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Article

Association of Serum IL-6, TNF-α, and HIF-1α Levels With Respiratory Tract Infection in Patients With Ischemic Stroke

Wenwen Wu[1], Qing Gao[2,*]

[1]Department of Geriatric Respiratory Medicine, The Fifth People's Hospital of Jinan, 250022 Jinan, Shandong, China
[2]Department of Neurology II, The Fifth People's Hospital of Jinan, 250022 Jinan, Shandong, China
*Correspondence: qingpiaopiao2026@163.com (Qing Gao)
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Abstract

Aims/Background: Patients with ischemic stroke are prone to developing respiratory tract infections, which can seriously affect prognosis. The objective of this study was to assess the association of the serum levels of interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), and hypoxia-inducible factor-1 alpha (HIF-1α) with the occurrence of respiratory tract infection, and to determine whether these biomarkers are independently associated with infection risk. **Methods:** A total of 140 patients with ischemic stroke admitted to The Fifth People's Hospital of Jinan between January 2024 and September 2025 were enrolled. Based on the presence or absence of respiratory tract infection, patients were divided into an infection group ($n = 41$) and a non-infection group ($n = 99$). Blood samples were collected within 24 hours after admission. Serum IL-6, TNF-α, and HIF-1α levels were measured using enzyme-linked immunosorbent assay (ELISA). Baseline characteristics were compared between the two groups. Point-biserial correlation and univariate logistic regression were used to assess the relationships between inflammatory markers (IL-6, TNF-α, HIF-1α) and respiratory tract infection, followed by multivariate logistic regression to identify independent influencing factors. **Results:** There were no significant differences between the two groups in terms of age, gender, body mass index, smoking and drinking history, hypertension, diabetes, coronary heart disease, hyperlipidemia, infarction site, National Institutes of Health Stroke Scale (NIHSS) score, Glasgow Coma Scale (GCS) score, mean respiratory rate, or mean oxygen saturation ($p > 0.05$). Serum levels of IL-6, TNF-α, and HIF-1α were significantly higher in the infection group than in the non-infection group ($p < 0.001$). Point-biserial correlation analysis revealed that IL-6, TNF-α, and HIF-1α were positively correlated with respiratory tract infection (r = 0.695, 0.738, and 0.655, respectively; $p < 0.001$). Univariate logistic regression indicated that all three biomarkers were influencing factors of respiratory tract infection ($p < 0.001$), and multivariate logistic regression confirmed them as independent influencing factors ($p < 0.05$). **Conclusion:** Elevated serum levels of IL-6, TNF-α, and HIF-1α are significantly associated with respiratory tract infection in patients with ischemic stroke. However, this association does not imply a causal relationship, and the observed increases in these inflammatory markers may reflect a consequence of infection rather than independent risk factors. Early monitoring of these biomarkers may help identify patients with increased risk of developing infection and facilitate timely clinical assessment and intervention to improve outcomes.

Keywords: ischemic stroke; respiratory tract infection; IL-6; TNF-α; HIF-1α

1. Introduction

Ischemic stroke is one of the primary causes of death and disability worldwide. It is characterized by cerebral vascular occlusion that results in ischemia and hypoxia of brain tissue, leading to neuronal injury and functional impairment [1,2]. With the accelerating trend of population aging, the incidence of ischemic stroke continues to rise, posing a significant burden on individual health, families, and socioeconomic systems [3]. Although acute-phase treatments such as thrombolysis, mechanical thrombectomy, and reperfusion therapy provide clear clinical benefits, patients with stroke remain at high risk for various complications, among which stroke-associated pneumonia (SAP) is the most common [4,5,6,7]. Studies have shown that the incidence of SAP within a short period after the onset of ischemic stroke can reach 10%–35%, and severe cases may progress to aspiration pneumonia, sepsis, or even death [8,9].

The mechanisms underlying SAP in patients with ischemic stroke are complex and multifactorial [10]. First, brain injury can lead to swallowing dysfunction, weakened cough reflex, and prolonged bed rest, all of which increase the risk of aspiration pneumonia [8]. Second, stroke can induce stroke-induced immunodepression, characterized by lymphopenia, imbalance of inflammatory cytokines, and impaired immune cell activity, resulting in an elevated risk of bacterial, viral, and fungal infections [8,11]. In addition, underlying conditions such as hypertension, diabetes, and cardiovascular diseases further elevate the risk of infection.

