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Original Article

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The CD4 cell level as a predictive factor for the outcome severity and prognosis of patients with COVID-19

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Abstract

***Background & Aims*:** Coronavirus disease 2019 (COVID-19) leads to the activation of immune cells, especially in patients developing severe disease, and induces lymphopenia, primarily affecting the cluster of differentiation 4 T-cell (CD4+ T) subset. The presence of lymphopenia and cytokine storm may play a major role in the pathogenesis of COVID-19. This prospective single-center study aimed to assess the association between CD4 cell levels and the severity and prognosis of COVID-19 pneumonia, comparing the differences in lymphocyte subsets and inflammatory biomarkers between severe and non-severe cases using flow cytometry.

***Materials & Methods*:** Between March 1 and June 30, 2020, a cohort of 122 RT-PCR-confirmed COVID-19 patients was enrolled in this prospective study. CD4 levels and other laboratory data were measured at the beginning of hospitalization.

***Results*:** Of the 122 patients, 56 were admitted to the respiratory ward and 66 to the ICU. ICU patients had significantly lower CD4 counts (368.93 cells/μL) compared to non-ICU patients (562.24 cells/μL) ($P = 0.001$). Serum C-reactive protein (CRP) levels were significantly higher in ICU patients (85.06 ± 41.85 mg/dL) than in non-ICU patients (57.29 ± 27.51 mg/dL) ($P = 0.01$), and a negative correlation was observed between CRP and CD4 levels ($P = 0.03$). Mortality was significantly higher in ICU patients (40.9%) compared to non-ICU patients (19.6%) (Odds Ratio = 2.83, $P = 0.006$).

***Conclusion*:** Our study demonstrates that lower CD4+ T-cell counts on admission are strongly associated with increased disease severity and poor prognosis in COVID-19 patients. The correlation between lower CD4 levels and higher CRP suggests that CD4+ T cell depletion may be a critical marker for predicting clinical outcomes. These findings highlight the potential role of CD4+ T-cell monitoring in managing severe COVID-19 cases and improving prognostic assessments.

***Keywords*:** COVID-19, CD4 cell, Immune response, Inflammatory biomarkers, Lymphopenia

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Introduction

Cytokines and innate immune cells regulate immune responses to viral infections, mediate inflammation, and are involved in tissue damage and repair (1). Following infection, the host's innate immune system acts first to curb viral invasion and replication, preceding the adaptive immune system (2). An excessive immune response can aggravate and damage the lungs (3). Dysregulated immune cell responses significantly contribute to the severity of virus-induced diseases (4).

Coronavirus disease 2019 (COVID-19) rapidly activates innate immune cells, particularly in severe cases (5). The infection induces lymphocytopenia, affecting CD4+ T cells, including effector, memory, and regulatory subsets (6). Systemic inflammation alters peripheral blood leukocytes, measurable by the neutrophil-to-lymphocyte ratio (NLR), a prognostic marker for inflammation, cancer, tuberculosis (TB), and autoimmune diseases (7-10).

Leukocytosis, characterized by increased neutrophils and monocytes, was observed in most Middle East respiratory syndrome coronavirus (MERS-CoV) patients, with rapid drops in lymphocyte counts in deceased patient. The inflammatory reaction may increase neutrophil production and lymphocyte apoptosis. Early glucocorticoid intervention during cytokine storms can reduce ARDS formation and protect organ function (11).

Cluster of differentiation 4 T-cells (CD4+ T) are crucial for mounting an adaptive immune response and coordinating immune function. A decrease in CD4+ T cell counts has been associated with severe immunosuppression, making patients more susceptible to severe forms of COVID-19 (12). Monitoring CD4+ T cell levels provides insight into the immune system's capacity to respond to the infection, making it a key predictor of clinical outcomes in COVID-19 patients (13). While previous studies have explored various immune markers, the specific relationship between CD4+ T cell levels, cytokine responses, and clinical prognosis in COVID-19 patients remains controversial (13). This research seeks to address this unmet need by providing evidence on the prognostic significance of CD4+ T cells in managing severe COVID-19.

With no standardized treatments available, identifying risk factors for severe COVID-19 prognosis is crucial. This prospective, single-center study aimed to analyze infection-related biomarkers, inflammatory cytokines, and lymphocyte subsets, including CD4+ T cells, by flow cytometry in laboratory-confirmed cases, comparing severe and non-severe cases. Specifically, biomarkers such as C-reactive protein (CRP), D-dimer, lactate dehydrogenase (LDH), and procalcitonin, as well as inflammatory cytokines like interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ), were analyzed.

