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Inflammation-related Parameters in Hospitalized Patients with COVID-19: A Retrospective Observational Study

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Abstract: Assessing biomarker levels during diagnosis may be useful for predicting disease severity when formulating patient care plans. Especially, C-reactive protein (CRP) levels are often used to indicate disease severity and to monitor the response of coronavirus disease (COVID-19) patients to treatment. Similarly, an elevated erythrocyte sedimentation rate (ESR) and white blood cell (WBC) count have been reported as indicators and predictors of disease severity. This retrospective study compared immune indicators, including CRP, ESR, and WBC count, in COVID-19 patients and control group with a standard age of approximately 50 years. Data analysis was performed for patients with COVID-19 hospitalized for two weeks in Gyeonggi Provincial Medical Center Anseong Hospital, South Korea between April and October 2020 and healthy controls who underwent a health checkup in January 2020. Two groups of patients were formed based on the collected data from electronic medical records: younger (<50 years) and older adults (≥50 years). CRP levels and ESR were elevated in both young people and older adults with COVID-19. In contrast, the WBC count were decreased in young people and increased in older adults with COVID-19. Compared to control group, individuals diagnosed with COVID-19 exhibited greater CRP and ESR, with more pronounced differences observed in older adults relative to younger ones. This study provides important data on age-specific immune indicators of COVID-19 by comparing and analyzing immune indicators in individuals with a standard age of approximately 50 years. The findings can also help understand diagnostic test results and characterize viral infection at a specific time, facilitating diagnosis of COVID-19, treatment of the disease, and prediction of patient response. These values may also be useful in assessing and responding to outbreaks of similar viral diseases.

Keywords: COVID-19, C-reactive Protein, ESR, Infection, Inflammatory Parameter

1. Introduction

Coronavirus disease (COVID-19) outcomes can range from a slight fever and cough to acute

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respiratory pain and even death, making it challenging to predict the progression of the disease[1][2]. Furthermore, the development of new coronavirus strains with varying levels of transmissibility and causing different levels of illness adds to the complexity of understanding and managing the pandemic [3][4]. Therefore, assessing biomarker levels during diagnosis may be useful for predicting disease severity when formulating patient care plans[5][6].

Hematological parameters and inflammatory indices based on blood cell analysis are useful prognostic indicators in patients with infections and many other diseases[7][8]. Laboratory testing is key to COVID-19 diagnosis[9]. At COVID-19 onset, doctors rely on a combination of hematological and biochemical measurements[10][11], including erythrocyte sedimentation rate (ESR), white blood cell (WBC) count and C-reactive protein (CRP), to ascertain the disease's severity[12].

Inflammatory responses, characterized by a surge of cytokine activity, are a typical characteristic of severe COVID-19 and other significant illnesses[13]. Several types of viral respiratory infections trigger an immune response accompanied by inflammation, which is significant during the development of COVID-19[14].

In South Korea, the COVID-19 case fatality rate increases sharply after 50 years of age[15]. Individuals aged ≥50 years are classified as a vulnerable group because they are prone to spread acute disease and have greater COVID-19 mortality rates than younger individuals[16][17]. The government has thus prioritized COVID-19 vaccination for this age group. Therefore, biomarker data of older individuals could be helpful for disease prevention and making prompt treatment decisions.

This retrospective study aimed to evaluate and to compare immune markers, in individuals diagnosed with COVID-19 and healthy individuals aged approximately 50 years to provide information on age-related immune markers in patients. The study was intended to offer useful information for establishing a patient's treatment plan or predicting disease severity. The research questions were as follows:

1) What are the correlations between individuals with COVID-19 diagnosis aged approximately 50 years and healthy individuals regarding immune markers?

2) Can the immune markers be evaluated and compared to provide information on age-related immune markers in the COVID-19 patients?

