Predictive value of inflammatory factors and lymphocyte counts in tracheal intubation and death after infection with COVID-19

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Research Article

Keywords:

DOI: https://doi.org/

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Additional Declarations: No competing interests reported.
Predictive value of inflammatory factors and lymphocyte counts in tracheal intubation and death after infection with COVID-19

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Total count 3097
Abstract

Objective: This study aims to investigate the prognostic significance of inflammatory cytokines and lymphocyte levels in predicting disease progression among patients with COVID-19 infection.

Methods: Ninety-two hospitalized COVID-19 patients were retrospectively included as subjects for this study. General clinical information and various indicators, including lymphocyte count, interleukin-2 (IL-2), interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-10 (IL-10), tumor necrosis factor (TNF), were collected. All patients received treatment according to the ninth edition of the guidelines for COVID-19. Incidences of endotracheal intubation and mortality within 28 days were observed.

Results: 1. Lymphocyte count and inflammatory factors demonstrated predictive value for endotracheal intubation in COVID-19 patients. The critical lymphocyte count value was 0.91, with a sensitivity of 38.8%, specificity of 92.9%, and AUC of 0.687 (95% CI: 0.580-0.795). The critical IL-6 value was 38.21, with a sensitivity of 81%, specificity of 63.3%, and AUC of 0.771 (95% CI: 0.6670.872). The critical IL-8 value was 54.09, with a sensitivity of 61.9%, specificity of 75.5%, and AUC of 0.665 (95% CI: 0.545-0.771). The critical IL-10 value was 5.05, with a sensitivity of 71.4%, specificity of 65.3%, and AUC of 0.712 (95% CI: 0.601-0.813). The tumor necrosis factor cutoff was 1.98, with
a sensitivity of 52.4%, specificity of 73.5%, and AUC of 0.648 (95% CI: 0.530-0.756). 2. Lymphocyte count and inflammatory factors also exhibited predictive value for death in COVID-19 patients. The critical lymphocyte count value was 0.56, with a sensitivity of 71.2%, specificity of 57.5%, and AUC of 0.641 (95% CI: 0.528-0.754). The critical IL-6 value was 53.05, with a sensitivity of 75%, specificity of 71.2%, and AUC of 0.770 (95% CI: 0.6690.870). The critical IL-8 value was 54.09, with a sensitivity of 62.5%, specificity of 63.5%, and AUC of 0.687 (95% CI: 0.5780.796). The critical IL-10 value was 5.05, with a sensitivity of 70%, specificity of 63.5%, and AUC of 0.683 (95% CI: 0.5740.792). The tumor necrosis factor cutoff was 0.98, with a sensitivity of 90%, specificity of 34.6%, and AUC of 0.636 (95% CI: 0.523-0.749).

**Conclusion**: Elevated inflammatory factors and decreased lymphocyte levels have prognostic value for predicting endotracheal intubation and mortality in COVID-19 patients, providing valuable insights for clinicians in anticipating disease progression.

**Key words** COVID-19 infection; Inflammatory factors; Lymphocyte; Tracheal intubation; Death

**Introduction**

Coronavirus (COVID-19) infection is an acute and severe respiratory infectious ailment induced by a novel coronavirus. Numerous recent studies have
substantiated a compelling association between the severity of COVID-19 and the heightened release of inflammatory factors coupled with lymphocytopenia. The vigilant monitoring of alterations in inflammatory factors and lymphocyte counts proves instrumental in tracking disease progression and conducting comprehensive disease assessments. In the present investigation, we retrospectively examined the dynamics of inflammatory factors and lymphocyte profiles in COVID-19 patients, delving into the predictive significance of their levels in the context of disease progression.

Materials and methods

General information

A retrospective study was executed, encompassing individuals afflicted with COVID-19 who were admitted to the Intensive Care Department in the North District of Suzhou City Hospital between December 1, 2022, and February 28, 2023. Comprehensive data were extracted from the inpatient medical records, and all subjects received treatment in accordance with the ninth edition of the Guidelines for the Diagnosis and Treatment of novel coronavirus infection. The dataset included general clinical information, results from laboratory tests, and prognostic outcomes for the patients under scrutiny.

Monitoring index and method

The laboratory tests encompassed a range of parameters, including white
blood cell count, lymphocyte count, hypersensitive C-reactive protein (CRP), procalcitonin, prealbumin, albumin, B-type natriuretic peptide (BNP), among others. Inflammatory factors under investigation included IL-1β, IL-2, IL-6, IL-8, IL-10, TNF, among others. The study monitored the occurrences of tracheal intubation and mortality within a 28-day period.

