

RESEARCH ARTICLE

Elevations of serum cancer biomarkers correlate with severity of COVID-19

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Abstract

In this retrospective study, we evaluated the levels of a series of serum biomarkers in coronavirus disease 2019 (COVID-19) patients (mild: 131; severe: 98; critical: 23). We found that there were significant increases in levels of human epididymis protein 4 (HE4) (73.6 ± 38.3 vs 46.5 ± 14.7 pmol/L; $P < .001$), cytokeratin-19 fragment (CYFRA21-1) (2.2 ± 0.9 vs 1.9 ± 0.8 $\mu\text{g/L}$; $P < .001$), carcinoembryonic antigen (CEA) (3.4 ± 2.2 vs 2.1 ± 1.2 $\mu\text{g/L}$; $P < .001$), carbohydrate antigens (CA) 125 (18.1 ± 13.5 vs 10.5 ± 4.6 $\mu\text{g/L}$; $P < .001$), and 153 (14.4 ± 8.9 vs 10.1 ± 4.4 $\mu\text{g/L}$; $P < .001$) 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 (SCC) and CA199 increased significantly 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 C-reactive protein and levels of HE4 ($R = .631$; $P < .001$), CYFRA21-1 ($R = .431$; $P < .001$), CEA ($R = .316$; $P < .001$), SCC ($R = .351$; $P < .001$), CA153 ($R = .359$; $P < .001$) and CA125 ($R = .223$; $P = .031$). We concluded that elevations of serum cancer biomarkers positively correlated with the pathological progressions of COVID-19, demonstrating diffuse and acute pathophysiological injuries in COVID-19.

KEYWORDS

cancer biomarker, carbohydrate antigens, carcinoembryonic antigen, COVID-19, cytokeratin-19 fragment, epididymis protein 4, SARS-COV-2

1 | INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has become a global threat to public health.¹ The disease is believed to be of zoonotic origin.^{2,3} Snakes, pangolins, and turtles are speculated to be an intermediate host(s).⁴ Severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) is the causative organism for

COVID-19.⁵ SARS-COV-2 is a single-strand RNA virus and belongs to the genus *Betacoronavirus*, which is based on the most conserved sequence of coronavirus genome, that is, the open reading frame 1a/1b (ORF1a/1b) responsible for replicases encoding.⁶ The RNA genome has 29 891 nucleotides and shares 79% sequence identity with SARS-COV and 50% sequence identity with Middle East respiratory syndrome coronavirus.^{6,7} The phylogeny of this

coronavirus shows that it is most close to the bat coronavirus RaTG13, with 96.3% sequence identity.³ The SARS-COV2 Spike (S) protein is thought to mediate the virus entering host cells via surface angiotensin-converting enzyme 2.^{7,8}

COVID-19 patients can be asymptomatic or symptomatic. The incubation period for symptomatic development in COVID-19 is approximately 4 to 7 days.⁹ Based on the severity of symptoms, COVID-19 can be classified into three categories.^{1,2,10} Mild cases are marked by the onset of symptoms such as fever, cough, fatigue, headache, diarrhea, and so forth, with or without mild pneumonia. Severe cases demonstrate dyspnea, acute respiratory stress, decrease in blood oxygen saturation, lung infiltrates, multiple peripheral ground-glass opacities on both lungs, and so forth. Critical cases present symptoms such as respiratory or multiple organ failure and septic shock. The mortality rate of COVID-19 is estimated to be about 2.3%, with a range from 6 to 41 days from the onset of symptoms to death.^{10,11} COVID-19 patients also develop dyslipidemia which is associated with the disease severity.^{12,13}

Many cancer biomarkers such as carcinoembryonic antigen (CEA) and carbohydrate antigens (CA) have shown an elevation in various inflammatory conditions in the lungs.¹⁴⁻¹⁶ We posit that SARS-CoV-2-induced acute lung injuries may be associated with elevations of some cancer biomarkers. In this study, we performed a thorough investigation of the pathological profiles of COVID-19 from a series of laboratory serum tests; these profiles may reflect the progression of the disease. We found that the levels of a panel of serum cancer biomarkers were positively associated with the severity of COVID-19, demonstrating the diffuse and acute lung injuries in patients.

