Impact on hospitalization and infection patterns of advanced lung cancer with lower respiratory tract infections: Targeted therapy vs. chemoradiotherapy

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Received October 3, 2023; Accepted January 25, 2024

DOI: 10.3892/ol.2024.14287

Abstract. Lung cancer is a prevalent and highly lethal disease often complicated by lower respiratory tract infections. Microbial patterns in these infections vary based on treatment modalities. The present study explored the impact of lung cancer treatments on pathogens and clinical characteristics in the presence of lower respiratory tract infections to inform antimicrobial drug selection. A retrospective analysis was performed that included data from 93 patients diagnosed with advanced lung cancer and lower respiratory tract infections between January 2019 and December 2021. Patients were divided into the targeted therapy and chemoradiotherapy groups. Clinical, nutritional, biochemical, infection and pathogenetic indicators were compared. Of the 93 cases, 24 were in the targeted therapy group and 69 were in the chemoradiotherapy group. Pathological type and hospitalization duration differed significantly ($P<0.05$), but age, sex, smoking history, alcohol consumption and underlying diseases did not ($P>0.05$). Lymphocyte counts differed ($P<0.05$), while body mass index, albumin, hemoglobin, alanine aminotransferase and creatinine levels, erythrocyte sedimentation rate, hypersensitive C-reactive protein and procalcitonin levels, and the percentage of neutrophils did not ($P>0.05$). Pathogenetic testing was negative in 15 patients and positive in 78 patients, with Gram-negative bacteria (61.77%), fungi (17.65%) and viruses (11.76%) predominant in the targeted therapy group. In the chemoradiotherapy group, Gram-negative bacteria (47.46%), fungi (28.81%) and viruses (16.95%) were also more prevalent. *Candida albicans* was the most frequent fungal infection in both groups, and mixed infections were common (50% in targeted therapy and 73.92% in chemoradiotherapy). The chemoradiotherapy group had significantly more mixed infections ($P<0.05$). Overall, common pathogens in both groups included Gram-negative bacteria, fungi and viruses. Chemoradiotherapy patients experienced longer hospital stays and a higher incidence of mixed infections, predominantly involving Gram-negative bacteria and fungi. The results provide valuable insights into the rational selection of empirical antibiotics and antifungals for critically ill patients with lung cancer and lower respiratory tract infections in targeted therapy or chemoradiotherapy.

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Key words: virus, bacteria, fungi, organ function, lymphocyte

Introduction

Cancer remains a global health challenge, posing a formidable obstacle to increasing life expectancy. Among the malignant tumors, lung cancer stands out as the foremost cause of mortality, responsible for 18% of cases, and ranks second in incidence worldwide, with 11.4% of cases (1).

The elevated mortality associated with lung cancer can be attributed to its inherent high malignancy rate. Additionally, the occurrence of complications further accelerates disease progression and contributes to the mortality rate. In individuals with cancer, infection represents the most prevalent complication (2). Lower respiratory tract infections occur with increased frequency in patients with lung cancer, primarily due to factors such as airway obstruction, mucosal surface damage and treatment-related interventions such as radiotherapy and chemotherapy (3).

Treatment strategies for lung cancer, depending on the disease phase, histology, genetic alterations and patient conditions, encompass surgical intervention, radiotherapy, chemotherapy, immunotherapy and targeted therapy, either as standalone therapies or in combination (4,5). Patients with early stage non-small cell lung cancer (NSCLC) who are in otherwise good physical health often benefit from a curative surgical resection (stage I, II and IIIA) (5). However, surgical treatment becomes unfeasible for patients with advanced lung cancer.

Several studies have identified the causative agents of lung infections induced by chemotherapy or radiotherapy, including bacteria (most notably *Pseudomonas aeruginosa*, *Pseudomonas maltophilia* and *Nocardia* spp), viruses (respiratory syncytial virus, influenza viruses A and B, and cytomegalovirus) and fungi (*Aspergillus* and *Fusarium*) (6,7). Nevertheless, a comparative analysis of pathogens and associated risk factors between the chemoradiotherapy and targeted therapy groups is conspicuously lacking.

The present study therefore centers on elucidating the impact of different lung cancer treatment modalities on pathogenic profiles and distinct clinical characteristics in the context of lower respiratory tract infections. Through a retrospective analysis, the clinical and pathogenic attributes of lung cancer coexisting with lower respiratory tract infections is examined in the targeted therapy and chemoradiotherapy cohorts. The insights gleaned from this investigation have the potential to furnish a theoretical foundation for clinical interventions and play a pivotal role in guiding the judicious selection of antibacterial agents.

