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The relationship between the incidence of pancytopenia and disease prognosis in hospitalized patients with Covid-19

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Abstract---Background: With the spread of the Covid-19 epidemic, complications, coagulation symptoms, and pancytopenia caused by the disease were observed in patients. Objectives: This study aimed to determine the relationship between the incidence of pancytopenia and disease prognosis in hospitalized Covid-19 patients. Methods: This descriptive-analytical cross-sectional study was performed on 51 Covid-19 patients with pancytopenia and 109 patients without pancytopenia referred to a referral hospital in Ahvaz (Iran) in 2021. We used descriptive and analytical statistics such as the independent t-test and Mann-Whitney test. Results: During the one-year study period, 51 out of 1839 hospitalized Covid-19 patients (2.8%) were

diagnosed with pancytopenia. The mean number of hospitalization days and the number of breaths, in the group of patients with pancytopenia (7.1 ± 5.6 days and 22.84 ± 9.2 per minute, respectively) were significantly higher than the group without pancytopenia (3.8 ± 1.8 days and 19.8 ± 3.6 per minute, respectively) ($P < 0.05$). In the group of patients with pancytopenia compared to the group without pancytopenia, we observed 13.7% vs. 0% of unconsciousness, 31.4% vs. 12.8% of severe lung involvement, 25.5% vs. 4.6% need for intubation, and 27.5% vs. 6.4 % death ($P < 0.05$). Conclusions: The results showed that the incidence of pancytopenia was not high in Covid-19 patients. It seems that its presence could be considered as a criterion for worse prognosis and higher mortality in the patients.

Keywords---Covid-19, Pancytopenia, Prognosis.

Introduction

Background

The 21st century has experienced an epidemic of three previously unknown types of coronaviruses: Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) in 2003, Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012, and finally the new virus named SARS-CoV-2 or coronavirus disease in 2019 (Covid-19) (1-3). All of the viruses belong to the family *coronaviridae*, a family with single-stranded RNA genome with positive polarity. Like other RNA viruses, this family is characterized by considerable genetic diversity and a high recombination rate, enabling them to spread rapidly among humans and animals around the globe. Therefore, many coronaviruses are present in the human and animal populations without causing any dangerous disease. However, sometimes the genetic recombination of the virus in a random intermediate host causes infectious and highly pathogenic species in humans. Although SARS-CoV-2 is structurally and genetically related to SARS-CoV, there is growing evidence of unique features of the virus that contribute to its rapid spread worldwide(4). Covid-19 was initially thought to be a respiratory infection. However, studies have shown that the virus can affect various systems, including cardiovascular, respiratory, gastrointestinal, nervous, and hematopoietic systems (5).

The most common symptoms of Covid-19 are high fever, cough, shortness of breath, and muscle aches that are similar to those of SARS and MERS. Some patients may experience sore throat, rhinorrhea, headache, and dizziness a few days before the onset of fever, which indicates that fever is an essential symptom but not the only early sign of the infection. A small percentage of patients have hemoptysis and a few patients are almost asymptomatic (4). Headache, diarrhea, and pneumonia are other symptoms observed (6).

Due to their low sensitivity and specificity, laboratory findings are not usually used to diagnose Covid-19 but are valuable prognostic indicators. The findings provide useful information about the severity and duration of the disease, and the response to treatment. According to studies in China and other countries,

hematology tests play an essential role in providing useful prognostic markers to the medical team (7, 8).

Although the studies are based on a limited number of data and need to be validated by further studies, according to current results, clinical hematology tests play an essential role in the triage and management of patients (9).

The most common abnormalities in the laboratory findings of Covid-19 patients are lymphopenia, pancytopenia, elevated levels of liver enzymes, lactate dehydrogenase (LDH), and reactive protein-C (CRP)(10), and elevated levels of troponin and D-dimer in severe cases (11).

Other disorders such as prolonged prothrombin time (PT) and partial thromboplastin time (PTT), increased fibrin degradation products, and severe thrombocytopenia leading to disseminated intravascular coagulation (DIC) can be dangerous. Biomarkers such as the level of procalcitonin have been suggested as poor prognostic factors (12).

Objectives

This study aimed to investigate the relationship between the incidence of pancytopenia and disease prognosis in hospitalized patients with Covid-19.

Methods

This was a descriptive-analytical cross-sectional study performed on all patients admitted to a referral hospital in Ahvaz (capital of Khuzestan Province, southwestern Iran) with a diagnosis of Covid-19 from March 2020 to March 2021. Inclusion criteria were patients with a definitive diagnosis of Covid-19 who developed pancytopenia during hospitalization or treatment. The results of laboratory findings were evaluated for a definitive diagnosis of pancytopenia. Exclusion criteria included: chemotherapy in the last six months, hematological diseases, solid malignancies, and history of immunosuppressive drugs.

