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ORIGINAL ARTICLE

The correlation between COVID-19 segmentation volume based on artificial intelligence technology and gastric wall edema: a multi-center study in Wuhan

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Abstract

Purpose This study aimed to investigate manifestations of the gastric wall and related risk factors in COVID-19 patients with gastrointestinal symptoms by CT.

Materials and methods Two hundred and forty patients diagnosed with COVID-19 by RT-PCR were enrolled from January 2020 to April 2020. Patients showed gastrointestinal symptoms, including nausea, vomiting, or diarrhea. Results of the initial laboratory examination were performed after admission. Chest CT was performed for all patients, with the lower bound including the gastric antrum. The volume of COVID-19 and lungs was segmented, and the ratio was calculated as follows: $PV/LV = Volume_{pneumonia}/Volume_{lungs}$.

Results Among the 240 patients, 109 presented with gastric wall edema (edema group), and 131 showed no gastric wall edema (non-edema group); the PV/LV values between the two groups were significantly different ($P = 0.002$). Univariate analysis revealed the following: fibrinogen (Fib), thrombin time (TT), activated partial thromboplastin time (APTT), and albumin (ALB) significantly differed between the two groups ($P < 0.05$). Binary logistic regression analysis showed that only APTT had a negative effect on gastric wall edema ($P = 0.003$).

Conclusions SARS-CoV-2 invades the gastrointestinal tract, gastric wall edema is the primary CT manifestation, and gastric wall edema is more likely to occur with a shorter APTT and severe pneumonia, with a slightly longer hospitalization time. Patients with gastric wall edema observed by CT should intervene early, which may improve digestive function, and further strengthen immune potency against COVID-19.

Keywords COVID-19 · SARS-CoV-2 · Gastrointestinal symptoms · Imaging · Edema

Introduction

Coronavirus disease 2019 (COVID-19) is caused by SARS-CoV-2 [1]. COVID-19 is highly infectious and can even be vertically transmitted [2]. In addition to life-threatening pulmonary complications [3], COVID-19 attacks the body's other organ systems. On the digestive system, the impact of COVID-19 is extensive, covering the liver, gallbladder, pancreas, and gastrointestinal tract [4].

COVID-19 patients often experience fever and respiratory symptoms, such as dry cough and dyspnea [5, 6]. Moreover, in nearly 20% of COVID-19 patients, combined gastrointestinal symptoms occur, and in 5%, gastrointestinal symptoms alone, such as diarrhea, abdominal pain, nausea, vomiting, and loss of appetite, have been note [7]. The New York Society for Gastrointestinal Endoscopy believes that in the time of a pandemic, acute gastrointestinal symptoms

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should be investigated as manifestations of COVID-19 [8]. The mechanism underlying the development of gastrointestinal symptoms in COVID-19 patients is similar to that in patients with severe acute respiratory syndrome (SARS) [9]. When SARS-CoV-2 reaches the digestive system, it binds to the angiotensin-converting enzyme 2 (ACE2) receptor expressed on epithelial cells [10], once inside these cells, it replicates in the cytoplasm, affecting the absorptive function of gastrointestinal epithelial cells and causing an imbalance in bacterial flora [11], thus inducing gastrointestinal symptoms. A study has reported that SARS-CoV-2 RNA was found in feces; therefore, even if a SARS-CoV-2 test result is negative based on respiratory secretions [12, 13], a patient may be a potential virus carrier through fecal–oral transmission. Hence, the digestive tract is a crucial transmission route for SARS-CoV-2 infection.

The small intestine has the most abundant ACE2 receptor expression among the organs of the digestive system; thus, it is most likely to be invaded by SARS-CoV-2 [14]. Regarding imaging manifestations of SARS-CoV-2 in the digestive tract, most studies have focused on abnormal imaging manifestations of the small intestine, including intestinal wall ischemia, infection, and necrosis, adjacent mesenteric hyperemia, and portal vein thrombosis or portal venous gas [15, 16]. In addition, imaging manifestations of the colon have been reported. In one COVID-19 patient, Nardi et al. [17] noted a significantly inflated colon with perforation, which may be related to virus invasion of the autonomic motor neurons. Pathological findings showed diffuse granulocytic infiltration and submucosal edema in the colon wall [18].

The ACE2 receptor is expressed in the gastric wall, however, its expression level is relatively low [19]. We hypothesized that SARS-CoV-2 may invade the gastric wall first, causing changes in the physiology of the gastric wall, hence resulting in gastrointestinal symptoms. However, there are few reports on whether it can cause abnormal changes seen on gastric wall imaging. On the basis of the above speculation, this study further explored whether COVID-19 patients with gastrointestinal symptoms have stomach wall abnormalities on CT and analyzed its risk factors.