Materials and methods

Study population. The present retrospective analysis included 93 patients who were diagnosed with advanced lung cancer and concurrent lower respiratory tract infection between January 1, 2019, and December 1, 2021. All patients were included from the North China University of Science and Technology Affiliated Hospital (Tangshan, China). Patients were categorized into two groups based on their tumor treatment protocols: The targeted therapy group, which received targeted lung cancer drugs exclusively, and the chemoradiotherapy group, consisting of patients treated with chemotherapy, radiotherapy or a combination of both, with or without concurrent targeted therapy. Tumor-Node-Metastasis staging (8th edition) was employed to determine lung cancer staging (8).

Inclusion criteria. The inclusion criteria for the study were as follows: i) An age ≥18 years; ii) a confirmed pathological diagnosis of advanced lung cancer; iii) patients who received appropriate antitumor therapy, including radiotherapy, chemotherapy and targeted agents, but not immunotherapy; and iv) the availability of complete clinical information.

Exclusion criteria. The exclusion criteria for the study were as follows: i) The presence of autoimmune or immunodeficiency diseases; ii) the coexistence of other systemic infections; iii) concurrent systemic tumors; iv) unclear pathogenetic test results; and v) the presence of severe complications and syndromes.

Clinical indicators and pathogenetic features. Clinical information encompassed age, sex, smoking and drinking history, pathological type, underlying diseases and the duration of hospitalization. Nutritional and Biochemical indicators included body mass index (BMI), hemoglobin (Hb) level, lymphocyte count, and albumin (ALB), alanine aminotransferase (ALT) and creatinine (Cr) levels. Infection indicators were erythrocyte sedimentation rate (ESR), hypersensitive C-reactive protein (hs-CRP), procalcitonin (PCT) and the percentage of neutrophils (NEU%). Pathogenetic indicators consisted of serology, general bacterial culture identification results and fungal culture identification results, as analyzed using the Guide to Utilization of the Microbiology Laboratory for Diagnosis of Infectious Diseases for specimen retention, submission and interpretation (9). All indicators and data were collected from hospital records.

Statistical analysis. Data analysis was performed using SPSS 22.0 statistical software (IBM Corp.). Normally distributed data are presented as mean ± standard deviation, and non-normally distributed data are expressed as median (interquartile range). The unpaired t-test was employed for between-group comparisons when data adhered to the normal distribution, while the Mann-Whitney rank sum test was utilized for non-normally distributed data. Count data are presented as n (%), and intergroup comparisons were conducted using the χ^2 test or Fisher's exact test. $P<0.05$ was used to indicate a statistically significant difference.

Results

General data comparison between groups. In the present study, a total of 93 cases were included, with 24 in the targeted therapy group and 69 in the chemoradiotherapy group. In the targeted therapy group, the median length of hospitalization was 8.5 days (interquartile range, 5.25-14 days), while in the chemoradiotherapy group it was 12 days (interquartile range, 8-19 days). Significant differences were observed between the groups in terms of length of hospitalization ($P<0.05$) (Fig. 1A). Notably, the targeted therapy group exhibited a shorter hospital stay compared with the chemoradiotherapy group. All patients treated with targeted therapy had NSCLC, while 18 patients with chemoradiotherapy had SCLC and 51 patients had NSCLC ($P<0.05$) (Table I). Conversely, no statistically significant differences were identified between the two groups with regard to age, sex, BMI, alcohol consumption and underlying diseases ($P>0.05$) (Table I).

Nutritional and biochemical indicator comparisons. A significant difference was observed between the two groups in terms of lymphocyte count ($P<0.05$). Specifically, the targeted therapy group displayed a lymphocyte count of $1.86x10^9$/l, while the chemoradiotherapy group had a count of $0.99x10^9$/l. Conversely, there were no statistically significant differences between the two groups in terms of Hb, ALB, ALT and Cr ($P>0.05$) (Table II).

Infection indicator comparisons. No statistically significant differences were detected between the two groups for ESR, hs-CRP, PCT and NEU% ($P>0.05$) (Table III).

