Am J Transl Res 2025;17(6):4723-4732
www.ajtr.org /ISSN:1943-8141/AJTR0164800

Original Article

Effect of interleukin-6 and interleukin-8 levels on pathogenic bacteria types in patients with advanced lung cancer and pulmonary infection during chemotherapy

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Received March 26, 2025; Accepted June 3, 2025; Epub June 15, 2025; Published June 30, 2025

Abstract: Objective: To investigate the levels of interleukin-6 (IL-6) and interleukin-8 (IL-8) in patients with advanced lung cancer complicated by pulmonary infection during chemotherapy and their effects on the type of pathogenic bacteria. Method: We retrospectively analyzed the clinical data of 196 patients from Wuhan Hankou Hospital (January 2021-June 2024). The incidence of pulmonary infection was assessed, and the levels of IL-6 and IL-8 were compared across different infection severities and pathogenic bacteria types. Spearman correlation analysis was used to determine associations, and logistic regression was performed to identify factors influencing different pathogenic bacteria infections. Result: The lung infection rate was 24.49% (48/196). Pathogenic bacteria included 36 strains (64.29%) of Gram-negative bacteria (G^-) and 20 strains (35.71%) of Gram-positive bacteria (G^+). The levels of IL-6 and IL-8 were significantly higher in infected patients than in uninfected patients ($P < 0.05$). These levels increased with the severity of infection and were positively correlated with the degree of infection. Elevated IL-6 and IL-8 levels were identified as independent risk factors for Gram-negative bacterial (G^-) infections in patients with pulmonary infection. The combined AUC, sensitivity, and specificity of IL-6 and IL-8 were 0.925, 81.80%, and 93.33%, respectively. Conclusion: In patients with advanced-stage lung cancer undergoing chemotherapy, elevated IL-6 and IL-8 levels were closely associated with pulmonary infection severity. Detection of these cytokines may help differentiate the types of pathogenic bacteria causing lung infections.

Keywords: Middle-late stage lung cancer, lung infection, pathogenic bacteria, interleukin-6, interleukin-8

Introduction

Lung cancer is the leading cause of cancer-related deaths in China, with the highest morbidity and mortality rates among malignant tumors, and a five-year survival rate of approximately 19.7% [1]. Patients with middle and advanced stages of lung cancer have poor prognoses due to the spread of cancer cells or metastasis [2]. Current treatments, such as chemotherapy and radiotherapy, offer limited benefit and are accompanied by significant side effects [3]. Chemotherapy drugs not only inhibit tumor cell proliferation but also suppress the immune system, decreasing the body's immunity and increasing the risk of infection. Additionally, lung cancer patients often experience local obstruction and atelectasis, which can lead to sputum accumulation in lung tissue, further heightening the risk of infection. Extended hospital stays and frequent invasive procedures also increase the likelihood of exposure to pathogenic bacteria, making patients more susceptible to lung infections [4].

Lung infection is one of the most common complications during chemotherapy in patients with advanced lung cancer. The occurrence of infection can not only worsen the patient's condition and extend their hospital stay but also significantly reduce the effectiveness of chemotherapy and lower the survival rate. Therefore, strengthening the prevention and management of pulmonary infections, as well as timely detection and treatment, are crucial for improving the prognosis of patients with moderate to advanced lung cancer. Studies have shown that

