0.369	0.779	0.628
Pneumocystis jirovecii	19 (30.2)	12 (28.6)	2 (2.0)	0.000	0.000	0.861
Atypical pathogen*	7 (11.1)	4 (9.5)	15 (15.2)	0.464	0.371	1.000
Polymicrobial	26 (41.3)	20 (47.6)	11 (11.1)	0.000	0.000	0.521

Notes: P^a:P values for HM group and immunocompetent group; P^b:P values for non-HM group and immunocompetent group; P^c:P values for HM group and non-HM group. * Atypical pathogen including M. Pneumoniae, C. Pneumoniae, and Legionella Pneumophila (L. Pneumophila), Rickettsia and Chlamydia psittaci.

HM immunocompromised patients. Despite the high detection rate of GGO in HM patients and the high detection rate of consolidation in non-HM patients, there was no significant difference between the two groups.

Diagnostic Efficacy of CT for Infections with Different Pathogens in Immunocompetent and Immunocompromised Patients with or without HM

The overall diagnostic accuracy was evaluated by assessing the rate at which the CT diagnosis and clinical composite diagnosis matched, and the final results are shown in Table 3 and Table 4. The rate of complete matching was significantly lower ($p<0.001$), and the rates of partial matching and complete mismatching were higher in the immunocompromised group than in the immunocompetent group. The rates of complete matching, partial matching and complete mismatching in the HM group were not significantly different from those in the non-HM immunocompromised group.

The diagnostic efficacy was evaluated by four indicators: sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), as detailed in Table 5 and Table 6. Cohen's kappa was used to analyze the concordance between CT diagnosis and comprehensive clinical diagnosis. Our results suggest that the CT diagnostic efficacy was poorer in the immunocompromised group than in the immunocompetent group, except for in the diagnosis of viral infection and *Pneumocystis jirovecii* infection, and CT showed better diagnostic performance in HM patients than in non-

Table 2 Comparison of CT Findings Between the Immunocompetent and Immunocompromised Groups

	Immunocompromised group (n=105)	Immunocompetent group (n=99)	p value
CT signs (n (%))			
Consolidation	62 (59.0)	76 (77.6)	0.005
GGA	52 (49.5)	37 (37.4)	0.080
Crazy-paving pattern	9 (8.6)	12 (12.1)	0.404
Mosaic pattern	1 (1.0)	1 (1.0)	1.000
Nodules	36 (34.3)	47 (47.5)	0.055
CT-halo sign	22 (21.0)	3 (3.0)	0.000
Tree-in-bud pattern	7 (6.7)	9 (9.1)	0.520
Bronchial wall thickening	5 (4.8)	8 (8.1)	0.332
ILS thickening	26 (24.8)	18 (18.2)	0.253
Hilar or mediastinal LN enlargement	5 (4.8)	9 (9.1)	0.222
The extent of the lesions * (n (%))			
0	0	0	
1	48 (45.7)	63 (63.6)	0.010
2	23 (21.9)	13 (13.1)	0.100
3	17 (16.2)	14 (14.1)	0.130
4	14 (13.3)	9 (9.1)	0.338
2–4	50 (47.6)	36 (36.4)	0.104
missing	3 (4.8)	0	0.057

Note: * The extent of the lesions within the entire lung field was graded subjectively on a five-point scale (0 =0%, 1 = 1–25%, 2 = 26–50%, 3 = 51–75%, and 4 = 76–100%).

