RESEARCH ARTICLE

Gastrointestinal system involvement characteristics in Covid -19 patients

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Abstract

Objective: To evaluate the involvement of gastrointestinal tract features in patients of coronavirus disease-2019, and to analyse the effects of these features on the development of critical illness, macrophage activation syndrome and mortality.

Method: The retrospective, cross-sectional study was conducted from January 2021 to December 2022 at a tertiary care facility after approval from the ethics review committee of Recep Tayyip Erdoğan University, Turkiye, and comprised data from March 30, 2020, to March 31, 2022, related to coronavirus disease-2019 inpatients. Gastrointestinal features, including nausea, vomiting, abdominal pain, diarrhoea, gastrointestinal bleeding, weight-loss and anorexia, and laboratory findings related to aspartate transaminase, alanine transaminase, total bilirubin, direct bilirubin, indirect bilirubin, alkaline phosphatase, gamma glutamyl transferase, amylase, C-reactive protein and ferritin levels were evaluated. The effects of biomarkers, clinical symptoms and findings on the development of macrophage activation syndrome, as well as the relationship with the development of critical illness and the effects on mortality were evaluated. Data was analysed using SPSS 22.0 statistical package programme.

Results: Of the 2,154 patients, 1,150(53.4%) were males and 1,004(46.6%) were females. The overall mean age was 61(61±16.8) years (range: 18-90 years). A total of 109(5.1%) patients died, 195(9.1%) developed critical illness and 158(7.3%) developed macrophage activation syndrome. Gastrointestinal symptom anorexia had significant association with the development of macrophage activation syndrome and mortality ($p<0.05$). There was a statistically significant relationship between nausea a and development of critical illness ($p <0.012$). Macrophage activation syndrome, critical illness and mortality were significant in patients with high ferritin levels ($p<0.05$). There was a significant relationship of high alanine transaminase levels with macrophage activation syndrome and critical illness ($p<0.05$). High aspartate transaminase levels were significantly associated with macrophage activation syndrome, critical illness and mortality ($p<0.05$). There was a significant association of elevated amylase levels with macrophage activation syndrome and mortality ($p<0.05$). High gamma glutamyl transferase levels were significantly associated with macrophage activation syndrome, critical illness and mortality ($p<0.05$).

Conclusion: Gastrointestinal feature anorexia and elevated levels of aspartate transaminase, alanine transaminase, gamma glutamyl transferase and amylase were found to be associated with poor prognosis in coronavirus disease-2019 patients.

Key Words: COVID-19, GI uptake characteristics, C-reactive protein, Ferritin, Macrophage activation syndrome, Liver function tests.

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Introduction

Coronaviruses are important microorganisms that are pathogenic to humans and animals. Towards the end of 2019, a new coronavirus, Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), was identified as the cause of pneumonia cases in Wuhan, a city in China's Hubei province. It resulted in an outbreak across China, followed by an increasing number of cases in other countries around the world. The World Health Organisation (WHO) named the disease coronavirus disease-2019 (COVID-19), and in March 2020, COVID-19 was recognised as a pandemic.[1] The first case infected with SARS-CoV-2 in Turkiye was detected on March 11, 2020. The number of people infected with COVID-19 was more than 500 million globally as of May 2022, according to WHO data. The total number of deaths in the world has been reported over 6 million. In Turkiye, the number of cases was over 15 million as of May 2022, and the total number of mortalities exceeded 98,000.[2] Although COVID-19 affects the upper respiratory tract, its most serious effects are due to the pneumonia it causes. COVID-19 pneumonia can cause many complications that can result in vital organ involvement and death. The SARS-CoV-2 virus, which enters the cells by binding to

