LETTER TO THE EDITOR

Elevated carcinoembryonic antigen in patients with COVID-19 pneumonia

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Abstract

Purpose Coronavirus disease 2019 (COVID-19) tends to affect multiple organs and induce abnormal laboratory parameters. We designed this study to investigate the association between carcinoembryonic antigen (CEA) elevation and SARS-CoV-2 infection.

Methods We retrospectively analyzed 177 patients with confirmed SARS-CoV-2 infection who received plasma CEA assays during hospitalization. Patients with other causes of CEA elevation were excluded. Data regarding epidemiological and demographical characteristics, clinical symptoms, laboratory tests, and outcomes were analyzed. Linear regression analysis was used to evaluate the correlation between CEA levels and inflammation severity.

Results 171 patients were included in the final study and 32 patients (18.7%) had raised serum of CEA (> 5 ng/ml), with a median (range) age of 66 (53–86). The median [interquartile range (IQR)] CEA level was 11.4 ng/ml (8.1–21.6), which was significantly higher than the upper limit of reference range. CEA level between 5–10 ng/ml was in 11 patients, 10–15 ng/ml in 10 patients, and > 15 ng/ml in 11 patients. No correlation was found between CEA levels and lymphocyte ($R^2 = 0.055$; $P = 0.10$) nor CRP ($R^2 = 0.026$; $P = 0.38$). The median levels of CEA were 20.0 ng/ml (IQR, 14.7–23.0) in non-survivors and 10.9 ng/ml (IQR 7.5–16.1) in survivors, and the difference between two groups was statistically significant ($P = 0.048$).

Conclusion SARS-CoV-2 infection might be another cause of CEA elevation, with nearly 20% of patients experienced transient and marked CEA increment during COVID-19 pneumonia. The false-positive results of CEA elevation might have clinical significance for patients with colorectal cancer.

Keywords Carcinoembryonic antigen · Coronavirus disease 2019 · SARS-CoV-2 · Gastrointestinal damage

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Coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 infection has now become an international public health crisis. Mounting evidence suggests that this novel disease can affect multiple organs despite lung, such as heart, liver and gastrointestinal tract, and results in abnormalities of several biomarkers (Lin et al. 2020; Guan et al. 2019). Carcinoembryonic antigen (CEA) is a glycoprotein formed in colonic epithelium during embryonic period, which has been widely utilized as a tumor marker to monitor tumor progression (Goldenberg et al. 1981). We found a portion of patients with COVID-19 pneumonia had raised serum of CEA, and we designed this study to investigate the association between CEA elevation and SARS-CoV-2 infection.

We retrospectively analyzed 177 consecutive patients with laboratory confirmed COVID-19 who admitted to Wuhan Jinyintan Hospital between January 1 and February 28, 2020. At the early stage of this epidemic, all patients admitted to our center received CEA tests as well as other

non-routine examinations. Patients with other potential causes of CEA elevation like recent smoking history, malignant tumors, or non-malignant conditions (such as inflammatory bowel disease or pancreatitis) were excluded. Nonparametric continuous variables were expressed as median (interquartile range) and compared using Mann–Whitney U test. Qualitative variables were expressed as number (percentage) and compared by means of Chi-squared or two-tailed Fisher's exact test. Linear regression analysis was used to evaluate the correlation between CEA levels and inflammation severity [judged by lymphocyte count and C-reactive protein (CRP)]. A two-sided α of less than 0.05 was considered statistically significant. All statistical analyses were processed using IBM SPSS (version 25.0). The study protocol was approved by the institutional ethics committee of Wuhan Union Hospital and Wuhan Jinyintan Hospital. Informed consent was waived given the retrospective nature of this study.

One hundred and seventy-one patients were enrolled in the final cohort, including 23 patients who were admitted to the intensive care unit. Among them, 32 patients (18.7%) had raised serum of CEA (> 5 ng/ml), with a median age of 66 years (range 53–86). The median [interquartile range (IQR)] CEA level was 11.4 ng/ml (8.1–21.6), which was significantly higher than the upper limit of reference range. CEA level between 5–10 ng/ml was in 11 patients, 10–15 ng/ml in 10 patients, and > 15 ng/ml in 11 patients. The highest level of CEA was 63 ng/ml. The median time from disease onset to the first detection of CEA was 12 days (IQR 9–16) (Table 1).

Serial determinations of CEA (CEA test ≥ 2 times) were available in 13 patients. CEA levels returned to normal in three patients, with an interval of 14, 26 and 40 days, respectively, from their disease onset. CEA levels of other ten patients remained abnormal until their last determination, but seven of them showed a decrease, with a median interval of 24 days (range 19–32) from disease onset.

All 32 patients had definite outcomes, of whom 7 died and 25 recovered and discharged from hospital. The median levels of CEA were 20.0 ng/ml (IQR 14.7–23.0) in non-survivors and 10.9 ng/ml (IQR 7.5–16.1) in survivors, and the difference between two groups was statistically significant ($P = 0.048$). No correlation was found between CEA levels and lymphocyte ($R^2 = 0.055$; $P = 0.10$) nor CRP ($R^2 = 0.026$; $P = 0.38$).