https://doi.org/10.62347/GRGQ7128

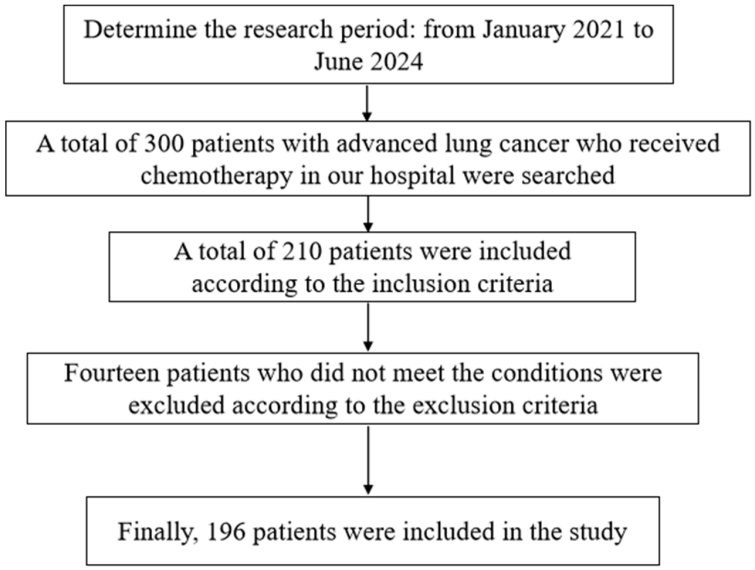

Figure 1. Flow chart of patient selection.

changes in immunoinflammatory markers are closely associated with the occurrence and progression of infection, and alterations in their levels can reflect the severity of infection [5]. Interleukin-6 (IL-6) and interleukin-8 (IL-8) are two critical immune-inflammatory factors that play significant roles in immune response and inflammatory regulation. Recent studies have increasingly focused on the relationship between immunoinflammatory markers and infections. Research has demonstrated that chemotherapy-induced immunosuppression can lead to an abnormal increase in immunoinflammatory markers [6]. However, there remains a limited amount of research examining the relationship between IL-6 and IL-8 levels and the type of pathogenic bacteria, particularly in the specific population of patients with advanced lung cancer undergoing chemotherapy. This study aimed to analyze the relationship between IL-6 and IL-8 levels and the types of pathogenic bacteria in patients with advanced lung cancer who develop pulmonary infections during chemotherapy, providing a reference for early clinical anti-infection treatment.

Patients and methods

General information

The clinical data of 196 patients with advanced lung cancer who received chemotherapy at Wuhan Hankou Hospital from January 2021 to June 2024 were retrospectively analyzed (see the flowchart in **Figure 1**).

Inclusion criteria: (1) Diagnosis of primary lung cancer [7], confirmed by pathological examination. (2) TNM stage II-IV. (3) Chemotherapy duration of more than one course. (4) All patients underwent pathogen testing. (5) Clinical data included IL-6 and IL-8 levels, as well as pathogen detection results.

Exclusion criteria: (1) Patients with lung infections, other types of lung disease, or other infectious diseases prior to the diagnosis of lung cancer. (2) Patients with other malignancies. (3) Patients with metabolic disorders or diseases of the blood and immune systems. (4) Patients with incomplete clinical data.

Based on the presence or absence of pulmonary infection, the patients were divided into two groups: the infected group (48 patients) and the non-infected group (148 patients). Among the infected group, patients were further classified according to the severity of the infection into three subgroups: mild infection (12 patients), moderate infection (26 patients), and severe infection (10 patients). Additionally, the infected patients were categorized based on the type of pathogen into Gram-negative (G^-) bacterial infection group (33 patients) and Gram-positive (G^+) bacterial infection group (15 patients).

This study was approved by the Ethics Committee of Wuhan Hankou Hospital.

Data extraction

The basic information of patients meeting the inclusion criteria was retrieved and entered into the hospital's information management system. This included age, sex, history of diabetes, history of hypertension, smoking history, history of chronic obstructive pulmonary disease, tumor type, TNM stage, chemotherapy cycle, IL-6, IL-8 levels, etc. IL-6 and IL-8 levels were determined by enzyme-linked immunosor-

bent assay (ELISA). Human IL-6 kit (JL14113) and IL-8 kit (JL19291) were used for detection. ELISA steps followed the manufacturer's instructions, including sample preparation, addition of standards and samples, incubation, washing, color development, and termination. Absorbance values were measured at specific wavelengths using an ELISA reader, and standard curves were plotted to calculate IL-6 and IL-8 concentrations in the samples.

Outcome measures

Primary outcomes: Pulmonary infection rate and IL-6 and IL-8 levels at different stages of infection.

Secondary outcomes: Factors influencing infections caused by different pathogenic bacteria and the diagnostic value of IL-6 and IL-8 in distinguishing types of pathogens.

Criteria for pulmonary infection: At least two of the following conditions must be present: (1) Body temperature < 36°C or ≥ 38°C. (2) Leukocyte count ≥ 10×10^9/L. (3) Positive pathogen detection results. (4) Significant increase in airway secretions or presence of purulent secretions.

