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The epidemiological characteristics of invasive pulmonary aspergillosis and risk factors for treatment failure: a retrospective study

Yun Wang[1†], Xiaoman Cui[1†], Ruixin Tian[1] and Ping Wang[1*]

Abstract

Objective The incidence of invasive pulmonary aspergillosis (IPA) is increasing gradually. This study analysed the epidemiological characteristics and prognostic factors of patients with IPA and explored the risk factors affecting prognosis.

Materials and methods The clinical data and treatment of 92 patients with IPA were retrospectively analysed, and the patients were followed for 12 weeks. Patients were divided into an effective treatment group and an ineffective treatment group, and the risk factors affecting prognosis were discussed.

Results A total of 92 patients met the IPA inclusion criteria, and the most common genus of *Aspergillus* was *Aspergillus fumigatus*. The incidence of IPA was highest in patients with malignant tumours. IPA often coexisted with infections caused by other pathogens. We divided the patients into an effective treatment group and an ineffective treatment group according to prognosis. Compared with those in the effective treatment group, the procalcitonin (PCT) level, lactate dehydrogenase-to-albumin ratio (LDH/ALB) and neutrophil-to-lymphocyte ratio (NLR) in the ineffective treatment group were greater, the serum albumin level was lower, and the imaging findings revealed less nodules and bronchial wall thickening ($P < 0.05$). Among these factors, a decrease in the serum albumin concentration, an increase in the PCT level, coinfection and less bronchial wall thickening on imaging were independent risk factors for aspergillosis treatment failure.

Conclusion A decreased albumin level, an elevated PCT level, coinfection, and less bronchial wall thickening were independent risk factors for treatment failure in patients with IPA. Attention should be given to the albumin level, coinfection status and imaging findings of patients.

Keywords Invasive pulmonary aspergillosis, Prognosis, Treatment, Risk factors, Clinical presentation

†Yun Wang, Xiaoman Cui these authors contributed equally to this work.

*Correspondence:
Ping Wang
17201367@hebmu.edu.cn
[1]Department of Respiratory Medicine, The Fourth Hospital of Hebei Medical University, Shijiazhuang 050011, China

Introduction

Aspergillus is widely found in nature and spreads through spores. *Aspergillus* infections in the lungs often cause Aspergillus pneumonia, which is the second most common fungal infection in hospitalized patients. Pulmonary aspergillosis (PA) is caused mainly by inhalation of *Aspergillus* and infection with *Aspergillus flavus* and *Aspergillus niger*. PA mainly includes invasive pulmonary aspergillosis (IPA), subacute invasive aspergillosis (SAIA) and chronic pulmonary aspergillosis (CPA). In recent years, reports of PA have increased in patients without neutropenia, including in patients with bronchiectasis, tuberculosis, chronic obstructive pulmonary disease (COPD), diabetes, chronic kidney disease, and cancer and those using glucocorticoids or immunosuppressants [1–3]. The clinical symptoms and imaging findings of early PA are not typical, the diagnosis is difficult, and the misdiagnosis rate and mortality rate are high. Once symptoms appear, they develop into a more severe form of invasive pulmonary aspergillosis. Owing to the lack of specificity in the clinical manifestations of the disease, diagnosis is often delayed. In addition, owing to the presence of multiple virulence factors and complex pathogenic mechanisms of *Aspergillus*, the prognosis of *Aspergillus* is poor, and the mortality rate is as high as 30-95% [4, 5].

The latest European Research and Treatment of Cancer Tissue and Mycosis Research Group (EORTC/MSG) guidelines suggest that in addition to the traditional galactomannan antigen (GM) test for *Aspergillus* culture, blood and bronchoalveolar lavage fluid (BALF) and specific polymerase chain reaction (PCR) tests can also be used for *Aspergillus* detection to further improve the diagnosis rate [6]. The improvement of detection methods has continuously increased the clinical diagnosis rate of IPA and can also enable patients to receive early treatment.

We included patients who were diagnosed with IPA in our department over the past 6 years. The most common clinical features of IPA were analysed for early detection and diagnosis. To further evaluate the prognosis of IPA and explore the risk factors affecting prognosis, more powerful data for clinical treatment are needed. The included patients were all treated with voriconazole, efficacy was evaluated after 12 weeks of treatment, and risk factors affecting prognosis were also identified. The main objective was to determine these prognostic risk factors to achieve good treatment outcomes for patients.

Data and methods

Patient population

Data from patients diagnosed with invasive pulmonary aspergillosis (IPA) at the Fourth Hospital of Hebei Medical University from January 1, 2018, to December 31, 2023, were retrospectively analysed. The patient selection criteria were as follows [5]: (1) age ≥ 18 years; (2) clinical manifestations of respiratory infectious diseases such as fever, cough, sputum, and dyspnoea; (3) one or more of the following chest CT findings: solid lesions or nodules with or without cavity formation, air crescent or halo signs, multiple patchy shadows in the airways and lungs, solid shadows, or tree bud signs; and (4) positive histopathology, a positive sputum or bronchoalveolar lavage fluid (BALF) culture, at least one positive serum galactomannan (GM) test, at least one positive BALF GM test, or BALF-based metagenomic next-generation sequencing (mNGS) analysis showing ≥ 1 *Aspergillus* reading according to the laboratory testing criteria recommended by the European Research and Treatment of Cancer Tissue and Mycosis Research Group (EORTC/MSG) [6]. The patient exclusion criterion was as follows: individuals with incomplete medical records. This study was approved by the Ethics Review Committee of the Fourth Hospital of Hebei Medical University.

