Computed tomography evaluation of pancreatic steatosis: correlation with COVID-19 prognosis

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Aim: To investigate the relationship between pancreatic steatosis (PS) assessed on computed tomography (CT) and COVID-19 prognosis. **Materials & methods:** This retrospective study covers 396 patients with COVID-19 (mean age: 52.50 ± 16.86 years), who underwent unenhanced chest CT. PS was compared with clinical findings, comorbidities, requirements for hospitalization, intubation and intensive care unit (ICU), length of hospitalization and death. **Results:** PS was found to be strongly correlated with the severity of clinical findings and hospitalization rates ($p < 0.001$). In hospitalized patients, length of hospitalization ($p = 0.002$) and rates of ICU requirement ($p = 0.003$) were higher in patients with PS. **Conclusion:** PS, correlated with clinical severity and hospitalization requirement, is an independent risk factor for COVID-19.

Plain language summary: Fat accumulation in the pancreas that is associated with obesity and metabolic syndrome can be used for estimating the clinical course of patients with COVID-19. Fat accumulation was determined by comparing the pancreas and spleen using computed tomography tools. In our study with 396 COVID-19 patients, the patients with fatty pancreas clearly seemed to have more severe clinical findings. Similarly, the rates of the requirement for hospitalization/intensive care unit and length of hospitalization were higher than in patients without fatty pancreas. The median length of hospitalization was 9 days in patients with fatty pancreas and 6 days in patients without fatty pancreas. However, death rates were only slightly higher in patients with fatty pancreas.

Tweetable abstract: In COVID-19 patients, the patients with fatty pancreas assessed using computed tomography have a more severe clinical course, higher rates of hospitalization/ICU requirement and increased length of hospitalization compared with the patients without fatty pancreas. #COVID-19 #computed tomography #fatty pancreas.

Graphical abstract:
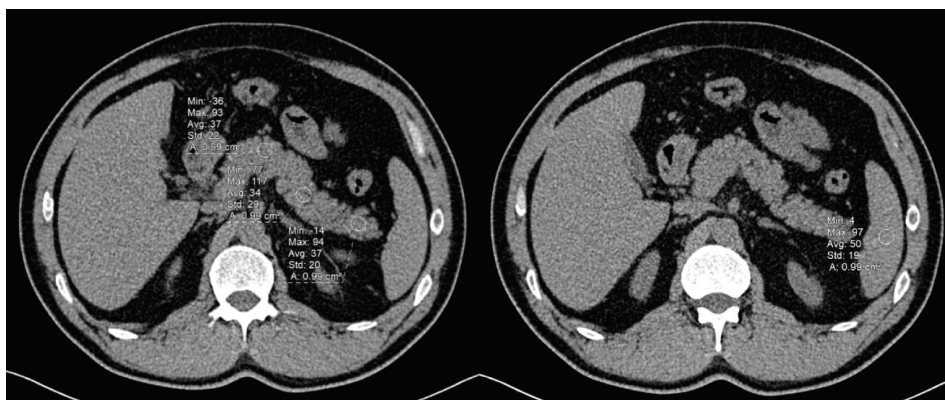
COVID-19, caused by SARS-CoV-2, first appeared in Wuhan, Hubei, China and it has rapidly spread worldwide [1]. Despite the gold standard, diagnosis remains to be a positive result of reverse transcription PCR (RT-PCR) test for the virus [2,3], chest computed tomography (CT) imaging has been playing an important role in the diagnosis and as well as in the prognosis of the disease [4–6].

Although there have been cases of asymptomatic patients and patients with mild symptoms until now, there have also been cases where the disease can progress rapidly and lead to death, especially in elderly patients and patients with accompanying chronic diseases [7]. Metabolic risk factors, such as obesity and hepatosteatosis were shown to increase the severity of the clinical findings in COVID-19 [8–10]. Hepatosteatosis is one of the pathologies which can be quantitatively evaluated on unenhanced CT. Several studies reported the relationship between hepatosteatosis and COVID-19 prognosis [8,11–13]. Similar to hepatosteatosis, pancreatic steatosis (PS) can be also assessed on CT, and its association with several diseases, such as metabolic syndrome and pancreatic cancer was reported in the literature [14,15]. To the best of our knowledge, the relationship between PS and the prognosis of COVID-19 has never been published.