2 | METHODS

2.1 | Study design and patients

This study was approved by the Institutional Review Board (IRB) at the Union Hospital of Tongji Medical College, Wuhan, Hubei, China. The requirement for informed consent was waived by the IRB committee. The study was carried out at the Cancer Center, Union Hospital of Tongji Medical College, Wuhan. A total of 252 patients who were admitted to the hospital from 13 February and 3 March 2020 were included in this study. Electronic data regarding epidemiological, demographic, clinical symptoms and diagnosis, laboratory tests, treatments, and outcomes were extracted. All patients were confirmed with an infection of SARS-COV-2 on nasal and pharyngeal swab specimens or induced sputum using a real-time reverse transcription-polymerase chain reaction (RT-PCR) assay before or on admission into our center for treatments. The primers and probe for real-time RT-PCR were reported previously.¹⁰ Pneumonia was diagnosed according to the guidelines from Chinese Thoracic Society, Chinese Medicine

Association, and the Infectious Diseases Society of America/American Thoracic Society guidelines. Patients were classified into three categories mild (n=131), severe (n=98), and critical (n=23) cases, according to the Chinese Center for Disease Control (CDC) guidelines and previous literature.¹ Patients were discharged if they met all of the following three criteria from the national CDC's guidelines: (a) with normal temperatures for more than 3 consecutive days; (b) remission of clinical symptoms, including cough, fever, and dyspnea; and (c) continuous twice negative RT-PCR results performed in every other day. All patients had an in-hospital lung computerized tomography or magnetic resonance imaging scan to exclude a lung cancer. Patients with a medical history of cancer were also excluded from this study.

Normal subjects who had laboratory tests of one or more cancer biomarkers in our hospital between 1 October and 1 November 2019 were included. Deidentified electronic data including only age, gender, and values of specific cancer biomarkers were extracted. Depending on the available data, we totally included the following age and gender-matched normal subjects in each cancer biomarker category: CEA (n = 190), CA125 (n = 245), CA153 (n = 197), squamous cell carcinoma antigen (SCC; n = 64), cytokeratin-19 fragment (CYFRA21-1; n = 88), and neuron-specific enolase (NSE; n = 78). Human epididymis protein 4 (HE4; n = 30) was only tested on female subjects in our hospital as a biomarker for ovarian cancer. The detailed demographic features for normal subjects in each cancer biomarker test category were listed in Table S1.

2.2 | Clinical laboratory tests

All tests were carried out at our certified clinical laboratory under standard procedures and practices that fully complied with regulations and guidelines of the Chinese Food and Drug Administration and CDC. The following clinical laboratory tests were performed on patient serum: a cancer biomarker profile, including NSE, CA724, CA242, CA199, CA125, CA153, free prostate-specific antigen (f-PSA), total PSA (t-PSA), alpha-fetoprotein (AFP), CEA, SCC, CYFRA21-1, and HE4; and an inflammatory and immunological profile including C-reactive protein (CRP), white blood cells (WBC), lymphocyte (LY), monocyte (MO), interleukin-2 (IL-2), IL-4, IL-6, IL-10, tumor necrosis factor-alpha (TNF- α), and interferon-gamma (IFN- γ). Other general laboratory tests were listed in Table S2. WBC, LY, and MO counts were performed on the Beckman LH750 analyzer using the manufacture's reagents (Beckman Coulter, Brea, CA). The general metabolic profiles were tested on the Beckman AU5800 chemistry analyzer using the manufacture's reagents (Beckman Coulter, Brea, CA). Cytokines and cancer biomarkers were tested on Abbott i2000 using manufacture's chemiluminescent immunoassay reagents (Abbott, Chicago, IL). CRP was performed using the BC-5390 reagent (MINDRAY, Shenzhen, Guangzhou, China).

2.3 | Statistical analysis

Statistical analyses were performed with the SPSS software (IBM, Armonk, NY). Differences among groups were analyzed by χ^2 . A Mann-Whitney *U* test was used to compare the differences between the two groups. A Pearson correlation analysis was used to calculate the correlation coefficient. The data was presented as "Mean \pm standard deviation (SD)" or "Mean \pm 95% confident interval (CI)". $P < .05$ was considered as statistical significance.