In this study, two experienced physicians were required to evaluate and identify patients who met the study inclusion criteria. Patient data were collected from medical records and electronic databases. We collected baseline data, such as age, sex, smoking history, clinical symptoms, and medical history, at the time of IPA diagnosis. At the same time, the patients' relevant examination data were collected, including the results of lung histological examinations, bacterial and fungal cultures of sputum or BALF, metagenomic next-generation sequencing (mNGS) detection of BALF, 1-3-β-D-glucan (G) detection, and GM detection. The white blood cell count, neutrophil count, lymphocyte count, albumin level, C-reactive protein (CRP) level, and procalcitonin (PCT) level were also measured.

Follow-up and grouping of treatment effects

All enrolled patients were treated with voriconazole, and efficacy was evaluated after 12 weeks of treatment. The efficacy evaluation criteria were based on the Mycoses Study Group and European Organization for Research and Treatment of Cancer Consensus Criteria [7]: (1) Complete remission (CR): After treatment, the patient's symptoms and signs of the disease were completely relieved, the microbial results revealed that the pathogenic bacteria at the infection site had completely disappeared, and the abnormal CT findings disappeared or only the imaging findings of scars existed; (2) Partial remission (PR): The symptoms and signs of the disease improved after treatment, and imaging revealed that the lung lesions had decreased by ≥ 25%; alternatively, imaging revealed that the lung lesions had decreased by less than 25%, and the symptoms and signs were completely relieved; (3) Stable disease (SD): After treatment, the

symptoms of the disease improved but were not very significant, and the microbiological results still showed mycelium; and (4) Progressive disease (PD): Symptoms did not improve and even worsened. In this study, patients were divided into an effective treatment group and an ineffective treatment group according to short-term efficacy (Fig. 1). The effective treatment group included patients with CR and PR, and the ineffective treatment group included patients with SD and PD. Baseline data from both groups were then analysed to identify independent risk factors for poor outcomes in the ineffective group.

Statistical analysis

All the statistical data were evaluated via SPSS 27.0 software. Normally distributed data are reported as the means ± standard deviations; skewed data are expressed as medians and quartile ranges. The chi-square test was used for comparisons of independent samples. All risk factors were analysed via single factor analysis. The factors with $P<0.2$ were subsequently included in the binary logistic regression model to determine the independent risk factors affecting prognosis. The Hosmer–Lemeshow statistical test was used to test the goodness of fit. $p<0.05$ was considered statistically significant.

Results

Patient characteristics

A total of 92 patients were evaluated according to the IPA diagnostic criteria. The median age of the patients was 63 years. Sixty-five (70.65%) patients were male, and 54 (58.70%) patients had a history of smoking. All patients had clinical manifestations of pneumonia, such as cough or sputum (75 patients, 81.52%), dyspnoea (36 patients, 39.13%), fever (34 patients, 36.96%), haemoptysis (4 patients, 4.35%), and chest pain (6 patients, 6.52%). The main CT imaging changes in patients with IPA were consolidation, patchy shadows, nodules, thickening of the bronchial wall, and lumen or crescent signs. The data are shown in Table 1.

Blood tests revealed that the mean leukocyte count of patients with IPA was 8.04 (5.87, 10.54)×10^9/L, the mean neutrophil count was 6.13 (4.10, 8.91)×10^9/L, the mean neutrophil count was 76.28 ± 14.71%, the mean eosinophil count was 0.02 (0.01, 0.05)×10^9/L, the mean CRP level was 23.13 (5.55, 117.10) mg/L, the mean procalcitonin level was 0.08 (0.04, 0.24) mg/L, the mean albumin level was 34.10 (30.63, 38.78) g/L, the mean white globule ratio was 1.34 (0.99, 1.58) %, the mean CRP level was 23.13 (5.55, 117.10) mg/L, the mean procalcitonin level was 0.08 (0.04, 0.24) mg/L, and the mean albumin level was 34.10 (30.63, 38.78) g/L. The mean lactate dehydrogenase level was 202.00 (168.70, 269.00) U/L, G test of serum was 54.19 (15.33, 111.73) pg/ml, GM test of serum was 0.34 (0.23, 0.67) μg/L. There were 6 (6.52%) cases of