We hypothesized that PS could correlate with the severity of clinical findings, the requirements for hospitalization or intensive care unit (ICU) and also the mortality of patients with COVID-19. The purpose of this study was to investigate the relationship between PS assessed with CT and the prognosis of COVID-19.

Materials & methods
Study population
We searched the patient records of 542 patients with a positive RT-PCR test result for SARS-CoV-2, who underwent chest CT using a 64-slice CT scanner (Siemens, Somatom Definition Flash, Erlangen, Germany) between March 2020 and December 2020 at a single center. The patients, who were under the age of 18 years (n = 5), with pancreatic mass (n = 3) or splenectomy (n = 1), who underwent contrast-enhanced chest CT (n = 16), in whom CT scans did not cover pancreas (n = 114) and in those who have significant artifacts (n = 7) were excluded, leaving 396 patients (227 males and 169 females) with a mean age of 52.50 ± 16.86 years.

The patient demographics, accompanying chronic diseases (diabetes mellitus, hypertension, coronary artery disease and cerebrovascular disease), the symptoms, the presence of positive findings on chest CT, respiratory rate and levels of oxygen saturation were noted throughout the research process. Additionally, the requirement for hospitalization or ICU, the length of stay in the hospital, need for intubation and mortality rates were logged as well. The patients were clinically classified under four groups according to mild, moderate, severe and critical findings [16]. Here, mild findings refer to mild clinical findings without positive findings on CT. Moderate findings refer to findings including fever and respiratory tract with positive findings on CT. Severe findings refer to respiratory distress with a respiratory rate ≥30-times/min and an oxygen saturation ≤93% in rest. Last, critical findings refer to respiratory failure requiring mechanical ventilation and failures of other organs requiring ICU care [16].

CT image acquisition
All CT scans were obtained using a 64-slice scanner without using contrast media. The patients were in a supine position, and the images were obtained under breath-hold condition. The entire thoracic cavity and upper
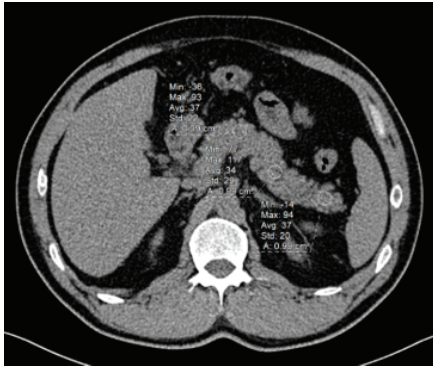
Figure 1.   Unenhanced axial computed tomography image of a 43-year-old male patient with COVID-19. Five different ROIs (using a circular ROI of 1 cm^2) were drawn over five anatomical parts of the pancreas to assess the attenuation value of the organ by taking the average of the 5 HU values collected from the ROIs. Shown here are the measurements from the neck, body and tail of the pancreas (37, 34 and 37 HU, respectively). The average attenuation value of the pancreas was 35 HU in this patient.
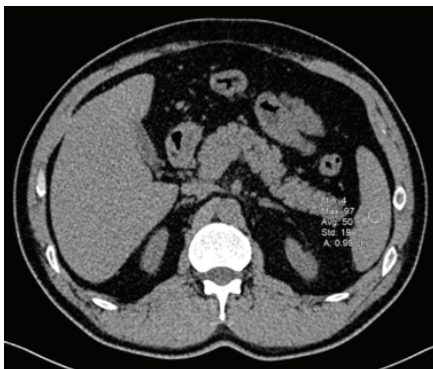HU: Hounsfield unit; ROI: Region of interest.