Materials and methods

Patient clinical data

This retrospective study was approved by the Ethics Committee of the First Affiliated Hospital, Army Medical University. From January 2020 to April 2020, patients with COVID-19 confirmed by RT-PCR at 3 Hospitals were enrolled, including Huoshenshan Hospital, Taikang Hospital and Guanggu Hospital at Wuhan. The inclusion criteria were initial clinical symptoms including digestive abnormalities, such as nausea and vomiting, and/or diarrhea; chest CT including the entire gastric; and laboratory examination after admission, including the white blood cell (WBC) count, lymphocyte (LYM) count, neutrophil (NEU) count, C-reactive protein (CRP), prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), fibrinogen (Fib), blood glucose, alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin (ALB), and total bilirubin (TB). Conversely, the exclusion criteria were poor CT image quality due to artifacts and incomplete laboratory test data or > 7 days between the CT scan and laboratory tests (Fig. 1). Overall, 240 patients were included in this study: 93 men and 147 women, with an age range of 19–94 years and an average age of 58.3 ± 14.3 years. No patient had a history of malignant tumor, chronic hepatitis B, alcoholic liver disease, nonalcoholic fatty liver disease, ascites, heart failure, gastritis, ulcer or shock (Table 1).

Scanning parameters and image analysis

For the patients included in this study, 64-row (Somatom, Siemens Healthcare), 128-row (uCT 760 scanner, United Imaging Healthcare), and 256-row (Brilliance-16P, Philips Healthcare) spiral CT scans were performed. All patients were asked to hold their breath after deep inhalation before the scan was started. The scanning parameters were as follows: tube voltage at default machine settings, with automatic tube current; layer thickness was 1 mm (64-row), 0.625 mm (128-row), and 1 mm (256-row); lung window width and level were 1200–1500 HU and − 600 to 700 HU, respectively; and mediastinal window width and level were 400 HU and 20–40 HU, respectively. The scan covered the area from the thoracic inlet to the costophrenic angle. After each examination, the staff disinfected the equipment room and machine.

The comprehensive 3D-UNet for COVID-19 segmentation model was used to identify and separate the volume of both lungs (LV, $\text{Volume}_{\text{lungs}}$) and pneumonia (PV, $\text{Volume}_{\text{pneumonia}}$) (refer to Y Bao for specific methods) [20]. The $\text{Volume}_{\text{pneumonia}}/\text{Volume}_{\text{lungs}}$ ratio was calculated as follows: $\text{PV/LV} = \text{Volume}_{\text{pneumonia}}/\text{Volume}_{\text{lungs}}$. In addition, all CT images were analyzed by two radiologists (Dr. Liu, 10 years' experience; Dr. Chen 5 years' experience) to observe any abnormality of the gastric wall, and any discrepancy in feature assessment was resolved by means of consensus discussion. If the following signs occurred simultaneously, we believed the presence of gastric wall edema. (i) The gastric lumen is well-filled, which is defined by full dilatation of gastric lumen and no folds on gastric mucosa displayed; (ii) layering appearance: mainly mucosa and muscle layer was separated by diffuse banding low-density (CT value 0-20HU) appeared in the gastric wall (greater and/or lesser curvature involved). (iii) The wall thickness at the level of the body is