During the one-year study period, 51 out of 1839 hospitalized Covid-19 patients (1036 males and 803 females) were diagnosed with pancytopenia. To compare patients with pancytopenia (51 patients) and patients without pancytopenia, about 109 hospitalized Covid-19 patients were considered. These patients were randomly selected from the Covid-19 patients during the study period.

A checklist was used to collect data based on patients' medical records. The checklist included variables of age, sex, history of coronary artery bypass graft, chronic kidney disease, asthma, chronic lung disease, diabetes, liver failure, fatty liver, hepatitis, the length of stay in hospital and ICU, number of breaths (per minute), systolic blood pressure (mmHg), heart rate (per minute), temperature (°C), the concentration of D-dimer (ng/mL) and , blood oxygen saturation (%), consciousness (yes, no), the severity of lung involvement (mild, moderate, severe), need for intubation (yes, no) and the patient's final condition (death, recovery).

Data Analysis

The study used descriptive statistics, including frequency, mean and standard deviation. The Shapiro-Wilk test was used to evaluate the normality of the data. A Chi-square test was applied to compare the frequency distribution of qualitative variables according to the groups under the study (pancytopenia, no pancytopenia). To compare the mean distribution of quantitative study variables by the groups, if the data were normal, the researchers used an independent two-sample t-test and otherwise non-parametric Mann-Whitney test. Analysis was performed using SPSS software version 16. A significance level of less than 0.05 was considered.

Results

The mean age in the group of patients with pancytopenia was 62.7 ± 8.8 years. In the group without pancytopenia, it was 58.3 ± 8.8 years. The difference in the mean age between the two groups was statistically significant ($P = 0.008$). At the beginning of the study, 49.0% of the patients with pancytopenia and 45.0% of patients without pancytopenia were male, and the rest were female. In the pancytopenia group, 0% and the non-pancytopenia group, 2.8% of the patients had chronic lung disease. In addition, 49.4% in the pancytopenia group and 52.3% in the non-pancytopenia group were diabetic. Finally, the results of the Chi-square test showed that at the beginning of the study, the frequency distribution of sex, Coronary Artery Bypass Graft, Chronic Kidney Disease, asthma, chronic lung disease, diabetes, liver failure, fatty liver, and hepatitis did not differ statistically according to the study groups ($P > 0.05$) (Table 1).

In terms of main clinical variables and laboratory findings, the results of the study showed that the mean number of hospitalization days and the number of breaths per minute in the pancytopenia group (7.1 ± 5.6 days and 22.8 ± 9.2 per minute, respectively) were significantly higher than the non-pancytopenia group (3.8 ± 1.8 days, 19.8 ± 3.6 per minute) ($P < 0.05$). However, there was no statistically significant difference between the two groups in terms of the other variables, such as the levels of blood oxygen saturation and D-Dimer ($P > 0.05$) (Table -2). Finally, the results showed that the frequency distribution of unconsciousness, severe lung involvement, need for intubation, and death was statistically different according to the groups. In the pancytopenia group compared to the non-pancytopenia group, the research observed 13.7% vs. 0% of unconsciousness, 31.4% vs. 12.8% of severe lung involvement, 25.5% vs. 4.6% need to use intubation, and 27.5% vs. 6.4 % death ($P < 0.05$) (Table 3).

Discussion

This study aimed to investigate the relationship between the incidence of pancytopenia and disease prognosis in hospitalized patients with Covid-19. This study showed that the mean age in the pancytopenia group was significantly higher than in the non-pancytopenia group. Studies by Hersby et al. (2020) and Singh et al. (2020) showed that in male patients over 40 years with influenza-like symptoms, at first, the number of platelets, neutrophils, and hemoglobin was steadily decreasing, and then the pancytopenia of patients improved with the elimination of infection (13,14).

The study results also showed that the mean number of hospitalization days and the number of breaths in the pancytopenia group were significantly higher than in the non-pancytopenia group. Moreover, the frequency of unconsciousness, severe lung involvement, the need for intubation, and deaths in the pancytopenia group was significantly higher than the non-pancytopenia group.

A similar study was not found on the incidence of pancytopenia and its association with the severity of lung involvement. However, in line with these results, the study of Yufei et al. (2020) showed that the level of C-reactive protein (CRP) and the neutrophil-to-lymphocyte ratio (NLR) in Covid-19 patients were significantly higher than in healthy individuals, while the percentage of lymphocytes in the patients were lower than healthy individuals. In the group of Covid-19 patients with severe, critical, and dead status, the levels of CRP and NLR were higher than in the patients with moderate status whereas the percentage of lymphocytes in these patients was lower than other the patients. Finally, the study results showed that the levels of CRP and NLR and the percentage of lymphocytes are independent risk factors in Covid-19 disease (15).