Figure 2.   Axial computed tomography image of the same patient. Three ROIs (using a circular ROI of 1 cm^2) were drawn from the upper, middle and lower parts of the spleen, to assess the attenuation value of the organ by taking the average of the three HU values collected from the ROIs. Shown here is the measurement from the lower a third of the spleen (50 HU). The average attenuation value was 51 HU in the patient. By dividing the attenuation value of the pancreas with the attenuation value of the spleen, a pancreas-to-spleen attenuation ratio of 0.68 was found, which was smaller than 0.70 (cut-off ratio of pancreas-to-spleen attenuation for pancreatic steatosis), confirming the diagnosis of pancreatic steatosis in this patient.
HU: Hounsfield unit; ROI: Region of interest.

abdominal region were scanned. The CT protocol was as follows: helical scanning mode; tube voltage: 120 kV; tube current-time product: 50–350 mAs; pitch: 1.2 and 1.375; matrix: 512 × 512; reconstructed in lung and soft tissue windows; reconstructed slice thickness: 1.00 mm.

Assessment of pancreatic steatosis

CT images were evaluated by two radiologists (S Guneyli and H Dogan with 11 and 2 years of experience, respectively) experienced in thoracic and abdominal radiology, who were blinded to the clinical and laboratory results of the patients, using a dedicated workstation based on consensus. Hounsfield unit (HU) of fat tissue ranges between -150 and -30 HU on unenhanced CT [14]. Both the pancreas-to-spleen (P/S) attenuation ratio and the pancreas minus spleen (P-S) attenuation difference significantly correlated with PS, proven histopathologically [17–19]. Five different regions of interest (ROIs) were drawn over the uncinate process, the head, neck, body and tail of the pancreas (Figure 1), while three ROIs were drawn from the upper, middle and lower parts of spleen (Figure 2) [15]. In both organs, a circular ROI of 1 cm^2 was drawn [14]. To ensure reproducibility of the measurements, the ROIs were drawn by avoiding vessels and parenchymal calcifications. The average of the ROIs was calculated, and then the P/S attenuation ratio was determined, by dividing the attenuation value of the pancreas with the attenuation value of the spleen. PS was considered present in a patient when the P/S attenuation ratio was found to be <0.70 [18].

Statistical analysis

The SPSS17.0 software (IL, USA) was used for statistical analysis. PS was compared with the severity of clinical findings, comorbidities and the requirement for hospitalization using the chi-square test. In hospitalized patients, PS was compared with the length of stay in the hospital using the Mann–Whitney U test, while it was compared with the requirement for ICU, intubation and mortality using the chi-square test. Age was expressed as mean ± standard deviation, and the length of stay in the hospital was expressed as median and range. A p value < 0.05 was considered statistically significant.

Table 1. Comparisons of the patients with and without pancreatic steatosis according to their clinical groups and their requirement for hospitalization among a total of 396 patients.

	PS + (n = 126)	PS − (n = 270)	p-value
Clinically mild group	9 (7.1%)	62 (22.9%)	<0.001[†]
Clinically moderate group	45 (35.7%)	159 (58.8%)	<0.001[†]
Clinically severe group	35 (27.7%)	29 (10.7%)	<0.001[†]
Clinically critical group	37 (29.3%)	20 (7.4%)	<0.001[†]
Hospitalization requirement	97 (76.9%)	104 (38.5%)	<0.001[†]

[†]Statistically significant values are p < 0.05.
PS: Pancreatic steatosis.

Table 2. Comparisons of the patients with and without pancreatic steatosis according to the length of their hospitalization, their requirement for intensive care unit, their need for intubation and their mortality rates among a total of 201 hospitalized patients.

	PS + (n = 97)	PS − (n = 104)	p-value
Length of hospitalization, days (range)	9 (2–48)	6 (1–92)	0.002[†]
Requirement for ICU	37 (38.1%)	20 (19.2%)	0.003[†]
Need for intubation	26 (26.8%)	18 (17.3%)	0.104
Mortality rates	18 (18.6%)	12 (11.5%)	0.163

[†]Statistically significant values are p < 0.05.
ICU: Intensive care unit, PS: Pancreatic steatosis.

Results

Among a total of 396 patients, 126 (31.8%) had PS, while 270 (68.2%) did not. The comparisons of the patients with and without PS according to their clinical groups and their requirement for hospitalization are presented in Table 1.