**Statistical method**

SPSS 20 statistical software was used for analysis. The mean of measurement data with normal distribution was expressed as (\(\bar{x} \pm s\)), and the median and quartile of measurement data with non-normal distribution were expressed as. Independent sample t test was used for quantitative variables conforming to normal distribution; otherwise, Wilcoxon rank sum test was used. Chi-square tests were used for both sets of qualitative data. The statistical data were expressed as frequency, and \(\chi^2\) test was used for comparison between groups. The ROC curve was drawn using the results of diagnostic tests to calculate the optimal critical value of inflammatory factors and lymphocyte counts for predicting tracheal intubation and death in patients infected with COVID-19. Bilateral test was used in all the comparisons, and \(P < 0.05\) was considered statistically significant.

**Results**

**Clinical characteristics of patients**
Following the exclusion of cases with incomplete data, a total of 92 patients ultimately fulfilled the enrollment criteria, as outlined in Table 1.

<table>
<thead>
<tr>
<th></th>
<th>Tracheal intubation</th>
<th>Control group</th>
<th>t/z</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>80.35±9.03</td>
<td>74.24±15.4</td>
<td>-</td>
<td>0.025</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>2.277</td>
<td></td>
</tr>
<tr>
<td>Sex n(male)</td>
<td>43(30)</td>
<td>49(34)</td>
<td>-</td>
<td>0.969</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.039</td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.39±0.06</td>
<td>7.39±0.06</td>
<td>-</td>
<td>0.614</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.506</td>
<td></td>
</tr>
<tr>
<td>PaCO₂ (mmHg)</td>
<td>38.31±10.01</td>
<td>36.25±7.73</td>
<td>-</td>
<td>0.269</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.113</td>
<td></td>
</tr>
<tr>
<td>PaO₂ (mmHg)</td>
<td>93.44±56.64</td>
<td>79.53±17.92</td>
<td>-</td>
<td>0.129</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.544</td>
<td></td>
</tr>
<tr>
<td>Lac (mmol/L)</td>
<td>1.80(1.50,2.20)</td>
<td>1.80(1.55,2.10)</td>
<td>-</td>
<td>0.878</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.153</td>
<td></td>
</tr>
<tr>
<td>BNP (pg/ml)</td>
<td>244.00(160.00,701.00)</td>
<td>172(64.00,341.50)</td>
<td>-</td>
<td>0.079</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.757</td>
<td></td>
</tr>
<tr>
<td>Prealbumin (mg/L)</td>
<td>72.58±45.99</td>
<td>107.49±70.77</td>
<td>2.762</td>
<td>0.007</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>30.55±3.95</td>
<td>30.68±4.18</td>
<td>0.156</td>
<td>0.876</td>
</tr>
<tr>
<td></td>
<td>Values</td>
<td>Control Values</td>
<td>p-value</td>
<td></td>
</tr>
<tr>
<td>--------------------------</td>
<td>-------------------------------</td>
<td>----------------</td>
<td>---------</td>
<td></td>
</tr>
<tr>
<td>Immunoglobulin (g/L)</td>
<td>31.45±4.18</td>
<td>28.14±6.25</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>105.31±70.77</td>
<td>89.73±62.29</td>
<td>0.264</td>
<td></td>
</tr>
<tr>
<td>Leucocyte (10^9/L)</td>
<td>9.20±5.49</td>
<td>6.21(4.87,9.74)</td>
<td>0.407</td>
<td></td>
</tr>
<tr>
<td>Neutrophil (10^9/L)</td>
<td>8.19±5.2</td>
<td>6.85±4.69</td>
<td>0.199</td>
<td></td>
</tr>
<tr>
<td>Lymphocyte (10^9/L)</td>
<td>0.57±0.28</td>
<td>0.96±0.89</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td>PCT (10^9/L)</td>
<td>0.82(0.22,2.93)</td>
<td>0.69(0.27,1.16)</td>
<td>0.253</td>
<td></td>
</tr>
</tbody>
</table>

### Comorbidities

<table>
<thead>
<tr>
<th>Condition</th>
<th>Patients</th>
<th>Control</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>diabetes</td>
<td>48(52.17%)</td>
<td>44(47.82%)</td>
<td>0.283</td>
</tr>
<tr>
<td>cardiovascular disease</td>
<td>47(51.08%)</td>
<td>45(48.91%)</td>
<td>0.686</td>
</tr>
<tr>
<td>cerebral infarction</td>
<td>32(34.78%)</td>
<td>60(65.21%)</td>
<td>0.370</td>
</tr>
<tr>
<td>hypertension</td>
<td>52(56.52%)</td>
<td>40(43.47%)</td>
<td>0.582</td>
</tr>
</tbody>
</table>