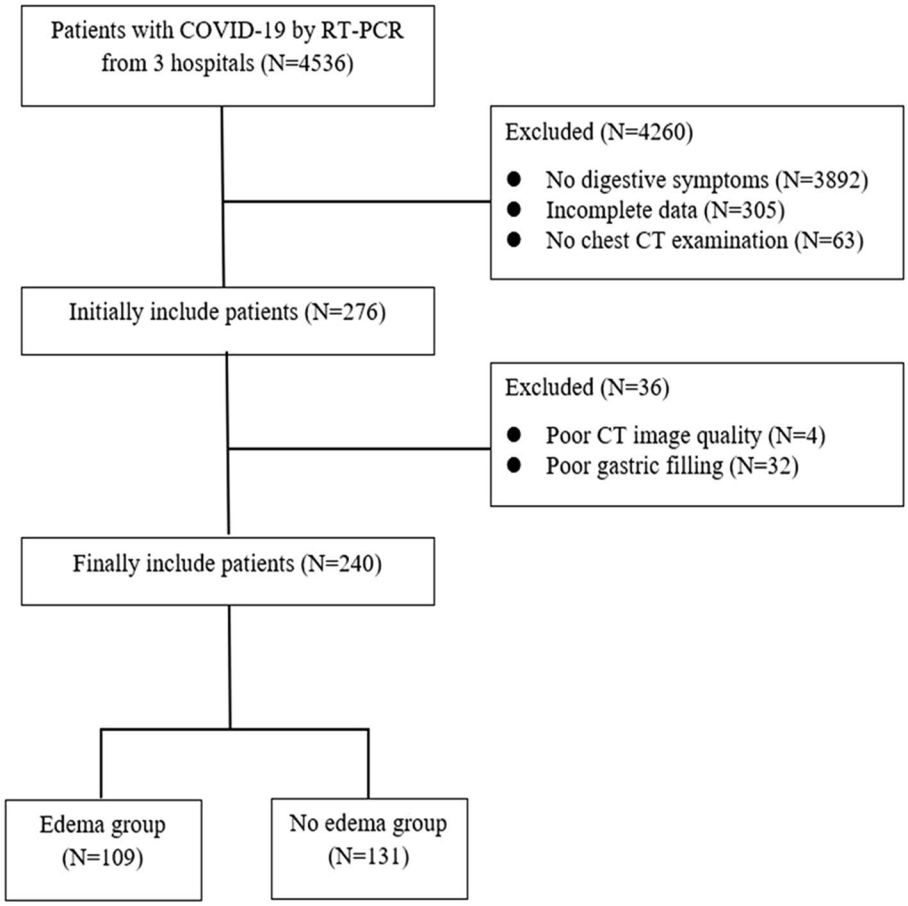

Fig. 1 Flowchart shows the patient exclusion criteria

measured from innermost edge of the mucosa to outer surface of the serosa perpendicular to the gastric wall, a radiologist (10 years' abdominal experience) manually measured twice, and obtain average value, > 2 mm was considered abnormal [21].

Statistical analysis

All statistical analyses were performed using SPSS 22.0 (IBM Corp). Measurement data with a normal distribution are expressed as the means ± standard deviation, and a *t* test was used for comparisons between the two groups. Data with a skewed distribution are presented as the median P_{50} (interquartile range P_{25} and P_{75}), and the rank sum test was used for comparisons between the two groups. Categorical variables were compared using the χ^2 test. Binary logistic regression was used to screen for related risk factors. $P < 0.05$ (two-sided) indicated a statistically significant difference.

Results

Among the 240 COVID-19 patients, 109 (45%) presented with gastric wall edema (edema group, Figs. 2, 3) and 131 (55%) did not present with gastric wall edema (non-edema group).

Chest CT images showed no obvious lesions in three patients diagnosed with mild COVID-19. The remaining 237 patients had different ground-glass opacities or consolidations. Statistical results showed that the PV/LV ratio (0.102 ± 0.113 vs. 0.066 ± 0.097) and PV (327,721.9 ± 319,021.6 *vs.* 209,753.7 ± 259,882 cm^3) were significantly different between the edema and non-edema groups ($P = 0.002$, 0.002) (Fig. 4). No significant difference in LV was noted between the two groups ($Z = -0.522$, $P = 0.602$).

Table 1 Baseline characteristics of the overall study population

Variable	Patients ($n=240$)	Variable	Patients ($n=240$)
Age (years)	19–92	PT (normal range 10–14 s)	
		Normal	223
		Over	17
Sex		TT (normal range 11–14 s)	
M	93	Normal	236
F	147	Over	4
Gastrointestinal symptoms		APTT (normal range 24.8–33.8 s)	
Diarrhea	149		
Nausea/vomiting	75	Normal	227
All of the above	16	Over	13
Other symptoms		Fib (normal range 1.8–3.7 g/L)	
Fever	164		
Cough	157		
Muscle soreness	40	Normal	213
Headache/dizziness	18	Elevated	27
Chronic diseases		Blood glucose (normal range 3.9–6.1 mmol/L)	
Hypothyroidism	4		
Hyperthyroidism	1	Normal	204
Chronic kidney diseases	2	Elevated	36
DM		CRP (normal range 0–5 mg/L)	
Presence	29	Normal	166
Absence	211	Elevated	74
Hypertension		TB (normal range 6–21 μmol/L)	
Presence	80	Normal	233
Absence	160	Elevated	7
WBC count (normal range $3.5–9.5\times10^9$/L)		ALT (normal range 0–42 IU/L)	
Normal	232	Normal	201
Elevated	8	Elevated	39
LYM count (normal range $1.1–3.2\times10^9$/L)		AST (normal range 0–42 IU/L)	
Normal	200	Normal	212
Decreased	40	Elevated	28
NEU count (normal range $1.8–6.3\times10^9$/L)		ALB (normal range 35–51 g/L)	
Normal	224	Normal	187
Elevated	16	Decrease	53

DM diabetes mellitus, *PT* prothrombin time, *TT* thrombin time, *APTT* activated partial thromboplastin time, *Fib* fibrinogen, *WBC* white blood cell, *LYM* lymphocyte, *NEU* neutrophil, *CRP* C-reactive protein, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *ALB* albumin, *TB* total bilirubin

The univariate analysis indicated significant differences in the coagulation parameters between the edema and non-edema groups: Fib level ($P=0.003$), TT ($P=0.025$), APTT ($P=0.001$), and the ALB level in the edema group was lower than that in the non-edema group ($P=0.018$). Regarding sex, age, WBC count, LYM count, NEU count, CRP, PT, blood glucose, ALT, AST, and TB, the intergroup differences were not statistically significant ($P>0.05$) (Table 2).

Binary logistic regression analysis showed that only APTT had a negative effect on gastric wall edema (odds ratio [OR] 0.896; 95% confidence interval [CI] 0.833–0.964; $P=0.003$) (Fig. 5) (Table 3).

The average hospitalization time was 15.7 ± 9.3 d for edema group, and 13.7 ± 6.4 d for non-edema group, there is a statistical difference between two groups ($t=-1.989$, $P=0.048$).