Inflammatory factors play a central role in ischemic stroke and its associated respiratory tract infections [12]. Interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) are classic pro-inflammatory cytokines that can be rapidly upregulated after cerebral ischemia, participating in inflammatory cascades and regulation of immune cell function, and these cytokines are closely correlated with tis-

sue injury and clinical outcomes [13]. Hypoxia-inducible factor-1 alpha (HIF-1α) is activated under the hypoxic conditions of cerebral ischemia and can modulate inflammatory responses, cell apoptosis, and immune homeostasis [14]. A previous study has suggested that serum levels of IL-6, TNF-α, and HIF-1α may be associated with the occurrence of infections [15]; however, systematic analyses focusing on respiratory tract infections in patients with ischemic stroke, with a particular emphasis on exploring the independent predictive value of these biomarkers, remain limited.

Based on this background, the present study examines the association of serum IL-6, TNF-α, and HIF-1α levels with the occurrence of respiratory tract infections in patients with ischemic stroke. The secondary objective of this study was to determine whether these factors are independently associated with respiratory tract infections. The findings may provide supporting evidence for early identification of patients at increased risk of infections, enabling more strategic clinical monitoring and further investigation of potential prevention and management strategies.

2. Methods

2.1 General Information

A total of 140 patients with ischemic stroke admitted to our hospital from January 2024 to September 2025 were enrolled in this study. All enrolled patients met the diagnostic criteria for ischemic stroke. Patients were then divided into an infection group and a non-infection group according to whether they developed stroke-associated pneumonia (SAP) during hospitalization. SAP was diagnosed based on expert consensus, taking into account the timing after stroke onset, clinical manifestations, imaging findings, and laboratory evidence of infection. Patients who met the diagnostic criteria for SAP were assigned to the infection group (n = 41), whereas those who did not meet the criteria were assigned to the non-infection group (n = 99). Baseline clinical characteristics of the two groups are shown in Table 1. This study was conducted in strict accordance with the ethical principles of the Declaration of Helsinki and approved by the Ethics Committee of The Fifth People's Hospital of Jinan (Approval No: 25-5-20). Informed consent was obtained from the patients or their immediate family members.

Inclusion criteria: (1) Adult patients (aged ≥18 years) who met the diagnostic criteria for ischemic stroke according to the criteria issued by the Chinese Stroke Association guidelines for clinical management of ischaemic cerebrovascular diseases: executive summary and 2023 update [16]; (2) patients admitted to the study hospital after stroke onset; (3) patients who were able to cooperate with clinical procedures during examination; (4) patients who received treatment at the study hospital after stroke onset and had complete clinical data, including baseline serum IL-6, TNF-α, and HIF-1α measurements; and (5) patients or their legal guardians who provided informed consent.

Exclusion criteria: (1) Patients with hemorrhagic stroke or transient ischemic attack (TIA); (2) patients with documented pneumonia, other active respiratory infections, or infections at other sites (e.g., urinary tract, bloodstream, skin or soft tissue) within 2 weeks prior to admission, confirmed by clinical, laboratory, or imaging findings; (3) patients with a history of immunosuppressive therapy, including the use of immunosuppressants, systemic glucocorticoids, or anti-inflammatory drugs within the 2 weeks prior to admission; (4) patients with severe cardiac, hepatic, or renal dysfunction, malignant tumors, or other conditions known to significantly impair immune function; (5) patients with chronic underlying lung diseases that could clearly affect the risk of respiratory infection; (6) pregnant or breastfeeding women; and (7) patients with incomplete clinical data or laboratory data.

2.2 Outcome Measures

Serum biomarkers: Blood samples from all patients were collected and tested within 24 hours of admission. Serum was obtained via centrifugation of 5 mL of morning venous blood at 3500 r/min for 10 minutes. Serum levels of IL-6 (PI330, Beyotime, Shanghai, China), TNF-α (PT518, Beyotime, Shanghai, China), and HIF-1α (EK1392, MULTI SCIENCES, Hangzhou, China) were measured using enzyme-linked immunosorbent assay (ELISA). Samples with concentrations exceeding the upper detection limit were diluted appropriately and subjected to repeated measurement.