3 | RESULTS

3.1 | Demographic, basic health conditions, and general metabolic profiles

A total of 252 confirmed COVID-19 cases were included in this study: 131 mild, 98 severe, and 23 critical cases. The average age for all patients was 64.8 ± 13.3 years. The average age for the critical and severe cases were 70.4 ± 15.7 and 69.7 ± 11.6 , respectively; the patients in these groups were significantly older than those mild cases (60.1 ± 12.4) ($P < .05$) (Table 1). Male cases represented 52% ($n = 130$) and female cases 48% ($n = 122$) of the patients; this ratio was consistent for the critical and severe groups. However, there were more female patients than male patients in the mild group (52% vs 45%). About half of the patients with severe and critical conditions had other chronic morbidities such as diabetes, hypertension, and cardiovascular disorders; such conditions were present in only 35% of patients with mild symptoms (Table 1).

CRP increased in 95% of all cases; the increases were significant for all groups (mild: 13.5 ± 13.1 ; severe: 35.0 ± 39.2 ; critical: 66.1 ± 67.3 ; in mg/L; $P = .002$) (Table 2). Patients showed a significant lymphopenia with a degree associated with the disease severity (mild: 1.6 ± 0.6 ; severe: 1.4 ± 0.7 ; critical: 0.9 ± 0.5 ; $\times 10^9/L$; $P < .001$) (Table 2). IL-6 levels dramatically increased in all categories of cases (Table 2). IL-4 and IFN- γ levels increased in critical cases. Changes in

WBC, IL-2, IL-10, TNF- α , and many other metabolic profiles in patients were not in evidence (Table 2 and Table S2).

3.2 | Elevations of serum cancer biomarkers in COVID-19 patients

There were significant increases in levels of HE4 (73.6 ± 38.3 vs 46.5 ± 14.7 ; pmol/L, $P < .001$), CYFRA21-1 (2.2 ± 0.9 vs 1.9 ± 0.8 ; $\mu\text{g/L}$, $P < .001$), CEA (3.4 ± 2.2 vs 2.1 ± 1.2 ; $\mu\text{g/L}$, $P < .001$), CA125 (18.1 ± 13.5 vs 10.5 ± 4.6 ; $\mu\text{g/L}$, $P < .001$) and 153 (14.4 ± 8.9 vs 10.1 ± 4.4 ; $\mu\text{g/L}$, $P < .001$) in COVID-19 mild cases as compared with levels in the normal subjects (Figure 1). The levels of all these biomarkers exhibited significantly gradual increases in patients across cases in all categories (Figure 1 and Table 2; $P < .02$). NSE, SCC, and CA199 levels increased significantly only in critical cases as compared with levels in normal subjects, mild, and critical cases (Figure 1F and Table 2; $P < .05$). We had all female subjects in the normal control group of HE4, which data had a gender bias. To determine whether the gender was a potential factor contributing to the elevation of HE4 in patients, we divided the cohort based on genders in each category. Both female and male patients with mild COVID-19 showed significantly higher levels of HE4 as compared with the normal subjects (Figure 1A; $P < .05$); they also showed gradual increases in HE4 levels in correlation with the disease severity, regardless of genders (Figure 1A; $P < .05$).

3.3 | Relationship of LY or CRP with biomarkers

The number of LYs inversely correlated with levels of HE4 ($R = -.375$; pmol/L; $P < .001$) in COVID-19 patients (Figure 2A), but was not associated with other cancer biomarkers we examined in this study (data not shown). CRP levels positively correlated with HE4 ($R = .631$; $P < .001$; Figure 2B), CYFRA21-1 ($R = .431$; $P < .001$; Figure 2C), CEA ($R = .316$; $P < .001$; Figure 2D), CA125 ($R = .223$; $P = .031$; Figure 2E), CA153