The number of patients in the four clinical groups classified from mild to critical was as follows: 71, 204, 64 and 57, respectively. There was a significant correlation between PS and the severity of clinical findings of COVID-19 (p < 0.001). Only 9 out of 126 (7.1%) patients with PS were classified in clinically mild group, whereas only 20 out of 270 (7.4%) patients without PS were classified under the clinically critical group. The rates of the patients with PS in the four clinical groups from mild to critical were respectively as follows: 12.7, 22.1, 54.7 and 64.9%. PS was found to be significantly correlated with the requirement for hospitalization in COVID-19 (p < 0.001), and the hospitalization rates in patients with and without PS were 76.9 and 38.5%, respectively. Diabetes mellitus (p = 0.810), hypertension (p = 0.057), coronary artery disease (p = 0.221) and cerebrovascular disease (p = 0.738) did not show any significant correlation with PS.

There were 201 (50.8%) in-patients and 195 (49.2%) out-patients. Out of the 201 hospitalized patients, 97 (48.2%) had PS, while 104 (51.8%) did not. Among the hospitalized patients, the comparisons of the patients with and without PS according to the four aforementioned prognostic parameters are presented in Table 2. The length of stay in the hospital among patients with PS (p = 0.002) and the requirement for ICU (p = 0.003) were higher than those without PS. The median values for the length of hospitalization in patients with PS and in those without PS were 9 (range: 2–48 days) and 6 (range: 1–92 days) days, respectively. Although, there was not any significance for the need for intubation (p = 0.104), mortality rates (p = 0.163) between the clinical groups were found to be higher in the patients with PS compared with those without PS.

Discussion

This study shows that PS is correlated with the prognostic factors, including the severity of clinical findings, the requirements for hospitalization or ICU and length of hospitalization in COVID-19 patients; while comorbidities, the need for intubation and mortality rates did not correlate with PS.

There is an increase in the research of PS in the literature recently, which can be attributed to the increasing prevalence of obesity and metabolic syndrome among patients worldwide. The metabolic syndrome causes fatty infiltration in many organs, including the heart, liver and subcutaneous tissues which can lead to chronic inflammation, fibrosis and organ dysfunction [20]. Chronic lipogenic and glucogenic inflammation are thought

to be associated with PS. It was reported that PS can lead to acute pancreatitis, diabetes mellitus and pancreatic malignancy [15,21].

CT is the most commonly used imaging modality in evaluating PS. Kim *et al.* reported that the histologic pancreatic fat fraction significantly correlated with the P-S attenuation difference assessed on CT, and the sensitivity and specificity of PS were stated as 79.3 and 42.4%, respectively [17]. In the study of Limanond *et al.*, unenhanced CT was used to investigate the correlation between PS and metabolic syndrome, and they considered PS to be present when there is a P-S attenuation difference that is less than -5 HU [22]. Unlike this study, we used the P/S attenuation ratio in the assessment of PS. In order to obtain more accurate density values, five ROIs were used instead of three or fewer ROIs. Additionally, obtaining these five ROIs from five anatomical parts of the pancreas can lead to acquiring more accurate density values on CT compared with when the ROIs are obtained randomly.

Obesity and hepatosteatosis were reported in the literature as potential risk factors in patients with COVID-19 [8,23]. Similar to hepatosteatosis, PS is associated with obesity and metabolic syndrome. This association can point to a potential relationship between PS and the clinical severity of COVID-19. Furthermore, compared with the evaluation of hepatosteatosis on chest CT, evaluating PS could prove to be a more efficient and reliable method. This is because the pancreas is an organ that is covered mostly on chest CT while the liver is not covered entirely, and because the fatty infiltration of pancreas is relatively more diffuse compared with the fatty changes of the liver on CT. In our study, the rates of the patients with PS were higher in patients who were in the clinically critical group and in patients requiring hospitalization. As the clinical group moved from mild to critical, in other words, as the clinical course worsened, the rate of patients with PS gradually increased, especially in the clinically severe and critical groups. However, the accompanying chronic diseases were not found to be significant when they were compared between the groups.

Among the 201 hospitalized patients, 97 patients had PS, whose length of hospitalization and rates of ICU requirement were higher than those without PS. Apart from the impact of the clinically severe disease and its complications on the prognosis, if the length of hospital or ICU stay increases, the patients may develop several hospital-related complications, such as nosocomial infections and iatrogenic complications. There were not any significant results gathered from comparing the need for intubation and the mortality rates between patients with and without PS. This can be explained by the relatively low numbers of patients requiring intubation and low mortality rates.