Pathogenetic indicator comparisons. In the present study, pathogenetic testing was conducted on a total of 93 patients, with 15 testing negative and 78 testing positive through pathogenetic culture or serum antibody testing. The targeted therapy group exhibited 5 cases with unspecified pathogens, while the chemoradiotherapy group had 10 such cases. Overall, a total of 152 pathogens were identified in both groups.

Table I. Clinical characteristics.

Characteristic	Targeted therapy (n=24)	Chemoradiotherapy (n=69)	P-value
Mean age ± SD, years	65.21±6.21	64.88±8.23	0.86
Sex, n (%)			
Male	16 (66.67)	50 (72.46)	0.59
Female	8 (33.33)	19 (27.54)	0.59
Mean BMI ± SD	22.22±3.34	23.58±3.30	0.09
Positive history of alcohol consumption, n (%)	6 (25.00)	29 (42.03)	0.14
Pathology, n (%)			
SCLC	0	18 (26.09)	0.01
NSCLC	24 (100.00)	51 (73.91)	0.01
Underlying diseases, n (%)			
Coronary heart disease	8 (33.33)	14 (20.29)	0.19
COPD	2 (8.33)	4 (5.80)	1.00
Cerebrovascular disease	4 (16.67)	17 (24.64)	0.60
Diabetes	5 (20.83)	14 (20.29)	0.96
Hypertensive disease	11 (45.83)	26 (37.68)	0.48

BMI, body mass index; NSCLC, non-small cell lung cancer; COPD, chronic obstructive pulmonary disease.

