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Erythrocyte levels in chronic obstructive pulmonary disease (COPD) patients with a history of positive and negative COVID-19

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ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) is a prevalent respiratory condition that predisposes patients to severe complications when infected with SARS-CoV-2 (COVID-19). Hematological alterations, particularly in erythrocyte levels, may influence the clinical course and outcomes in these high-risk individuals.

Objective: This study aimed to evaluate the erythrocyte profile of COPD patients with and without COVID-19 at RS Paru Dr. Ario Wirawan Salatiga.

Methods: An analytic study design was employed. Participants were recruited using consecutive sampling. All COPD patients admitted between March 2019 and December 2023 were included. A total of 53 COPD patients participated, comprising 27 COVID-19-positive and 26 COVID-19-negative patients.

Results: The mean erythrocyte level in the COVID-19-positive COPD group was 4.23 ± 0.73 million/µl, while in the COVID-19-negative COPD group, it was 4.77 ± 0.78 million/µl. Although a statistically significant difference was observed between the two groups ($p = 0.012$), both values remain within the normal reference range.

Conclusion: Erythrocyte levels in both the COVID-19-positive and COVID-19-negative COPD groups remained within the normal range, although the levels were relatively lower in the COVID-19-positive group with statistical significance. Further research is needed to explore the underlying mechanisms contributing to this difference.

Keywords: COPD, COVID-19, erythrocyte count

Introduction

Chronic obstructive pulmonary disease (COPD) is a collective term for long-lasting lung conditions marked by ongoing symptoms and reduced airflow. This limitation in airflow is mainly caused by the blockage of small airways (bronchiolitis) and the destruction of lung tissue (emphysema) [1]. The disease is linked to an abnormal inflammatory reaction to harmful particles or gases, with common symptoms including breathlessness and coughing, which may or may not be accompanied by sputum [2]. Major risk factors for developing COPD include cigarette smoking and exposure to environmental pollutants, such as biomass smoke and air pollution. In Indonesia, COPD is one of the four major non-communicable diseases accounting for 60% of all deaths; basic health research from 35 provinces indicates the highest prevalence in Papua (7%) and the lowest in Bali (2.5%) and Central Java (3%) [3].

The occurrence of anemia in individuals with COPD has been reported to vary between 7.5% and 33%. For example, the ANTADIR study identified anemia in 13.6% of COPD patients. The World Health Organization (WHO) defines anemia in the general population as having a hemoglobin level below 13.0 g/dL for men and below 12.0 g/dL for women [4, 5]. The etiology of anemia in COPD is

likely multifactorial, involving chronic inflammation, iron deficiency, vitamin deficiencies, comorbidities, hypogonadism, and treatment-related factors. Genetic factors, such as mutations in *SERPINA1*—which encodes for alpha-1 antitrypsin and contributes to its deficiency—have also been implicated [6, 7]. Moreover, genes encoding matrix metalloproteinase 12 (MMP-12) and glutathione-S-transferase, both associated with lung function and COPD risk, may play contributory roles [7, 8]. Anemia of chronic disease (ACD), largely resulting from systemic inflammation due to COPD, appears to be the most prevalent type of anemia in these patients. In COPD, the presence of anemia is associated with higher healthcare utilization, lower quality of life, decreased survival, and an elevated risk of hospitalization [6].

COVID-19 is an infectious illness triggered by SARS-CoV-2, a member of the Coronaviridae family. This virus, characterized by its enveloped structure and positive-sense single-stranded RNA, is known to cause infections in both the respiratory and gastrointestinal systems [2]. In patients with severe COVID-19, hematological alterations have been observed, suggesting that progressive changes in blood parameters may reflect disease severity. Monitoring these hematological parameters, including erythrocyte levels, may therefore be crucial for managing COVID-19 and mitigating the risk of severe outcomes. Furthermore, such changes may contribute to the pathogenesis of long COVID. Consequently, this study aimed to assess the erythrocyte levels in COPD patients with and without COVID-19 at RS Paru Dr. Ario Wirawan in Salatiga, Central Java, Indonesia.