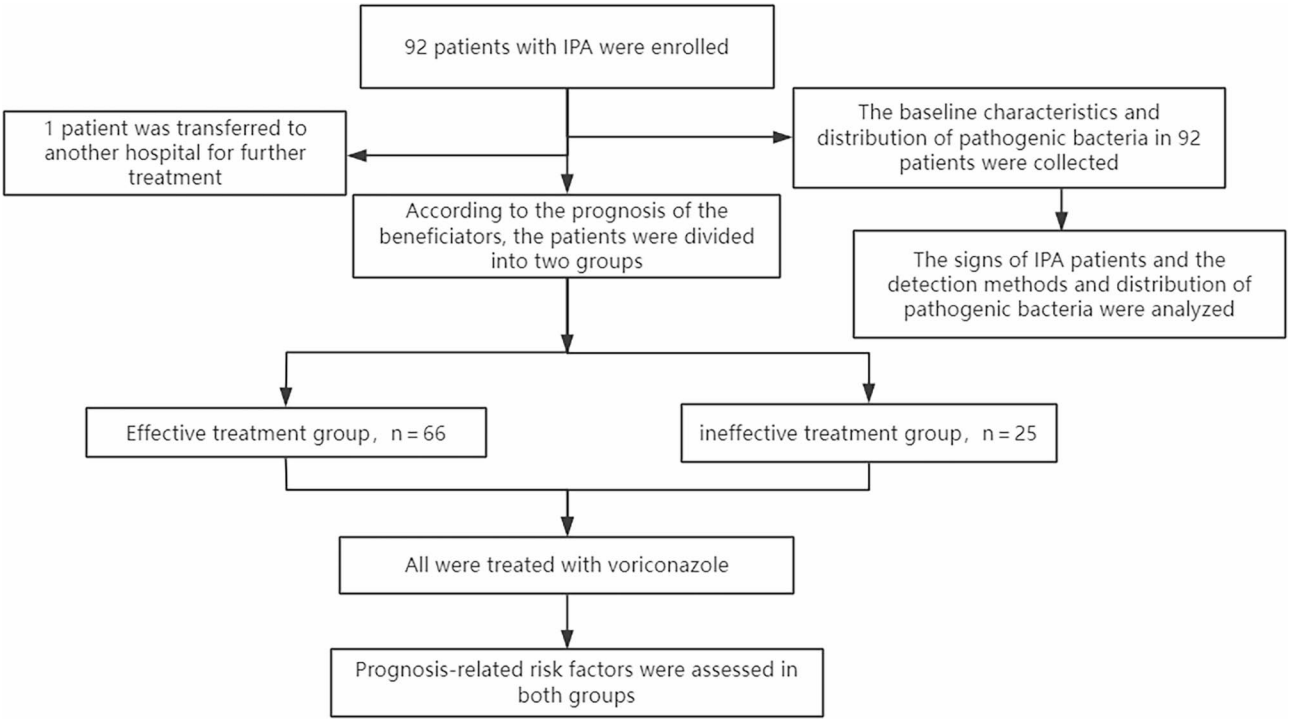

Fig. 1 The flowchart of the study

Table 1 Baseline characteristics of patients with IPA

Items	Baseline level	Results
Characteristic	Age (years)	63.00(54.00, 68.75)
	Sex (male) (n (%))	65(70.65%)
	Smoking history (n (%))	54(58.70%)
	Cough and/or expectoration (n (%))	75(81.52%)
	Breathe hard (n (%))	36(39.13%)
	Fever (n (%))	34(36.96%)
	Hemoptysis (n (%))	4(4.35%)
	Chest pain (n (%))	6(6.52%)
Imaging changes	Nodule (n (%))	80(86.96%)
	Plaque exudation and consolidation (n (%))	75(81.52%)
	Cavity or air crescent sign (n (%))	31(33.70%)
	Tube wall thickening (n (%))	25(27.17%)
	Ground glass shadow (n (%))	13(14.13%)
Blood test	White blood cell count ($\times 10^9$/L)	8.04(5.87, 10.54)
	Neutrophil count ($\times 10^9$/L)	6.13(4.10, 8.91)
	Ratio of neutrophils (%)	76.28 ± 14.71
	C-reactive protein (CRP) (mg/L)	23.13(5.55, 117.10)
	Eosinophil ($\times 10^9$/L)	0.02(0.01, 0.05)
	Lymphocyte ($\times 10^9$/L)	1.07(0.74, 1.66)
	G test (pg/ml)	54.19(15.33, 111.73)
	GM test (ug/L)	0.34(0.23, 0.67)
	Lactate dehydrogenase (U/L)	202.00(168.70, 269.00)
	Procalcitonin (ng/ml)	0.08(0.04, 0.24)
	Albumin (g/L)	34.10(30.63, 38.78)
	White-sphere ratio	1.34(0.99, 1.58)
Underlying disease	Malignant tumor (n (%))	44(47.83%)
	Hypertension (n (%))	34(36.96%)
	Diabetes (n (%))	20(21.74%)
	Chronic liver disease (n (%))	18 (19.57%)
	Chronic obstructive pulmonary disease (COPD) (n (%))	16(17.39%)
	Coronary heart disease (n (%))	10(10.87%)
	Chronic kidney disease (n (%))	6(6.52%)
	Obsolete pulmonary tuberculosis (n (%))	6(6.52%)
	Bronchiectasia (n (%))	4(4.35%)
	Interstitial pneumonia (n (%))	3 (3.26%)
Other factors	Received radiotherapy and chemotherapy in the past month	17(27.42%)
	Received immunotherapy in the past month	9(14.52%)
	Use of glucocorticoids within 14 days of diagnosis	8(12.90%)

old pulmonary tuberculosis, 16 (17.39%) cases of chronic obstructive pulmonary disease, 4 (4.35%) cases of bronchiectasis, 3 (3.26%) cases of interstitial pneumonia, 44 (47.83%) cases of malignant tumour, 20 (21.74%) cases of diabetes mellitus, 34 (36.96%) cases of hypertension, 10 (10.87%) cases of coronary heart disease, 6 (6.52%) cases of chronic kidney disease, and 18 (19.57%) cases of chronic liver disease. Eight patients (12.90%) used glucocorticoids within 14 days of diagnosis, 17 patients (27.42%) had received radiotherapy and chemotherapy in the past month, and 9 patients (14.52%) had received immunotherapy in the past month. The clinical characteristics of the patients are shown in Table 1.

Confirmation of detection methods for *aspergillus* and distribution of pathogens causing coinfection

The diagnosis of *Aspergillus* infection mainly relies on histopathology, sputum or BALF culture, BALF mNGS, and GM detection. Through the histopathological examination of 2 patients, sputum culture of 32 patients, BALF culture of 7 patients, body fluid culture of 37 patients, lavage fluid mNGS of 39 patients, serum GM experimental diagnosis of 21 patients, and lavage fluid GM experimental results of 7 patients (Fig. 2), we found that the main types of *Aspergillus* in patients with IPA were *Aspergillus fumigatus* in 49 patients, *Aspergillus flavus* in 17 patients, and *Aspergillus niger* in 5 patients. Patients with IPA were infected with other pathogens, including