TABLE 1 Demographic and clinical features for COVID-19 patients

Characteristics	All patients (n = 252)	Mild (n = 131)	Severe (n = 98)	Critical (n = 23)	P
Age, y	64.8 (13.3)	60.1 (12.4)	69.7 (11.6)	70.4 (15.7)	<.01
Sex					ns
Male	130 (52%)	59 (45%)	59 (60%)	12 (52%)	
Female	122 (48%)	72 (55%)	39 (40%)	11 (48%)	
Comorbidities					
Any	106 (42%)	46 (35%)	49 (50%)	11 (48%)	ns
2-DM	31 (12%)	16 (12%)	11 (11%)	4 (17%)	ns
Hypertension	81 (32%)	32 (24%)	42 (43%)	7 (30%)	<.02
Cardiovascular disease	20 (8%)	5 (4%)	11 (11%)	4 (17%)	<.05
HIV	1 (0.4%)	0 (0%)	0 (0%)	1 (4%)	na
Hyperlipidemia	6 (2%)	3 (2%)	2 (2%)	1 (4%)	ns

Note: Data were mean (SD) or n (%). The χ^2 was used to compare differences among groups.

Abbreviations: HIV, human immunodeficiency viruses; na, no available; ns, no significance; SD, standard deviation.

TABLE 2 Serum cancer biomarkers, inflammatory, and immunological profiles from COVID-19 patients

Category	Reference	All patients	Mild	Severe	Critical	P
f-PSA	<0.93 µg/L	0.3 (0.6)	0.3 (0.6)	0.2 (0.4)	0.4 (0.9)	ns
t-PSA	<4 µg/L	1.1 (3.3)	1.2 (4.4)	0.8 (1.1)	1.3 (2.4)	ns
HE4	^a 46.5 (14.7) pmol/L	121 (117)	73.6 (38.3)	145.7 (118.4)	284.0 (201.6)	<.001
CYFRA21-1	^a 1.9 (0.8) µg/L	2.8 (2.1)	2.2 (0.9)	3.3 (2.9)	3.9 (2.4)	<.05
CEA	^a 2.1 (1.2) µg/L	5.1 (8.9)	3.4 (2.2)	5.3 (6.3)	12.8 (24.7)	<.02
CA125	^a 10.5 (4.6) µg/L	28.9 (35.3)	18.1 (13.6)	33.1 (40.4)	72.3 (56.1)	<.01
CA153	^a 10.1(4.4) µg/L	16.6 (12.5)	14.4 (8.9)	17.7 (13.9)	24.6 (18.9)	<.05
NSE	^a 12.5(6.1) µg/L	14.4 (7.2)	13.6 (3.9)	13.8 (5.7)	21.1 (17.5)	<.05
SCC	^a 0.8 (0.3) µg/L	0.8 (0.8)	0.7 (0.5)	0.7 (0.5)	1.6 (2.0)	<.05
AFP	0.9-8.8 µg/L	3.5 (5)	3.2 (1.5)	4.1 (7.8)	2.6 (1.3)	<.05
CA242	<20U/ML	3.5 (3.0)	3.3 (3.2)	3.6 (2.9)	4.1 (2.6)	ns
CA724	<7U/ML	4.9 (9.9)	4.2 (6.8)	5.4 (12.8)	7.0 (10.9)	ns
CA199	<37 µg/L	10.4 (12.6)	8.9 (11.9)	11.2 (13.8)	14.2 (9.1)	<.01
CRP	<4 mg/L	16.2 (34.8)	4.29 (8.33)	18.8 (32.7)	66.1 (67.3)	<.01
IL-2	0.1-4 pg/ML	6 (37.9)	9 (53.4)	2.8 (0.7)	2.9 (0.9)	ns
IL-4	0.1-3.2 pg/ML	3 (5.7)	2.6 (1)	2.3 (0.8)	8.4 (20)	ns
IL-6	0.1-2.9 pg/ML	99.6 (307.9)	64.6 (137.7)	150.7(449.2)	57.4 (105.6)	ns
IL-10	0.1-5 pg/ML	4.2 (2)	3.9 (1.8)	4.3 (1.7)	5.6 (3.6)	ns
TNF-α	0.1-23 pg/ML	5.4 (6.1)	5.6 (6.6)	5.5 (6.1)	3.2 (2)	ns
IFNγ	0.1-18 pg/ML	3.2 (7.6)	2.5 (1.1)	2.9 (4.5)	9.5 (24.7)	ns
WBC	3.5-9.5 (× 10 ⁹ /L)	6.4 (2.7)	6.2 (2.0)	6.2 (2.4)	8.6 (5.7)	ns
LY	1.1-3.2 (× 10 ⁹ /L)	1.5 (0.7)	1.6 (0.6)	1.4 (0.7)	0.9 (0.5)	<.01
MO	0.1-0.6 (× 10 ⁹ /L)	0.6 (0.5)	0.51 (0.25)	0.6 (0.7)	0.6 (0.3)	n.s

