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RESEARCH ARTICLE

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Effect of the coronavirus pandemic on tumor markers

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Abstract

The new type of coronavirus could cause severe acute respiratory syndrome and injuries in other systems as well. Multiple organ damage can occur rapidly in patients infected with coronavirus disease 2019 (COVID-19). Previous studies have shown that many laboratory biomarkers were not within the normal ranges in COVID-19 patients. We aimed to summarize laboratory parameters and the tumor markers in COVID-19 patients. This is a retrospective cohort study conducted on 53 women between the ages of 19–85 years infected with COVID-19 at a training and research hospital between May 2020 and August 2020. Of the 53 women, 16 (30.2%) had leukopenia. The mean C-reactive protein level was 18.42 ± 59.33 mg/L. The mean procalcitonin level was 0.1 ± 0.21 µg/L. The liver function tests were within normal limits. The mean creatinine level was 0.58 ± 0.37 mg/dl. Elevated levels of α-fetoprotein (AFP) in 1 patient, elevated levels of carcinoembryonic antigen (CEA) in 2 patients, elevated levels of cancer antigen 125 (CA125) in 4 patients, elevated levels of CA19-9 in 2 patients, and elevated levels of CA15-3 in 2 patients were detected. One of 4 patients who were taken to the intensive care unit had elevated levels of AFP. In addition, 2 of 4 patients who were taken to the intensive care unit had elevated levels of CA125 and CA15-3. Except for AFP, levels of all tumor markers of the patient who died were high. We found that COVID-19 had no effect on tumor markers (CA125, CA19-9, CA15-3, AFP, and CEA).

KEYWORDS
coronavirus disease-2019, laboratory, tumor markers

1 | INTRODUCTION

The disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been recently named coronavirus disease-2019 (COVID-19) by the World Health Organization (WHO). COVID-19 has rapidly spread to multiple countries of the world within months. The WHO has defined COVID-19 as a pandemic due to the speed and scale of transmission. This new type of coronavirus could cause severe acute respiratory syndrome and injuries in other systems as well. Multiple organ damage can occur rapidly in patients infected with COVID-19.

Previous studies have shown that many laboratory biomarkers were not within the normal ranges in COVID-19 patients.[1–3] Some of the cancer biomarkers including carbohydrate antigens have shown an elevation in various inflammatory conditions.[4,5]

In this study, we aimed to summarize laboratory parameters and the tumor markers, including α-fetoprotein (AFP), cancer antigen 125 (CA125), carbohydrate antigen 15-3 (CA15-3), carbohydrate antigen 19-9 (CA19-9), and carcinoembryonic antigen (CEA), among COVID-19 patients.

2 | PATIENTS AND METHODS

This is a retrospective cohort study conducted on 53 women between the ages of 19–85 years infected with COVID-19 at a training and research hospital between May 2020 and August 2020. Data were recorded and collected from the joint electronic medical database system that included examination notes, clinical and laboratory parameters.

There was no disease in the patients except COVID-19. Patients with cancer diagnoses were excluded. The patients' laboratory parameters including age, white blood cell (WBC), neutrophil, lymphocyte, platelet, hemoglobin, C-reactive protein (CRP), d-dimer, lactate, fibrinogen, procalcitonin, troponin, ferritin, lactate dehydrogenase (LDH), alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, AFP, CA125, CA15-3, CA19-9, and CEA levels were recorded. The patients or relatives gave informed and voluntary consent to the publication of their clinical data and they agreed to participate in this study. The trial was approved by the local ethical review committee (approval number: 2020/1453).

Data were analyzed by SPSS (Version 20.0. 2011, IBM SPSS Statistics for Windows; IBM Corp.). Median, mean, standard deviation, frequency, and ratio values were used for descriptive statistics.