2. Methods

2.1 Investigation Design

This study was a retrospective analysis of COVID-19 patients hospitalized for 2 weeks after confirmation of a positive COVID-19 diagnosis at the Gyeonggi Medical Center. The hospital is a domestic COVID-19 base hospital, and the data was collected from April 2020 to October 2020. During the study period, the inspection agency conducted temporary emergency work to efficiently respond to the COVID-19 pandemic and treated only patients diagnosed with COVID-19. The analysis of COVID-19 was proved by conducting reverse-transcription quantitative polymerase chain reaction (RT-qPCR) tests on respiratory samples. Patients who underwent a health checkup at the hospital in January 2020, before the COVID-19 pandemic started in South Korea, were selected as a control group. The study divided patients into two groups based on their age: younger (<50 years) and older (≥50 years) adults.

2.2 Ethical Approval

This investigation received acceptance from Dankook University's Clinical Research Review Committee (Certificate No. 2020-12-010). Being a retrospective study using only data on sex and age, the research review team renounced the need for informed agreement.

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2.3 Data Collection

Figures were compiled from electronic charts of patients and controls. Blood tests for detecting inflammatory parameters (CRP level and WBC count) were performed using a hematology analyzer (ADIVA2120i; Siemens Healthcare Diagnostics, Tarrytown, NY, USA). An ESR analyzer (TEST-1; Alifax SRL, Polverara, Italy) was used to measure the ESR. These data were evaluated by the diagnostic test department at Anseong Hospital of Gyeonggi Medical Center according to standard blood testing procedures. In patients with COVID-19, data on inflammation parameters were obtained from the first blood test on the day of hospitalization after confirmation of the COVID-19 diagnosis.

2.4 Statistical Analyses

For each group, we calculated the mean and standard deviation and used an independent samples t-test to determine whether there were any significant differences between the two groups. The area under the curve (AUC), based on receiver operating characteristic (ROC) curve analysis, was utilized to establish optimal cut-off values of the biomarkers in younger and older adults. All numerical analyses were completed using Microsoft Excel program (Microsoft Inc., Redmond, WA, USA) and MedCalc Ver. 20.027 (MedCalc® Ostend, Belgium). An effect or difference between groups is considered statistically significant if the probability of observing such an effect or difference due to chance is low, measured by a p-value of less than 0.05.

3. Results

3.1 Participant Characteristics and Clinical Data

The 612 patients were incorporated in the analysis, comprising 492 COVID-19 patients and 120 healthy controls (112 [23%] were younger adults and 380 [77%] were older adults). Among the healthy controls, 49 (41%) were younger adults and 71 (59%) were older adults [Table 1]. The mean age was 36 years (±10 years) for younger adults and 70 years (±11 years) for older adults.

3.2 Levels of Inflammatory Parameters by Age

In younger adults with COVID-19, the CRP, ESR, and WBC count were 1.08±2.07 mg/dL (standard range: ≤0.5 mg/dL), 27.49±20.37 mm/h (standard range: ≤20 mm/h), and $5.59±1.66×10^3$/μL (standard range: 4.00 – $10.00×10^3$/μL), respectively, whereas in older adults with COVID-19, the CRP, ESR, and WBC count were 3.57±4.82 mg/dL, 49.89±28.29 mm/h, and $6.22±3.13×10^3$/μL, respectively [Table 1].

3.3 Inflammatory Markers and Laboratory Parameters between COVID-19 Positive Cases and Controls according to Age Groups

Patients diagnosed with COVID-19 had significantly elevated CRP levels and ESR compared to healthy individuals. Younger adults with COVID-19 had a higher CRP level (1.08±2.07 mg/dL vs. 0.13±0.22 mg/dL : $p<0.001$) and ESR (27.49±20.37 mm/h vs 10.69±6.8 mm/h : $p<0.001$) than healthy controls. On the contrary, younger adults with COVID-19 showed a lower WBC count ($6.33±1.92×10^3$/μL vs. $5.59±1.66×10^3$/μL, $p=0.014$). In the older age group, there were significantly higher CRP, ESR, and WBC count in COVID-19 positive patients compared to the healthy controls (CRP level, 3.54±4.82 mg/dL vs. 0.15±0.26 mg/dL, <0.001; ESR, 15.45±0.26 mm/h vs. 3.57±4.82 mm/h, $p<0.001$; WBC count, $6.22±3.13×10^3$/μL vs. $6.15±1.63×10^3$/μL $p=0.777$). However, the