The severity of pulmonary infection was assessed using the Clinical Pulmonary Infection Score [8], which includes data such as body temperature, white blood cell count, oxygenation, chest X-ray lung infiltration, and tracheal secretions. The score ranged from 0 to 12, with higher scores indicating more severe infections. Scores < 6 indicated mild infection, 6-9 indicated moderate infection, and > 9 indicated severe infection.

Pathogen detection: Sputum was collected from patients in the morning, placed in sterile containers, and sent for pathogen isolation and culture. Pathogens were identified using a fully automated microbiological analysis system (VITEK-2 Compact, Merieux Biotech, France).

Statistical methods

Statistical analysis was performed using SPSS 23.0. Continuous data were expressed as mean ± standard deviation ($\bar{x}$ ± sd), and comparisons between groups were made using the independent samples t-test. Categorical data were expressed as counts and percentages [n (%)], with the chi-square test used for group comparisons. One-way ANOVA was used to compare IL-6 and IL-8 levels across different infection severities, and pairwise comparisons were conducted using the LSD-t test. Spearman correlation analysis was used to assess the relationship between IL-6 and IL-8 levels and infection severity. Logistic regression analysis was performed to identify factors influencing infection. The diagnostic value of IL-6 and IL-8 levels for different pathogens was evaluated using receiver operating characteristic (ROC) curves. A *p*-value of < 0.05 was considered significant.

Results

Comparison of baseline data

Among the 196 lung cancer patients, 48 were diagnosed with pulmonary infection, resulting in an infection rate of 24.49%. The levels of IL-6 and IL-8 in patients with pulmonary infection were significantly higher than those of patients without pulmonary infection (both P < 0.001). No significant differences were found in the general data between the two groups (all P > 0.05, **Table 1**).

Comparison of IL-6 and IL-8 levels in patients with different levels of infection

Among the 48 patients with pulmonary infection, 12 had mild infection, 26 had moderate infection, and 10 had severe infection. Univariate analysis of variance revealed statistically significant differences in serum IL-6 and IL-8 levels among patients with varying infection severities. Pairwise comparisons showed that the serum levels of IL-6 and IL-8 increased with the severity of infection (both P < 0.05, **Table 2**).

Correlation between IL-6 and IL-8 levels and infection degree in patients with pulmonary infection

Spearman correlation analysis showed that serum IL-6 and IL-8 levels were positively correlated with the degree of pulmonary infection (r = 0.631, and 0.543, P < 0.001, **Table 3**). The scatter plot is presented in **Figure 2**.

Distribution of pathogenic bacteria in patients with pulmonary infection

A total of 56 strains of pathogenic bacteria were isolated from 48 patients with pulmonary

Table 1. Comparison of general information

Factor	Uninfected group (n = 148)	Infected group (n = 48)	χ^2/t	*P*
Age (yrs)	60.57 ± 4.98	60.00 ± 5.00	0.685	0.494
Gender				
female	77 (52.03)	20 (41.67)	1.556	0.212
male	71 (47.97)	28 (58.33)		
Diabetes				
no	74 (50.00)	25 (52.08)	0.063	0.802
yes	74 (50.00)	23 (47.92)		
Hypertension				
no	71 (47.97)	28 (58.33)	1.556	0.212
yes	77 (52.03)	20 (41.67)		
Smoking				
no	75 (50.68)	26 (54.17)	0.177	0.674
yes	73 (49.32)	22 (45.83)		
History of chronic obstructive pulmonary disease				
no	81 (54.73)	19 (39.58)	3.327	0.068
yes	67 (45.27)	29 (60.42)		
Tumor type				
Squamous carcinoma	71 (47.97)	30 (62.5)	3.070	0.215
adenocarcinoma	48 (32.43)	11 (22.92)		
Others	29 (19.59)	7 (14.58)		
TNM				
II	46 (31.08)	23 (47.92)	4.611	0.100
III	49 (33.11)	13 (27.08)		
IV	53 (35.81)	12 (25.00)		
Chemotherapy cycle				
≤ 2	70 (47.30)	21 (43.75)	0.183	0.668
> 3	78 (52.70)	27 (56.25)		
IL-6 (ng/L)	214.64 ± 54.24	288.37 ± 50.94	8.303	< 0.001
IL-8 (ng/L)	19.11 ± 4.31	27.62 ± 4.38	11.838	< 0.001