Lac, lactate; CRP, hypersensitive C-reactive protein; PCT, procalcitonin

The predictive efficacy of tracheal intubation in patients infected with COVID-19 is depicted through the assessment of inflammatory factors.
and lymphocyte counts. Figure 1

The predictive parameters for tracheal intubation in COVID-19 infection were determined as follows: a critical value of 0.91 for lymphocyte count, exhibiting a sensitivity of 38.8%, specificity of 92.9%, and an AUC of 0.687 (95% CI: 0.580-0.795). For IL-6, the critical value was 38.21, with a sensitivity of 81%, specificity of 63.3%, and an AUC of 0.771 (95% CI: 0.6670.872). In the case of IL-8, a critical value of 54.09 corresponded to a sensitivity of 61.9%, specificity of 75.5%, and an AUC of 0.665 (95% CI: 0.545-0.771). For IL-10, the critical value was 5.05, demonstrating a sensitivity of 71.4%, specificity of 65.3%, and an AUC of 0.712 (95% CI: 0.6010.813). The tumor necrosis factor cutoff was 1.98, with a sensitivity of 52.4%, specificity of 73.5%, and an AUC of 0.648 (95% CI: 0.530-0.756). All p-values were less than 0.05.

![Fig1. ROC curve analysis of endotracheal intubation in predicting novel coronavirus infection by inflammatory factors and lymphocytes](image)

The predictive efficacy of death in patients infected with COVID-19 is
depicted through the assessment of inflammatory factors and lymphocyte counts. Figure 2

For predicting death in COVID-19 infection, the critical values and associated parameters were determined as follows: a lymphocyte count critical value of 0.56, with a sensitivity of 71.2%, specificity of 57.5%, and an AUC of 0.641 (95% CI: 0.528-0.754). The critical value for IL-6 was 53.05, with a sensitivity of 75%, specificity of 71.2%, and an AUC of 0.770 (95% CI: 0.669-0.870). In the case of IL-8, a critical value of 54.09 corresponded to a sensitivity of 62.5%, specificity of 63.5%, and an AUC of 0.687 (95% CI: 0.5780.796). For IL-10, the critical value was 5.05, with a sensitivity of 70%, specificity of 63.5%, and an AUC of 0.683 (95% CI: 0.5740.792). The tumor necrosis factor threshold was 0.98, demonstrating a sensitivity of 90%, specificity of 34.6%, and an AUC of 0.636 (95% CI: 0.5230.749). All p-values were less than 0.05.

Fig2. ROC curve analysis of inflammatory factors and lymphocytes predicting death from COVID-19 infection
**Discussion**

Over the preceding three years, the global dissemination of COVID-19 infection has been widespread. While the majority of patients exhibit mild symptoms and a favorable prognosis, a noteworthy subset, comprising 14% of cases, progresses to severe illness, and an additional 5% reach a critical state \[^1\]. The global mortality rate stands at approximately 3.4%, with observational studies underscoring the heightened risk associated with comorbidities such as obesity, cardiovascular disease, diabetes, chronic respiratory disease, hypertension, and cancer, which contribute to an increased mortality rate \[^2\]. Consequently, there is a pressing need to identify and monitor early-stage disease progression through the exploration of markers for timely intervention and improved clinical outcomes.

The immune response and the emergence of a cytokine storm are pivotal factors in the onset and progression of COVID-19. Numerous studies have consistently demonstrated elevated serum levels of proinflammatory cytokines in individuals affected by COVID-19. Moreover, the administration of anti-inflammatory drugs in the treatment of COVID-19 further underscores the fundamental role of inflammation in the disease's evolution \[^3\]. Through a retrospective analysis of medical records encompassing 92 patients, our study revealed a positive correlation between inflammatory markers, notably the extent of lymphocyte count decline, as well as the levels of IL-6, IL-8, IL-10, and tumor necrosis factor, and the severity of the disease.