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angiotensin converting enzyme 2 (ACE2) receptors in cells with its spike proteins, causes acute respiratory distress syndrome (ARDS) characterised by alveolar-capillary membrane destruction and exudation. The resulting hypoxia and diffuse inflammation lead to septic shock and multiple organ failure. ARDS is the most fatal complication in patients with a severe clinical picture and may occur shortly after the onset of dyspnoea.[3] In addition to respiratory system involvement, gastrointestinal tract (GI) symptoms were also common in COVID-19 patients. In addition, elevated liver enzyme levels were observed in these patients at the onset of the disease and during hospitalisation. Symptoms such as diarrhoea, loss of appetite, nausea and vomiting may occur during the onset and course of COVID-19 and should be suspected in patients at risk.[4]

Coronaviruses are medium-sized enveloped positive-strand ribonucleic acid (RNA) viruses, named for their characteristic crown-like appearance in electron micrographs.[5,6] Figure.[6]

During COVID-19 infection, the GI tract is affected to varying degrees. Liver and intestines are affected commonly. Diagnostic and therapeutic endoscopy procedures in infected patients have become risky for nosocomial transmission due to the presence of SARS-CoV-2 virus in both oral mucosa and the intestinal tract.

It has been observed that GI symptoms often start early in the disease and 1-2 days before the respiratory symptoms. In addition, studies have shown that GI symptoms were more frequently reported and hospitalisation rates were higher in cases with severe disease than in cases without severe disease. These findings support the theory of GI entry and infection of SARS-CoV-2 via the ACE2 receptor.[4]

Macrophage activation syndrome (MAS), also known as cytokine storm, is characterised by fever, variable hepatosplenomegaly, an increase in C-reactive protein (CRP) concentration, hyperferritinaemia, haemophagocytosis, cytopenias and coagulopathy due