Table 3 Comparison of Overall Diagnostic Accuracy Between the Immunocompromised and Immunocompetent Groups

	Immunocompromised group (n=105)	Immunocompetent group (n=99)	p value
Complete match, n(%)	27 (25.7)	50 (50.5)	0.000
Partial match, n(%)	48 (45.7)	31 (31.3)	0.035
Complete mismatch, n(%)	30 (28.6)	18 (18.2)	0.080

Table 4 Comparison of Overall Diagnostic Accuracy Between the HM and Non-HM Groups

	HM group (n=63)	Non-HM group (n=42)	p value
Complete match, n(%)	16 (25.4)	11 (26.2)	0.927
Partial match, n(%)	32 (50.8)	16 (38.1)	0.201
Complete mismatch, n(%)	15 (23.8)	15 (35.7)	0.186

HM patients, except for in the diagnosis of tuberculosis infection. Details of the diagnostic efficacy of CT in the three groups were as follows. In the immunocompetent group, CT had superior efficacy in the diagnosis of bacterial infection and *tuberculosis* infection. In the HM group, we found that CT had superior efficacy in diagnosing fungal infections and *Pneumocystis jirovecii* infections. The sensitivity of CT for the detection of fungal pneumonia was 61.1%, and the specificity was 88.9%. The sensitivity of CT for the detection of *Pneumocystis jirovecii* pneumonia was 42.1%, the specificity was 93.2%, and the positive predictive value in detecting this type of infection was the highest (72.7%). In the

Table 5 Comparison of Diagnostic Efficacy and Concordance Analysis Between the Immunocompromised and Immunocompetent Groups

	Immunocompromised group (n=105)					Immunocompetent group (n=99)				
	Sensitivity %	Specificity %	PPV %	NPV %	Kappa value	Sensitivity %	Specificity %	PPV %	NPV %	Kappa value
Bacteria	71.7	55.6	68.3	59.5	0.275	96.7	43.6	72.5	89.5	0.442
Virus	52.4	75.0	34.4	86.3	0.229	50.0	84.5	6.3	98.8	0.078
Fungi	50.0	83.1	51.9	82.1	0.335	56.3	91.6	56.3	91.6	0.478
Tuberculosis	46.2	95.7	60.0	92.6	0.464	86.7	90.5	61.9	97.4	0.663
Pneumocystis jirovecii	38.7	94.6	75.0	78.7	0.388	0	97.9	0	97.9	0.021
Atypical pathogen	0	100.0	0	89.5	0.000	7.7	98.8	50.0	87.6	0.102
Polymicrobial	43.5	69.5	52.6	61.2	0.132	55.6	67.8	14.7	93.8	0.104

Table 6 Comparison of Diagnostic Efficacy and Concordance Analysis Between the HM and Non-HM Groups

	HM group (n=63)					Non-HM group (n=42)				
	Sensitivity %	Specificity %	PPV %	NPV %	Kappa value	Sensitivity %	Specificity %	PPV %	NPV %	Kappa value
Bacteria	86.7	57.6	65.0	82.6	0.436	56.7	50.0	73.9	31.6	0.057
Virus	62.5	68.1	40.0	84.2	0.258	20.0	83.8	14.3	88.6	0.032
Fungi	61.1	88.9	68.8	85.1	0.517	30.0	75.0	27.3	77.4	0.048
Tuberculosis	28.6	94.6	40.0	91.4	0.265	66.7	97.2	80.0	94.6	0.687
Pneumocystis jirovecii	42.1	93.2	72.7	78.8	0.401	33.3	96.7	80.0	78.4	0.364
Atypical pathogen	0	100.0	0	88.9	0.000	0	100	0	90.5	0.000
Polymicrobial	57.7	64.9	53.6	68.6	0.223	25.0	77.3	50.0	53.1	0.014

non-HM group, the diagnostic method only showed a higher efficacy for the diagnosis of tuberculosis, which had a sensitivity of 66.7%, specificity of 97.2%, PPV of 80.0%, and NPV of 94.6%.