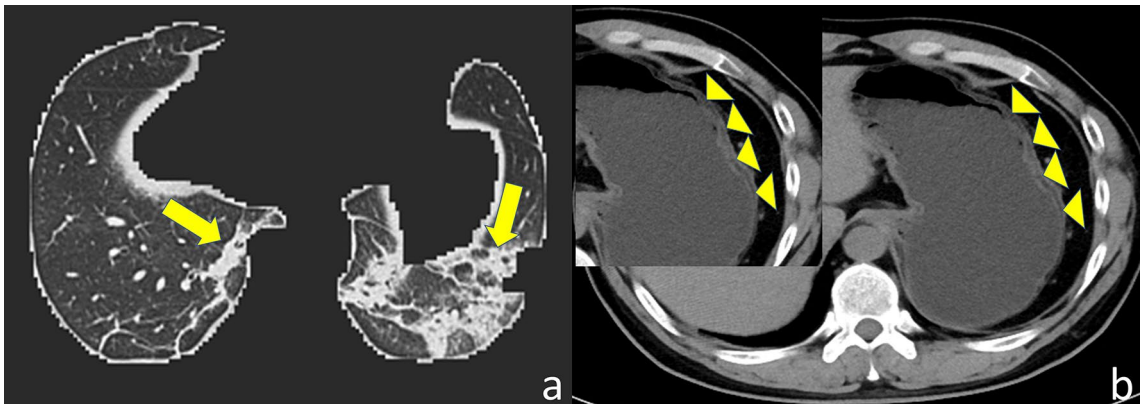

Fig. 2 Male, 44 years old, positive for COVID-19 (nucleic acid test). The patient had nausea and diarrhea for 3 weeks. **a** Segmentation results of lung and pneumonia lesions (yellow arrows). **b** CT axial scan shows diffuse edema on the large curvature of the gastric wall (triangles). The upper right corner showed the magnified image

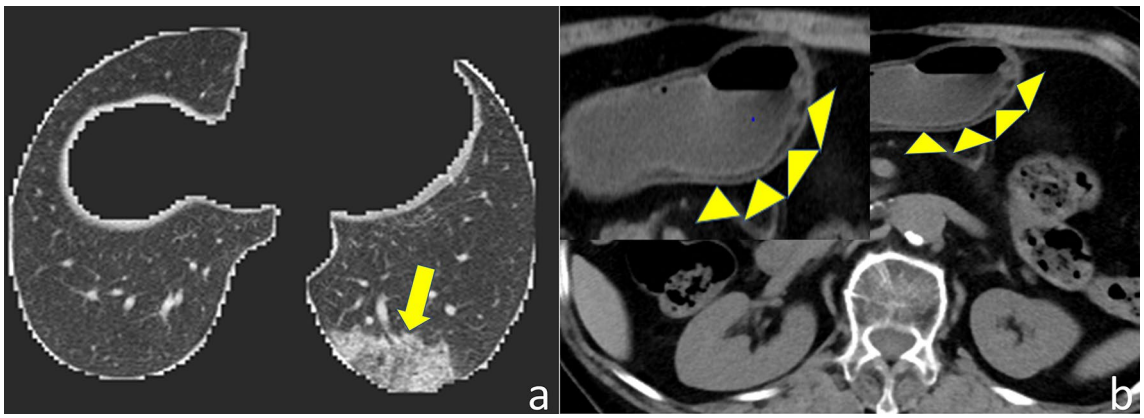

Fig. 3 Female, 58 years old, positive for COVID-19 (nucleic acid test). The patient had vomiting and fever for 2 weeks, accompanied with diarrhea. **a** Segmentation results of lung and pneumonia lesions (yellow arrow). **b** CT axial scan showing diffuse edema of the gastric wall (triangles). The upper right corner showed the magnified image

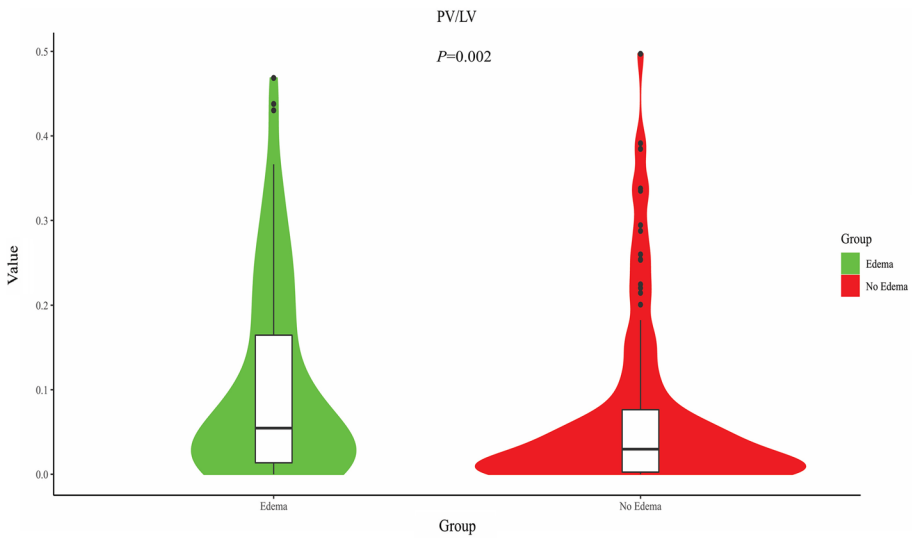

Fig. 4 Comparison of PV/LV ratio between the edema and non-edema groups. Gastric wall edema in COVID-19 patients with gastrointestinal symptoms is correlated with the PV/LV ratio: the greater the ratio, the higher the occurrence of edema