3 | RESULTS

The present study included 53 women with COVID-19. The mean age of the women infected with COVID-19 was 42.49 ± 20.31 years. All laboratory parameters of the patients are shown in Table 1. Of the 53 women, 16 (30.2%) had leukopenia (serum level less than 4.49×10^3 cells/μl). The mean CRP level was 18.42 ± 59.33 mg/L (range, 0.3–430 mg/L). The mean procalcitonin level was 0.1 ± 0.21 μg/L (range, 0.02–1 μg/L). The liver function tests (AST and ALT) were within normal limits (26.76 ± 15.87 and 23.45 ± 11.32 IU/L, respectively). The mean creatinine level was 0.58 ± 0.37 mg/dl (range, 0.2–1.8 mg/dl).

Elevated levels of AFP in 1 patient, elevated levels of CEA in 2 patients, elevated levels of CA125 in 4 patients, elevated levels of CA19-9 in 2 patients, and elevated levels of CA15-3 in 2 patients were detected (Table 2). Four patients (7.5%) were critical and they were taken to the intensive care unit. One of 4 patients who taken to the intensive care unit had elevated levels of AFP. In addition, 2 of 4 patients who taken to the intensive care unit had elevated levels of CA125 and CA15-3. One of 4 patients (aged 85 years) (1.9%) in the intensive care unit died. Except for AFP, levels of all tumor markers of the patient who died were high.

4 | DISCUSSION

The prevalence of COVID-19 began in December 2019, then spread worldwide, and now is an ongoing pandemic caused by SARS-CoV-2.[3–5] All over the world scientists are trying to understand viral tropism better and the main problem is to develop therapeutic approaches for preventing virus infection and spreading. As this situation has become an urgent public health challenge, it aroused our curiosity to investigate a set of some significant tumor biomarkers in patients with COVID-19. In our study, we retrospectively summarized an outcome of clinical laboratory tests on serum from COVID-19 patients and a set of 5 cancer biomarkers. Besides this, changes of blood lymphocytes (L), neutrophils (N), d-dimer, lactate, hemoglobin (HGB), CRP, platelets (PLT), WBC, fibrinogen, AST, ALT, creatinine, procalcitonin (PCT), troponin, ferritin, and LDH progression were also studied. We wanted to detect if these parameters have any clinical value in COVID-19 infection.

TABLE 1 The laboratory parameters of the patients with COVID-19

	n = 53
Hemogram	
WBC (10^3 cells/μl)	6.06 ± 4.8 (1.4–24.8)
Neutrophil (10^3 cells/μl)	3.88 ± 4.29 (0.9–22)
Lymphocyte (10^3 cells/μl)	1.71 ± 0.77 (0.4–4)
Platelet (10^3 cells/μl)	228.26 ± 75.72 (80–481)
Hemoglobin (g/dL)	13.06 ± 1.63 (8.1–18)
Acute phase reactants	
CRP (mg/L)	18.42 ± 59.33 (0.3–430)
Ferritin (ng/ml)	168. 8 ± 345.06 (0.1–2000)
Procalcitonin (ng/ml)	0.1 ± 0.21 (0.02–1)
Markers of organ dysfunction	
Troponin (ng/ml)	0.16 ± 0.34 (0.1–2.3)
Creatinine (mg/dl)	0.58 ± 0.37 (0.2–1.8)
ALT (IU/L)	26.39 ± 14.53 (7–65)
AST (IU/L)	28.06 ± 13.31 (5–54)
LDH (IU/L)	243.27 ± 136.71 (137–919)
Coagulation markers	
d-Dimer (ng/ml)	608.62 ± 1203.28 (18–7788)
Fibrinogen (mg/dL)	286.84 ± 126.69 (49–608)
Other	
Lactate (mmol/L)	2.54 ± 2.32 (0.8–7.5)

Note: Values are presented as mean ± *SD* and range (minimum–maximum).
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; LDH, lactate dehydrogenase; WBC, white blood cell.

