COVID-19 is more dangerous for older people and its severity is increasing: a case-control study

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Abstract

Coronavirus disease 2019 (COVID-19) triggers important changes in routine blood tests. In this retrospective case-control study, biochemical, hematological and inflammatory biomarkers between March 10, 2020, and November 30, 2020 from 3969 COVID-19 patients (3746 in the non-intensive care unit (non-ICU) group and 223 in the ICU group) were analyzed by dividing into three groups as spring, summer and autumn. In the non-ICU group, lymphocyte to monocyte ratio was lower in autumn than the other two seasons and neutrophil to lymphocyte ratio was higher in autumn than the other two seasons. Also, monocyte and platelet were higher in spring than autumn; and eosinophil, hematocrit, hemoglobin, lymphocyte, and red blood cells decreased from spring to autumn. In the non-ICU group, alanine aminotransferase and gamma-glutamyltransferase gradually increased from spring to autumn, while albumin, alkaline phosphatase, calcium, total bilirubin and total protein gradually decreased. Additionally, C-reactive protein was higher in autumn than the other seasons, erythrocyte sedimentation rate was higher in autumn than summer. The changes in routine blood biomarkers in COVID-19 varied from the emergence of the disease until now. Also, the timely changes of blood biomarkers were mostly more negative, indicating that the disease progresses severely. The study was approved by the Erzincan Binali Yildirim University Non-interventional Clinical Trials Ethic Committee (approval No. 86041) on June 21, 2021.

Key words: biochemical; hematological and inflammatory biomarkers; neutrophil to lymphocyte ratio; lymphocyte to monocyte ratio; platelet to lymphocyte ratio; systemic immune-inflammation index

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Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2), which emerged in Wuhan, China in December 2019 and was declared as a pandemic by the World Health Organization on March 11, 2020, continues to spread. A total of 93,805,612 confirmed cases have been detected in more than 200 countries until now and the disease has caused 2,026,093 deaths.[1] As reported, climate and seasonal changes have important effects on COVID-19.[2-5] On the other hand, important mutations have occurred in the genetic structure of SARS-CoV-2.[6,7]

Many studies have shown that there have been important changes in the routine laboratory test in COVID-19.[8-12] However, most of these studies include data from the early period of the disease. The changes in the structure of the virus and the clinical characteristics of the disease within the process or seasonal changes may cause changes in routine laboratory tests. Thus, this study examined the changes in routine laboratory tests by seasons by constituting three periods of 3 months each, beginning with the emergence of COVID-19 disease in Turkey. This study also examined the increases and decreases in the routine laboratory tests of the patients based on the reference range.

Subjects and Methods

This retrospective case-control study was conducted by examining the records between March 10, 2020, and November 30, 2020 from the laboratory information system of the hospital. Only adults older than 18 years were included in the study. An ethic approval was obtained from Erzincan Binali Yildirim University Non-interventional Clinical Trials Ethic Committee (approval No. 86041) on June 21, 2021 (**Additional file 1**). This study protocol followed the *Declaration of Helsinki*. This study follows the STrengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. The diagnosis of "COVID-19 identified virus" was searched with indicated parameters and testing data from a total of 3969 patients, including 3746 in non-intensive care unit (non-ICU) group and 223 in ICU group, were collected. The diagnosis of COVID-19 was only made with a real-time polymerase chain reaction test and SARS-CoV-2 virus nasal and pharyngeal swab specimens in the hospital when the study was conducted. The patients in the intensive care unit were included in the ICU group and the patients in other patient wards and clinics were included in the non-ICU group. Their laboratory data were compared within 3 months period. The results between March 10, 2020 and May 31, 2020 were grouped as spring, the results between June 1, 2020 and August 31, 2020 were

grouped as summer, and the results between September 1, 2020 and November 30, 2020 were grouped as autumn. The test results obtained from the first measurements of the patients recorded in the system were evaluated in this study.

The whole blood count was measured with Sysmex XN-1000 instrument (Sysmex Corporation, Kobe, Japan) autoanalyzer, and biochemical tests were made with the spectrophotometric method from serum in the Olympus AU2700 Plus Chemistry Analyzer (Beckman Coulter, Tokyo, Japan) autoanalyzer. Serum ferritin was measured by chemiluminescence method in the autoanalyzer (Centaur XP, Siemens Healthcare, Germany). Prothrombin time, activated partial prothrombin time and fibrinogen on plasma was measured with a fully automated photo-optical coagulation device Ceveron-Alpha (Diapharma Group Inc., West Chester, Canada). C-reactive protein (CRP) was measured on serum by nephelometric method on BN™ II device (Siemens, Munich, Germany). Procalcitonin, D-dimer, and Troponin I were measured from the whole blood with AQT90 flex Radiometer® (Bronshoj, Denmark) device. The erythrocyte sedimentation rate (ESR) was analyzed on whole blood using TEST 1 BCL (Alifax, Padova, Italy).