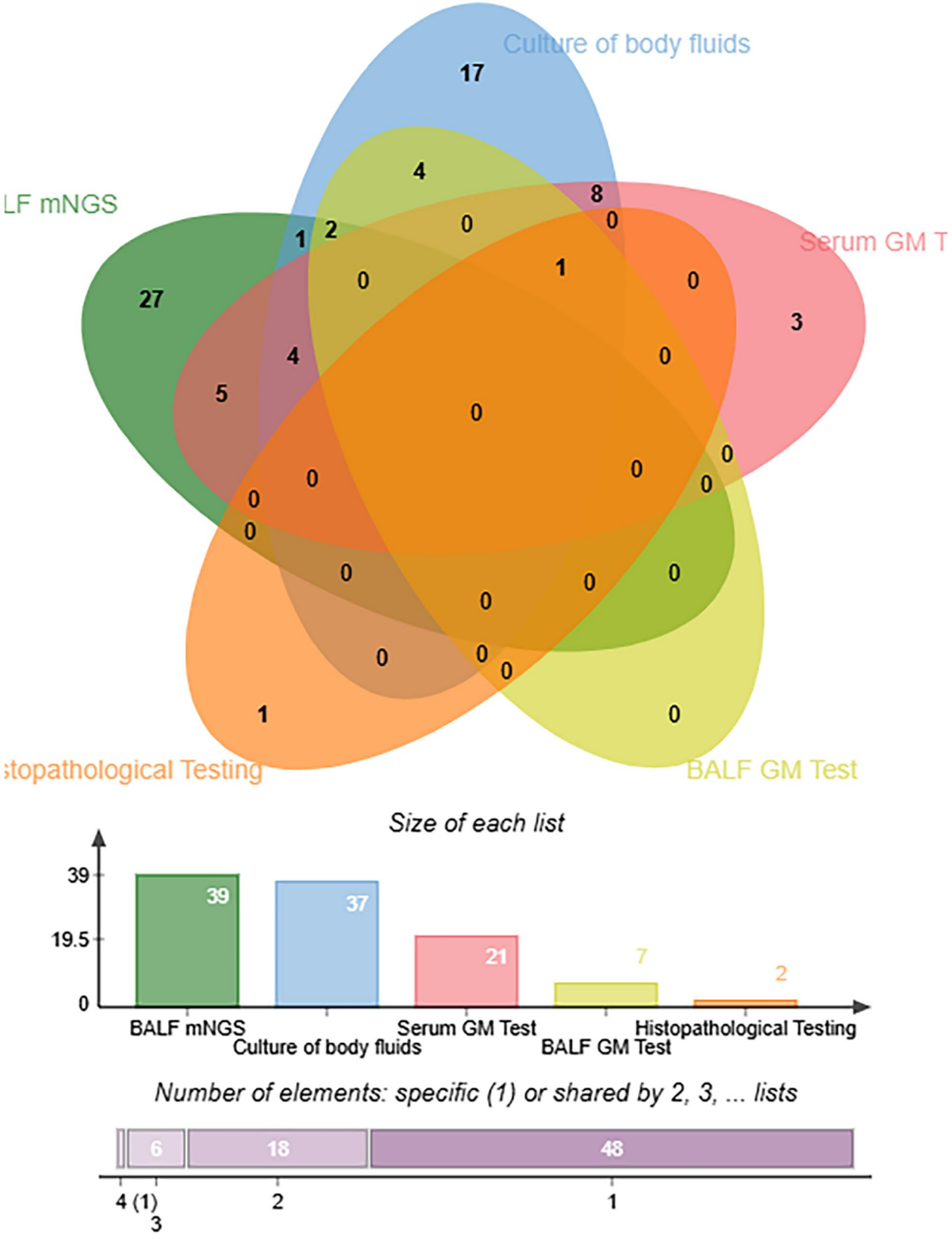

Fig. 2 Detection methods of IPA. Note: Veen diagram in patients with IPA. The abscissa represents the detection results of different methods. The ordinate represents the number of *Aspergillus* detected. Abbreviation: IPA, invasive pulmonary aspergillosis; GM, galactomannan antigen; BALF, bronchoalveolar lavage fluid; mNGS, metagenomic next-generation sequencing

Candida in 12 patients, *Cryptococcus* in 1 patient, *Pseudomonas aeruginosa* in 3 patients, *Klebsiella pneumoniae* in 2 patients, *Haemophilus influenzae* in 4 patients, *Staphylococcus aureus* in 5 patients, *Streptococcus pneumoniae* in 2 patients, *EB virus* in 2 patients, and *herpes virus in* 8 patients (Fig. 3). The data are shown in Table 2.

After a patient was diagnosed with IPA, voriconazole was given as the preferred treatment option. Follow-up CT imaging was performed during the initial stage of treatment. After 4 weeks of treatment, treatment status was evaluated, and the patients were divided into an effective treatment group and an ineffective treatment group on the basis of clinical symptoms and imaging changes. One patient was transferred to another hospital for the treatment of other primary diseases; therefore, the patients were divided into an effective treatment group including 66 patients and an ineffective treatment group including 25 patients (Fig. 4).

Single-factor analysis of prognostic factors in patients with IPA

The PCT level, serum albumin level, LDH/ALB, NLR, presence of coinfection, and imaging findings of nodules or bronchial wall thickening in patients with IPA were related to the prognosis of IPA ($P<0.05$), whereas the other indicators were not related to the prognosis of IPA ($P>0.05$). The results are shown in Table 3.

Multivariate analysis of prognostic factors in IPA patients

With the prognosis of IPA as the dependent variable (effective=1, ineffective=2), the factors with $P<0.2$ in the univariate analysis were used as independent variables in the multivariate logistic regression analysis. The results revealed that the serum albumin level, PCT level, the presence of coinfection, and the presence of bronchial wall thickening on imaging were independent risk factors affecting the prognosis of IPA ($P<0.05$). The results are shown in Table 4.