TABLE 2 Tumor markers of the patients with COVID-19

	n = 53
AFP (IU/ml)	7.75 ± 44.32 (0.5–321)
CA125 (IU/ml)	16.1 ± 18.58 (2.7–92)
CA15-3 (IU/ml)	18.88 ± 18.75 (6–118)
CA19-9 (IU/ml)	11.09 ± 18.62 (0.6–106)
CEA (ng/ml)	1.74 ± 2.29 (0.24–14.13)

Note: Values are presented as mean ± *SD* and range (minimum–maximum).
Abbreviations: AFP, α-fetoprotein; CA125, cancer antigen 125; CA15-3, carbohydrate antigen 15-3; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen.

A great number of studies have shown that cancer biomarkers such as CEA, CA, and human epididymis protein 4 (HE4) are also increased in various inflammatory diseases in the lungs.[6] For example, CEA is increased in smoking subjects and CA-125 is increased in chronic obstructive pulmonary disease.[4,6,7]

In our study, we found elevated values of some tumor markers in patients who were diagnosed with COVID-19. Our results were consistent with the other authors' research results. Yu et al.[5] in their study found that CEA was highly expressed in the serum of COVID-19 patients without cancer. During the pandemic, the serum levels of CEA in 433 of 1876 (23.08%) patients infected with COVID-19 were found to be higher than the normal level (5 ng/ml) at Jinyintan Hospital; however, no difference in afp levels was detected. They aimed to summarize the clinical significance of CEA in predicting the prognosis of COVID-19 using Nomograms analysis. The serum CEA levels were found to be increased in patients with severe or critically severe SARS-CoV-2 infection. Otherwise, the initial levels of CEA were associated with the prognosis of patients with COVID-19. Initial CEA levels of over 29.75 ng/ml predicted fatal outcomes in patients. Hence, their findings suggest that CEA may serve as a novel prognostic marker of COVID-19.[5]

Wei et al.[6] in their retrospective study have evaluated the levels of serum biomarkers in COVID-19 patients (mild: 131; severe: 98; critical: 23). They found that there were significant increases in levels of HE4 (73.6 ± 38.3 vs. 46.5 ± 14.7, $p <. 001$), cytokeratin-19 fragment (CYFRA21-1) (2.2 ± 0.9 vs. 1.9 ± 0.8, $p < . 001$), CEA (3.4 ± 2.2 vs. 2.1 ± 1.2, $p < .001$), carbohydrate antigens; CA-125 (18.1 ± 13.5 vs. 10.5 ± 4.6, $p < .001$) and CA15-3 (14.4 ± 8.9 vs. 10.1 ± 4.4, $p < .001$) in COVID-19 mild cases as compared to normal control subjects; their levels showed continuous and significant increases in severe and critical cases (HE4, CYFRA21-1 and CA125 $p < .001$; CEA and CA153: $p < .01$). Squamous cell carcinoma antigen (SCCA) and CA19-9 increased only in critical cases of COVID-19 as compared with mild and severe cases and normal controls ($p < .01$). There were positive associations between levels of CRP and levels of HE4 ($R = 0.631$, $p < .001$), CYFRA21-1 ($R = 0.431$, $p < .001$), CEA ($R = 0.316$, $p < .001$), SCC ($R = 0.351$, $p < .001$), CA153 ($R = 0.359$, $p < .001$) and CA125 ($R = 0.223$, $p = .031$). They concluded that elevations of serum cancer biomarkers positively correlated with the pathological progressions of COVID-19, demonstrating diffuse and acute lung injuries.

As we know CRP is a significant factor that correlates with the severity of the COVID-19 cases.[6] Our study unveils that a positive correlation between CRP and a series of cancer biomarkers can inform us about an acute pathophysiological injury in COVID-19. Positive correlations between CRP and CEA or CA biomarkers have been found in other diseases such as gastric and colon cancer and Parkinson's disease.[8,9]