Neutrophil to lymphocyte ratio (NLR), lymphocyte to monocyte ratio (LMR) and platelet to lymphocyte ratio (PLR) calculated as neutrophil/lymphocyte, lymphocyte/monocyte and platelet/lymphocyte, respectively. Derived NLR ratio was calculated neutrophil count divided by the result of white blood cell (WBC) count minus neutrophil count. Lymphocyte to CRP ratio (LCR), a systemic immune-inflammation index, was calculated using the following formula: platelet × neutrophil / lymphocyte. The atherogenic index of plasma is the logarithmically transformed ratio of triglycerides and high-density lipoprotein cholesterol. The values of the group with increased biomarker levels were defined as the upper threshold of the reference range and the values of the group with decreased biomarker levels were defined as the lower threshold of the reference range. Thus, how much they changed was determined.

Statistical analysis

The one-way analysis of variance was used when the data were normally distributed in the three groups; otherwise, the Kruskal-Wallis test was carried out. An independent *t*-test or Mann-Whitney *U* test was used to evaluate the continuous variables between groups. Using the chi-square test, proportions for categorical variables were compared. All statistical analyses were conducted by using SPSS software (version 20.0, IBM, Armonk, NY, USA). Statistical significance could be shown as the *P*-values < 0.05.

Results

In the non-ICU group, the ratio of men to women was higher in spring, while the ratio of women to men was higher in summer and autumn. The ratio of men was always higher in the ICU group. The mean age in the non-ICU group gradually increased from spring to autumn, which was similar in the ICU group. In the non-ICU group, basophil count was higher in spring than other two seasons, mean corpuscular hemoglobin value was only higher in spring than autumn, and mean corpuscular hemoglobin concentration (MCHC), neutrophil, platelet distribution width and red cell distribution width (RDW) values were higher in autumn than spring and higher in spring than summer. Additionally, mean corpuscular volume, platelet large cell ratio and LMR values were lower in autumn than other two seasons, monocyte, platelet and WBC (in women) were higher in spring than autumn and higher in autumn than summer, while mean platelet volume, NLR and dNLR values were higher in autumn than the other seasons, and PCT and WBC (in men) were lower in summer than the other seasons. Moreover, PLR value gradually increased from spring to autumn while eosinophil, hematocrit, hemoglobin, lymphocyte and red blood cells (RBC) values gradually decreased (**Additional Table 1**). In the ICU group, MCHC was higher in autumn than in other seasons, monocyte was higher in spring than autumn while neutrophil, WBC (in women), NLR, dNLR and PLR were lower in summer than autumn. Age, mean corpuscular volume, neutrophil, plateletcrit, platelet distribution width, RDW, WBC, platelet large cell ratio, NLR, derived NLR ratio and PLR values were higher and eosinophil, hematocrit, hemoglobin, lymphocyte, MCHC, monocyte, RBC, WBC and LMR were lower in the ICU group compared with the non-ICU group (**Additional Table 2**).

In the non-ICU group, alanine aminotransferase (ALT) and gamma-glutamyltransferase (GGT) values gradually increased from spring to autumn, while albumin, alkaline phosphatase (ALP), calcium, total bilirubin, total protein, and estimated glomerular filtration rate (eGFR) gradually decreased. Additionally, aspartate aminotransferase (AST) was lower in spring than the other seasons and HDL was higher in spring than the other seasons, while AST/ALT, direct bilirubin and chlorine were lower in autumn than the other seasons. Moreover, glucose, creatinine (only in men), urea and uric acid were higher in autumn than the other seasons, and lactate dehydrogenase (LDH) was higher in summer than the other seasons, while creatine kinase myocardial band, creatinine (only in women) and lipase were lower in summer than autumn and cholesterol were higher in spring than autumn. Also, sodium level was higher in summer than autumn and atherogenic index of plasma was higher in summer than spring. In the ICU group, ALT, GGT, and creatinine (only in men) increased in summer than autumn, and AST, glucose and urea were higher in autumn than the other seasons, while calcium and eGFR were lower in autumn than the other seasons, and albumin and ALP were higher in spring than the other seasons. Additionally, LDH was higher in autumn than spring and the total protein value was lower in autumn than spring (**Additional Table 3**).