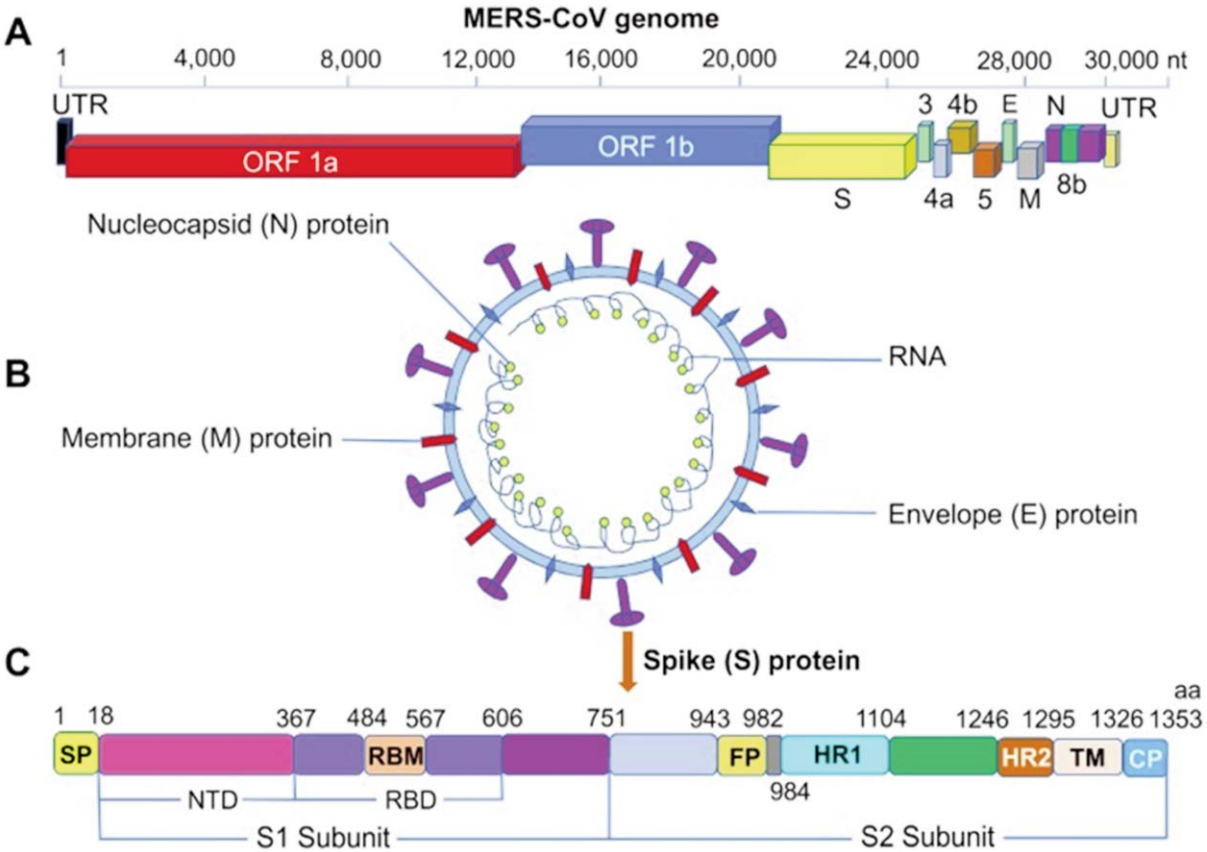

Figure: The schematic structure of the coronavirus[6].

Schematic structures of MERS-CoV S protein. (A) MERS-CoV genomic structure, with the untranslated region (UTR), open reading frame regions ORF1a and ORF1b, spike (S), envelope (E), membrane (M), and nucleocapsid (N) genes. (B) Schematic structure of the MERS-CoV virion and its major structural proteins. (C) Schematic structure of the MERS-CoV S protein and its functional domains, including the N-terminal domain (NTD), receptor-binding domain (RBD), receptor-binding motif (RBM), fusion peptide (FP), heptad repeat region 1 and 2 (HR1 and HR2), transmembrane region (TM), and cytoplasmic tail (CP). aa, amino acid; MERS-CoV, Middle East respiratory syndrome coronavirus; nt, nucleotide.

to liver dysfunction and disseminated intravascular coagulation (DIC). Critical illness describes patients who need intensive care due to pneumonia, respiratory failure and multiorgan failure.[7,8]

The current study was planned to evaluate the involvement of GI tract (GIT) features in COVID-19 patients, and to analyse the effects of these features on the development of critical illness, and mortality.

Materials and Methods

The retrospective, cross-sectional study was conducted from January 2021 to December 2022 at the Recep Tayyip Erdoğan University Training and Research Hospital, Turkiye, a tertiary care facility, after approval from the institutional ethics review committee, and comprised data from March 30, 2020, to March 31, 2022, related to COVID-19 inpatients aged 18-90 years. Patients hospitalised for <3 days were excluded, and so were those with terminal cancer and chronic liver disease as well patients receiving palliative care. All laboratory results used in the diagnosis and examination of the patients, treatments administered, length of hospital stay (LOS) and demographic characteristics were retrieved from computer records. Laboratory parameters included aspartate transaminase (AST), alanine transaminase (ALT), total bilirubin (TBIL), direct bilirubin (DBIL), indirect bilirubin (IBIL), alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), amylase and CRP. GI symptoms included nausea, vomiting, abdominal pain, diarrhoea, dyspeptic complaints, anorexia, GI bleeding and weight-loss.

Data was analysed using SPSS 22.0 statistical package programmer. Data was expressed as frequencies and percentage as well as mean and standard deviations, as appropriate. Students t test was used to compare the means of continuous variables, while chi-square test was used to compare the laboratory values, development of critical illness, development of MAS, and mortality status of the patients. Pearson correlation test was used for correlation evaluation between laboratory parameters of the patients. Receiver operating characteristic (ROC) curve regression analysis was used to evaluate the effect of laboratory parameters on mortality. P<0.05 was considered statistically significant.

Results

Of the 2,154 patients, 1,150(53.4%) were males and 1,004(46.6%) were females. The overall mean age was 61±16.8 years (range: 18-90 years). A total of 2,045(94.9%) patients were discharged, while 109(5.1%) died. Besides, 195(9.1%) developed critical illness and 158(7.3%) developed MAS.