Discussion

Invasive pulmonary aspergillosis (IA) is a serious opportunistic infection in the human body. Under normal circumstances, *Aspergillus* usually colonizes the respiratory tract and airways. Owing to the body's own immune mechanism, *Aspergillus* usually does not cause disease [8]. However, when the body's immune function is impaired, it cannot prevent the growth of *Aspergillus* spores and hyphae, leading to the growth of *Aspergillus* in the lungs, which can even cause tissue damage and vascular invasion. Eventually, *Aspergillus* hyphae spread throughout the body through the bloodstream, causing multisystem infections [5, 9]. With the abuse of antibiotics and hormones, the use of antitumour drugs and immunosuppressants, and the development of organ transplantation, studies have shown that the incidence rate and prevalence rate of IPA are increasing annually. Owing to the lack of specificity in the clinical manifestations of IPA, the common symptoms are cough, expectoration, chest tightness, and shortness of breath [3, 10], which is the same as our conclusions. *Aspergillus* affects mainly patients with impaired immune function, such as those with long-term neutropenia and cancer [4]. In this study, the majority of patients with IPA had malignant tumours and required antitumour treatment, such as chemotherapy, radiotherapy, immunotherapy, and other related therapies, which can reduce immune function and lead to IPA. Many studies have shown that patients with cancer, chronic lung disease, diabetes and other basic diseases constitute the main population with IPA. Invasive aspergillosis is also common in solid organ transplant recipients, patients with renal failure and patients with other complications [10, 11]. Since 2019, there have been increasing reports of COVID-19-associated pulmonary aspergillosis (CAPA), a fungal co-infection associated with increased morbidity and mortality, with the emergence of *coronavirus disease 2019* (COVID-19) [12]. Patients with *influenza viruses* are also susceptible to IPA due to the reduced ability of neutrophils and monocytes to kill and eliminate Aspergillus conidia and other mechanisms [13].

In this research group, the most common genus of *Aspergillus* was *Aspergillus fumigatus*, followed by *Aspergillus flavus* and *Aspergillus niger*. This finding is consistent with the research of SArunmozhi Balajee et al. [14]. IPA coinfection is a common complication, and when patients are infected with *Aspergillus*, they may also have other infections, with bacteria being the main pathogen causing coinfection [3]. Research has revealed that viral infections also play a certain role in coinfection by IPA and other pathogens, such as *cytomegalovirus* and *influenza virus* [15].

The disease manifestations of invasive aspergillosis are usually nonspecific and vary from patient to patient. Invasive aspergillosis begins in the lungs and then spreads through the bloodstream, causing infections in multiple organs. Infected patients may experience symptoms such as coughing, sputum production, fever, and chills [3, 10, 18]. This study revealed that patients with IPA often present with clinical manifestations of pneumonia, such as cough, sputum production, difficulty breathing, and fever. If patients experience chest pain or haemoptysis, invasion of the pulmonary vascular system may have occurred. The typical imaging manifestations of IPA are scattered nodules, halo signs, consolidation, cavities, air crescents, etc [16–18]. , but they are also related to the location of the lesion and the source of pathogenic bacteria. The EORTC/MSG standard considers air