2.3 Statistical Analysis

Statistical analyses were performed using SPSS version 27.0 (IBM, Chicago, IL, USA). Continuous variables were first tested for normality using the Kolmogorov-Smirnov test. Normally distributed data were presented as mean ± standard deviation (SD) and compared between groups using independent samples *t*-tests, while non-normally distributed data were expressed as medians (interquartiles), and the Mann-Whitney *U* test is used for comparisons between groups. Categorical variables were expressed as frequencies and percentages (n/%) and compared using the chi-square test. Point-biserial correlation analysis was used to evaluate the relationships between ischemic stroke complicated with respiratory tract infection and continuous variables. Multicollinearity among the variables included in the multivariate model was assessed using the variance inflation factor (VIF). All variables were examined, and no significant multicollinearity was detected, with all VIF values being <2.0. Univariate logistic regression was conducted to determine whether IL-6, TNF-α, and HIF-1α are influencing factors for respiratory tract infection, and multivariate logistic regression was performed to identify independent influencing factors. A p-value < 0.05 was considered statistically significant.

3. Results

3.1 Comparison of Baseline Characteristics

According to the diagnostic criteria, patients were divided into a non-infection group (n = 99) and an infection group (n = 41). The non-infection group comprised 53 males and 46 females, with a mean age of 67.16 ± 8.89 years and a mean body mass index (BMI) of 22.61 ± 5.79 kg/m^2. Among these patients, 56 had a history of alcohol consumption, 47 had a history of smoking, 42 had a history of hypertension, 44 had diabetes, 55 had coronary heart disease, and 39 had hyperlipidemia. The ischemic regions were located in the cerebellum in 5 cases, the cerebral lobes in 55 cases, and the basal ganglia in 39 cases. In the non-infection group, the mean National Institutes of Health Stroke Scale (NIHSS) score was 13.32 ± 3.16, and the mean Glasgow Coma Scale (GCS) score was 13.12 ± 3.13. The mean respiratory rate was 15.36 ± 3.11 breaths per minute, and the mean oxygen saturation was 94.71 ± 4.88%. The infection group comprised 21 males and 20 females, with a mean age of 66.85 ± 7.75 years and a mean BMI of 22.68 ± 5.35 kg/m^2. Among these patients, 21 had a history of alcohol consumption, 18 had a history of smoking, 19 had hypertension, 20 had diabetes, 25 had coronary heart disease, and 17 had hyperlipidemia. The ischemic regions were located in the cerebellum in 2 cases, the cerebral lobes in 21 cases, and the basal ganglia in 18 cases. The mean NIHSS score was 13.35 ± 4.11, and the mean GCS score was 13.47 ± 3.85. The mean respiratory rate was 15.04 ± 2.86 breaths per minute, and the mean oxygen saturation was 95.43 ± 4.80%. There were no statistically significant differences in the baseline or clinical characteristics between the two groups ($p > 0.05$) (Table 1).

3.2 Comparison of Serum IL-6, TNF-α, and HIF-1α Levels Between the Two Groups

Serum levels of IL-6, TNF-α, and HIF-1α in the infection group were significantly higher than those in the non-infection group ($p < 0.001$) (Table 2).

3.3 Correlations of IL-6, TNF-α, and HIF-1α Levels With Respiratory Tract Infection

Respiratory tract infection in ischemic stroke patients was positively correlated with serum IL-6, TNF-α, and HIF-1α levels (r = 0.695, 0.738, 0.655, respectively; $p < 0.001$) (Table 3).

3.4 Univariate Logistic Regression Analysis

The univariate logistic regression analysis demonstrated that IL-6, TNF-α, and HIF-1α were all influencing factors of the occurrence of respiratory tract infection in ischemic stroke patients ($p < 0.001$) (Table 4).

3.5 Multivariate Logistic Regression Analysis

According to multivariate logistic regression analysis, IL-6, TNF-α, and HIF-1α were independent influencing factors of respiratory tract infection in ischemic stroke patients ($p < 0.05$) (Table 5).

4. Discussion

The present study demonstrated that in patients with ischemic stroke complicated by respiratory tract infection, serum levels of IL-6, TNF-α, and HIF-1α were significantly higher than those in non-infected patients, and these indicators were positively associated with the occurrence of infection. Univariate and multivariate logistic regression analyses further demonstrated that IL-6, TNF-α, and HIF-1α were independently associated with respiratory tract infection in patients with ischemic stroke. However, these findings reflect statistical associations rather than causal relationships, and the elevated inflammatory markers may be a consequence of infection rather than true risk factors. These results suggest that increased levels of inflammatory markers may reflect the presence or severity of infection and could serve as potential biomarkers for identifying patients with a higher risk of infection.