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\[^2\] The immune response and the emergence of a cytokine storm are pivotal factors in the onset and progression of COVID-19. Numerous studies have consistently demonstrated elevated serum levels of proinflammatory cytokines in individuals affected by COVID-19. Moreover, the administration of anti-inflammatory drugs in the treatment of COVID-19 further underscores the fundamental role of inflammation in the disease's evolution \[^3\]. Through a retrospective analysis of medical records encompassing 92 patients, our study revealed a positive correlation between inflammatory markers, notably the extent of lymphocyte count decline, as well as the levels of IL-6, IL-8, IL-10, and tumor necrosis factor, and the severity of the disease.
A plethora of experimental studies and clinical trials have consistently established a direct correlation between the occurrence of a "cytokine storm" and the ensuing tissue damage, as well as the unfavorable prognosis associated with severe lung disease in COVID-19 [4]. The pathogenesis of COVID-19 triggers a robust inflammatory response involving a complex array of mediators, prominently including IL-6 and IL-10 [5]. These versatile cytokines are synthesized at the site of inflammation and are subsequently released into the bloodstream by various cell types, including macrophages, lymphocytes, endothelial cells, epithelial cells, and fibroblasts, particularly during instances of sepsis and acute organ dysfunction.

Recent investigations have delineated that, during COVID-19 infection, pathogenic T cells can actively secrete IL-6 and granulocyte-macrophage colony-stimulating factor (GM-CSF). Furthermore, CD14+ and CD16+ inflammatory monocytes activated by GM-CSF exhibit an increased secretion of inflammatory factors, including IL-6 [6]. Given the pivotal role of IL-6 in orchestrating the acute phase response, its potential as a prognostic biomarker has been extensively explored in the context of sepsis and various acute organ dysfunctions. Plasma and/or bronchoalveolar IL-6 levels have emerged as early biomarkers of lung injury in COVID-19 patients, with predictive value extending to prolonged mechanical ventilation time, organ dysfunction, and the incidence and mortality associated with lung disease [7].

A comprehensive systematic review and meta-analysis, encompassing 10
cohort studies and involving 1798 patients, revealed elevated IL-6 levels in individuals affected by COVID-19 [8]. Among hospitalized COVID-19 patients grappling with severe complications, a staggering 86.8% exhibited significantly heightened IL-6 levels, with 22.9% experiencing an elevation exceeding tenfold [9]. Another study reported serum IL-6 levels reaching 517±796 pg/mL in patients with severe acute respiratory syndrome. In contrast, recovered patients demonstrated a gradual decline in cytokine levels, stabilizing at 68.8±25.9 pg/mL [10].

In the comparison of cytokine levels between COVID-19 patients and healthy controls, most cytokines exhibited a moderate increase of approximately 20%. Notably, IL-10 demonstrated a 37% increase, while IL-6 showed a substantial elevation of 100% [7]. Regarding disease severity, the levels of TNF-α, IL-2, IL-6, and IL-10 in the severe group were significantly higher than those in the moderate group, with statistical significance. However, when compared to the critical group, only the levels of IL-6 and IL-10 exhibited an increase [7]. Specifically, the IL-6 level in the severe group was markedly higher than that in the moderate group [46.4 (10.0-205.0) vs. 20.05 (5.40-41.75)], and the moderate group demonstrated higher levels than the mild group [20.05 (5.40-41.75) vs. 9.30 (3.9-15.0)]. A statistically significant difference in IL-6 levels was observed between the severe and mild COVID-19 groups [11].

The findings from this study underscore a direct correlation between the extent of lymphocyte reduction and the heightened risk of tracheal intubation.
and mortality among patients, aligning with similar conclusions. Specifically, the percentage of lymphocytes in the severe group was significantly lower than that in the mild group [8.90 (5.6-16.7) vs. 21.90 (10.90-29.8)], and the percentage of lymphocytes in the moderate group was also lower than that in the mild group \[^{[12,15]}\] (7.52-21.62) vs. 21.90 (10.90-29.8)]. Notably, there was no significant difference in the percentage of lymphocytes between moderate and severe patients\[^{[11]}\].

Numerous studies have reported a noteworthy increase in the neutrophil-lymphocyte ratio among severe COVID-19 patients after a one-month follow-up \[^{[12]}\], with the ability to predict 28-day mortality\[^{[13]}\]. Laboratory indicators, including low lymphocyte count, elevated CRP, D-dimer, ferritin, cardiac troponin, and IL-6 levels, have been identified in various studies as valuable tools for assessing the severity of COVID-19. Moreover, these indicators can serve as effective means for risk stratification among severe and fatal COVID-19 patients\[^{[14]}\].