Materials & Methods

Study Design

This was a prospective observational study conducted at Firoozabadi General Hospital, a single-center located in Tehran, Iran. We investigated the association of CD4 cell levels with the severity and prognosis of pneumonia caused by COVID-19, through a prospective cohort. A consecutive series of 122 RT-PCR-confirmed COVID-19 patients were enrolled between March 1st and June 30th, 2020.

Study Population

Participants were categorized into severe and non-severe cases based on clinical presentation: Severe cases were defined as patients requiring ICU admission, mechanical ventilation, or experiencing organ failure. Non-severe cases included patients who were managed in the general ward without requiring ICU care or mechanical ventilation. The inclusion criteria for the study were as follows: patients aged 18 years or older with a laboratory-confirmed diagnosis of COVID-19 (positive PCR of nasopharyngeal swab), with or without specific lung involvement. We also excluded patients with a history of HIV infection, lymphoproliferative or hematologic diseases, rheumatologic diseases, or those using antiviral chemotherapy or immunomodulatory therapy.

Data Collection

At the beginning of hospitalization, a pre-prepared checklist was used to collect relevant patient data, including demographic characteristics (sex, age, smoking history, and opium consumption), a complete medical history (diabetes, hypertension, cardiovascular disease, hematologic disorders, and HIV), drug history, and clinical symptoms (fever, myalgia, cough, dyspnea, and olfactory disorder). Laboratory data and imaging were requested as needed. Radiological findings from chest CT scans were reviewed by an experienced radiologist using a standardized scoring system to assess the extent of lung involvement.

Measurement of CD4 Levels

CD4 levels were measured by flow cytometry. Blood samples were collected at the time of admission, prior to the initiation of any treatment. A BD FACSCalibur™ flow cytometer was used to assess the CD4+ T cell counts, following standard procedures. Monoclonal antibodies specific for CD4+ T cells were used to label the samples, and results were expressed as the number of CD4+ T cells per microliter of blood. The laboratory team strictly adhered to the recommended protocol for flow cytometry to ensure accurate measurements.

Statistical Analysis

Data were presented as means ± SD for continuous variables and as frequencies (percentages) for categorical variables. Statistical analyses were performed using SPSS software for Windows (version 26.0, SPSS Inc., Chicago, IL, USA). The Student's t-test was used for continuous variables, while the chi-squared test was employed for categorical variables. Statistical significance of *P-values* less than 0.05 were considered. Multiple imputation was used to handle missing data, to ensure missing information was accounted for. We excluded cases we could not impute from the specific analysis.

Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki. The research protocol was registered with and approved by the Ethical Committee of Iran University of Medical Sciences (Ethics Code: IR.IUMS.REC.1399.007). Informed written consent was obtained from each patient prior to participation. To ensure confidentiality and anonymity, patient data were anonymized before being analyzed, and all participants' personal information was kept strictly confidential throughout the study.

Outcome Measures

The duration and outcome of hospitalization were recorded for both ICU and non-ICU patients. Outcomes included either recovery (discharge) or death.

Results

The mean age of the patients was 64.8 ± 15.4 years (range: 28-99 years). Data from a consecutive series of 122 patients, comprising 70 (57.3%) males and 52 (43.7%) females, were analyzed. Baseline and demographic characteristics of the participants are presented in Table 1.

Table 1. Baseline and demographic characteristics of participants

S.No.	Parameters	Mean ± SD
1	Age (y/o)	64.11 ± 15.65
2	BUN (mg/dl)	25.44 ± 22.87
3	Creatinin (mg/dl)	1.51 ± 1.28
4	CPK (mg/dl)	273.48 ± 249.86
5	LDH (mg/dl)	749.96 ± 421.66
6	Troponin-I	247.67 ± 885.97
7	D-dimer	2381.59 ± 684.45
8	SGOT (mg/dl)	53.21 ± 43.01

S.No.	Parameters	Mean ± SD
9	SGPT (mg/dl)	43.24 ± 42.81
10	CD4	458.05 ± 331.62
11	WBC	8.09 ± 3.42
12	HB (mg/dl)	12.32 ± 2.94
13	MCV	86.17 ± 9.91
14	RDW	15.07 ± 2.67
15	PMN	76.79 ± 12.84
16	PLT	233.4 ± 96.51
17	LYM	15.78 ± 10
18	MPV	10.32 ± 1.08
19	BS (mg/dl)	173.32 ± 89.22
20	CRP (mg/dl)	72.04 ± 62.94
21	ESR (mg/dl)	47.06 ± 27.96

Among the 122 patients, 44 (36%) had either diabetes mellitus, essential hypertension or ischemic heart disease; with prevalence rates of 34 (27.8%), 37 (30.3%), and 16 (13.1%), respectively. The average duration from symptom onset to admission was 11.3 ± 4.6 days.