Note: Data are presented as mean (SD). The χ^2 was used for comparisons.

Abbreviations: AFP, alpha-fetoprotein; CEA, carcinoembryonic antigen; CRP, C-reactive protein; CYFRA21-1, cytokeratin-19 fragment; f-PSA, free prostate-specific antigen; HE4, Human epididymis protein 4; IFN- γ , interferon-gamma; IL, interleukin; LY, lymphocyte; MO, monocyte; ns, no significance; NSE, neuron-specific enolase; SCC, squamous cell carcinoma antigen; TNF- α , tumor necrosis factor-alpha; t-PSA, total PSA; WBC, white blood cells.

^aData were measured from the normal subjects in each control group in Table S1.

($R = .359$; $P < .001$; Figure 2F), SCC ($R = .351$; $P < .001$; Figure 2G), and NSE ($R = .316$; $P < .001$; Figure 2H), respectively.

4 | DISCUSSION

In this study, we retrospectively summarized a series of clinical laboratory tests on serum from COVID-19 patients, including metabolic panels and a set of 13 cancer biomarkers. This is the first report with such a substantial evaluation of cancer biomarkers on a large patient population of COVID-19. Our data demonstrate that levels of serum HE4, CYFRA21-1, CEA, CA125, CA153, SCC, and NSE are positively associated with CRP, a crucial factor in correlation with the severity of the disease. Our findings provide insights into the detailed pathological evolution of COVID-19 in patients; this will not only aid in understanding the disease's molecular pathology, and facilitate early diagnosis, but will also help in assessing long-term outcomes.

In this study, we did not include any patients with cancer diagnoses; therefore, the elevation of these cancer biomarkers was not associated to preexisting conditions of tumorigenesis. Many studies have shown that cancer biomarkers such as CEA, CA and HE4 are also elevated in various inflammatory conditions in the lungs. For example, CEA is increased in smoking subjects;¹⁴ CYFRA21-1 is increased in pulmonary alveolar proteinosis;¹⁵ and CA125 is increased in chronic obstructive pulmonary disease.¹⁶ HE4 levels are correlated with the severity of cystic fibrosis.¹⁷ More interestingly, a recent study has shown that CA such as CA199 can cause rapid and severe pancreatitis with hyperactivation of epidermal growth factor receptor signaling and promote pancreatic cancer in an animal model.¹⁸ A potential mechanism underlying our data is that upregulation of HE4, CEA, and CYFRA21-1 can reflect an acute alveolar injury. CRP is an inflammatory marker. The 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.^{19,20} CRP is a crucial factor