Discussion

CT imaging is well established as a valuable technique for detecting and managing pulmonary infection in immunocompetent patients.[21] Several studies have reported that CT findings are potentially useful for the differential diagnosis of some pulmonary infections in immunocompromised patients.[14] HM patients have various types of immunodeficiencies that differ from those observed in patients with other immunocompromised statuses. Previous studies only focused on documenting CT scan abnormalities in patients with pulmonary infection and HMs.[22,23] To the best of our knowledge, there have been no comparisons of the CT findings in HM patients and other groups with different immune statuses. Moreover, the role of CT in distinguishing the etiologic pathogens of pulmonary infections in HM is unclear. In this study, we sought to compare clinical characteristics and radiologic features between patients with different immune statuses and evaluated the potential application of CT in pathogen identification in HM patients with pulmonary infections.

The clinical manifestations and distribution of pathogens in HM patients were different from those in immunocompetent and non-HM immunocompromised patients. The clinical presentation of pneumonia varies widely, ranging from mild pneumonia characterized by fever and cough to severe pneumonia with sepsis and respiratory failure, and depends on the interaction between the patient's immune system and characteristics and the virulence of the pathogen.[24] Previous studies have described findings of clinical features that have suggested that HM patients with pneumonia present with atypical symptoms.[25] Accordingly, we found that the presence of respiratory symptoms, including cough, chest pain, shortness of breath, hemoptysis, and abnormal breath sounds, was significantly less frequent in HM patients than in

immunocompetent patients. Systemic syndromes such as fever occurred in up to 76.2% of the HM group, which was significantly higher than in the immunocompetent and non-HM immunocompromised groups. The reason for the higher frequency of systemic symptoms in HM patients might have been due to the deficiency in immune surveillance in HM patients, resulting in failure to develop an immune response to infection.[26,27] This deficiency in immune surveillance results in the intrapulmonary or even systemic spread of pathogens. In immunocompetent patients, infection tends to be localized due to phagocytosis by macrophages and granulomatosis formation.[28] Therefore, immunocompetent patients tend to have mild pulmonary dissemination and fewer systemic symptoms. In terms of pathogen distribution, immunocompromised patients are susceptible to opportunistic infections. In our study, viral, *Pneumocystis jirovecii*, and mixed infections were significantly more common in the immunocompromised group than in the immunocompetent group. The incidence of viral infections was significantly higher in HM patients than in non-HM patients. The reason for these findings may relate to the fact that the type and degree of the immune defect dictate the profile of potential opportunistic pathogens.[29] The results of our study showed that the HM group had neutropenia, lymphopenia, and hypoglobulinemia, whereas the non-HM group showed only lymphopenia. In conclusion, early diagnosis and treatment of pulmonary infections in HM patients are often delayed due to the presence of atypical clinical features. These clinical manifestations and characteristics of pathogen distribution should be taken into account when identifying the causative pathogen of pulmonary infection in HM patients.

Regarding the CT findings, our study suggests that the radiological features of pulmonary infection in immunocompromised patients differ from those seen in immunocompetent patients. Among immunocompromised patients, the radiological features of pulmonary infection in HM patients are quite similar to those in non-HM patients. The immunocompromised group showed more diverse findings and tended to have a larger extent of pulmonary involvement than the immunocompetent group. Regarding the predominant CT pattern in patients with each infection, both immunocompetent and immunocompromised patients showed typical consolidation in the presence of bacterial pneumonia, but the incidence of consolidation was higher in the immunocompetent group, which may have been due to the decrease in neutrophil counts and inflammatory exudation in immunocompromised patients. On the other hand, both groups of patients had used antibiotics before CT, which may have caused the lesions to be atypical.[30] Regarding fungal infections, consolidation and nodules were the most frequent radiologic abnormalities in both groups, while the CT halo sign was significantly more common in the immunocompromised group than in the immunocompetent group. The CT halo sign corresponds to ground glass opacity surrounding the circumference of a nodule or mass. Histopathologically, it represents a focus of pulmonary infarction surrounded by alveolar hemorrhage.[31] In neutropenic patients, *Aspergillus* invades small and medium-sized pulmonary vessels, causing thrombosis and subsequent ischemic necrosis of the lung parenchyma.[32] Therefore, the CT halo sign was more common in the immunocompromised group. CT findings were similar in the HM and non-HM patients, but the HM group had more diverse findings and tended to have a larger extent of pulmonary involvement. However, there were differences in the characteristic findings of patients with different infections. The main difference was that the signs were more atypical in the HM group, such as less consolidation in patients with bacterial infections and more consolidation and nodules in patients with fungal infections. The general presence of bacteria is shown as consolidation, and fungal infections typically present as halo signs.[33] Overall, HM patients showed more atypical and diverse CT findings, making identification more difficult. Our findings that the accuracy of CT in the diagnosis of HM patients is significantly lower than that in immunocompetent patients supported this conclusion.