Rapidly upregulated in the early stages of cerebral ischemia, IL-6 is a typical pro-inflammatory cytokine that activates downstream inflammatory signaling pathways. Previous studies have demonstrated that elevated serum IL-6 levels in patients with ischemic stroke are closely associated with the degree of neurological impairment, infarct volume, and the risk of complications [17,18]. For example, Zhang et al. [19] reported that increased IL-6 levels in patients with acute ischemic stroke could predict the risk of in-hospital infection, which is consistent with the findings of this study.

TNF-α, another key pro-inflammatory cytokine, contributes to infection susceptibility by modulating immune cell function, blood-brain barrier permeability, and phagocyte activity. Our findings showed that elevated TNF-α levels were strongly correlated with the occurrence of respiratory tract infection. Notably, this observation differs from previous reports describing a decrease in circulating TNF-α in the context of stroke-induced immunosuppression [20], highlighting that TNF-α dynamics may vary depending on disease stage, sampling time, and patient heterogeneity.

HIF-1α is a central regulator of cellular adaptation to hypoxia and plays a pivotal role in coordinating immune and inflammatory responses. In patients with ischemic stroke, cerebral ischemia itself creates a hypoxic microenvironment that stabilizes HIF-1α and activates downstream pathways involved in inflammation, apoptosis, and immune modulation. In parallel, respiratory tract infection may further exacerbate systemic hypoxia and inflammatory stress, leading to additional upregulation of HIF-1α. Therefore, the elevated serum HIF-1α observed in this study likely reflects the combined effects of stroke-related cerebral hypoxia and infection-associated systemic inflammation, rather than a single pathological process. Importantly, because serum HIF-1α levels in our cohort were measured within 24 hours of admission—prior to the clinical diag-

Table 1. Comparison of baseline characteristics between the two groups.

Factor	Non-infection group (n = 99)	Infection group (n = 41)	t/χ^2	p
Age (years)	67.16 ± 8.89	66.85 ± 7.75	0.197	0.844
Gender, n (%)			0.062	0.803
Male	53 (53.54)	21 (51.22)		
Female	46 (46.46)	20 (48.78)		
BMI (kg/m^2)	22.61 ± 5.79	22.68 ± 5.35	0.069	0.945
Drinking history, n (%)			0.335	0.563
Yes	56 (56.57)	21 (51.22)		
No	43 (43.43)	20 (48.78)		
Smoking history, n (%)			0.149	0.700
Yes	47 (47.47)	18 (43.90)		
No	52 (52.53)	23 (56.10)		
Complications, n (%)				
Hypertension			0.181	0.671
Yes	42 (42.42)	19 (46.34)		
No	57 (57.58)	22 (53.66)		
Diabetes			0.220	0.639
Yes	44 (44.44)	20 (48.78)		
No	55 (55.56)	21 (51.22)		
Coronary heart disease			0.348	0.555
Yes	55 (55.56)	25 (60.98)		
No	44 (44.44)	16 (39.02)		
Hyperlipidemia			0.052	0.820
Yes	39 (39.39)	17 (41.46)		
No	60 (60.61)	24 (58.54)		
Ischemic region, n (%)			0.247	0.884
Cerebellum	5 (5.05)	2 (4.88)		
Cerebral lobe	55 (55.56)	21 (51.22)		
Basal ganglia	39 (39.39)	18 (43.90)		
NIHSS score	13.32 ± 3.16	13.35 ± 4.11	0.056	0.955
GCS score	13.12 ± 3.13	13.47 ± 3.85	0.558	0.578
Respiratory rate (bpm)	15.36 ± 3.11	15.04 ± 2.86	0.563	0.574
Oxygen saturation (%)	94.71 ± 4.88	95.43 ± 4.80	0.800	0.425

Abbreviation: BMI, body mass index; NIHSS, National Institutes of Health Stroke Scale; GCS, Glasgow Coma Scale.

Table 2. Comparison of serum IL-6, TNF-α, and HIF-1α levels between the two groups.