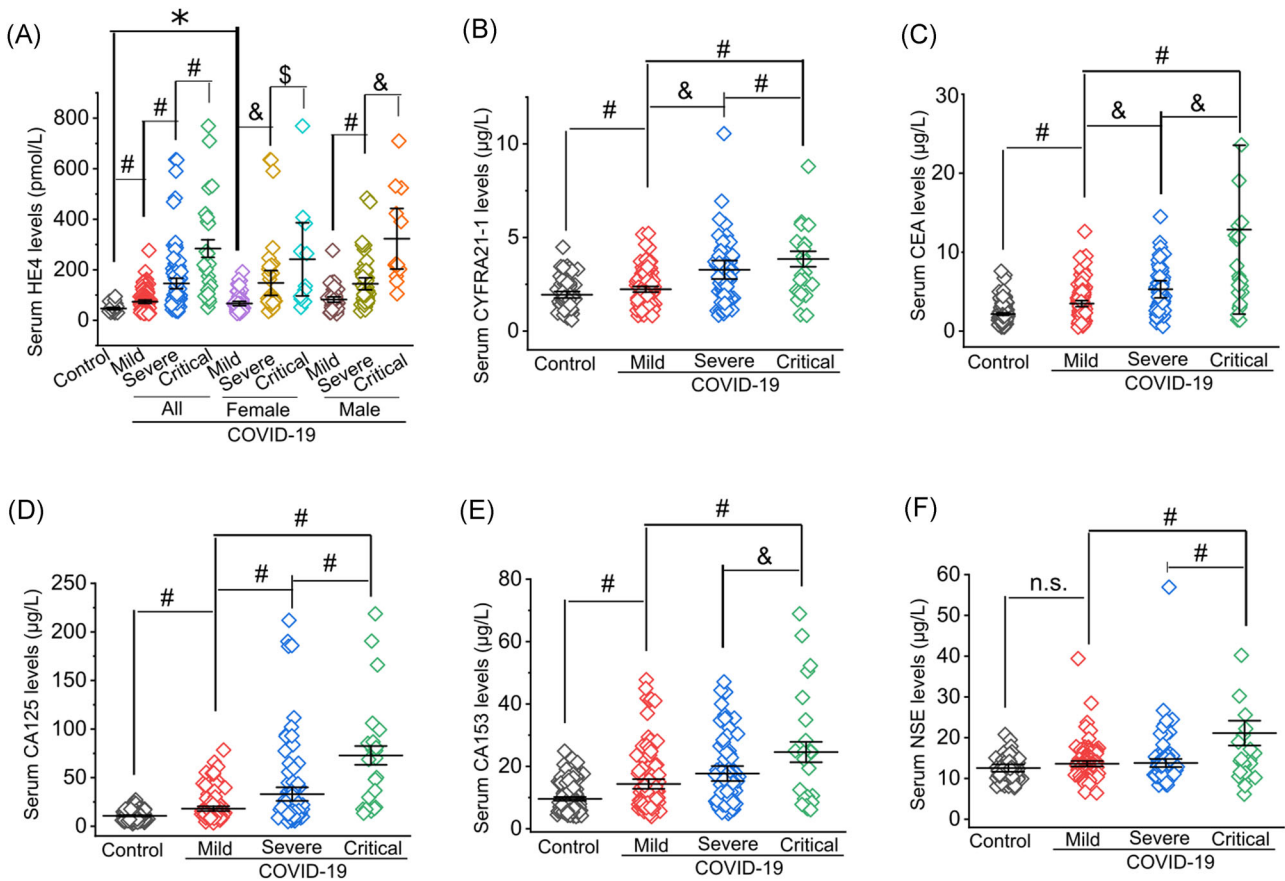


FIGURE 1 Elevation of cancer biomarkers in COVID-19 patients with critical, severe, or mild symptoms as compared with normal control subjects. Serum levels of cancer biomarkers, HE4 (A), CYFRA21-1 (B), CEA (C), CA125 (D), CA153 (E), and NSE (F) are plotted as “Mean \pm 95% CI” in each figure. The χ^2 and the Mann-Whitney U tests were used for intergroup analysis. * $P < .05$, $^{\$}P < .01$, $^{\#}P < .001$, $^{\&}P = .05$.

CA, carbohydrate antigens; CEA, carcinoembryonic antigen; CI, confidence interval; COVID-19, coronavirus disease 2019; CYFRA21-1, cytokeratin-19 fragment; HE4, Human epididymis protein 4; NSE, neuron-specific enolase