The most common symptoms at the time of admission were dry cough, myalgia, fever, and shortness of breath. As shown in Table 2, of the 122 hospitalized patients, 56 were admitted to the respiratory ward (group 1) and 66 were admitted to the intensive care unit (ICU) due to disease severity (group 2).

Table 2. Comparison clinical and laboratory data between ICU and non-ICU patients

Parameters	ICU patients (N = 66)	Non-ICU patients (N = 56)	*P-value*
Age (y/o)	67.45 ± 16.48	60.16 ± 13.73	0.009
WBC count	8359 ± 3271	7785 ± 3591	0.36
Hemoglobin (mg/dl)	11.83 ± 3.22	12.87 ± 2.47	0.04
Platelet count	231 ± 90 × 1000	235 ± 104.33	0.25
PMN	76.84 ± 12.71	76.72 ± 13.09	0.96
Lymphocytes	15.60 ± 10.02	15.98 ± 10.06	0.83
BS (mg/dl)	166 ± 84.96	180 ± 93.75	0.42
D-dimer	2061 ± 280.31	2012 ± 858.75	0.52
LDH (mg/dl)	665 ± 415.59	829 ± 422.02	0.15
Troponin-I	3.96 ± 1189.83	986.4 ± 357.54	0.12
CD4	368.93 ± 275.71	562.24 ± 361.86	0.001
ESR (mg/dl)	46.05 ± 26.44	48.30 ± 29.98	0.69
CRP (mg/dl)	85.06 ± 41.85	57.29 ± 27.51	0.01

WBC: White blood cells PMN: Polymorphonuclear cells
BS: Blood sugar LDH: Lactate dehydrogenase
ESR: Erythrocyte sedimentation rate CRP: C-Reactive protein

Our results revealed that older patients were more likely to be admitted to the ICU. The mean ages were 60.16 ± 13.2 and 67.45 ± 16.48 years in groups 1 and 2, respectively, which were significantly different (P = 0.03). According to our study, there was no statistically significant relationship between gender and disease severity, including ICU admission (Odds Ratio = 1.12, 95% CI: 0.56 to 2.31, P = 0.74) and mortality during admission (Odds Ratio = 1.15, 95% CI: 0.53 to 2.47, P = 0.86). The mortality rate was significantly higher in ICU patients compared to non-ICU patients (40.9% vs. 19.6%, Odds Ratio = 2.83, 95% CI: 1.24 to 2.31, P = 0.006).

As shown in Table 2, serum CRP levels were significantly higher in critically ill patients admitted to the ICU compared to non-ICU patients (80.76 ± 8.9 vs. 60.75 ± 6.92, P = 0.01). Serum CRP levels were also higher in patients who died compared to those who survived (92.83 ± 14.17 vs. 62.71 ± 5.51, P = 0.01), indicating that CRP can be a predictive marker for mortality.

Our results demonstrated that ICU patients had lower hemoglobin levels compared to non-ICU patients (11.83 ± 3.22 vs. 12.87 ± 2.47, P = 0.04). White blood cell counts (WBCs) on admission were not significantly different between ICU and non-ICU patients (8359 ± 3271 vs. 7785 ± 3591, P = 0.36). However, serum CD4 levels were significantly lower among ICU patients compared to non-ICU patients (P = 0.001).

As shown by figure 1, linear regression analysis showed a significant correlation between serum CRP and CD4 levels (Pearson correlation -2.27, P = 0.03).