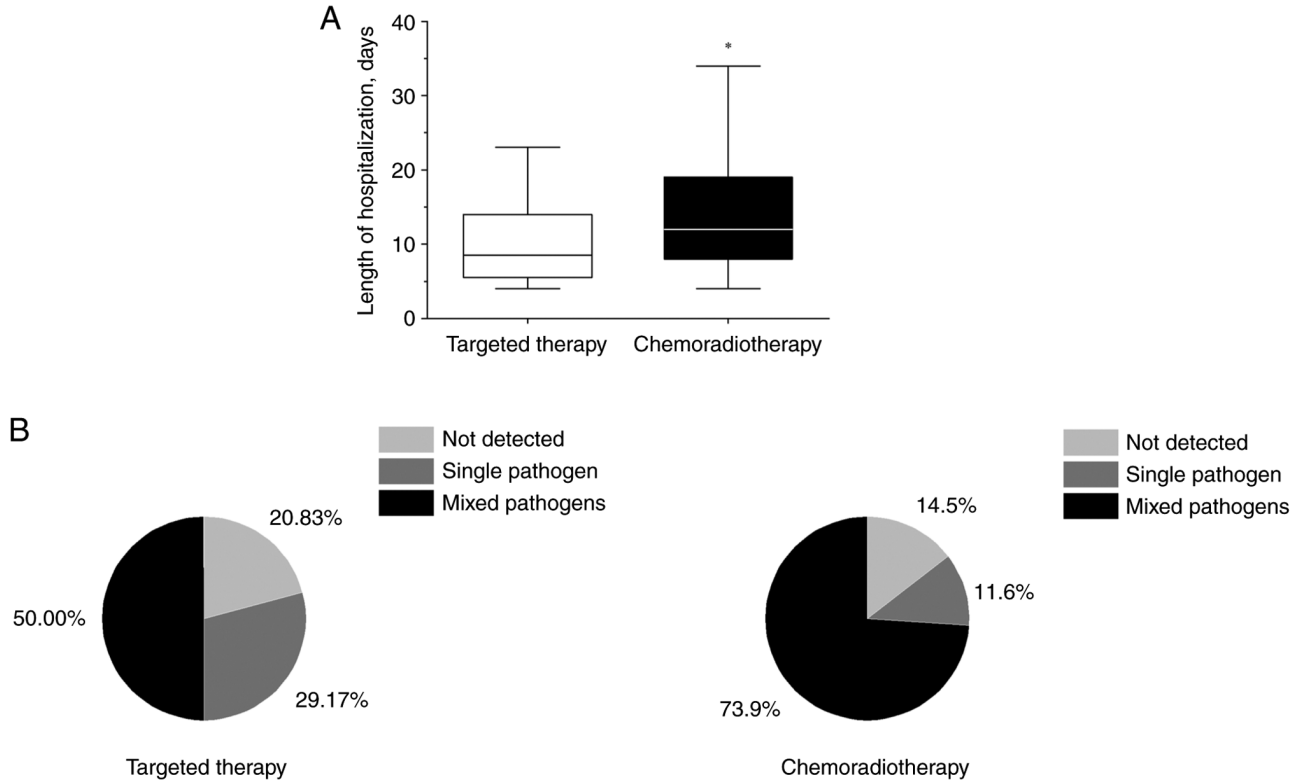

Figure 1. (A) Length of hospitalization comparing between the targeted therapy and chemoradiotherapy groups. Data are presented as the median and interquartile range. *P<0.05 vs. targeted therapy. (B) Pathological categories comparison between the targeted therapy and chemoradiotherapy groups. Data are presented as percentages. Intergroup comparisons were performed using the χ^2 test, revealing statistically significant differences for single pathogens and mixed pathogens (P<0.05).

Significant differences were observed between the two groups regarding fungal infections (P<0.05), with a higher prevalence in the chemoradiotherapy group compared with that in the targeted therapy group (Table IV). However, no statistically significant differences were noted between the two groups in terms of viruses, Gram-negative

Table II. Biochemical variables.

Variable	Targeted therapy (n=24)	Chemoradiotherapy (n=69)	P-value
Hb, g/l	124.75±17.23	130.13±17.02	0.19
Lymphocyte count ($x10^9$/l)	1.86 (1.00-2.41)	0.99 (0.62-1.96)	0.04
ALB, g/l	37.94±5.80	39.40±4.63	0.23
ALT, U/l	15 (12.25-33.75)	17 (13.00-29.00)	0.70
Cr, μmol/l	62.5 (44.00-79.25)	62 (50.00-78.5)	0.95

Data are presented as mean ± standard deviation or median (interquartile range). Hb, hemoglobin; ALB, albumin; ALT, alanine aminotransferase; Cr, creatinine.

Table III. Infection indicators.

Indicator	Targeted therapy (n=24)	Chemoradiotherapy (n=69)	P-value
ESR	80 (25.50-94.00)	55 (32.50-82.00)	0.27
hs-CRP	47.71 (10.56-75.20)	21.40 (6.10-74.30)	0.46
PCT	0.08 (0.06-0.15)	0.05 (0.03-0.10)	0.08
NEU%	76.85 (64.60-84.73)	69.3 (61.40-77.55)	0.10

Data are presented as median (interquartile range). ESR, erythrocyte sedimentation rate; hs-CRP, hypersensitive C-reactive protein; PCT, procalcitonin; NEU%, percentage of neutrophils.

bacteria, Gram-positive bacteria, atypical pathogens and *Mycobacterium tuberculosis*/non-tuberculous mycobacteria (P>0.05) (Table IV). In the targeted therapy group, 20.83% of results were recorded as not detected, a single pathogen accounted for 29.17% and mixed pathogens accounted for 50%. In the chemoradiotherapy group, 14.49% of results were recorded as not detected, while a single pathogen accounted for 14.49% and mixed pathogens accounted for 73.92%. There were more single-pathogen infections in the targeted therapy group than in the chemoradiotherapy group (P<0.05), while the chemoradiotherapy group exhibited a higher incidence of mixed-pathogen infections than the targeted therapy group (P<0.05) (Fig. 1B).

Discussion

Lung cancer is broadly categorized into SCLC and NSCLC (10). The treatment approaches for these two categories differ (11,12). Among the various treatment modalities for advanced lung cancer, targeted therapy and chemoradiotherapy are the most frequently employed. Targeted drugs for cancer treatment can be classified into two main categories (13): The first category involves targeted antitumor angiogenesis, which includes monoclonal antibodies against vascular endothelial growth factor (VEGF) and endothelial inhibitors. These drugs function by impeding tumor neo-angiogenesis, thereby inhibiting the growth, proliferation and metastasis of tumor cells. An example of a VEGF-targeted therapy is bevacizumab. While studies have generally demonstrated the safety of bevacizumab combination therapy, it is essential to note potential adverse events such as high blood pressure or pulmonary hemorrhage (14). Bevacizumab reduces VEGF levels, affecting endothelial repair and potentially weakening blood vessels, thereby increasing the risk of rupture (15). The second category comprises small molecules that act on the tumor cell signal transduction pathway by inhibiting key components, effectively halting the proliferation of tumor cells. Pathway-targeted therapy is particularly suitable for patients with driver mutations and is associated with minimal adverse effects, although it may be prone to secondary resistance. In stage IV NSCLC, chemotherapy is commonly employed. Chemotherapeutic drugs leverage the higher mitogenic activity of tumor cells compared with host cells, rendering them more toxic to tumors. The choice of medication is determined based on the patient's physical condition, as indicated by their performance status scores (16). However, chemotherapy is associated with a relatively short survival period, and patients treated with platinum-containing two-drug chemotherapy typically survive for only 8-10 months. Cross-resistance is also a consideration in this context (16). Radiotherapy constitutes a crucial treatment modality for NSCLC, applicable as adjuvant or neoadjuvant therapy across all stages of the disease (17).