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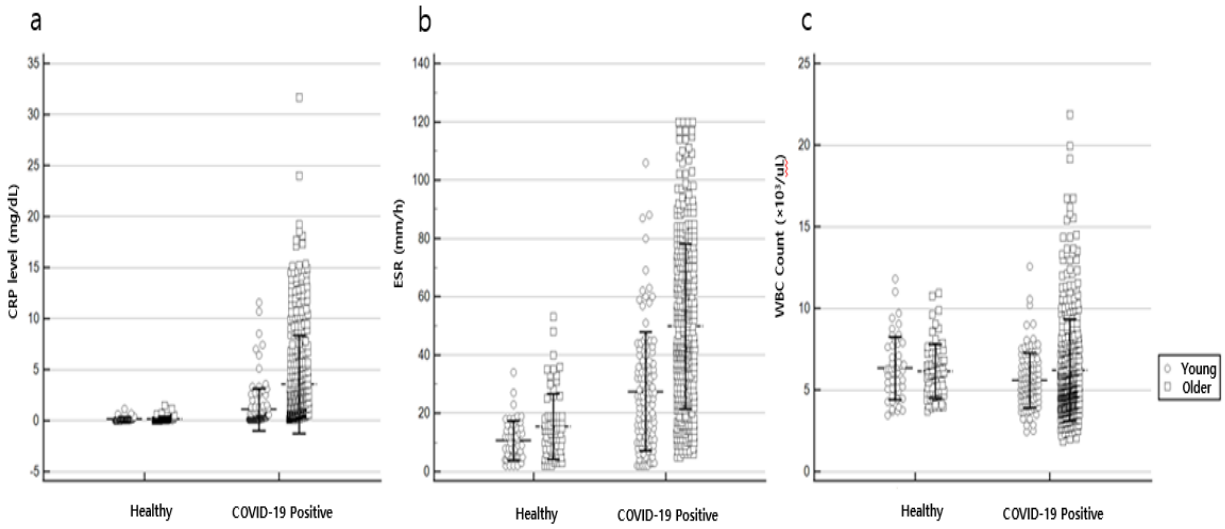
differences were only significant for the CRP (p<0.001) and ESR (p<0.001). The difference in WBC count was not significant (p=0.777) [Table 1], [Fig. 1].

[Table 1] Participant Characteristics and Laboratory Results

Parameter	age <50 years			age ≥50 years		
	Healthy controls (n = 49)	**COVID-19 (n = 112)**	**p**	**Healthy controls (n = 71)**	**COVID-19 (n = 380)**	**p**
Sex (n, %)						
Male	29 (59%)	68 (61%)	0.855	44 (62%)	175 (46%)	0.014
Female	20 (41%)	44 (39%)		27 (38%)	205 (54%)	
CRP (mg/dL), mean ± SD	0.13 ± 0.22	1.08 ± 2.07	<0.001	0.15 ± 0.26	3.57 ± 4.82	<0.001
ESR (mm/h), mean ± SD	10.69 ±6.86	27.49 ±20.37	<0.001	15.45±11.17	49.89±28.29	<0.001
WBC (× 103/μL), mean ± SD	6.33 ± 1.92	5.59 ± 1.66	0.014	6.15 ± 1.63	6.22 ± 3.13	0.777



[Fig. 1] Comparison of Inflammatory Parameters (a, b) and White Blood Cell Count Among Younger and Older Adults and between COVID-19 positive patients and Healthy Controls

(a) CRP; (b) ESR; (c) WBC count.