Table-1: Gastrointestinal (GI) symptoms and their gender distribution.

Sign and symptom	Number of patients with signs or symptoms - M/F	Percentage
Nausea	171-73/105	% 8.7
Vomiting	125-55/70	% 5.8
Abdominal pain	56-25/31	% 2.6
Diarrhoea	76-42/34	% 4
Dyspeptic complaint	81-40/41	% 3.7
Loss of appetite	153-82/71	% 7.4
GI bleeding	32-19/13	% 1.4
Weight loss	2-2/0	% 0.1

Table-2: Gastrointestinal (GI) laboratory abnormalities.

Laboratory parameter	Number of patients with elevated / Number of patients examined	Percentage
ALT	694/2044	
% 33.9		
AST	554/2044	% 27.1
TBIL	119/1992	% 6
Direct bilirubin	112/1984	% 5.6
İndirect bilirubin	89/1984	% 4.5
Amylase	344/1683	% 20.4
GGT	558/1856	% 30
ALP	160/1394	% 11.4
Ferritin	985/1907	% 51.6
CRP	1693/2139	% 79.1

ALT: Alanine transaminase, AST: Aspartate transaminase, TBIL: Total bilirubin, GGT: Gamma glutamyl transferase, ALP: Alkaline phosphatase, CRP: C-reactive protein.

Of the patients discharged from the ward, 951(46%) were female and 1,094(53.4%) were male. Of the patients transferred to the intensive care unit (ICU), 75(38.4%) were female and 120(61.5%) were male. Among patients who developed MAS, 44(27.8%) were female and 1114(72.1%) were male. Overall, 53(48.6%) of the patients who died were female and 56(51.3%) were male (p=0.187). The mean age of the patients who survived was 59±16.2 years, while the mean age of the patients who died was 73.3 years (p<0.0001). The mean age of patients who developed MAS was 64.6±17.7 years, the mean age of patients who died after development of MAS was 71.4±19.6 years, and the mean age of patients who survived after development of MAS was 57.7±15.8 years.

Ferritin level was elevated in 985(51.6%) of 1,907 patients. In discharged patients, ferritin was high in 876(89%) of 985 patients, and the highest ferritin level was 1,109ng/ml, while ferritin was high in 102(93.6%) of 109 patients who died, and the highest ferritin level was 3446ng/ml (p<0.001). The association of ferritin elevation (>1,000ng/ml) with mortality was a significant predictor of mortality (p<0.001) with 78.2% sensitivity and 64.6%

specificity.

Each GI symptom was noted along with gender distribution (Table 1).

With respect to laboratory parameters, ALT level was in the normal range in 1,350(66.1%) of the patients discharged from the ward, while it was high in 694(33.9%). While it was in the normal range in 74(67%) of the deceased patients, it was elevated in 35(33%). AST levels were in the normal range in 1,490(72.9%) and elevated in 554(27.1%) of the patients discharged from the ward. In patients who died, 55(50.4%) had AST in the normal range, and 54(49.6%) had it elevated.

GGT level was normal in 1,298(70%) and elevated in 558(30%) of the patients discharged from the ward. ALP level was normal in 1,234(88.5%) and elevated in 160(11.5%) patients who were tested. Amylase levels were elevated in 344(20.4%) patients.

CRP level was elevated in 1,693(79.1%) of 2,140 patients. Of these, 745(44%) were female and 948(55.9%) were male. CRP level was elevated in 1,693(79.1%) of 2,140 patients. While CRP was high in 79% of discharged patients, it was high in 100% of the patients who died. The highest CRP value was 58.8IU in discharged patients, and 94.8IU in patients who died. Ferritin level was elevated in 985(51.6%) of 1,907 patients. Of these, 331(33.6%) were female and 654(66.3%) were male (Table 2).