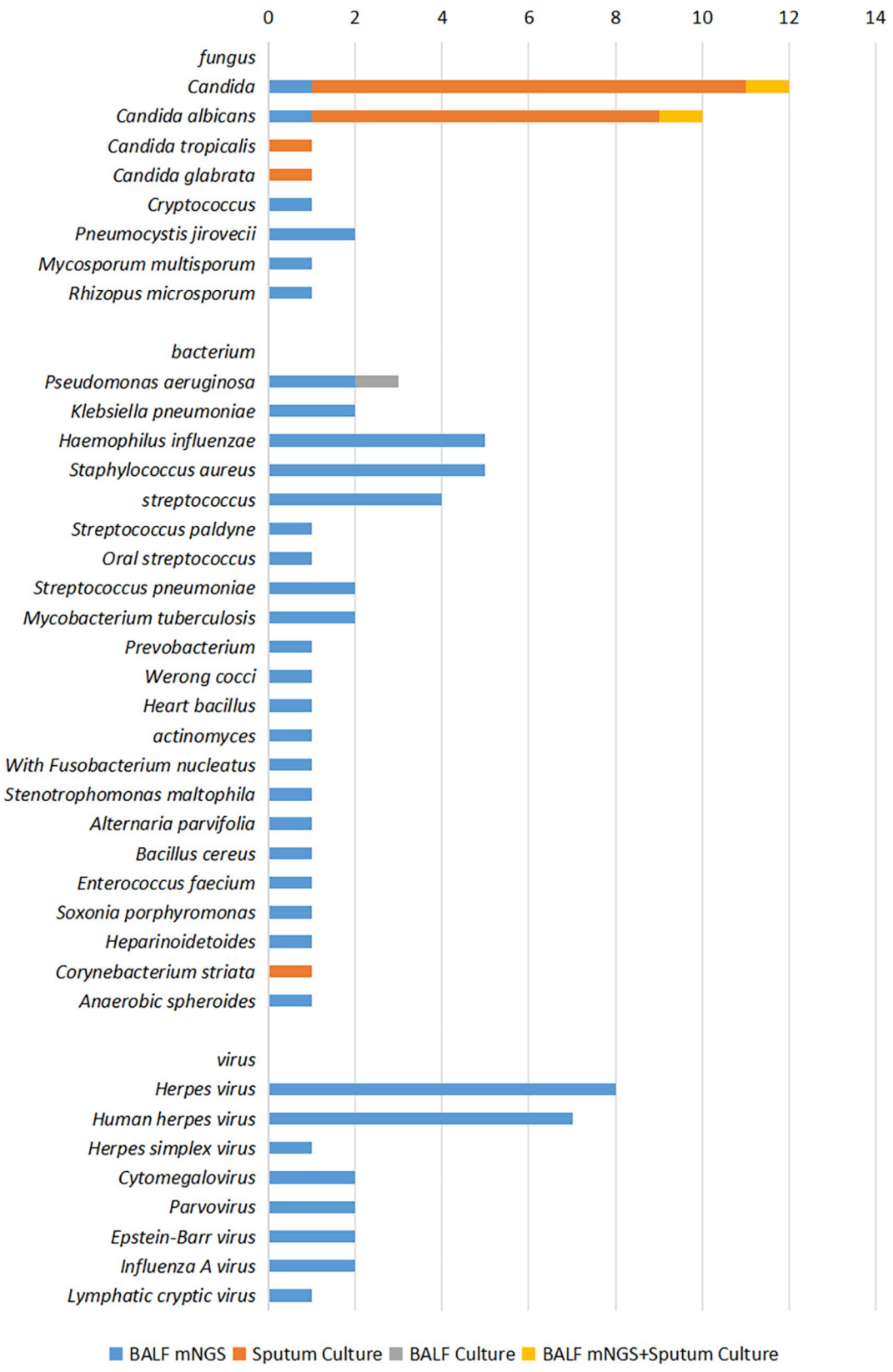

Fig. 3 Distribution of IPA patients combined with other pathogens. Note: The bar chart of patients infected with bacteria, fungi, and viruses. Different colors represent the detection results of different methods. The abscissa represents the number of pathogens detected. The ordinate represents the detection of different pathogens. "+" for the same checkout. Abbreviation: IPA, invasive pulmonary aspergillosis; BALF, bronchoalveolar lavage fluid; mNGS, metagenomic next-generation sequencing

Table 2 Detection methods and pathogenic bacteria

Pathogen types	BALF mNGS (+)	Sputum culture (+)	BALF culture (+)	Histopathological examination (+)	Serum GM test (+)	BALF GM test (+)
Aspergillus fungus(n)	39	32	7	2	21	7
Aspergillus fumigatus(n)	25	27	4	1	0	0
Aspergillus flavus(n)	5	6	2	0	0	0
Aspergillus niger(n)	1	3	1	0	0	0
Grey green Aspergillus(n)	2	0	0	0	0	0
Centennial Orchid Aspergillus(n)	1	0	0	0	0	0
Aspergillus nidulans(n)	0	0	0	1	0	0
Unclassified Aspergillus types(n)	7	1	0	0	0	0
Candida(n)	2	11	0	0	0	0
Candida albicans(n)	2	9	0	0	0	0
Cryptococcus(n)	1	0	0	0	0	0
Haemophilus influenzae(n)	5	0	0	0	0	0
Staphylococcus aureus(n)	5	0	0	0	0	0
Pseudomonas aeruginosa(n)	2	0	1	0	0	0
Klebsiella pneumoniae(n)	2	0	0	0	0	0
Streptococcus pneumoniae(n)	2	0	0	0	0	0
Human herpesvirus(n)	7	0	0	0	0	0
EB virus(n)	2	0	0	0	0	0
Influenza A virus(n)	2	0	0	0	0	0
Cytomegalovirus(n)	2	0	0	0	0	0
Parvovirus(n)	2	0	0	0	0	0

Note: "+" means test positive

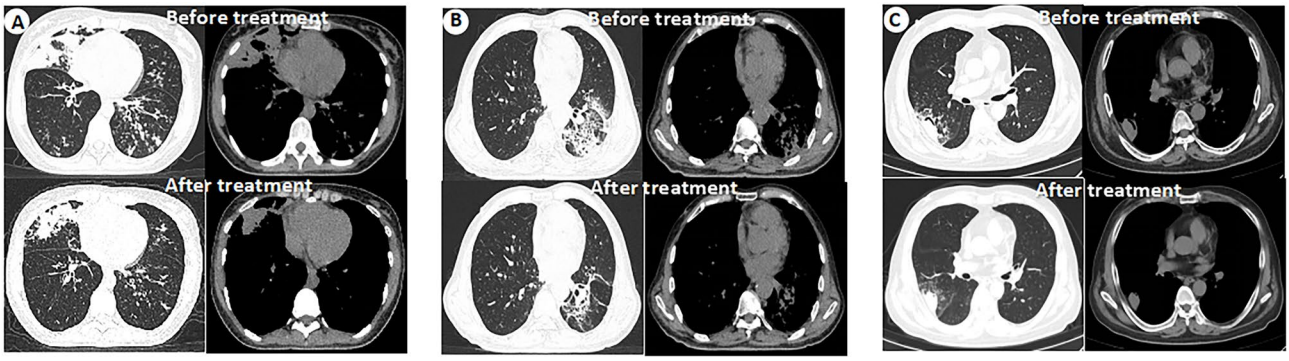

Fig. 4 The images of computed tomography for the patients in effective treatment group. **A**, **B** and **C** represent the imaging changes of the same computed tomography plane in three patients before and after treatment with voriconazole. It can be seen that the IPA images have improved after treatment. Abbreviation: IPA, invasive pulmonary aspergillosis

crescents, halos, and cavities as relatively typical early manifestations of IPA [6].

However, some typical CT manifestations of IPA are transient, most commonly occurring in the first week after symptom onset, and are also related to the degree of immune suppression [19]. Both immunocompromised and nonimmunocompromised patients were included in this study, and most of the patients did not seek medical attention in a timely manner, had unclear diagnoses, and did not receive antifungal treatment in a timely manner, leading to disease progression and spread, resulting in diverse CT manifestations of the lungs, as well as signs of airway invasion and vascular infiltration. Studies have shown that bronchial wall thickening is more common in nonimmunocompromised patients [20], while the results of this study suggest that bronchial wall thickening is associated with prognosis. Neofytos D et al. reported that the nonspecific clinical features and diagnostic difficulties of patients with IPA, especially those with nonneutropenia, are likely to lead to poor treatment effects and delayed treatment [21]. Fran ç oisDanion et al. reported that, owing to new risk factors and the lack of completely specific imaging findings, missed diagnoses are likely to occur [22]. Owing to the high mortality rate among