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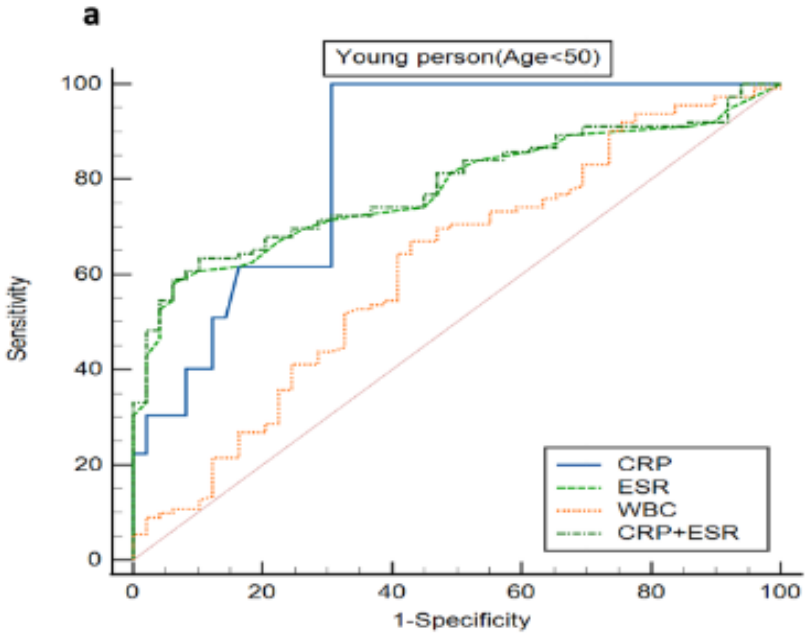
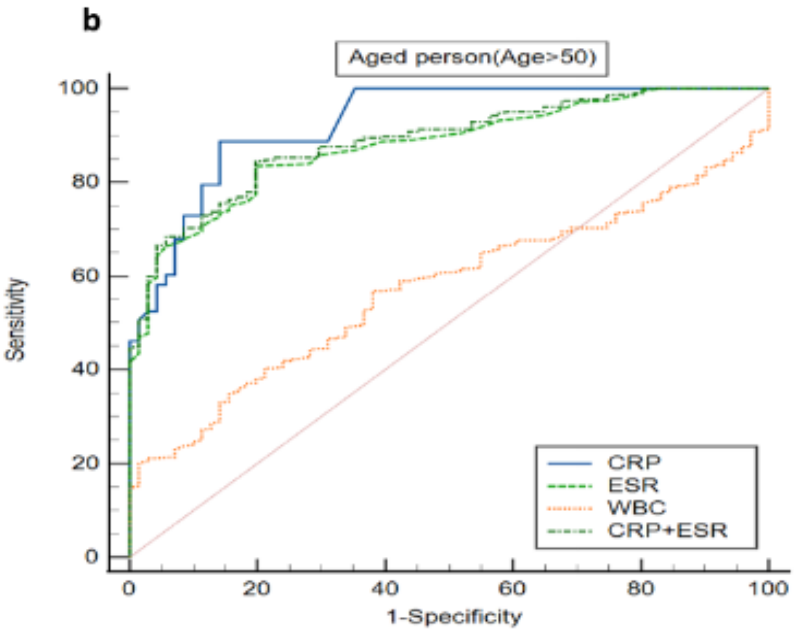


	AUC	Standard division	95% Confidence interval
CRP	0.843	0.038	0.778~0.896
ESR	0.777	0.036	0.705~0.839
WBC	0.615	0.050	0.535~0.690
CRP+ESR	0.786	0.035	0.714~0.847



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	AUC	Standard division	95% Confidence interval
CRP	0.928	0.017	0.900~0.950
ESR	0.878	0.018	0.844~0.907
WBC	0.572	0.030	0.525~0.618
CRP+ESR	0.888	0.018	0.855~0.915

[Fig. 2] Receiver Operating Characteristic Curve of the Accuracy of Inflammatory Parameters for Diagnosing COVID-19 According to Age

(a) Diagnostic accuracy of CRP level, ESR, and WBC count in distinguishing between individuals with and without COVID-19 among younger adults (age <50 years). (b) Diagnostic accuracy of CRP level, ESR, and WBC count in distinguishing between individuals with and without COVID-19 among older adults (age ≥50 years).

3.4 Differences in Inflammatory Parameters in COVID-19 Patients and Controls

The AUCs for differentiating between COVID-19 positive cases and controls according to the CRP, ESR, WBC count, and CRP combined with ESR were 0.843 (95% confidence interval [CI]; 0.778–0.896), 0.777 (95% CI; 0.705–0.839), 0.615 (95% CI; 0.535–0.690), and 0.786 (95% CI; 0.714–0.847), in younger adults. In older adults, AUC values for distinguishing COVID-19 from healthy controls according to the CRP level, ESR, WBC count, and CRP level combined with ESR, were 0.928 (95% CI; 0.900–0.950), 0.878 (95% CI; 0.844–0.907), 0.572 (95% CI; 0.525–0618), and 0.888 (95% CI; 0.0.855–0.915), respectively [Fig. 2]. The AUCs were interpreted as excellent (0.9 <AUC), good (0.8 <AUC <0.9), fair (0.7 <AUC <0.8), poor (0.6 <AUC <0.7), or failed (0.5 <AUC <0.6).