Also, the study by Zheng et al. (2020) showed that the most patients with Covid-19, the number of white blood cells, neutrophils, and platelets were normal at the time of hospitalization. However, as the disease progressed and the symptoms worsened, patients developed lymphopenia. Eventually, the results of this study showed that the number of neutrophils, lymphocytes, and platelets are independent risk factors in the disease progression and are associated with improvements in disease risk classification and management of Covid-19 patients(16).

In a systematic review and meta-analysis study by Zong et al. (2020), the results showed that platelet counts were lower in Covid-19 patients with severe conditions and those who died than in other patients. The results also showed that the incidence of pancytopenia in Covid-19 patients increases the risk of hospitalization in ICU, progression to acute respiratory distress syndrome, and mortality by three times. Overall, the results of this study revealed that approximately 12% of hospitalized Covid-19 patients had pancytopenia, which was a sign of more severe disease and poor treatment outcomes (17). In another systematic review and meta-analysis study by Lippi et al. (2020), the results showed that platelet counts were significantly lower in severe Covid-19 patients. Low platelet counts were associated with a 5-fold increased risk of developing severe Covid-19. A significant relationship was observed between low platelet counts and higher mortality (18). Finally, the results of a systematic review and meta-analysis of 21 studies by Hersby et al. (2020) showed that significantly increased in the number of white blood cells in Covid-19 patients and decreased the number of lymphocytes and platelets were with severe and fatal condition compared to the patients with the non-severe disease (13).

The results showed no statistically significant relationship between the level of D-Dimer and pancytopenia. In the study by Liao et al. (2020), the results showed that the incidence of thrombocytopenia and the decrease in the number of lymphocytes and eosinophils in critical cases of Covid-19 were significantly higher

than the moderate and severe cases. The levels of D-dimer and PT significantly associated with disease severity. Additionally, the results of multivariate analysis showed that higher mortality was associated with increased NLR and D-dimer, the incidence of thrombocytopenia, and prolonged PT (19).

The present study showed no statistically significant relationship between the incidence of pancytopenia and length of stay in ICU, systolic blood pressure, heart rate, and blood oxygen saturation. Since only severe and critical cases of Covid-19 are admitted the ICU, it was not possible to identify the relationship between pancytopenia and disease prognosis and length of stay in the ICU. This might be due to insufficient sample size.

Although in viral infections, bone marrow aplasia occurs by different mechanisms, King and Goodell categorized four different mechanisms by which viral infections can affect hematopoietic stem cells. Two mechanisms work through direct effects on HSC hematopoietic stem cells including:

- A. Direct viral infection causes changes in the expression of intracellular factors and cellular pathways or even interrupts the translation of host cells
- B. Direct detection of a pathogen that, through molecular patterns, alters the expression of chemokine receptors and induces apoptosis.

The other two mechanisms are indirect and include: either proinflammatory cytokines released by other cells or through changes in the bone marrow micro-environment (20). Because it is well known that stromal cells play an essential role in signaling during hematopoietic, these four scenarios are not mutually exclusive and can even reinforce or weaken each other (21). In addition to the above mechanisms, the cause of pancytopenia in Covid-19 patients can be an overwhelming bacterial infection, septicemia, and even DIC, which can create a poor prognosis in these patients. Drug side effects may also play a role in developing of pancytopenia in the patients.

Pancytopenia in Covid-19 infection has been reported as case reports, and there is a lack of primary studies in this regard. In most case reports, pancytopenia has been self-limiting and has improved significantly with the treatment of Covid-19 infection. Eventually, in some cases where bone marrow biopsy was performed, no specific pathology was observed (13).

One of the strengths of this study was that it is the first study that investigated the relationship between the incidence of pancytopenia and the prognosis of the disease, especially in terms of disease severity and mortality in Covid-19 patients. One of the limitations of this study was the lack of sufficient studies to compare the results of the present study. Thus, further studies with higher sample sizes are recommended.

Conclusions

The results showed that the incidence of pancytopenia was not high in Covid-19 patients, and that its presence could be considered as a criterion for worse prognosis and higher mortality in the patients. In other words, considering all the mechanisms that cause pancytopenia in Covid-19 patients, this factor indicates a worse prognosis and higher mortality.

Declarations

Availability of data and materials

Data sharing: Participant level data are available from the corresponding author.

Competing interests

The authors declare that they have no competing interests.

Ethical considerations

Ethics License of the study was acquired from the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (Code of ethics:

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Authors' contributions

ZM, SHB and HR conceived and designed the project. AP and HR acquired the data. AP and HR analyzed and interpreted the data. TV and HT wrote the paper.

All authors approved the final text.

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