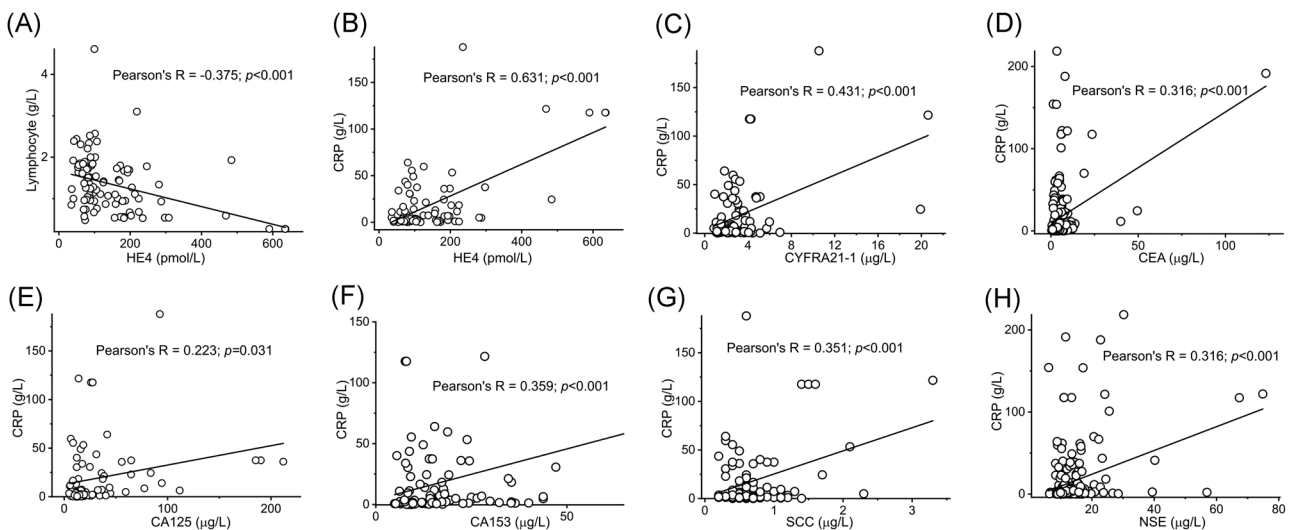


FIGURE 2 Correlations of numbers of lymphocyte and HE4 (A), and CRP and biomarkers HE4 (B), CYFRA21-1 (C), CEA (D), CA125 (E), CA153 (F), SCC (G) and NSE (H) in COVID-19 patients. A Pearson correlation analysis was used. CEA, carcinoembryonic antigen; COVID-19, coronavirus disease 2019; CYFRA21-1, cytokeratin-19 fragment; HE4, Human epididymis protein 4; NSE, neuron-specific enolase; SCC, squamous cell carcinoma antigen

associated with the severity of COVID-19.^{12,13} The positive correlations between CRP and a series of cancer biomarkers we showed in this study demonstrate that these cancer biomarkers can present the diffuse and acute pathophysiological injuries in COVID-19.

There are several limitations to this study. First, a long-term follow-up is needed to determine whether elevated cancer biomarkers in patients are transient or long-term as a risk of tumorigenesis. Second, surveillance of these serum markers during treatment is very important to provide a molecular basis for how this disease responds to various treatments. Third, the normal control subjects for HE4 were all female, which data had a gender bias.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

HW and WT supervised and designed the study. WX, JS, JW, and HW performed the tests and collected the data. WX, JS, KY, and XC contributed to the data analysis. HW and WT contributed to the manuscript writing and data interpretation.