Patients with lung cancer who have compromised immune systems are susceptible to lower respiratory tract infections. Thus, understanding the pathogenic and clinical aspects of these infections is crucial for guiding the selection of appropriate antimicrobial agents.

The present study identified a significant disparity in case types between the two groups. Specifically, the targeted therapy group exclusively comprised NSCLC cases, whereas the chemoradiotherapy group consisted of 51 NSCLC cases and 18 SCLC cases. This aligns with the existing literature indicating that NSCLC is more prevalent than SCLC (18). It is important to note that targeted therapy primarily focuses

Table IV. Pathogenic characteristics.

Characteristic	Targeted therapy	Chemoradiotherapy	P-value
Total pathogens, n	34	118	
Virus, n (%)	4 (11.76)	20 (16.95)	0.36
Respiratory syncytial viruses	1 (2.94)	5 (4.24)	0.96
Parainfluenza viruses	0 (0.00)	1 (0.85)	>0.99
A and B viruses	2 (5.88)	2 (1.69)	0.59
Cytomegaloviruses	1 (2.94)	0 (0.00)	0.26
Epstein-barr virus	0 (0.00)	6 (5.08)	0.33
Coxsackie virus	0 (0.00)	4 (3.39)	0.60
Others	0 (0.00)	2 (1.69)	>0.99
Gram-negative, n (%)	21 (61.77)	56 (47.46)	0.69
Klebsiella pneumoniae	6 (17.65)	21 (17.80)	0.61
Pseudomonas aeruginosa	3 (8.82)	8 (6.78)	>0.99
Acinetobacter baumannii	4 (11.76)	9 (7.63)	0.92
Haemophilus influenzae	3 (8.82)	4 (3.39)	0.53
Haemophilus parainfluenzae	1 (2.94)	3 (2.54)	>0.99
Escherichia coli	2 (5.88)	6 (5.08)	>0.99
Others	2 (5.88)	5 (4.24)	>0.99
Gram-positive, n (%)	2 (5.88)	2 (1.69)	0.59
Streptococcus pneumoniae	0 (0.00)	0 (0.00)	
Staphylococcus aureus	2 (5.88)	0 (0.00)	0.07
Staphylococcus haemolyticus	0 (0.00)	2 (1.69)	>0.99
Others	0 (0.00)	0 (0.00)	
Atypical pathogen	1 (2.94)	5 (4.24)	0.96
Mycoplasma	1 (2.94)	5 (4.24)	0.96
Others	0 (0.00)	0 (0.00)	
Mycobacterium tuberculosis/NTM	0 (0.00)	1 (0.85)	>0.99
Fungi, n (%)	6 (17.65)	34 (28.81)	0.04
Candida albicans	4 (11.76)	23 (19.49)	0.20
Aspergillus	1 (2.94)	4 (3.39)	>0.99
Penicillium	1 (2.94)	4 (3.39)	>0.99
Others	0 (0.00)	3 (2.54)	0.57

NTM, non-tuberculous mycobacteria.

on NSCLC due to genetic mutations and rearrangements (18). Consequently, the SCLC patients in the present study did not receive targeted therapies.

Additionally, a statistically significant difference in lymphocyte count was observed between the two groups, with the chemoradiotherapy group exhibiting lower lymphocyte levels. Lymphocyte levels are indicative of systemic immune status and inflammatory response, with reduced levels signifying immunodeficiency (19,20).