Another author Li et al.[10] in their research bring up an important consideration for COVID-19 patients who had significantly increased serum amyloid A protein (SAA) and CRP levels, while lymphocyte count decreased, and procalcitonin, WBC, and PLT were in the normal range. SAA is a nonspecific acute phase protein mainly produced by cytokines interleukin-1β (IL-1β), IL-6, and tumor necrosis factor-α (TNF-α) in liver cells. As a marker of inflammation, its clinical value is obtaining more attention recently. As COVID-19 disease progressed from mild to critically severe, SAA and CRP gradually increased, while lymphocytes decreased, and PLT, WBC, and PCT had no significant changes. All in all, they suggested that SAA and lymphocytes are sensitive indicators in evaluating the severity and prognosis of COVID-19, and monitoring of these dynamic changes of SAA combined with CT imaging could be valuable in the diagnosis and treatment of COVID-19. Studies report that patients with severe acute respiratory syndrome had a significantly increased level of SAA, suggesting that SAA is a reliable indicator in distinguishing severe COVID-19 infection cases from mild ones.

Smith et al.[11] have reported the case of a woman with FIGO stage IV A ovarian high-grade serous carcinoma (HGSC) during the COVID-19 pandemic, who had a transient increase in CA125 without evidence of progression of disease on imaging, and who was later found to have a positive COVID-19 antibody test. The patient had a peak CA125 of 4499 U/ml, an increase of 2617 U/ml from the presumed pre-COVID-19 level, and only had mild infection not requiring hospitalization. This case illustrates that in the presence of underlying malignancy and elevated CA125, COVID-19 infection may produce a dramatic increase in CA125 that resembles cancer progression.[11]

Remarkably, the Hou et al.[12] study is relevant to our study. They investigated that leukocytes, neutrophils, infection biomarkers such as CRP, PCT, and ferritin and the concentrations of cytokines (IL-2R, IL-6, IL-8, IL-10, and TNF-α) were significantly increased, while lymphocytes were significantly decreased with increased severity of illness. The amount of IL-2R was positively correlated with the other cytokines and negatively correlated with lymphocyte number. The ratio of IL-2R to lymphocytes was found to be elevated in severe and critical patients. Lymphopenia and increased levels of cytokines were closely associated with disease severity. The IL-2R/lymphocyte was a prominent biomarker for early identification of severe COVID-19 and predicting the clinical progression of the disease.

He et al.[13] firstly reported the role of tumor biomarkers in COVID-19 patients. Tumor biomarkers; CEA, cytokeratin 19 fragment (CYFRA21-1), neuron-specific enolase (NSE), SCCA, and Pro-Gastrin Releasing Peptide (ProGRP) were previously reported to be elevated in the pneumonia patients or benign lung diseases. In this study, they observed that all five tumor biomarkers were significantly increased in the plasma of COVID-19 patients than those in healthy controls. CEA, CYFRA21-1, and SCCA were significantly different among the subgroups of the severity of disease and they revealed that CEA, CYFRA21-1, SCCA could predict the clinical outcome of COVID-19 patients.

Therefore, early diagnosis and appropriate treatment are important in reducing the morbidity and mortality of COVID-19-infected patients.[4,14] Inflammatory factors, such as SAA, CRP, L, PCT, WBC, and PLT are frequently used to predict, diagnose and evaluate many inflammatory diseases. Similarly, lymphopenia was also very common in COVID-19 and this was more obvious in intensive care unit (ICU) patients.[12]

Our study also has several limitations. First, the number of patients can be increased in our study for the future. Second, if the patients' number increased in groups, we could determine and divide the patients accordingly into mild, severe and critical groups. Third, we can add other cancer biomarkers to our study and it will be more comprehensive. Fourth, a long-term follow-up is needed to determine if elevated cancer biomarkers in patients are transient or long-term as a risk of tumorigenesis. And the fifth and last limitation is not all routine laboratory tests have been included, as other markers are also valuable in COVID-19, such as coagulation and chemistry markers.

5 | CONCLUSION

As gynecologist oncologists, we tried to reveal a deeper understanding of the interaction between the immune system and cancer biomarkers developed parallel in patients with COVID-19. We found that COVID-19 had no effect on tumor markers (CA125, CA19-9, CA15-3, AFP, and CEA).

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Data are available on request from the authors.

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