The exact mechanism of CEA elevation during COVID-19 pneumonia remains elusive. One possible explanation is that CEA as an acute phase protein, its increment may be associated with inflammation induced by viral infection. However, no correlation was found between CEA level and severity of inflammation in the present study, indicating this assumption may not be reasonable. Another possible mechanism may be related to the gastrointestinal damage caused by viral infection. As previously reported, the regeneration

Table 1 Baseline characteristics of patients with elevated serum of CEA concentrations

	Total ($n = 32$)	Survivor ($n = 25$)	Non-survivor ($n = 7$)	P value
Age—years[a]	66.0 (61.0–76.0)	65.0 (59.0–71.0)	74.0 (63.0–84.0)	0.242
Sex (male)[b]	18 (56.2%)	11 (44.0%)	7 (100%)	0.01
Co-existing disease[b]				0.614
COPD	2 (6.2%)	1 (4%)	1 (14.2%)	
Hypertension	17 (52.1%)	14 (56%)	3 (42.8%)	
Diabetes	10 (31.2%)	9 (36%)	1 (14.2%)	
Cerebrovascular disease	1 (3.1%)	1 (4%)	0 (0%)	
Laboratory parameters[a]				
Leucocyte count (× 109/l)	8.1 (6.1–10.4)	7.8 (5.9–9.9)	9.3 (6.9–13.0)	0.281
Neutrophil count (× 109/l)	6.6 (4.9–9.0)	6.2 (4.9–8.6)	7.9 (6.1–12.5)	0.148
Lymphocyte count (× 109/l)	0.87 (0.61–1.25)	0.95 (0.63–1.5)	0.69 (0.35–1.1)	0.175
C-reactive protein (mg/l)	59 (24–139)	48 (18–115)	148 (45–160)	0.02
ESR (mm/h)	56 (30–71)	67 (35–76)	35 (7–44)	0.0
Serum CEA levels (ng/ml)[a]	11.4 (8.1–21.6)	10.9 (7.5–16.1)	20.0 (14.7–23.0)	0.048
Time from disease onset to[a]				
Hospital admission—days	11 (8–15)	10 (8–15)	15 (12–23)	0.161
First CEA test—days	12 (9–16)	11 (8–16)	15 (12–24)	0.191

COPD chronic obstructive pulmonary disease; *CEA* carcinoembryonic antigen; *ESR* erythrocyte sedimentation rate

[a]Nonparametric continuous variables were expressed as median (interquartile range) and compared using Mann–Whitney U test

[b]Qualitative variables were expressed as number (percentage) and compared by means of Chi-squared or two-tailed Fisher's exact test

and/or degeneration of intestinal mucosa in patients with gastrointestinal disease was similar to the process of embryonic development and carcinoma progression, which was the leading course of CEA increment (Rule et al. 1973). SARS-CoV-2, which can identify angiotensin-converting enzyme 2 (ACE2) through its spike protein and consequently enter target cells, has been proved to infect gastrointestinal glandular cells (Hoffmann et al. 2020; Jin et al. 2019; Xiao et al. 2020). These evidences indicate that SARS-CoV-2 infection might contribute to CEA elevation secondary to mucosal damage.

Previous studies showed that elevated CEA was correlated with disease severity (manifested by declined pulmonary function) in patients with idiopathic pulmonary fibrosis (Fahim et al. 2012). Similarly, CEA level was significantly higher in non-survivors in our study, suggesting this biomarker may be predictive of poor prognosis. In addition, considering the clinical and prognostic value of CEA in patients with confirmed colorectal malignancy, as its failure to decrease to normal after surgical resection indicates residual lesion and its rapid and marked increment indicates recurrence or metastasis, regular assays of CEA is widely used as an effective non-invasive method for postoperative surveillance. Our results demonstrated that transient and marked CEA elevation was not rare during the clinical course of COVID-19. Thus, physicians should be aware that a single measurement of CEA in COVID-19 patients may be a false-positive result induced by viral infection and may not be suggestive of tumor progression or remission, and sequential assays should be conducted subsequently. However, as none of our participants had any clinical indication of malignancy, further studies are needed to investigate the role of CEA level in COVID-19 patients accompanied with colorectal cancer.

The present study has several limitations. First, since CEA increment was not frequent in COVID-19 patients and we enrolled patients within a short period, the sample size was relatively small and thus no firm conclusions could be drawn. Second, as a pilot study which focused on reporting an abnormal increment of a biomarker during COVID-19 pneumonia, we did not perform basic research to confirm this hypothesis. Therefore, further studies are needed to investigate the underlying pathophysiological mechanisms.

In conclusion, SARS-CoV-2 infection might cause transient and marked CEA elevation especially in non-survivors, and this abnormal increment was not correlated with the severity of inflammation. Future studies on the mechanisms of CEA elevation and the role of CEA in predicting prognosis are warranted.

Compliance with ethical standards

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