Of the 158(7.3%) patients who developed MAS, 44(27.8%) were female and 114(72.2%) were male, and 39(24.7%) of them died. Of the 195(9.1%) patients admitted to ICU, 75(38.5%) were female and 120(61.5%) were male, and 109(55.9%) of them died; 53(48.6%) females and 56(51.4%) males.

When the relationship between ALT levels and development of MAS was analysed, 94(14.8%) patients with elevated ALT levels developed MAS compared to 64(4.7%) of patients with normal ALT levels (p<0.001). When the relationship between ALT and development of critical illness was analysed, 89(13.9%) patients with elevated ALT levels developed critical illness compared to 106(8%) patients with ALT values in the normal range (p<0.003). When the relationship between ALT levels and mortality was analysed, 35(5%) patients with elevated ALT levels died compared to 74(5.5%) with ALT values in the normal range (p=0.692). When the relationship between AST levels and development of MAS was analysed, 96(18.8%) patients with elevated AST levels developed MAS compared to 62(4.2%) patients with AST values in the normal range (p<0.001). When the relationship between AST level and development of critical illness was analysed, 71(13.2%) patients with elevated AST levels developed critical illness compared to 124(8.7%) patients with AST values in the normal range (p<0.007). When the relationship between AST level and mortality was analysed, 54(9.7%) patients with elevated AST levels died compared to

Table-3: Association of biochemical tests and gastrointestinal complaints with macrophage activation syndrome (MAS) development, critical illness and mortality.

Biochemical tests and gastrointestinal complaints	MAS development No, %	P value	Presence of critical illness No, %	Pvalue	Mortality No, %	Pvalue
ALT	Normal High 1360 635 MAS developing 64(%4.7)94(%14.8)	**<0.001**	Normal High 1318 640 Presence of critical illness 106(%8) 89(%13.9)	**<0.003**	Normal High 1350 694 Mortality 74(%5.5) 35(%5)	<0.692
AST	Normal High 1483 512 MAS developing 62(%4.2) 96(%18.8)	**<0.001**	Normal High 1421 537 Presence of critical illness 124(%8.7) 71(%13.2)	**<0.007**	Normal High 1490 554 Mortality 55(%3.7) 54(%9.7)	**<0.001**
GGT	Normal High 1293 525 Mas developing 60(%4.6) 84(%16)	**<0.001**	Normal High 1254 542 Presence of critical illness 99(%7.9) 67(%12.4)	**<0.006**	Normal High 1298 558 Mortality 55(%4.2) 51(%9.1)	**<0.001**
Amylase	Normal High 1313 330 Mas developing 84(%6.4) 46(%13.9)	**<0.002**	Normal High 1279 71 Presence of critical illness 118(%9.2) 8(%11.3)	<0.071	Normal High 1339 344 Mortality 58(%4.3) 32(%9.3)	**<0.002**
Loss of appetite	None Exist 1864 132 Mas developing 137(%7.3)21(%15.9)	**<0.001**	None Exist 1815 144 Presence of critical illness 186(%10.2) 9(%6.2)	<0.156	None Exist 1912 153 Mortality 89(%4.6) 20(%13)	**<0.001**
Nausea	None Exist 1829 166 Mas developing 146(%8) 12(%7.2)	<0.749	None Exist 1787 171 Presence of critical illness 188(%10.5) 7(%4)	**<0.012**	None Exist Yok Var 1877 167 Mortality 98(%5.2) 11(%6.5)	<0.413
Diarrhoea	None Exist 1832 76 Mas developing 37(%2) 3 (%3.9)	p<0.248	None Exist 1832 76 Presence of critical Illness 34(%1.9) 3(%3.9)	p<0.114	None Exist 1832 76 Mortality 41(%2.2) 5 (%6.5)	p<0.538

ALT: Alanine transaminase, AST: Aspartate transaminase, GGT: Gamma glutamyl transfer.