Cytotoxic chemotherapeutic agents have the capacity to directly or indirectly eliminate immune effector cells. Direct impairment of immune cells by chemotherapy results in a reduction of overall immune function (21). The abrupt destruction of a substantial number of tumor cells induced by chemotherapy leads to the release of significant amounts of tumor antigens. This release, in turn, causes damage to effector T cells. Radiotherapy, on the other hand, has the capability to target and eliminate various immune cells in the body, including $CD4^+$ and $CD8^+$ cells, contributing to a decline in overall immune function. Within the tumor microenvironment, $CD8^+$ T cells play a pivotal role in antitumor defense, while $CD4^+$ T cells impede blood vessel formation, hindering tumor progression (22,23). Before the initiation of radiotherapy and chemotherapy, absolute levels of natural killer (NK) cells and intracellular interferon-γ levels are notably higher (24). Therefore, managing advanced lung cancer concurrent with lower respiratory tract infections is paramount for improving the patient prognosis.

The present analysis of pathogenetic characteristics revealed noteworthy differences between the two groups. Notably, the pathogens causing lower respiratory tract infections in patients with advanced lung cancer differed significantly from those found in community-acquired pneumonia. Both groups exhibited a high rate of Gram-negative

bacterial infections, necessitating empirical Gram-negative bacterial coverage in antibiotic selection. *Klebsiella pneumoniae* was the most commonly isolated pathogen in both groups and is a leading cause of sepsis, bacteremia and abscess formation (25). *Acinetobacter baumannii* was the second most common pathogen, with a higher detection rate in the targeted therapy group than the chemoradiotherapy group. Previous studies have associated *Acinetobacter baumannii* with radiation pneumonitis in patients with cancer (26), and its presence indicates an increased likelihood of mortality (27).

In addition, in the present study, both groups showed a high detection rate of fungi, with significantly more cases in the chemoradiotherapy group. *Candida albicans* was the most frequent fungal infection in both groups, particularly in immunocompromised hosts. Factors contributing to fungal infections in lung cancer patients include underlying diseases, immunodeficiency, prolonged use of broad-spectrum antibiotics and glucocorticoid therapy during chemotherapy (28). Therefore, clinicians should consider antifungal therapy when patients with advanced lung cancer and lower respiratory tract infections do not respond to broad-spectrum antibiotics.

Viral infections were less common in the present study, likely due to the timeframe of the study, which did not encompass the COVID-19 pandemic (29). However, it is important to note that COVID-19 infections among patients with lung cancer have increased significantly since 2023 (30). Respiratory syncytial viruses, influenza A and B viruses, and epstein-barr virus were the predominant viruses detected in the present study. Awareness of viral infections, particularly COVID-19, is crucial in patients with advanced lung cancer and lower respiratory tract infections.

Mixed infections were prevalent in both groups in the present study, consistent with previous findings by Qiao *et al* (31). These polymicrobial infections significantly impact quality of life and lead to severe morbidity. The primary pattern of mixed infections involved a combination of Gram-negative bacteria and fungi. The chemoradiotherapy group exhibited fewer single infections, which was possibly associated with host factors. Studies have shown that peripheral blood leukocyte and neutrophil levels are significantly reduced in patients treated with chemoradiotherapy, and bone marrow haematopoiesis is impaired, resulting in decreased immune function (32). Prolonged hospitalization was observed in the chemoradiotherapy group following the occurrence of lower respiratory tract infections.

The small sample size, the absence of lymphocyte classification tests, and the absence of NK cell and leukocyte data are limitations of the present study. Blood specimens were not preserved from the collected patient samples, and routine lymphocyte classification tests are not standard in hospital procedures, contributing to the inadequacy of this data segment. Patients receiving chemoradiotherapy exhibited a poorer overall prognosis for lower respiratory tract infections compared with those individuals receiving targeted therapy alone. These patients were also more susceptible to multiple infections and drug-resistant Gram-negative bacilli co-infections. Routine bacterial and fungal studies should be considered in specialized populations to improve patient management. The findings of the present study provide valuable insights for the appropriate selection of empiric antibiotics and antifungal agents in severely ill patients.

Acknowledgements

Not applicable.

Funding

The present study was funded by a grant from Basic Research Operating Expenses of Universities in Hebei Province (grant no. JQN2021028).

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

DZ and YH designed the research and revised the manuscript. DZ and JD collected data and drafted the manuscript. JJ performed the data analysis. HZ designed the research and revised the manuscript critically for important intellectual content. DZ and YH confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The Ethics Committee of North China University of Science and Technology Affiliated Hospital (Tangshan, China) approved this study (approval no. 20221108017).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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