4. Discussion

While molecular identification through PCR is recommended for determining COVID-19, analyzing biomarkers and hematological parameters can be valuable for tracking patient progress and predicting outcomes. A previous study reported minor hematologic changes in early COVID-19, although significant changes were observed in progressive disease; thus, hematological data can guide treatment planning and predict patient outcomes[18].

The assessment of biomarker levels during the diagnosis phase could be valuable in predicting disease severity, thereby aiding the formulation of patient care plans[19]. CRP is a biomarker that indicates inflammation. It is formed by the liver and released into the blood in reaction to infection, helping the body fight infections caused by invading pathogens. Severe COVID-19 patients, the greater CRP levels may be due to several factors, including a secondary bacterial co-infection; a strong inflammatory response caused by the virus itself, or both. Therefore, CRP levels are often used as an indicator of illness severity and to monitor the reaction to treatment in patients with COVID-19[9][19][20]. An elevated ESR has also been stated to be a predictor of infection severity[18]. Recent studies have shown that the WBC count is also an indicator of disease seriousness[18][21-23].

As reported previously[21][24-27], comparisons by age have shown that CRP levels and ESR are

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elevated in both young people and older adults with COVID-19, whereas the WBC count is decreased in young people and increased in older adults with COVID-19[28]. Therefore, no major difference in the WBC count was found among the COVID-19 positive cases and controls in the older age group.

COVID-19 cases had higher CRP and ESR than healthy controls, and the differences were more marked in older than in younger adults, possibly because older adults are more susceptible to developing severe COVID-19[6][14][22]. In the ROC curve analysis, the AUCs showed that the CRP and ESR were both effective predictors of COVID-19 in older adults, and that the CRP was an effective predictor of COVID-19 in younger adults.

The ESR and CRP level, which predict the severity of inflammation and infection, were higher in older patients with COVID-19 than in controls, the ROC curve analysis confirmed they are effective predictors of COVID-19. The findings of this study provide evidence of hematological alterations in the initial stages of COVID-19 and suggest the potential utility of hematological data as a predictor of COVID-19 patient prognosis.

This research has some limitations. Owing to the design and retrospective nature of data collection, data on other inflammatory biomarkers, such as procalcitonin (an indicator of bacterial infection[29]) and lactate dehydrogenase[30-32], were not available for analysis. However, since biomarkers were measured after confirmation and hospitalization of patients with COVID-19, immune indicators such as CRP, ESR, and WBC count, studied in this research, may be useful for checking and predicting the progress of COVID-19. Furthermore, owing to the administrative approach and temporary operations of the COVID-19 hospital, only patients with definite positive COVID-19 diagnosis were admitted and managed. Therefore, the presence or absence of other respiratory illnesses in inpatients and severity of COVID-19 could not be determined. Future research should explore other potential biomarkers for predicting COVID-19 prognosis.

Nevertheless, this study is important because it compared and analyzed immune markers in the COVID-19 patients and controls with a standard age of approximately 50 years to provide data on age-specific immune indicators of COVID-19 positive patients.

5. Conclusions

The aim of this study was to compare immune markers in individuals with COVID-19 and healthy individuals aged around 50 years, with the objective of providing insights into age-related immune marker changes. The results revealed that the CRP level and ESR, which are immune-related markers, were particularly increased in older adults with COVID-19. Evaluation of biomarker levels during the diagnosis can be important in assessing the disease severity or establishing a treatment plan for a patient. The findings can help to understand the diagnostic test results and characterize the viral infection at a specific time, which may be important in diagnosing COVID-19, treating the disease, and predicting patient response. In addition, these results provide age-specific information on immune markers and fundamental clinical data for follow-up studies on COVID-19.

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