Method

This analytical, cross-sectional study" was conducted at RS Paru Dr. Ario Wirawan Salatiga from March 2019 to December 2023. RS Paru Dr. Ario Wirawan Salatiga is a referral hospital specializing in pulmonary diseases, and COPD is among the top 10 most common diagnoses in both outpatient and inpatient care at this institution. Patients admitted to RS Paru Dr. Ario Wirawan Salatiga with a diagnosis of SARS-CoV-2 pneumonia, according to WHO interim guidance, were enrolled. The inclusion criteria comprised COPD patients aged 18 years or older, with COVID-19 status confirmed as either positive or negative using standard PCR tests. Patients were excluded if (a) their COVID-19 test results were obtained from a different PCR test, or (b) data on erythrocyte levels and outcomes were missing. Ultimately, 53 patients were included during the study period, with 27 testing positive for COVID-19 and 26 testing negative. The sample size was deemed statistically adequate. The study protocol was approved by the Ethics Commission of RSI Sultan Agung Semarang (approval number 285/KEPK-RSISA/X/2023).

Data were collected from secondary sources through electronic medical records. The primary variable, erythrocyte level, was measured using standard procedures with an automated hematology analyzer. Normal red blood cell counts were defined as 4.7–6.1 million cells per microliter for men and 4.2–5.4 million cells per microliter for women [7, 8].

Demographic information was recorded, and the data were presented as frequencies and percentages in tables. All collected data were subsequently recorded and analyzed. COPD was designated as the primary endpoint in assessing the association between erythrocyte levels and COVID-19 status among hospitalized patients. Continuous variables were expressed as means and compared using paired sample T-tests (or analysis of variance tests) to confirm normal distribution. All analyses were conducted using SPSS, and a two-tailed p-value below 0.05 was deemed statistically significant.

Results

Out of 281 patients admitted to the hospital, 228 were excluded due to the absence of PCR results and 31 were omitted because of incomplete erythrocyte data. This left 53 patients for the study, comprising 27 COPD patients who tested positive for COVID-19 (50.9%) and 26 who tested

negative (49.1%). Most of the patients were male (77.3%), with females accounting for 22.7%. The age groups were distributed as follows: 30–39 years (5.7%), 40–49 years (7.5%), 50–59 years (13.2%), 60–69 years (35.8%), 70–79 years (32.1%), and 80–89 years (5.7%) (Table 1).

Table 1. Demographic characteristics of COPD patients

Demographic	n (percentage)
COVID-19 status	
Positive	27 (50.9%)
Negative	26 (49.1%)
Gender	
Male	41 (77.3%)
Female	12 (22.7%)
Age group	
30-39 years	3 (5.7%)
40-49 years	4 (7.5%)
50-59 years	7 (13.2%)
60-69 years	19 (35.8%)
70-69 years	17 (32.1%)
80-89 years	3 (5.7%)

Based on the available electronic medical records, 53 patients were selected for the study. Data normality was evaluated using the Kolmogorov–Smirnov test, which revealed that the mean erythrocyte count was 4.23 ± 0.73 million cells/µL for COVID-19–positive COPD patients and 4.77 ± 0.78 million cells/µL for COVID-19–negative COPD patients. With a p-value of 0.2—exceeding the 0.05 threshold—the data were confirmed to be normally distributed, thereby meeting the criteria for a paired sample T-test. This T-test was subsequently employed to compare the erythrocyte levels between the two groups (Figure 1).

The paired sample T-test produced a p-value of 0.012 ($p < 0.05$), demonstrating a statistically significant difference in erythrocyte levels between COPD patients with and without COVID-19. Notably, the COVID-19–positive group exhibited a lower average erythrocyte count compared to the COVID-19–negative group.

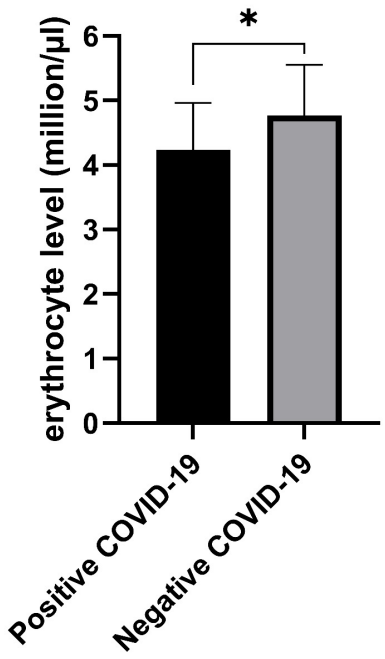

Figure 1. Erythrocyte level T-test results in COPD patients with positive and negative COVID-19. * $p < 0.05$

Discussion

Erythrocyte levels in both groups remained within the normal range, despite being relatively lower in the COVID-19–positive group. This decrease in erythrocyte count among COVID-19–positive COPD patients may be due to several factors, including increased red blood cell lysis and disruptions in the erythropoiesis process. Further research is also needed to assess potential confounding factors that may have influenced these findings.