Factor	Non-infection group (n = 99)	Infection group (n = 41)	t	p
IL-6 (ng/L)	71.09 ± 7.01	86.06 ± 7.31	11.356	<0.001
TNF-α (ng/L)	6.40 ± 0.93	9.05 ± 1.46	12.848	<0.001
HIF-1α (ng/mL)	41.51 ± 6.18	54.80 ± 8.74	10.195	<0.001

Abbreviations: HIF-1α, hypoxia-inducible factor-1 alpha; IL-6, interleukin-6; TNF-α, tumor necrosis factor alpha.

Table 3. Correlation of IL-6, TNF-α, and HIF-1α levels with respiratory tract infection in ischemic stroke patients.

	r	p
IL-6 (ng/L)	0.695	<0.001
TNF-α (ng/L)	0.738	<0.001
HIF-1α (ng/mL)	0.655	<0.001

nosis of infection—our findings suggest that HIF-1α elevation is at least partly driven by the ischemic insult itself and may represent a predisposing immunoregulatory state that increases susceptibility to subsequent respiratory tract infection. Mechanistically, previous studies have demonstrated that HIF-1α activation in ischemic tissues can amplify local inflammatory responses while impairing innate immune cell function, particularly macrophage phagocyto-

Table 4. Univariate logistic regression analysis of IL-6, TNF-α, and HIF-1α levels for respiratory tract infection in ischemic stroke patients.

	β	Standard error (SE)	Wald	*p*	OR	95% CI
IL-6 (ng/L)	0.322	0.058	30.475	<0.001	1.380	1.231–1.548
TNF-α (ng/L)	2.312	0.419	30.416	<0.001	10.095	4.439–22.958
HIF-1α (ng/mL)	0.251	0.043	34.675	<0.001	1.285	1.182–1.397

OR, odds ratio; CI, confidence interval.

Table 5. Multivariate logistic regression analysis of IL-6, TNF-α, and HIF-1α levels for respiratory tract infection in ischemic stroke patients.

	β	Standard error (SE)	Wald	*p*	OR	95% CI
IL-6 (ng/L)	0.312	0.105	8.812	0.003	1.366	1.112–1.678
TNF-α (ng/L)	2.380	0.762	9.759	0.002	10.807	2.427–48.111
HIF-1α (ng/mL)	0.253	0.097	6.854	0.009	1.288	1.066–1.558

IL-6, TNF-α, and HIF-1α were entered simultaneously into the multivariate logistic regression model. Because the number of infection events was relatively limited (n = 41), age, gender, NIHSS score, and comorbidities were not included in this model to avoid overfitting. Therefore, the results represent mutual adjustment among the three biomarkers rather than adjustment for all clinical confounders.

sis and bactericidal capacity, thereby compromising host defense against pathogens [21]. Consistent with these biological mechanisms, we systematically evaluated for the first time the association between serum HIF-1α levels and respiratory tract infection in patients with ischemic stroke and identified HIF-1α as an independent risk factor. These findings provide novel clinical evidence supporting the role of HIF-1α as a link between ischemia-induced hypoxia, immune dysregulation, and increased infection susceptibility following stroke.

From a clinical perspective, the identification of reliable biomarkers for early risk stratification of infection following ischemic stroke is of substantial importance. The present findings suggest that elevated serum levels of IL-6, TNF-α, and HIF-1α at admission may serve as early indicators of an increased risk of subsequent respiratory tract infection. Measurement of these biomarkers could assist clinicians in identifying high-risk patients at an early stage, even before overt clinical signs of infection appear.

In clinical practice, patients with markedly elevated levels of these biomarkers may benefit from closer clinical surveillance, early assessment of swallowing function, intensified respiratory care, and proactive preventive strategies such as aspiration precautions and optimized nutritional support. Moreover, recognition of a heightened inflammatory and hypoxia-related state may help guide individualized management plans, including timely consultation with respiratory specialists and judicious use of preventive interventions.

Importantly, these biomarkers are not intended to replace routine clinical assessment or standard inflammatory markers, but rather to complement existing risk evaluation tools by providing additional insight into immune dysregulation and hypoxia-related vulnerability after stroke. Although the present study does not establish specific clinical cutoff values, it provides preliminary evidence supporting the potential role of IL-6, TNF-α, and HIF-1α in infection risk stratification. Future prospective studies are warranted to define optimal thresholds, integrate these biomarkers into predictive models, and evaluate whether biomarker-guided preventive strategies can effectively reduce infection incidence and improve outcomes in patients with ischemic stroke.