Table 2. Comparison of IL-6 and IL-8 levels in patients with different levels of infection ($\bar{x}$ ± s)

Variable	Mild infection (n = 12)	Moderate infection (n = 26)	Severe infection (n = 10)	*F* value	*P* value
IL-6 (ng/L)	245.98 ± 57.63	285.25 ± 31.23[a]	347.35 ± 22.17[a,b]	19.490	< 0.001
IL-8 (ng/L)	24.48 ± 2.92	26.80 ± 3.26[a]	33.51 ± 2.58[a,b]	25.963	< 0.001

Note: Compared to mild infection, [a]*P* < 0.05; Compared to moderate infection, [b]*P* < 0.05.

Table 3. Correlation analysis of pulmonary infection degree and each index

Variable	r value	*P* value
IL-6 (ng/L)	0.631	< 0.001
IL-8 (ng/L)	0.543	< 0.001

infection. These included 36 strains (64.29%) of G^- bacteria and 20 strains (35.71%) of G^+ bacteria. Among the 48 patients, 33 were infected with G^- bacteria and 15 with G^+ bacteria (**Figure 3**).

Comparison of general data of patients infected with different pathogens

Among the 48 patients, serum IL-6 and IL-8 levels in those infected with G^- bacteria were significantly higher than those in patients infected with G^+ bacteria (both P < 0.05) (**Table 4**).

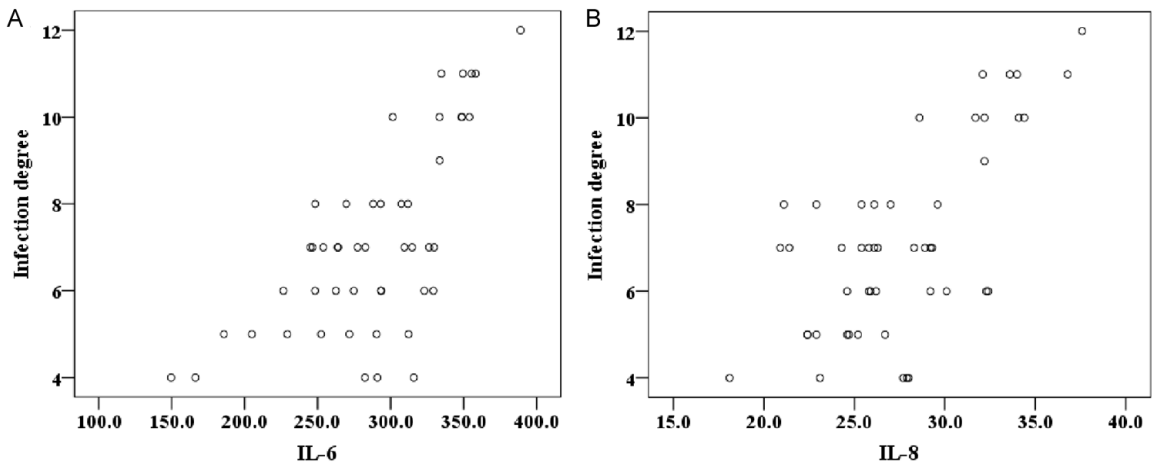

Figure 2. Scatter plot of the relationship between the degree of pulmonary infection, IL-6, and IL-8. Note: (A) Relationship between the degree of pulmonary infection and IL-6; (B) Relationship between the degree of pulmonary infection and IL-8.