Table 3 Univariate analysis of factors affecting the prognosis of IPA patients

Items	Factor	Effective treatment group, $n=66$	Ineffective treatment group, $n=25$	*P*
Basic features	Age (year)	61.36 ± 13.21	57.68 ± 15.96	0.237
	Smoke (n)	37	16	0.495
	Gender (Male, n)	45	19	0.469
Blood testing	G test (pg/ml)	53.08(19.3,106.10)	40.95(11.78,116.58)	0.768
	GM test (ug/L)	0.32(0.22,0.76)	0.36(0.27,0.54)	0.564
	White blood cell($\times10^9$/L)	8.09(5.82,9.93)	8.47(6.14,12.44)	0.356
	Neutrophils ($\times10^9$/L)	6.09(3.80,8.03)	7.59(4.56,10.99)	0.066
	Eosinophils ($\times10^9$/L)	0.02(0.01,0.06)	0.02(0.01,0.04)	0.509
	Lymphocyte ($\times10^9$/L)	1.19(0.75,1.66)	0.94(0.72,1.41)	0.163
	NLR	4.84(2.57,9.14)	10.54(4.63,15.50)	0.012
	LDH (U/L)	204.50(168.18,262.75)	216.00(167.00,641.00)	0.219
	PCT (ng/dl)	6.00(4.00,10.00)	16.00(6.00,32.00)	0.001
	Albumin (g/L)	36.00 ± 5.72	32.30 ± 4.36	0.005
	White ball ratio	1.38(1.00,1.60)	1.22(0.91,1.43)	0.276
	LDH/ALB	6.07(4.72,7.39)	7.59(5.85,21.13)	0.001
	CAR	0.40(0.11,2.26)	1.18(0.31,4.56)	0.059
Primary disease	Malignant tumor (n)	33	10	0.396
	Hypertension (n)	24	8	0.699
	Lung cancer (n)	23	6	0.324
	Diabetes (n)	16	3	0.202
	COPD (n)	11	5	0.711
	Pulmonary tuberculosis (n)	5	2	0.946
Characteristics of chest CT imaging	Tubercle (n)	59	17	0.015
	Patchy exudation and consolidation (n)	54	16	0.073
	Hollow or air crescent symbol (n)	23	8	0.799
	Thickening of bronchial wall (n)	22	2	0.015
	Ground glass opacity (n)	10	2	0.371
Other factors	Mixed bacterial infection (n)	29	15	0.084
	Received radiotherapy and chemotherapy in the past month (n)	13	4	0.688
	Received immunotherapy in the past month (n)	7	2	0.680
	Use of glucocorticoids in the past 14 days (n)	5	3	0.508

Table 4 Multivariate analysis of factors affecting the prognosis of IPA patients

Items	B	*P*	OR	95% CI of OR	
				lower limit	upper limit
Neutrophils($\times10^9$/L)	0.083	0.475	1.087	0.865	1.366
Lymphocyte($\times10^9$/L)	0.290	0.733	1.336	0.252	7.077
NLR	0.106	0.288	1.112	0.914	1.352
ALB(g/L)	-0.270	0.003	0.763	0.638	0.914
LDH/ALB	0.223	0.093	1.249	0.964	1.619
CAR	-0.206	0.385	0.814	0.511	1.296
PCT(ng/dl)	0.093	0.037	1.097	1.005	1.197
Merge infection(n)	6.670	0.018	788.177	3.145	197531.123
Patchy exudation and consolidation(n)	-0.896	0.575	0.408	0.018	9.313
Tubercle(n)	-1.245	0.549	0.288	0.005	16.944
Thickening of bronchial wall(n)	-2.921	0.037	0.054	0.003	0.838

patients with IPA, timely and accurate diagnoses should be made. We also urgently need effective antifungal treatment to reduce the IPA incidence and mortality rates.

IPA diagnostic methods include pathological examination, imaging examination, microbiological examination, serum antigen antibody detection, and molecular biology methods [6, 23]. The gold standard for diagnosing IPA is pathological examination, which is an invasive procedure that is difficult to perform. Only 2 cases were confirmed in this study. Imaging examinations have poor sensitivity and are prone to missed diagnoses [6]. Fungal culture is a commonly used diagnostic method, but owing to its long cultivation time, it is usually not used for early diagnosis. The GM test is recommended as an early and rapid diagnostic method for IPA, and the selection of GM test samples mainly includes serum and BALF, with BALF having higher accuracy [24]. This study also included results obtained via these two detection methods as diagnostic criteria. mNGS has shown great potential in identifying pathogens and can provide new evidence for the diagnosis of IPA [25]. Some scholars have applied mNGS to detect viruses, bacteria, fungi, etc., in various host samples for rapid diagnosis. A multicentre study has shown that mNGS has excellent performance and reliability in the diagnosis of pulmonary infections [26], and there is also evidence that BALF mNGS may be a supplementary option for diagnosing IPA [27]. This study used mainly sputum culture, lavage fluid culture, BALF mNGS, serum GM test, BALF GM test, and histopathological examination results as the diagnostic criteria for diagnosis.

Currently, the treatment options for IPA include drug therapy, local treatment and surgical treatment, the most common of which is drug therapy, including new antimicrobial drugs, combination therapy and immunomodulatory therapy, among which there are currently recognized three classes of antifungal drugs are used for IPA treatment: azoles, polyenes, and echinocandins. Among them, triazole drugs, including voriconazole, posaconazole, and esoconazole, are recommended as first-line antifungal treatments for IPA [23, 28, 29] and have better therapeutic effects than amphotericin B [30]. In this study, the first-line treatment regimen of voriconazole was the first choice. Studies have shown that the relief rate of IPA symptoms is between 33% and 75%, which is similar to the results of this study [31].