Table 2 Comparison of general information between the edema and non-edema groups

Baseline characteristic	Edema group ($n=109$)	Non-edema group ($n=131$)	χ^2/Z	P
Sex (male)	46 (42.2%)	48 (36.6%)	1.606	0.205
Age	59.9 ± 13.3	57.1 ± 14.6	− 1.452	0.147
DM	15	14	0.529	0.467
Hypertension	43	37	3.362	0.067
WBC count	5.8 (4.7, 7.1)	5.5 (4.7, 6.9)	− 0.806	0.42
LYM count	1.5 (1.1, 1.8)	1.6 (1.2, 2.0)	− 1.677	0.094
NEU count	3.7 (2.7, 4.6)	3.1 (2.4, 4.9)	− 1.661	0.097
CRP	1.9 (0.5, 6.0)	1.2 (0.5, 4.8)	− 1.041	0.298
PT	12.5 (11.9, 13.4)	12.6 (11.9, 13.2)	− 0.1	0.92
TT	15.4 ± 1.1	15.1 ± 1.2	− 2.247	0.025*
APTT	27.3 (25.2, 29.2)	29.1 (27.1, 30.0)	− 3.243	0.001*
Fib	3.1 (2.7, 3.5)	2.8 (2.5, 3.2)	− 3.009	0.003*
Glucose	5.1 (4.5, 5.8)	4.8 (4.5, 5.4)	− 2.158	0.056
ALT	24.7 (15.3, 38.3)	19.7 (12.9, 34.6)	− 1.634	0.102
AST	20.3 (16.3, 29.0)	19.0 (15.3, 25.4)	− 1.239	0.215
ALB	37.1 ± 4.3	38.3 ± 4.1	− 2.362	0.018*
TB	9.3 (7.1, 12.5)	9.3 (7.2, 12.2)	− 0.065	0.948

DM diabetes mellitus, *TT* thrombin time, *TB* total bilirubin, *CRP* C-reactive protein, *PLT* platelet, *ALB* albumin, *AST* aspartate aminotransferase, *NEU* neutrophil, *ALT* alanine aminotransferase; *LYM* lymphocyte, *WBC* white blood cell, *Fib* fibrinogen, *PT* prothrombin time, *APTT* activated partial thromboplastin time

*Represents a statistically significant difference in TT, APTT, Fib, and ALB

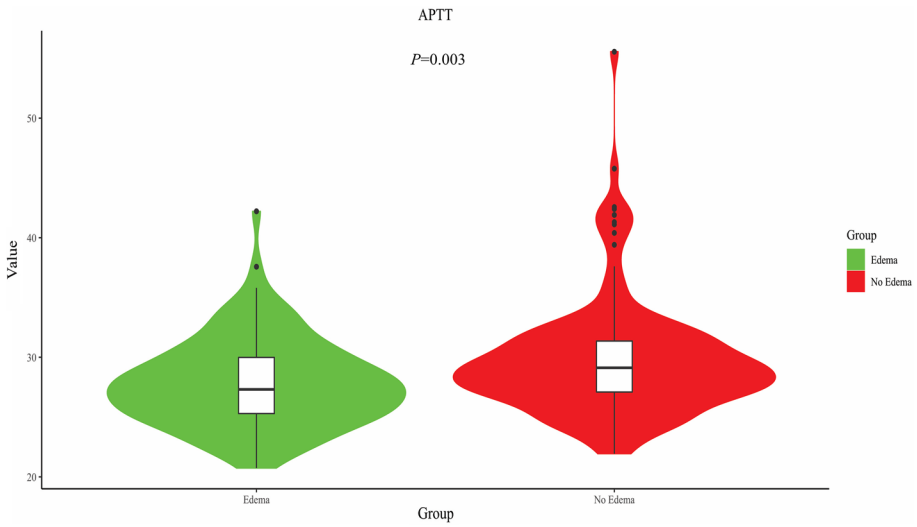

Fig. 5 Comparison of APTT in the edema and non-edema groups. Gastric wall edema in COVID-19 patients with gastrointestinal symptoms is correlated with a short APTT: the shorter the APTT, the higher the occurrence of edema

Table 3 Analysis of risk factors related to gastric wall edema

	P	OR	95% CI
Fib	0.331	1.206	0.826–1.762
APTT	0.003*	0.896	0.833–0.964
ALB	0.089	0.936	0.868–1.010
TT	0.207	1.249	0.885–1.762