This study has several limitations. First, the study had a retrospective design and was conducted in a single center. Second, the baseline data for the patients was absent. Third, the degree of PS severity was not considered as a parameter in our study, and the assessment of PS, by using a cut-off ratio on CT seemed to be less specific compared with that which was obtained from histopathologic specimens. Additionally, some patients did not have a homogeneous fat distribution in their pancreas. However, the use of five ROIs obtained from five anatomical parts of the pancreas, which is more than the average amount of ROIs used in similar studies from the literature, is thought to minimize this limitation. Finally, the HU values of the pancreas were obtained with the consensus of two radiologists instead of having two separate assessments.

Conclusion

PS can be effectively demonstrated using unenhanced chest CT in patients with COVID-19, which can readily be performed in most of the COVID-19 patients. It can be used as a prognostic factor in COVID-19, since it is in correlation with the severity of clinical findings in COVID-19, the requirement for hospitalization or ICU, and the length of hospitalization in COVID-19 cases. Although the need for intubation and the mortality rates were not found to be of significance, they were observed to be higher in patients with PS. Future studies with larger sample sizes can demonstrate the possible associations between PS and other prognostic factors. With the further investigation of PS and the degree of PS severity in future studies, the clinical importance and the use as a prognostic factor of this phenomenon in COVID-19 can be shown to be even more crucial.

Summary points

- Pancreatic steatosis (PS) that is associated with metabolic syndrome can be also used for estimating the prognosis in patients with COVID-19.
- Both the pancreas-to-spleen attenuation ratio and the pancreas-minus-spleen attenuation difference were reported to be in correlation with PS, which were proven via histopathologic confirmation.
- The mean age of 396 patients (227 males and 169 females) was 52.50 ± 16.86 years, and PS was found to be present in 126 of 396 (31.8%) patients.
- There was a strong correlation between PS and severity of clinical findings in COVID-19, and the rates of the patients with PS gradually increased from the clinically mild to the clinically critical groups, in the order of 12.7, 22.1, 54.7 and 64.9%, respectively.
- PS was in correlation with the requirement for hospitalization or intensive care unit, and with the length of hospitalization.
- The median values of the length of hospitalization in patients with PS and without PS were 9 (range: 2–48 days) and 6 (range: 1–92 days) days, respectively.
- Although the need for intubation and mortality rates among hospitalized COVID-19 patients with PS were higher than those without PS, these parameters did not reach a significant level.

References

Papers of special note have been highlighted as: ● of interest; ●● of considerable interest

1. Han R, Huang L, Jiang H, Dong J, Peng H, Zhang D. Early clinical and CT manifestations of coronavirus disease 2019 (COVID-19) pneumonia. *AJR Am. J. Roentgenol.* 215(2), 338–343 (2020).

2. Corman VM, Landt O, Kaiser M *et al.* Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. *Euro. Surveill.* 25(3), 3–11 (2020).

3. Rubin EJ, Baden LR, Morrissey S, Campion EW. Medical journals and the 2019-nCoV outbreak. *N. Engl. J. Med.* 382(9), 866 (2020).

4. Chung M, Bernheim A, Mei X *et al.* CT imaging deatures of 2019 novel coronavirus (2019-nCoV). *Radiology* 295(1), 202–207 (2020).

5. Pan Y, Guan H, Zhou S *et al.* Initial CT findings and temporal changes in patients with the novel coronavirus pneumonia (2019-nCoV): a study of 63 patients in Wuhan, China. *Eur. Radiol.* 30(6), 3306–3309 (2020).

6. Güneyli S, Atçeken Z, Doğan H, Altınmakas E, Atasoy KÇ. Radiological approach to COVID-19 pneumonia with an emphasis on chest CT. *Diagn. Interv. Radiol.* 26(4), 323–332 (2020).