A previous report revealed that the inflammatory process can inhibit or stimulate tumour growth and that the activity of inflammatory cells and the levels of inflammatory regulatory factors can affect the progression of cancer [32]. CRP is an acute phase protein produced by the liver and is a recognized biomarker for systemic inflammation and the acute phase response. CRP levels can continue to increase with the progression of infection and worsening tissue damage during the acute phase but lack specificity. PCT is a prohormone of calcitonin, which is usually secreted by thyroid C cells. Under normal circumstances, PCT is rarely secreted from cells, and the blood concentration of PCT is extremely low. However, when bacterial infection occurs, a series of molecular events lead to a rapid increase in the blood PCT concentration, which can increase over 1000 times [33, 34]. A series of studies have shown that PCT rapidly increases only in patients with infectious bacteria; therefore, PCT is commonly used to identify bacterial and viral infections [34]. PCT is more sensitive and specific for the diagnosis and evaluation of prognosis in infected patients [35, 36]. This study confirmed that PCT has greater sensitivity in patients with fungal infections.

Lactate dehydrogenase (LDH) is a key enzyme in glycolysis that promotes the conversion of pyruvate to lactate. Numerous studies have shown that LDH is a nonspecific indicator and that its elevation exists in many clinical diseases, such as cancer, severe infections, and sepsis [37–40]. Albumin is produced by the liver, and its levels decrease in patients with various diseases, including malnutrition, inflammation, and kidney disease. It usually affects the body's nutritional and immune status and is therefore often used as a nutritional and inflammatory response indicator [41]. One study revealed that hypoalbuminaemia is not the cause of the increased incidence or mortality rate but can indicate prognosis [42]. In recent years, the ratio of LDH to albumin (LDH/ALB) has become a new inflammatory biomarker. Although the LDH/ALB ratio is used mainly in the study of malignant tumours [43], recent evidence suggests that it is also associated with the prognosis of infection [44, 45]. LDH/ALB indeed has high diagnostic value and performs well in various combinations of inflammatory biomarkers. The ratio of C-reactive protein (CRP) to the albumin receptor (CAR) is an emerging biomarker that reflects systemic inflammation and nutritional status, and studies suggest that its elevation is significantly correlated with the prognosis of various malignant tumours. Similarly, studies have shown that the CAR can be used to assess the progression and severity of diseases [46, 47]. This may be related to the fact that when the body is infected, the immune system is activated, CRP levels remain elevated, and ALB levels tend to decrease. The results of this study revealed that the CAR had no statistically significant effect on prognosis, but the CAR in the disease progression group was greater than that in the effective treatment group.

Neutrophils are the most abundant white blood cells in the human body and play a crucial role in host immune defence. When inflammation occurs, many neutrophils are released into the bloodstream, leading to an increase in the proportion of neutrophils. In contrast, lymphocytes are also essential cellular components. When

pathogens enter the human body, the number of lymphocytes significantly decreases. In this study, there was no statistically significant difference in the lymphocyte count. Studies have shown that the lymphocyte count is associated with the prognosis of pneumonia [48], which differs from the findings of this study and may be due to limited statistical data. The neutrophil-to-lymphocyte (NLR) reflects systemic inflammation in cancer patients and the ability of the immune system to attack malignant cells. Numerous studies have also shown that an elevated NLR is associated with the prognosis of cancer and can be used as a prognostic marker for various malignant tumours [49, 50], which is consistent with the results of this study. Studies have shown that elevated NLR is associated with the prognosis of patients and can be used as a prognostic marker for a variety of diseases.

Further analysis of laboratory indicators in patients with IPA revealed that albumin and PCT levels, the presence of coinfections, and imaging findings of bronchial wall thickening affect prognosis in immunocompromised patients.

However, this study also has certain limitations. First, single-centre retrospective studies inevitably have the option of being inexpensive, without the use of dynamic monitoring and predictive indicators and a small sample size. Second, the observation time was relatively short, and long-term observation may have greater guiding significance for clinical practice. In the future, we will continue to collect data and conduct dynamic monitoring in our work to provide more comprehensive and reliable data for clinical practice.

Conclusions

A decreased albumin level, an increased PCT level, an increased incidence of concurrent infections, and thickening of the bronchial wall on imaging are associated with poor prognosis in patients with invasive pulmonary aspergillosis and can serve as predictive indicators, providing a basis for clinical diagnosis and treatment.

Abbreviations

IPA	Invasive pulmonary Aspergillosis
PA	Pulmonary aspergillosis
PCT	Procalcitonin
LDH/ALB	Lactate dehydrogenase to albumin ratio
NLR	Neutrophil-to-lymphocyte ratio
SAIA	Subacute invasive aspergillosis
CPA	Chronic pulmonary aspergillosis
COVID-19	Associated pulmonary aspergillosis (CAPA)
COPD	Chronic obstructive pulmonary disease
EORTC/MSG	The European Research and Treatment of Cancer Tissue and Mycosis Research Group
COVID-19	Coronavirus disease 2019
GM	Galactomannan antigen
BALF	Bronchoalveolar lavage fluid
PCR	Polymerase chain reaction
mNGS	Metagenomic next-generation sequencing
G	1-3-β-D-glucan
CRP	C-reactive protein
CR	Complete remission
PR	Partial remission
SD	Stable disease
PD	Progression disease

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Author contributions

Ping Wang contributed to the study concept and design. Yun Wang, Xiaoman Cui Ruixin Tian and Ruixin Tian contributed to data acquisition and analysis, and interpretation of the data. The primary literature search was conducted and the manuscript was drafted by Yun Wang and Xiaoman Cui.Yun Wang, Xiaoman Cui, and Ping Wang critically reviewed and revised the manuscript for intellectual content. All authors reviewed the final version of the manuscript prior to submission and all accept responsibility for the integrity of the research process and findings. All authors read and approved the final manuscript.

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Data availability

Data is provided within the manuscript. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the Institutional Review board at the Ethics Review Committee of the Fourth Hospital of Hebei Medical University (No. 2023KS206). The Ethics Review Committee of the Fourth Hospital of Hebei Medical University waived the requirement for written informed consent owing to the retrospective nature of the study; participants were also given the option to opt-out.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Clinical trial number

Not applicable.

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