TT thrombin time, *ALB* albumin, *Fib* fibrinogen, *APTT* activated partial thromboplastin time, *CI* confidence interval

*Represents a statistically significant difference

Discussion

In this study, as shown in the CT images, approximately 45% of COVID-19 patients with gastrointestinal symptoms had gastric wall edema. After ruling out edema caused by other diseases, such as heart, liver, and kidney diseases and malignant tumors, gastric wall edema was suspected to be correlated with SARS-CoV-2. On autopsy, SARS-CoV-2 (positive) was found in the gastric wall, and the

epithelium of the gastric wall had degenerated and was necrotic and exfoliated to different degrees by microscopy [22]. Another study observed yellow discoloration of the gastric wall, supporting the possibility that SARS-CoV-2 affects the gastric wall [15]. Pathological abnormalities in the gastric wall may be the result of the interaction of many factors, and statistical analyses in this study indicated that gastric wall edema was associated with the PV/LV ratio, ALB, Fib, TT, and APTT.

The comprehensive 3D-UNet segmentation model was used to quantitatively study pulmonary inflammation in COVID-19. The results showed that more severe pneumonia (COVID-19) correlated with a greater possibility of gastric wall edema, a result believed to involve the "gut-lung" axis. The "gut-lung" axis plays crucial roles in the mediation of the immune response and the release of inflammatory mediators through interactions among gastrointestinal microflora and the lungs [23]. After SARS-CoV-2 binds to the ACE2 receptor in the lungs, effector CD4 + T cells reach the gastric wall through the "gut-lung" axis. The disturbance of gastrointestinal microflora and the release of proinflammatory cytokines can promote the accumulation of NEUs, leading to the destruction of the gastric mucosal barrier. Furthermore, inflammatory cytokines and bacteria can enter the lungs through the blood circulation, further aggravating pulmonary inflammation [24, 25].

COVID-19 patients often suffer from a variety of coagulation disorders, and both a bleeding-prone state and a hypercoagulable state [26] indirectly reflect impaired liver cell function. This study also found that coagulation parameters, including Fib, TT, and APTT, were critical factors affecting gastric wall edema; in particular, the relative shortening of the APTT was an independent risk factor for the development of gastric wall edema. The S (spike) protein on the surface of SARS-CoV-2 binds to the ACE2 receptor expressed on the endothelial surface of the vessels, stimulating entry of the virus into host cells [27] and directly causing vascular endothelial injury in multiple organs (e.g., the lungs, stomach, small intestine, and liver) [28], inflammatory cytokine stimulation, and impaired endothelial glycocalyx function. The functions of the endothelial glycocalyx include the maintenance of an oncotic gradient across the endothelial barrier, regulation of leukocyte adhesion/migration, and inhibition of intravascular thrombosis [29]. Activating the endogenous coagulation pathway is an important cause of thrombosis [28, 30, 31], and APTT is an important indicator for the detection of endogenous coagulation pathways. A shortened APTT reflects a hypercoagulable state, and thrombosis may occur in blood vessels. In addition, vascular endothelial dysfunction further promotes vasoconstriction [32], thus causing acute ischemia and hypoxia in the gastric wall. SARS-CoV-2 has also been shown to bind directly to the ACE2 receptor in the gastric gland cells, resulting in numerous infiltrating plasma cells, lymphocytes, and interstitial edema [33]. The imaging findings were similar to those of the small intestine, mainly manifesting as submucosal edema. In contrast-enhanced scans, the intestinal wall is weakened due to ischemia [15, 34].

In addition, a correlation between gastric wall edema and reduced ALB levels was observed, mainly because SARS-CoV-2 causes liver cell dysfunction [35]. Impaired liver function can result in decreased ALB synthesis [36], which can lead to edema formation. In addition, a reduction in ALB may also be associated with ALB loss during the presence of gastrointestinal symptoms and a decrease in nutrition intake [37]. Our results suggested that patients with gastric wall edema had slightly longer hospitalization time than without edema, so CT might be helpful for clinical hierarchical management and treatment of patients.

This study had several limitations. First, the patients underwent chest CT plain scan only because the impact of the epidemic and clinical requirements; therefore, no other digestive tract images, such as images of the colon and small intestine, could be observed in this study to identify abnormalities. Second, all patients did not perform gastroscope and colonoscopy due to the risk of aerosol infection. Third, other immune cells subsets such as CD3, CD4, and CD8 could not be statistically analyzed due to incomplete data. Finally, all patients with gastric wall edema were not followed up because of missing data.

Conclusions

COVID-19 patients with gastrointestinal symptoms may present with gastric wall edema related to both lung inflammation severity and APTT. This finding suggests that in addition to chest CT manifestations, clinicians should also pay attention to APTT. Patients with gastric wall edema observed by CT should intervene early, which may improve digestive function, and further strengthen immunopotency against COVID-19. COVID-19 patients with gastrointestinal symptoms should undergo routine abdominal CT. If necessary, contrast-enhanced CT scans should be performed to obtain images of the entire gastrointestinal tract and vessels.