ALT, AST, AST/ALT, ALP, creatine kinase myocardial band, direct bilirubin, GGT, glucose, creatinine, creatine kinase, LDH, magnesium, sodium, total bilirubin, and urea were higher, while albumin, iron, calcium, total protein and eGFR were lower in the ICU group compared with the non-ICU group (**Additional Table 4**).

In the non-ICU group, CRP was higher in autumn than the other seasons and ferritin (only in men) gradually increased from spring to autumn, while ferritin (in women) was lower in spring than the other seasons. Additionally, procalcitonin was higher in summer than autumn, and ESR was higher in autumn

than summer, while activated partial prothrombin time was higher in summer than spring as well as higher in spring than autumn. Moreover, LCR and systemic immune-inflammation index were lower in autumn than the other seasons. In the ICU group, ferritin gradually increased from spring to autumn, while procalcitonin and systemic immune-inflammation index were higher in summer than autumn and ESR was higher in autumn than spring (**Additional Table 5**).

CRP, D-dimer, ferritin, fibrinogen, international normalized ratio, prothrombin time, procalcitonin, ESR, and troponin were higher and LCR was lower in the ICU group compared with the non-ICU group (**Additional Table 6**).

Discussion

While COVID-19 continues to rapidly spread in the world, the disease and mortality ratios are increasing. Unfortunately, the epidemic has not been prevented as an effective treatment for the disease has yet to be found.[1] The vaccination has begun but it is too soon to see its effect. On the other hand, important mutations have been detected in the structure of the virus while the disease continues to spread.[6,7] Therefore, it is possible that COVID-19 will be in our lives for a long time. It is essential to explain this disease with all its aspects and to reveal the differences that may develop in time. In this regard, this study is important as it shows the real-time changes in routine blood biomarkers in COVID-19. Also, these changes are important for the diagnosis of the disease but the fact that the test results changed negatively indicates that the severity of the disease increased over time.

This study showed that aged patients and male individuals are more likely to be hospitalized in the intensive care unit. It is known that advanced age is a bad prognostic indicator.[13] The increase in mean platelet volume, NLR, dNLR and decreased eosinophil, hematocrit, hemoglobin, lymphocyte, and RBC values indicates that the disease progresses more severely in autumn, the third period of the disease, than the early period. NLR is also an independent risk factor for mortality.[14] These results might be effective in conditions such as the increased possibility of infection of the elderly and people with chronic diseases. Increased glucose, creatinine, urea, uric acid, ALT, AST, GGT and decreased albumin, ALP, calcium, total bilirubin, total protein and eGFR in autumn show that organ damage such as pancreas, kidney and live damage is more serious in these patients. Additionally, the mutations in the virus structure or changes in the clinical characteristics of the disease might have caused this result. As CRP, ferritin, and ESR were increased while LCR was decreased in autumn, the patients might produce a more powerful inflammatory response in this last period. Previous studies reported that increased CRP, ESR, LDH and decreased albumin, eosinophil, and lymphocyte are the most important laboratory findings of the disease.[9,10,12]

In the ICU group, mean corpuscular volume, neutrophil, plateletcrit, platelet distribution width, RDW, WBC, platelet large cell ratio, NLR, derived NLR ratio and PLR were increased, while eosinophil, hematocrit, hemoglobin, lymphocyte, MCHC, monocyte, RBC and LMR were lowered, which indicates that the immune response is defective in this group, i.e., lymphocytic and erythrocyte series in the bone marrow might have been suppressed and there might be platelet and erythrocyte deformities. Lymphopenia is the most important laboratory findings that show defective immune response and risk of hospitalization in the intensive care unit in COVID-19.[9] Neutrophil might be related to hyperinflammation and cytokine storm or superimposed bacterial infection.[15] NLR shows the severity of inflammation and it is a powerful predictive and prognostic indicator.[8,16] Also, the PLR value is asserted to be correlated with the severity of cytokine storm.[17] It was asserted that eosinopenia can be used in diagnosis in combination with lymphopenia.[18] Additionally, changes in the RBC parameters are related to distorted erythropoiesis.[8] High RDW is reported to be related to high mortality.[19]