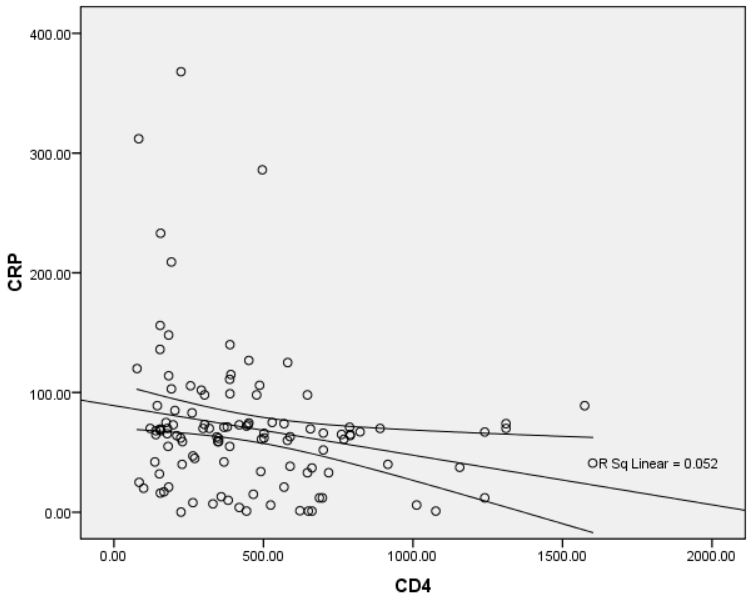

Fig. 1. Correlation between serum CD4 and CRP levels

Discussion

In this study, we found that abnormal lymphocyte and CD4+ T cell counts at the time of admission in patients with COVID-19 could predict their prognosis. Lower counts of CD4+ T cells were closely related to disease severity and clinical outcomes, showing a negative correlation with CRP levels. Since the primary target of most COVID-19 vaccines is the spike protein and CD4+ T cell responses to this protein are correlated with the production of anti-SARS-CoV-2 IgG and IgA, it is predictable that CD4+ counts are associated with COVID-19 severity (14). The mean CD4+ T cell count

in ICU patients was 368.93 cells/μL, compared to 562.24 cells/μL in non-ICU patients. To establish a cut-off for CD4+ count as a prognostic factor, the sensitivity of CD4+ counts should be analyzed. One study estimated that a CD4+ count of less than 355 cells/μL indicates a poor prognosis for COVID-19 patients (15). Our results align with these findings, demonstrating that CD4+ depletion can serve as a useful prognostic marker for severe COVID-19 cases. From a clinical standpoint, CD4+ T cell monitoring should be integrated into standard care protocols for hospitalized COVID-19 patients, especially those requiring intensive care. In terms of clinical implications, identifying patients with significantly depleted CD4+ counts could prompt earlier and more targeted interventions, such as aggressive monitoring or early ICU admission. Patients with CD4+ counts below a certain threshold may benefit from immunomodulatory therapies or corticosteroids to prevent progression to critical illness.

Similar to our study, Previous studies on infections caused by MERS, SARS, and SARS-CoV-2 demonstrated that severe cases were marked by lymphopenia, including a dramatic loss of CD4+ T cells and elevated NLR, which correlated with disease severity (16-18). Moreover, previous studies demonstrated that COVID-19 patients who died had lower lymphocyte levels (19). Additionally, the total number of CD8+ T cells also decreased alongside CD4+ T cells, particularly in patients over 60 years old and those admitted to the ICU (20). This is consistent with our results, where older ICU patients had significantly lower CD4+ counts, highlighting the impact of age on immune depletion. This lymphopenia is attributed to the production of inflammatory cytokines such as IL-1, IFN-γ, and IL-6, which inhibit T cell proliferation (21). Chronic infections like COVID-19 cause T cell exhaustion and death, similar to the mechanism observed in Hepatitis C virus infections. However, the exact mechanism of T cell apoptosis in COVID-19 remains unclear (17).

Consistent with the findings of Seung Mi Oh et al., our study compared the clinical and laboratory findings in severe and critically ill COVID-19 cases, demonstrating that decreased hemoglobin and the presence of anemia at admission are correlated with increased mortality and could be independent risk factors for severe COVID-19 (22). We already know that SpO2, lymphocytes, CRP, procalcitonin, and LDH are established predictors COVID-19 severity (23). Lower lymphocyte counts and higher levels of CRP, procalcitonin, IL-6, neutrophils, LDH, D-dimer, cardiac troponin I, and brain natriuretic peptide, along with an increased CD4+/CD8+ T-lymphocyte ratio, are associated with COVID-19 severity (24). While lower CD4+ counts are related to COVID-19 severity, an increased CD4+/CD8+ T-lymphocyte ratio is another biomarker indicating poor prognosis. Thus, profiling immune system markers in COVID-19 patients can help predict their prognosis and the need for ICU admission (25).

Study Limitations

While this prospective study provides valuable insights, the sample size of 122 patients may limit expanding of our findings to general population. Bigger sample sizes are needed to confirm the use of CD4+ T cells as a prognostic marker across different populations. Additionally, the study did not include sensitivity and specificity analyses, which could further refine CD4+ T cell thresholds for clinical use. Future research should address these gaps and consider confounding factors such as pre-existing immunosuppressive conditions.

Conclusion

Lower CD4+ T cell counts on admission in COVID-19 patients reflect disease severity and can predict illness prognosis, making them valuable indicators of COVID-19 activity. The reduction in CD4+ T cells, increase in CRP levels, patient age, and presence of anemia should be considered critical factors in monitoring and treating COVID-19.

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Ethical statement

This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the Ethical Committee of Iran University of Medical Sciences (Approval number: IR.IUMS.REC.1399.007). All included patients were asked for an informed consent prior to their enrollment.

Data availability

The corresponding author could be requested to provide access to the data. Due to the sensitive nature of the COVID-19 information, restrictions apply to the availability of some data.

Conflict of interest

The authors declare that they have no conflicts of interest related to this study.

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Author contributions

None declared.

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