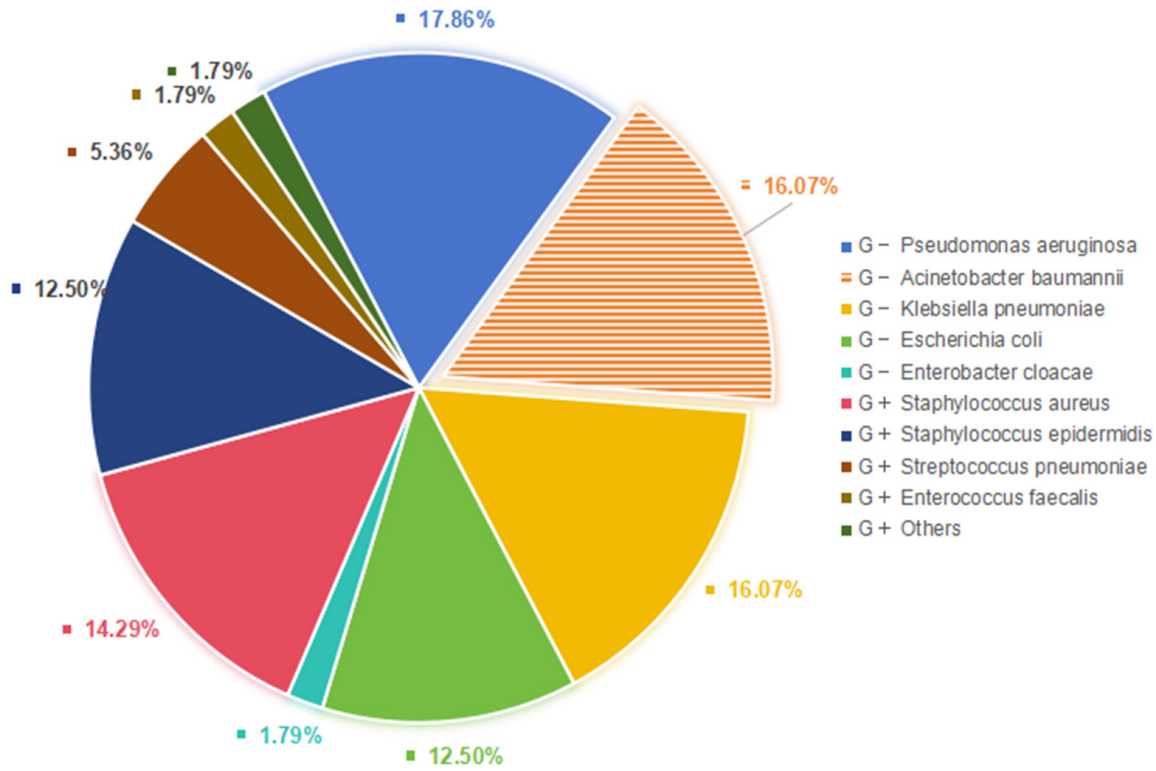

Figure 3. Distribution of pathogenic bacteria in patients with pulmonary infection. Note: G^-: Gram-negative bacteria; G^+: Gram-positive bacteria.

Multi-factor analysis of different pathogenic bacteria

The infection types ($G^- = 1$, $G^+ = 0$) were used as dependent variables, while IL-6 and IL-8 levels were considered independent variables. Logistic regression analysis revealed that increased levels of IL-6 and IL-8 were independent risk factors for G^- infection in lung cancer patients undergoing chemotherapy ($P < 0.05$) (**Table 5**).

Table 4. Comparison of general data of patients infected with different pathogens

Factor	G^+ (n = 15)	G^- (n = 33)	χ^2/t	*P*
Age (yrs)	60.67 ± 3.99	59.70 ± 5.43	0.618	0.539
Gender				
female	5 (33.33)	15 (45.45)	0.623	0.430
male	10 (66.67)	18 (54.55)		
Diabetes				
no	5 (33.33)	20 (60.61)	3.074	0.080
yes	10 (66.67)	13 (39.39)		
Hypertension				
no	9 (60.00)	19 (57.58)	0.025	0.875
yes	6 (40.00)	14 (42.42)		
Smoking				
no	7 (46.67)	19 (57.58)	0.494	0.482
yes	8 (53.33)	14 (42.42)		
History of chronic obstructive pulmonary disease				
no	5 (33.33)	14 (42.42)	0.356	0.551
yes	10 (66.67)	19 (57.58)		
Tumor type				
Squamous carcinoma	10 (66.67)	20 (60.61)	1.405	0.498
adenocarcinoma	2 (13.33)	9 (27.27)		
Others	3 (20.00)	4 (12.12)		
TNM				
II	7 (46.67)	16 (48.48)	0.599	0.850
III	5 (33.33)	8 (24.24)		
IV	3 (20.00)	9 (27.27)		
Chemotherapy cycle				
≤ 2	5 (33.33)	16 (48.48)	0.962	0.327
> 3	10 (66.67)	17 (51.51)		
Infection degree				
Mild infection	4 (26.67)	8 (24.24)	2.681	0.293
Moderate infection	10 (66.67)	16 (48.48)		
Severe infection	1 (6.67)	9 (27.27)		
IL-6 (ng/L)	240.86 ± 45.58	309.96 ± 36.93	5.581	< 0.001
IL-8 (ng/L)	23.71 ± 2.62	29.39 ± 3.84	5.191	< 0.001