We found that the role of CT in the diagnosis of fungal pneumonia and *Pneumocystis jirovecii* pneumonia in HM patients is promising. In our study, the sensitivity of CT for the detection of fungal pneumonia was 61.1%, and the specificity was 88.9%, which implied that there were fewer false positives and that there was moderate agreement with the comprehensive clinical diagnosis. Yeghen et al and Bernard et al demonstrated that the presence of the CT-halo sign had a high positive predictive value (90%) for presumptive diagnosis of IPA in neutropenic patients with hematological disease.[31] Therefore, antifungal therapies could be actively initiated when CT suggests the presence of fungal infections. For patients with suspected fungal infections, when the CT finding is atypical, the CT results should be reviewed dynamically and combined with the results of Aspergillus galactomannan (GM) and[1–3]-β-D-glucan (βDG) analyses.[34] Similarly, the sensitivity of CT for the detection of *Pneumocystis jirovecii* pneumonia was 42.1%, the specificity was 93.2%, and the positive predictive value was the highest (72.7%) in the detection of all pathogens. This finding indicated

a high true positive rate for the detection of *Pneumocystis jirovecii* pneumonia. Previous studies also suggest that CT has better efficacy for diagnosing infections with *Pneumocystis jirovecii* in immunocompromised patients.[14] Therefore, treatment can be initiated when CT suggests *Pneumocystis jirovecii* infection. Other detection methods, such as NGS, should be taken into account when CT results are negative and other antibiotic treatments elicit no response. In addition, for the diagnosis of infections with pathogens such as bacteria, viruses, and tuberculosis, the combination of other conventional microbiological test results can be considered to improve the sensitivity and specificity.

Our research also has certain limitations. First, this study was conducted in a single center, with a small sample size and potential selection bias. But this is also the case in clinical practice. Second, this study was retrospective in nature, therefore, the CT protocols and diagnostic procedures used to evaluate the included participants were not uniform. A prospective clinical trial is sufficient to overcome these limitations. Third, patients aged >65 years were excluded from the study, which may affect the generalizability of the findings. Lastly, there are many polymicrobial infections, which may affect the reliability of CT sign recognition. Both the comprehensive clinical diagnosis and CT diagnosis are subjective. The reliability of the diagnosis may be controversial. However, all discrepancies were reviewed by a senior clinician, so consistency was ensured. It is worth clarifying that although our inclusion period partially overlapped with the COVID-19 pandemic, none of the patients included in this article were infected with the COVID-19. Thus we consider the influence of the COVID-19 on this article to be minor.

In conclusion, HM patients with pulmonary infections have atypical clinical symptoms and multiple pathogens, and the diagnostic efficiency of CT is lower in these patients.

Abbreviations

CT, computed tomography; HM, hematological malignancies; GGO, ground-glass opacities; NGS, next-generation sequencing; HIV, human immunodeficiency virus; GM, galactomannan; βDG, (1-3)-β-D-glucan.

Acknowledgment

We would like to thank Dr. Qi Liang for his support in the implementation of the study, the interpretation of the imaging results, the revision of the manuscript. We also would like to thank Lingyan Yan for her help in drafting, revising or critically reviewing the article.

Disclosure

The authors declare that they have no competing interests in this work.

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