Moreover, more pathologies of the muscle, liver, heart, pancreas, lung and kidney were indicated in the ICU group, in which ALT, AST, AST/ALT, ALP, creatine kinase myocardial band, direct bilirubin, GGT, glucose, creatinine, creatine kinase, LDH, magnesium, sodium, total bilirubin, urea and troponin values were increased while albumin, iron, calcium, total protein and eGFR were decreased. This multi-organ involvement in COVID-19 was associated with the widespread distribution of angiotensin-converting enzyme receptors in the body.[20] High creatinine, AST, LDH, troponin, CRP, ferritin, procalcitonin, D-dimer, and fibrinogen values were reported to be the indicator of clinical deterioration and mortality in these patients.[21,22] It is asserted that live function tests such as ALT, AST, GGT, ALP and bilirubin often increase in COVID-19 but they do not require treatment and the underlying reasons for these increased values are hyper inflammation and thrombotic microangiopathy.[23] The ratio of AST/ALT (De Ritis ratio) was found to be an important indicator especially in women.[24] It was reported that fasting hyperglycemia increases mortality as well as the development of complications.[25] It was stated that sodium, potassium and calcium are low in severe COVID-19 patients; thus, electrolytes should be monitored.[26] The reason for high sodium in the ICU group in the present study might have been iatrogenic.

Additionally, increased CRP, ferritin, procalcitonin, ESR and decreased LCR values in the ICU group show that this group had a more powerful inflammatory response. CRP is a sensitive indicator of inflammation and tissue damage and it increases in most COVID-19 patients.[27,28] Previous study reported that high CRP and LDH and lymphopenia may show the necessity to transfer the patient to intensive care.[10] It is asserted that low LCR is an indicator of high mortality and the need for mechanical ventilation.[29] A high level of procalcitonin might be due to secondary bacterial infection.[11] Increased d-Dimer and fibrinogen are the indicators of intravascular blood clot coagulation and high prothrombin time and international normalized ratio values. Therefore, these patients should be monitored in terms of the development of disseminated intravascular coagulopathy and acute respiratory distress.[11,20,30]

Another new information provided by this study is that the ratio of the changes in routine blood biomarkers was revealed clearly. Accordingly, the increases in these tests were mostly lower than twice while decreases were lower than half (bigger than 0.5 times). Thus, even small changes in the laboratory tests of these patients must be considered.

The limitations of this study are that it was designed retrospectively and single-center and that comorbidities and medications received were not included in the study.

In conclusion, this study showed that the changes in routine laboratory tests in COVID-19 vary in the period from the emergence of the disease until now. There were increases in some tests, decreases in some and similarities in some during this period. Thus, the real-time changes in the routine laboratory tests in COVID-19 should be checked with new studies. Also, the real-time changes in the routine laboratory tests were mostly negative in this study, indicating that the disease progresses compared with the period when it first emerged.

Author contributions

CM; conception, design, supervision, data collection and processing, analysis and interpretation, literature review, writer, critical review. MTH; conception, design, data collection and processing, analysis and interpretation, critical review. HO and MT; data collection and processing, analysis and interpretation, critical review. MK and TAC; conception, design, supervision, critical review.

Conflicts of interest

Authors declares that there is no conflict of interest.

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None.

Institutional review board statement

The study was approved by the Erzincan Binali Yildirim University Non-interventional Clinical Trials Ethic Committee (approval No. 86041) on June 21, 2021.

Declaration of participant consent

Based on the regulations of the Ministry of Health of Turkey, retrospective studies do not require the informed consent from patients.

Reporting statement

This study follows the STrengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Biostatistics statement

The statistical methods of this study were reviewed by the biostatistician of Erzincan Binali Yildirim University, Faculty of Medicine, Departmant of Biostatistics.

Data sharing statement

Datasets analyzed during the current study are available from the corresponding author on reasonable request.

Plagiarism check

Checked twice by iThenticate.

Peer review

Externally peer reviewed.

Additional files

Additional file 1: Hospital ethics approval document.

Additional Table 1: Seasonal comparison of age, gender and hematological biomarkers between the groups on admission.

Additional Table 2: Comparison of gender and hematological biomarkers between the groups on admission.

Additional Table 3: Seasonal differences in biochemical biomarkers between the groups on admission.

Additional Table 4: Differences in biochemical biomarkers between the groups on admission.

Additional Table 5: Seasonal differences in inflammatory, cardiac and coagulation biomarkers between the groups on admission.

Additional Table 6: Differences in inflammatory, cardiac and coagulation biomarkers between the groups on admission.

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