Author contributions XML and FXC: conceived and designed the study; XML: wrote the manuscript; JC and YML: collected the images; CL and FXC: reviewed the image; JuW: analyzed the data; JiW: performed extensive editing of the manuscript; all the authors reviewed and approved the final manuscript for submission.

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Availability of data and materials All data generated or analyzed during this study are included in this published paper.

Declarations

Conflict of interest The authors declare that they have no competing interests.

Ethics approval and consent to participate This study followed the ethical guidelines of the Declaration of Helsinki, and was approved by the Ethics Committee of the Army Medical University.

References

1. Gorbalenya AE, Baker SC, Baric RS, Groot RJD, Drosten C, Gulyaeva AA, Haagmans BL, Lauber C, Leontovich AM, Neuman BW, Penzar D, Perlman S, Poon LLM, Samborskiy DV, Sidorov IA, Sola I, Ziebuhr J. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol. 2020;5:536–44.
2. Dong L, Tian J, He S, Zhu C, Wang J, Liu C, Yang J. Possible vertical transmission of SARS-CoV-2 from an infected mother to her newborn. JAMA. 2020;323:1846–8.
3. Li X, Zeng W, Li X, Chen H, Shi L, Li X, Xiang H, Cao Y, Chen H, Liu C, Wang J. CT imaging changes of corona virus disease 2019(COVID-19): a multi-center study in Southwest China. J Transl Med. 2020;18:154.
4. Gupta A, Madhavan MV, Sehgal K, Nair N, Landry DW. Extrapulmonary manifestations of COVID-19. Nat Med. 2020;26:1017–32.
5. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323:1061–9.
6. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS; China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020;382:1708–20.
7. Pan L, Mu M, Yang P, Sun Y, Wang R, Yan J, Li P, Hu B, Wang J, Hu C, Jin Y, Niu X, Ping R, Du Y, Li T, Xu G, Hu Q, Tu L. Clinical Characteristics of COVID-19 Patients With Digestive Symptoms in Hubei, China: A Descriptive, Cross-Sectional, Multicenter Study. Am J Gastroenterol. 2020;115:766–73.
8. Sethi A, Swaminath A, Latorre M, Behin D, Jodorkovsky D, Calo D, Aroniadis O, Mone A, Mendelsohn R, Sharaiha R, Gonda T, Khanna L, Bucobo J, Nagula S, Ho S, Carr-Locke D, Robbins D. Donning a new approach to the practice of gastroenterology: perspectives from the COVID-19 pandemic epicenter. Clin Gastroenterol Hepatol. 2020;18:1673–81.
9. Liang W, Feng Z, Rao S, Xiao C, Xue X, Lin Z, Zhang Q, Qi W. Diarrhoea may be underestimated: a missing link in 2019 novel coronavirus. Gut. 2020;69:1141–3.
10. Zhang H, Li HB, Lyu JR, Lei XM, Li W, Wu G, Lyu J, Dai ZM. Specific ACE2 expression in small intestinal enterocytes may cause gastrointestinal symptoms and injury after 2019-nCoV infection. Int J Infect Dis. 2020;96:19–24.
11. Tian Y, Rong L, Nian W, He Y. Review article: gastrointestinal features in COVID-19 and the possibility of faecal transmission. Aliment Pharmacol Ther. 2020;51:843–51.
12. Holshue M, DeBolt C, Lindquist S, Lofy K, Wiesman J, Bruce H, Spitters C, Ericson K, Wilkerson S, Tural A, Diaz G, Cohn A, Fox L, Patel A, Gerber S, Kim L, Tong S, Lu X, Lindstrom S, Pallansch M, Weldon W, Biggs H, Uyeki T, Pillai S. First case of 2019 novel coronavirus in the United States. N Engl J Med. 2020;382:929–36.
13. Uno Y. Why does SARS-CoV-2 invade the gastrointestinal epithelium? Gastroenterology. 2020;159:1622–3.
14. Lamers M, Beumer J, van der Vaart J, Knoops K, Puschhof J, Breugem T, Ravelli R, Paul van Schayck J, Mykytyn A, Duimel H, van Donselaar E, Riesebosch S, Kuijpers H, Schipper D, van de Wetering W, de Graaf M, Koopmans M, Cuppen E, Peters P, Haagmans B, Clevers H. SARS-CoV-2 productively infects human gut enterocytes. Science (New York, NY). 2020;369:50–4.
15. Bhayana R, Som A, Li M, Carey D, Anderson M, Blake M, Catalano O, Gee M, Hahn P, Harisinghani M, Kilcoyne A, Lee S, Mojtahed A, Pandharipande P, Pierce T, Rosman D, Saini S, Samir A, Simeone J, Gervais D, Velmahos G, Misdraji J, Kambadakone A. Abdominal imaging findings in COVID-19: preliminary observations. Radiology. 2020;2020: 201908.
16. Ignat M, Philouze G, Aussenac-Belle L, Faucher V, Collange O, Mutter D, Pessaux P. Small bowel ischemia and SARS-CoV-2 infection: an underdiagnosed distinct clinical entity. Surgery. 2020;168:14–6.
17. De Nardi P, Parolini DC, Ripa M, Racca S, Rosati R. Bowel perforation in a Covid-19 patient: case report. Int J Colorectal Dis. 2020;35:1797–800.
18. Cardona GC, Pájaro LD, Marzola ID, Villegas YR, Salazar LR. Neurotropism of SARS-CoV 2: mechanisms and manifestations. J Neurol Sci. 2020;412: 116824.
19. Hikmet F, Méar L, Edvinsson Å, Micke P, Uhlén M, Lindskog C. The protein expression profile of ACE2 in human tissues. Mol Syst Biol. 2020;16: e9610.
20. Bao Y, Zeng H, Zhou C, Liu C, Zhang L, Qian D, Wang J, Lu H. C3D-UNET: a comprehensive 3D Unet for Covid-19 segmentation with intact encoding and local attention. In: Annual international conference of the IEEE engineering in medicine & biology society; 2021. p. 2592–6.
21. Hameed S, Caro-Domínguez P, Daneman A, Zani-Ruttenstock E, Zani A, Navarro O. The role of sonography in differentiating congenital intrinsic duodenal anomalies from midgut malrotation: emphasizing the new signs of duodenal and gastric wall thickening and hyperechogenicity. Pediatr Radiol. 2020;50:673–83.
22. Bian XW, the COVID-19 Pathology Team. Autopsy of COVID-19 victims in China. Nat Sci Rev 2020;7:1414–8.
23. Budden K, Gellatly S, Wood D, Cooper M, Morrison M, Hugenholtz P, Hansbro P. Emerging pathogenic links between microbiota and the gut-lung axis. Nat Rev Microbiol. 2017;15:55–63.
24. Zhang D, Li S, Wang N, Tan H, Zhang Z, Feng Y. The cross-talk between gut microbiota and lungs in common lung diseases. Front Microbiol. 2020;11:301.
25. Ye Q, Wang B, Zhang T, Xu J, Shang S. The mechanism and treatment of gastrointestinal symptoms in patients with COVID-19. Am J Physiol. 2020;319:G245–52.
26. Grobler C, Maphumulo S, Grobbelaar L, Bredenkamp J, Laubscher G, Lourens P, Steenkamp J, Kell D, Pretorius E. Covid-19: the rollercoaster of Fibrin(Ogen), D-Dimer, Von Willebrand Factor, P-selectin and their interactions with endothelial cells, platelets and erythrocytes. Int J Mol Sci. 2020;21:5168.
27. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens T, Herrler G, Wu N, Nitsche A, Müller M, Drosten C, Pöhlmann S. SARS-CoV-2 cell entry depends