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REFERENCES

- Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (covid-19) outbreak in china: summary of a report of 72314 cases from the chinese center for disease control and prevention. *JAMA*. 2020;323:1239. <https://doi.org/10.1001/jama.2020.2648> 2762130.
- Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in wuhan, china. *Lancet*. 2020;395:497-506. S0140-6736(20)30183-5.
- Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*. 2020;579:270-273. <https://doi.org/10.1038/s41586-020-2012-7>
- Liu Z, Xiao X, Wei X, et al. Composition and divergence of coronavirus spike proteins and host ace2 receptors predict potential intermediate hosts of sars-cov-2. *J Med Virol*. 2020;92:595-601. <https://doi.org/10.1002/jmv.25726>
- Xu X, Chen P, Wang J, et al. Evolution of the novel coronavirus from the ongoing wuhan outbreak and modeling of its spike protein for risk of human transmission. *Sci China: Life Sci*. 2020;63:457-460. <https://doi.org/10.1007/s11427-020-1637-5>
- The species severe acute respiratory syndrome-related coronavirus. Classifying 2019-ncov and naming it sars-cov-2. *Nat Microbiol*. 2020;5:2020-2544. <https://doi.org/10.1038/s41564-020-0695-z>
- Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet*. 2020;395:565-574. S0140-6736(20)30251-8.
- Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by novel coronavirus from wuhan: an analysis based on decade-long structural studies of sars. *J Virol*. 2020;94(7):e00127-20. <https://doi.org/10.1128/JVI.00127-20>
- Li Q, Guan X, Wu P, et al. Early transmission dynamics in wuhan, china, of novel coronavirus-infected pneumonia. *N Engl J Med*. 2020;382:1199-1207. <https://doi.org/10.1056/NEJMoa2001316>
- Shi H, Han X, Jiang N, et al. Radiological findings from 81 patients with covid-19 pneumonia in wuhan, china: a descriptive study. *Lancet Infect Dis*. 2020;20:425-434. [https://doi.org/10.1016/S1473-3099\(20\)30086-4](https://doi.org/10.1016/S1473-3099(20)30086-4)
- Wang W, Tang J, Wei F. Updated understanding of the outbreak of 2019 novel coronavirus (2019-ncov) in wuhan, china. *J Med Virol*. 2020;92:441-447. <https://doi.org/10.1002/jmv.25689>
- Fan J, Wang H, Ye G, et al. Low-density lipoprotein is a potential predictor of poor prognosis in patients with coronavirus disease 2019. *Metabolism*. 2020:154243. <https://doi.org/10.1016/j.metabol.2020.154243>
- Wei X, Zeng W, Su J, et al. Hypolipidemia is associated with the severity of covid-19. *J Clinical Lipidology*. 2020. <https://doi.org/10.1016/j.jacl.2020.04.008>
- Stockley RA, Shaw J, Whitfield AG, Whitehead TP, Clarke CA, Burnett D. Effect of cigarette smoking, pulmonary inflammation, and lung disease on concentrations of carcinoembryonic antigen in serum and secretions. *Thorax*. 1986;41:17-24. <https://doi.org/10.1136/thx.41.1.17>
- Hirakata Y, Kobayashi J, Sugama Y, Kitamura S. Elevation of tumour markers in serum and bronchoalveolar lavage fluid in pulmonary alveolar proteinosis. *Eur Respir J*. 1995;8:689-696.
- Barouchos N, Papazafiropoulou A, Iacovidou N, et al. Comparison of tumor markers and inflammatory biomarkers in chronic obstructive pulmonary disease (copd) exacerbations. *Scand J Clin Lab Invest*. 2015;75:126-132. <https://doi.org/10.3109/00365513.2014.992944>
- Nagy B Jr Jr., Bene Z, Fejes Z, et al. Human epididymis protein 4 (he4) levels inversely correlate with lung function improvement (delta fev1) in cystic fibrosis patients receiving ivacaftor treatment. *J Cyst Fibros*. 2019;18:271-277. <https://doi.org/10.1016/j.jcf.2018.08.013>
- Engle DD, Tiriach H, Rivera KD, et al. The glycan ca19-9 promotes pancreatitis and pancreatic cancer in mice. *Science*. 2019;364(6446):1156-1162. <https://doi.org/10.1126/science.aaw3145>
- Akil E, Bulut A, Kaplan I, Özdemir HH, Arslan D, Aluçlu MU. The increase of carcinoembryonic antigen (cea), high-sensitivity c-reactive protein, and neutrophil/lymphocyte ratio in parkinson's disease. *Neurol Sci*. 2015;36:423-428. <https://doi.org/10.1007/s10072-014-1976-1>
- Bagaria B, Bagaria A, Sharma R, Sood S, Lalwani S. Significance of correlation between levels of carcinoembryonic antigen and carbohydrate antigen 19-9, carcinoembryonic antigen and c-reactive protein, carcinoembryonic antigen and alpha-1 antitrypsin in gastric and colon cancer patients. *Clin Cancer Investig J*. 2014;3:291-298. <https://doi.org/10.4103/2278-0513.134477>

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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