Table 5. Multi-factor analysis

Factor	*β* value	*SE* value	*Wald* χ^2 value	*P value*	*OR* (95% *CI*)
IL-6	0.035	0.017	4.270	0.039	1.035 (1.002-1.070)
IL-8	0.468	0.214	4.765	0.029	1.596 (1.049-2.428)
Constant	-20.850	6.889	9.160	0.002	-

Diagnostic Value of IL-6 and IL-8 levels in identifying pathogenic bacteria types in patients with pulmonary infection

ROC curves for IL-6 and IL-8 levels were constructed using G^- patient data as positive and G^+ patient data as negative to identify different types of pathogenic bacteria infections. The AUC values for IL-6 and IL-8 were 0.889 and 0.903, respectively, with the highest AUC of 0.925 for combined identification (**Table 6**; **Figure 4**).

Table 6. The value of IL-6 and IL-8 in identifying pathogenic bacteria types in patients with pulmonary infection

Factor	AUC	95% *CI*	*P*	Cutoff value	Sensitivity (%)	Specificity (%)
IL-6	0.889	0.799-0.979	< 0.001	289.20	75.80	93.30
IL-8	0.903	0.816-0.990	< 0.001	26.15	78.80	93.00
Combined detection	0.925	0.847-1.000	< 0.001	-	81.80	93.30

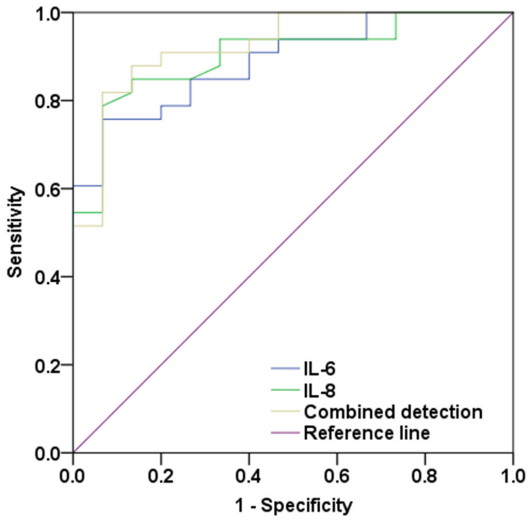

Figure 4. ROC curve.

Discussion

Lung cancer refers to malignant tumors originating from the bronchus, bronchial mucosa, or lung glands. It has high incidence and mortality rates in male malignancies and ranks third among female malignant tumors [9]. Early-stage lung cancer is often asymptomatic, leading to diagnosis at an advanced stage, when surgery is no longer an option. Most patients must undergo chemotherapy, radiotherapy, or immunotherapy, with surgical treatment considered later based on the patient's condition. The combination of chemotherapy and radiotherapy causes significant harm to the body. While chemotherapy kills cancer cells, it also inhibits the growth of normal cells and induces gastrointestinal side effects such as nausea, vomiting, and abdominal pain [10]. Moreover, chemotherapy can cause liver damage, inhibit hematopoietic stem cell differentiation, and reduce immunity [11]. Pulmonary infections in advanced lung cancer patients not only complicate anti-tumor treatment but are also a critical factor affecting prognosis.