on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020;181:271–80.e278.
28. Varga Z, Flammer A, Steiger P, Haberecker M, Andermatt R, Zinkernagel A, Mehra M, Schuepbach R, Ruschitzka F, Moch H. Endothelial cell infection and endotheliitis in COVID-19. Lancet (London, England). 2020;395:1417–8.
29. Lee W, Slutsky A. Sepsis and endothelial permeability. N Engl J Med. 2010;363:689–91.
30. Arachchillage D, Laffan M. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost JTH. 2020;18:1233–4.
31. Gonzalez Cañas E, Gimenez Gaibar A, Rodriguez Lorenzo L, Castro Rios JG, Martinez Toiran A, Bella Cueto MR, Bella Burgos B, Espasa Soley M. Acute peripheral arterial thrombosis in COVID-19. Role of endothelial inflammation. Br J Surg. 2020;107:e444–5.
32. Cipolloni L, Sessa F, Bertozzi G, Baldari B, Cantatore S, Testi R, D'Errico S, Di Mizio G, Asmundo A, Castorina S, Salerno M, Pomara C. Preliminary post-mortem COVID-19 evidence of endothelial injury and factor VIII hyperexpression. Diagnostics (Basel, Switzerland). 2020;10:575.
33. Xiao F, Tang M, Zheng X, Liu Y, Li X, Shan H. Evidence for gastrointestinal infection of SARS-CoV-2. Gastroenterology. 2020;158:1831-1833.e1833.
34. Azouz E, Yang S, Monnier-Cholley L, Arrivé L. Systemic arterial thrombosis and acute mesenteric ischemia in a patient with COVID-19. Intensive Care Med. 2020;46:1464–5.
35. Wu F, Zhao S, Yu B, Chen Y, Wang W, Song Z, Hu Y, Tao Z, Tian J, Pei Y, Yuan M, Zhang Y, Dai F, Liu Y, Wang Q, Zheng J, Xu L, Holmes E, Zhang Y. A new coronavirus associated with human respiratory disease in China. Nature. 2020;579:265–9.
36. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395:507–13.
37. Huang W, Li C, Wang Z, Wang H, Zhou N, Jiang J, Ni L, Zhang X, Wang D. Decreased serum albumin level indicates poor prognosis of COVID-19 patients: hepatic injury analysis from 2,623 hospitalized cases. Science China. Life Sci. 2020;63:1678–87.