● **Describes the chest computed tomography (CT) findings and the role of chest CT in management of COVID-19.**

7. Zhou F, Yu T, Du R *et al.* Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 395(10229), 1054–1062 (2020).

8. Çoraplı M, Çil E, Oktay C, Kaçmaz H, Çoraplı G, Bulut HT. Role of hepatosteatosis in the prognosis of COVID 19 disease. *Clin. Imaging* 80, 1–5 (2021).

9.   Guo W, Li M, Dong Y *et al.* Diabetes is a risk factor for the progression and prognosis of COVID-19. *Diabetes. Metab. Res. Rev.* doi: 10.1002/dmrr.3319. (2020) (Epub ahead of print).

10.   Cai Q, Chen F, Wang T *et al.* Obesity and COVID-19 severity in a designated hospital in Shenzhen, China. *Diabetes Care* 43(7), 1392–1398 (2020).

11.   Gao F, Zheng KI, Wang XB *et al.* Metabolic associated fatty liver disease increases coronavirus disease 2019 disease severity in nondiabetic patients. *J. Gastroenterol. Hepatol.* 36(1), 204–207 (2021).

12.   Medeiros AK, Barbisan CC, Cruz IR *et al.* Higher frequency of hepatic steatosis at CT among COVID-19-positive patients. *Abdom. Radiol.* 45(9), 2748–2754 (2020).

13.   Palomar-Lever A, Barraza G, Galicia-Alba J *et al.* Hepatic steatosis as an independent risk factor for severe disease in patients with COVID-19: a computed tomography study. *JGH. Open* 4(6), 1102–1107 (2020).

•   **Describes the relationship between hepatosteatosis and severe COVID-19.**

14.   Hoogenboom SA, Bolan CW, Chuprin A *et al.* Pancreatic steatosis on computed tomography is an early imaging feature of pre-diagnostic pancreatic cancer: a preliminary study in overweight patients. *Pancreatology* 21(2), 428–433 (2021).

••   **Describes the assessment method of pancreatic steatosis on CT and the relationship between pancreatic steatosis and pancreatic cancer.**

15.   Lee JS, Kim SH, Jun DW *et al.* Clinical implications of fatty pancreas: correlations between fatty pancreas and metabolic syndrome. *World. J. Gastroenterol.* 15(15), 1869–1875 (2009).

•   **Describes the assessment method of pancreatic steatosis by using five regions of interest obtained from five anatomical parts of the pancreas.**

16.   Li K, Fang Y, Li W *et al.* CT image visual quantitative evaluation and clinical classification of coronavirus disease (COVID-19). *Eur. Radiol.* 30(8), 4407–4416 (2020).

••   **Describes a classification system arranged according to the severity of clinical findings in COVID-19.**

17.   Kim SY, Kim H, Cho JY *et al.* Quantitative assessment of pancreatic fat by using unenhanced CT: pathologic correlation and clinical implications. *Radiology* 271(1), 104–112 (2014).

••   **Describes the assessment methods of pancreatic steatosis and pathologic correlation.**

18.   Fukuda Y, Yamada D, Eguchi H *et al.* CT density in the pancreas is a promising imaging predictor for pancreatic ductal adenocarcinoma. *Ann. Surg. Oncol.* 24(9), 2762–2769 (2017).

19.   Navina S, Acharya C, DeLany JP *et al.* Lipotoxicity causes multisystem organ failure and exacerbates acute pancreatitis in obesity. *Sci. Transl. Med.* 3(107), 107ra110 (2011).

20.   Tran V, De Silva TM, Sobey CG *et al.* The vascular consequences of metabolic syndrome: rodent models, endothelial dysfunction, and current therapies. *Front. Pharmacol.* 11, 148 (2020).

21.   Guglielmi V, Sbraccia P. Type 2 diabetes: does pancreatic fat really matter? *Diabetes. Metab. Res. Rev.* 34(2), e2955 (2018).

22.   Limanond P, Raman SS, Lassman C *et al.* Macrovesicular hepatic steatosis in living related liver donors: correlation between CT and histologic findings. *Radiology* 230(1), 276–280 (2004).

23.   Sachdeva S, Khandait H, Kopel J, Aloysius MM, Desai R, Goyal H. NAFLD and COVID-19: a pooled analysis. *SN. Compr. Clin. Med.* 6, 1–4 (2020).