Patients with COPD are particularly vulnerable to COVID-19 infection due to the virus's affinity for the respiratory system and its ability to weaken the immune response. SARS-CoV-2 utilizes angiotensin-converting enzyme II (ACE2) as a receptor to gain access to host cells. ACE2 is widely expressed in various tissues, including the epithelial cells of the upper and lower respiratory tracts. The virus exhibits a high binding affinity to ACE2, facilitating its rapid transmission among humans. Notably, COPD patients have significantly higher ACE2 expression levels than individuals without COPD, increasing their susceptibility to SARS-CoV-2 infection [7-9].

Previous studies have suggested that red blood cells serve as a potential entry point for SARS-CoV-2. The virus infiltrates the alveolar membrane in the lungs and subsequently enters the bloodstream [10, 11]. It binds to erythrocytes through an interaction between the S1 spike protein and the Band-3 protein on the erythrocyte membrane [12]. Although viral binding to the Band-3 protein does not promote viral replication, it alters erythrocyte characteristics and impairs their ability to release oxygen efficiently [12, 13].

Furthermore, previous research has identified significant metabolic alterations in infected individuals, particularly an upregulation of glycolysis. The increased demand for glucose leads to the accumulation of glycolytic intermediates and elevated levels of phosphofructokinase, a rate-limiting enzyme in glycolysis. This metabolic shift affects other pathways, including the pentose phosphate pathway, resulting in an increased non-oxidative phase and the conversion of glycolysis intermediates into ribose-5-phosphate, a molecule essential for viral replication [14]. Additionally, oxidative stress plays a critical role in erythrocyte damage. A marked increase in oxidized glutathione and a decline in antioxidant enzymes, such as superoxide dismutase 1 (SOD1), glucose-6-phosphate dehydrogenase, and peroxiredoxin, contribute to red blood cell destruction. Consequently, erythrocytes become increasingly susceptible to reactive oxygen species (ROS), leading to hemolysis and impaired oxygen transport [15-17].

Given the crucial role of the Band-3 protein in erythrocyte metabolism and oxygenation, viral binding to this protein may disrupt its interactions with glycolytic enzymes and deoxygenated hemoglobin, leading to metabolic dysregulation [18, 19]. The Band-3 protein is integral to erythrocyte membrane function, regulating cell shape, carbon dioxide uptake, and oxygen release. COVID-19-positive patients often exhibit excess intracellular iron accumulation and reduced serum iron levels [11, 12]. This decline in serum iron availability lowers transferrin saturation, thereby impairing hemoglobin synthesis and erythropoiesis.

Another pathological mechanism contributing to erythrocyte dysfunction in COVID-19 patients is oxidative stress. During viral infections, neutrophils rapidly migrate to infected tissues, releasing large quantities of ROS to neutralize pathogens [13]. Excessive ROS production triggers an inflammatory cascade that, if uncontrolled, can result in oxidative stress and tissue damage. Violi et al. reported that NADPH oxidase 2 (NOX2) is overexpressed in hospitalized COVID-19 patients [14]. NOX activation is a major driver of ROS formation, exacerbating oxidative stress, inflammation, and disease severity. The lungs, as the primary target of SARS-CoV-2, are particularly affected, with the virus inducing pulmonary edema, inflammation, and hypoxia—conditions further worsened by oxidative stress.

Oxidative stress also contributes to erythrocyte membrane damage. High ROS levels oxidize polyunsaturated fatty acids in the erythrocyte membrane, altering lipid distribution and compromising cell deformability. These structural changes impair oxygen and carbon dioxide exchange and may increase the risk of thrombotic events in critically ill COVID-19 patients [15].

Conclusion

A significant difference in erythrocyte levels was observed between COPD patients with and without COVID-19 ($p = 0.012$). However, erythrocyte levels in both groups remained within the normal range, despite being relatively lower in the COVID-19–positive group. Further studies with rigorous sampling criteria and a larger sample size are required to provide a more comprehensive understanding of these findings.

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Author contributions

All authors equally contribute to the study from the conceptual framework, data acquisition, data

analysis, and reporting the study results through publication.

Declaration of interest

None.

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