The results of this study showed that the incidence of pulmonary infection during chemotherapy in advanced lung cancer patients was 24.49%. Among the isolated pathogens, 64.29% were G^- bacteria and 35.71% were G^+ bacteria. This finding is consistent with research by Wang [12], who reported an infection rate of 23.56% in 208 lung cancer patients, with 49 cases of pulmonary infection. The study also found that IL-6 and IL-8 levels were significantly higher in patients with lung infection than in those without, which aligns with the findings of Fan [13]. These two inflammatory markers play a crucial role in the onset and progression of lung infection. It is hypothesized that IL-6 and IL-8 levels may be related to the occurrence of infection. Further analysis revealed that IL-6 and IL-8 levels increased with infection severity, and their levels were positively correlated with the degree of infection. This finding is consistent with previous studies [14, 15], indicating that changes in inflammatory factor levels are closely linked to infection severity.

IL-6 is a pleiotropic cytokine primarily produced by monocytes and macrophages, involved in inflammatory responses and immune regulation. During infection, IL-6 promotes the activation of B cells and T cells, enhancing the immune response [16, 17]. However, excessive IL-6 can lead to uncontrolled inflammatory responses and exacerbate tissue damage [18]. Research [19] has shown that chemotherapy-induced immunosuppression weakens the body's defense against infections, leading to elevated IL-6 levels. IL-8, a chemokine mainly secreted by neutrophils and macrophages, attracts neutrophils and monocytes to the site of infection, intensifying the inflammatory response [20, 21]. As the infection worsens, the immune response increases, requiring more inflammatory cells at the infection site. Continuous IL-8 secretion guides these cells to the site, enhancing pathogen clearance and further promoting IL-6 and IL-8 release, thereby

exacerbating the inflammatory response [22, 23]. This confirms that IL-6 and IL-8 levels are linked to infection occurrence, and the severity of infection is associated with more pronounced changes in these markers.

While pathogen detection remains the gold standard for diagnosing infection, it often lags behind, limiting its applicability for early clinical anti-infection treatment. Identifying pathogenic bacteria through early warning factor levels is an important direction in clinical anti-infection research. This study confirmed the abnormal expression of IL-6 and IL-8 in patients with pulmonary infection and found a significant correlation with infection severity. Furthermore, logistic regression multivariate analysis showed that elevated IL-6 and IL-8 levels were independent risk factors for G^- bacterial infection. ROC curve analysis further demonstrated that IL-6 and IL-8 can distinguish between G^- and G^+ bacterial infections, likely due to the more intense inflammation caused by G^- bacteria. The cell wall of G^- bacteria contains endotoxins that trigger inflammatory responses by inducing macrophages, smooth muscle cells, and endothelial cells to secrete inflammatory mediators [24, 25]. Additionally, G^- bacteria activate cell responses through toll-like receptor-4, initiating inflammatory responses by expressing interleukin-1, IL-6, tumor necrosis factor-α, and other pre-inflammatory factors [26, 27]. Lu [28] noted that serum inflammatory indicators such as procalcitonin, C-reactive protein, and brain natriuretic peptide were higher in patients infected with G^- bacteria than in those infected with G^+ bacteria, indicating a more severe inflammatory response in the former. Other studies [29] highlighted that lipopolysaccharide, a major component of G^- bacteria, can activate platelets through toll-like receptors, increasing the risk of immune-inflammatory response and platelet apoptosis compared to G^+ bacteria. Therefore, detecting IL-6 and IL-8 levels to identify pathogenic bacteria offers high clinical value and aids in guiding early anti-infection treatment.

Conclusion

This study analyzed the levels of immunoinflammatory indicators and their effect on pathogenic bacteria types in advanced lung cancer patients undergoing chemotherapy. The findings revealed that IL-6 and IL-8 are closely related to lung infection, with higher levels indicating more severe infection. Moreover, detecting IL-6 and IL-8 levels can help differentiate between G^- and G^+ infections, assisting in the rational use of antibiotics in clinical practice. While this study provides valuable insights, it has some limitations. It is a single-center, retrospective study with a limited sample size, and it only examined IL-6 and IL-8 levels without considering other immune markers, which may not fully capture the complexity of immune-inflammatory responses. Future research should expand the sample size, conduct multi-center studies, and incorporate additional inflammatory factors and immune markers to more comprehensively assess their role in lung infection during chemotherapy for lung cancer.

Acknowledgements

This work was supported by the Traditional Chinese Medicine Research Project of Wuhan Municipal Health Commission (WZ24A25).

Disclosure of conflict of interest

None.

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