Compared with previous studies, this study has several distinct features. First, we simultaneously measured three inflammation-related biomarkers—IL-6, TNF-α, and HIF-1α. This comprehensive set of clinical biomarker data was subject to correlation analysis with respiratory tract infection, and the findings are critical for determining their independent predictive values for this condition. Second, patients who had pre-existing infections or severe comorbidities prior to admission were excluded from this study in order to minimize potential confounding factors and enhance the reliability of the findings. Our results suggest that early detection of serum IL-6, TNF-α, and HIF-1α levels in patients with ischemic stroke may help identify high-risk individuals. This enables clinicians to implement targeted preventive strategies in advance, such as optimizing respiratory management, strengthening immune monitoring, and initiating timely anti-infective interventions.

Certain limitations of this study should be acknowledged. First, the single-center, retrospective design and limited sample size may have introduced selection bias. Future multicenter, large-scale prospective studies are needed to further validate these findings. In addition, the distribution of comorbidities in this cohort differed from that commonly reported in the general ischemic stroke population. The relatively low prevalence of hypertension and the

higher proportions of diabetes and coronary heart disease may be related to the single-center nature of the study, the limited sample size, the characteristics of hospitalized patients, and the exclusion of patients with severe comorbidities or incomplete clinical data. Therefore, these baseline characteristics should be interpreted with caution and may not fully represent the broader ischemic stroke population. Second, only a small selection of biomarkers, namely serum IL-6, TNF-α, and HIF-1α, were measured in this study, while other potentially relevant inflammatory cytokines and immune cell function markers were not assessed. This may underestimate the complexity of the immune network involved in post-stroke infections. Third, relatively high odds ratios were observed when the inflammatory biomarkers were analyzed on their original measurement scales, particularly for TNF-α (odds ratio [OR] = 10.807), indicating a strong association between small absolute changes in biomarker levels and the risk of respiratory tract infection. These odds ratios should not be interpreted as precise multipliers of clinical risk for minimal biological changes, but rather as indicators of the direction and relative strength of the associations. Therefore, caution is warranted when comparing the magnitude of odds ratios across different biomarkers or across studies using different measurement scales. Finally, we did not differentiate respiratory tract infections according to pathogen type (e.g., bacterial, viral, or fungal). Different pathogens are known to induce distinct immune and cytokine response patterns, which may influence the levels of inflammatory markers such as IL-6, TNF-α, and HIF-1α. Due to the retrospective nature of this study and the incomplete microbiological data in a subset of patients, pathogen-specific subgroup analyses could not be performed. Therefore, the observed associations reflect overall infection status rather than pathogen-specific effects. Future prospective studies with systematic pathogen identification are warranted to further elucidate the differential immune responses associated with specific infectious agents.

5. Conclusion

In conclusion, elevated serum levels of IL-6, TNF-α, and HIF-1α are closely associated with the occurrence of respiratory tract infections in patients with ischemic stroke. These markers may reflect the degree of systemic inflammation and hypoxic response. However, this association does not imply a causal relationship, and the observed increases in these inflammatory markers are more likely to reflect a consequence of infection rather than independent risk factors. Early clinical monitoring of IL-6, TNF-α, and HIF-1α levels may help identify patients at higher risk of infection and facilitate timely clinical assessment and management, thereby potentially improving the prognosis of patients with ischemic stroke.

Key Points

- Patients with ischemic stroke and respiratory infection had higher serum IL-6, TNF-α, and HIF-1α levels than non-infected patients.
- IL-6, TNF-α, and HIF-1α were positively associated with respiratory tract infection.
- Univariate analysis showed significant associations between these biomarkers and infection.
- Multivariate analysis confirmed they were independent correlates of infection.
- Findings indicate association, not causation; elevated markers may reflect infection rather than risk.
- Early monitoring of IL-6, TNF-α, and HIF-1α may help identify high-risk patients.

Availability of Data and Materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions

WW conceived the study, designed the methodology, collected and analyzed the data, and drafted the initial manuscript. QG was responsible for the overall study design, supervision of the research process, and validation of data analysis. Both authors have revised the manuscript for important intellectual content and approved the final version. Both authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

This study was conducted in strict accordance with the ethical principles of the Declaration of Helsinki and approved by the Ethics Committee of The Fifth People's Hospital of Jinan (Approval No: 25-5-20). Informed consent was obtained from the patients or their immediate family members.

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Conflicts of Interest

The authors declare no conflicts of interest.

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