Elevated plasma levels of IL-2, IL-6, IL-10, G-CSF, IFN-γ, and TNF-α were observed in ICU patients compared to non-ICU patients \[^{[15]}\], suggesting an association between cytokine storms and disease severity, as well as adverse outcomes including death. The trio of IL-10, IL-6, and IP-10 has been identified as predictive of the subsequent clinical progression of COVID-19 \[^{[16]}\]. TNF-α, primarily produced by monocytes and macrophages, is synthesized by B cells, T cells, and fibroblasts. Notably, TNF-α is implicated in bronchial
hyperreactivity, directly exacerbating respiratory epithelial inflammation by
inducing the release of inflammatory cytokines such as GM-CSF, IL-8, and
intercellular adhesion molecules (ICAMs). This cascade results in a reduction
of airway diameter and an increase in respiratory epithelial neutrophils.
Additionally, TNF-α induces neutrophils to release MMP-9, contributing to
irreversible changes through pulmonary fibrosis\textsuperscript{[17]}. As a pivotal inflammatory
amplifier and coordinator in acute inflammatory responses, TNF-α exerts its
activity by interacting with and activating two receptors, TNF receptor (TNFR)
1 and TNFR2, to transduce signals\textsuperscript{[18]}.
Blocking the TNF-mediated inflammatory response has been shown to rapidly
reduce IL-6 and IL-1 levels in individuals with active inflammation. Notably,
data from inflammatory bowel disease patients revealed that out of 116
individuals infected with COVID-19, 99 patients who received anti-tumor
necrosis factor treatment recovered without hospitalization. Moreover, those
undergoing anti-TNF treatment exhibited a more favorable prognosis\textsuperscript{[19]}.
While IL-6 proves to be a valuable indicator for severe COVID-19 cases, IL-8
demonstrates enhanced efficacy in signaling the progression from mild to
severe disease. The serum IL-8 level in mild patients surpassed that in healthy
individuals, and in severe patients, it exhibited a further increase. ROC
analysis revealed that the area under the curve for IL-8 (0.9776) was higher
than that for IL-6 (0.8417), signifying that IL-8 outperformed IL-6 in
distinguishing COVID-19 patients from healthy individuals\textsuperscript{[20]}.
To assess the prognostic impact of IL-6 and IL-8 on disease outcomes, Li et al. monitored the fluctuations in IL-6 and IL-8 concentrations during disease progression in COVID-19 patients with varying clinical scores, representing a composite of multiple physiological indicators associated with COVID-19. Notably, IL-8 levels exhibited a strong correlation with the clinical scores of diverse patients across multiple time points. In contrast, IL-6 levels remained comparatively low at most time points, except in patients with exceptionally high clinical scores. Consequently, Li et al. demonstrated that IL-8 may serve as a promising biomarker for predicting the prognosis of COVID-19.[20]

In conclusion, inflammatory markers, particularly IL-6, IL-8, IL-10, tumor necrosis factor, and lymphocyte counts, exhibit a positive correlation with the severity of COVID-19. Controlling the cytokine storm through the use of cytokine antagonists and immunomodulators has been shown to enhance the survival rate among infected patients. Therefore, targeted therapy focusing on inflammatory cytokines holds promise for benefiting patients and improving the efficacy of antiviral treatment for those with COVID-19. However, given the intricate nature of the inflammatory network, targeting a singular inflammatory signaling pathway may prompt a compensatory immune response downstream. Consequently, simultaneous targeting of multiple inflammatory targets emerges as a promising treatment approach. The data presented in this paper, coupled with the authors' perspective, suggests that combining inflammation inhibitors with other COVID-19 treatment modalities
may yield greater efficacy than standalone treatments. The detection of inflammatory markers can assist clinicians in monitoring and evaluating the severity and prognosis of COVID-19. A dynamic analysis of the fluctuating levels of inflammatory factors and lymphocytes can contribute to the development of more scientific and rational treatment plans in subsequent stages of patient care.

**Declarations:**

**Ethics approval and consent to participate**: This study was granted ethical approval (KL901392) by the Affiliated Suzhou Hospital of Nanjing Medical University Review Board. Written informed consent was obtained from patients or their delegates.

**Consent for publication**: Not applicable.

**Availability of data and materials**: All data generated or analyzed during this study are included in this published article and its additional information files.

**Competing interests**: All co-authors declare that they have no competing interests.

**Funding**: Not applicable.

**Authors' contributions**: Zy Xu is responsible for collecting and organizing research data and writing the paper. Db Zhang is responsible for designing the research plan and reviewing the paper. All authors reviewed the
Acknowledgements: Not applicable.

REFERENCES


Figures

Figure 1

Figure 2

Figure 3

Supplementary Files

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- table1.docx
- DATA1.sav
- DATA2.sav
- DATA1d1.sav
- DATA2d1.sav