55(3.7%) patients with AST values in the normal range (p<0.001).

When the relationship between amylase levels and development of MAS was analysed, 46(13.9%) patients with elevated amylase levels developed MAS compared to 84(6.4%) patients with amylase values in the normal range (p<0.002). When the relationship between amylase level and development of critical illness was analysed, 8(11.3%) patients with elevated amylase levels developed critical illness compared to 118(9.2%) patients with amylase values in the normal range (p=0.071). When the relationship between amylase level and mortality was analysed, 32(9.3%) patients with elevated amylase levels died compared to 58(4.3%) patients with amylase values in the normal range (p<0.002).

When the relationship between GGT level and development of MAS was analysed, 84(16%) patients with elevated GGT levels developed MAS compared to 60(4.6%) patients with normal GGT levels (p<0.001). When the relationship between GGT level and development of critical illness was analysed, 67(12.4%) patients with elevated GGT levels developed critical illness compared to 99(7.9%) patients with GGT values in the normal range (p<0.006). When the relationship between GGT level and mortality was analysed, 51(9.1%) patients with elevated GGT died compared to 55(4.2%) patients with GGT values in the normal range (p<0.001).

Of the 76 patients with diarrhoea, 3(3.9%) developed MAS (p<0.248). Critical illness developed in 3(3.9%) patients with diarrhoea (p=0.114). Of the patients with diarrhoea, 5(6.5%) died (p=0.538).

Of the 132 patients with anorexia, 21(15.9%) developed MAS (p<0.001). Critical illness development was observed in 9(6.2%) of 144 patients with anorexia (p=0.156). Of 153 patients with anorexia, 20(13%) died (p<0.001).

Of the 166 patients with nausea, 12(7.2%) developed MAS (p=0.749). Critical illness developed in 7(4%) of 171 patients with nausea (p=0.012). Besides, 11(6.5%) of 167 patients with nausea died (p<0,413) (Table 3).

Discussion

COVID-19 does not affect only the respiratory system, but has multisystemic effects, inlcuding GI effects.

It has been observed that increased ferritin level is one of the most important predictors of MAS, development of critical illness and mortality during the course of the disease.[9] In the current study, ferritin elevation was not associated with liver function tests (LFTs). Ferritin is an indicator of iron stores in the body and the liver is the storage area.[10] These findings may indicate that ferritin is elevated by a mechanism independent of enzymes and biomarkers related to GItract, such as ALT, AST, DBIL, GGT and may show that liver damage in COVID-19 is not caused by ferritin.

The presence of GI symptoms related to COVID-19 is not the result of systematic disease, but of the virus directly affecting the GIT. This needs to be considered independently of patients' respiratory symptomatology. For example, in patients with suspected or known COVID-19 disease, it may be desirable to exclude secondary causes for abdominal pain. Abdominal organs with high concentrations of ACE2 expression may theoretically be vulnerable to COVID-19-related infections. These organs particularly include the oesophagus, ileum, kidneys and bladder.[11]

Non-GI symptoms for COVID-19 include fever, cough, shortness of breath, chills, muscle pain, headache, sore throat, and loss of taste or smell. GI-related symptoms, such as nausea, vomiting, abdominal pain, diarrhoea, anorexia, GI bleeding, weight-loss have been reported.[12-16]

Abnormal liver enzyme levels have also been observed. However, there are significant differences between studies in the reporting of GI and hepatobiliary system symptoms.[12] According to the current study, the most commonly reported GI symptoms in COVID-19 patients receiving inpatient treatment were nausea 8.7%, anorexia 7.4%, and vomiting 5.8%.

In endoscopic examinations, no significant damage was observed in the mucosal epithelium of the oesophagus, stomach, duodenum and rectum with hematoxylin and eosin (H&E) staining, whereas ACE2 enzyme and viral nucleocapsid protein were positively stained in the cytoplasm of GI epithelial cells in the stomach, duodenum and rectum. These results suggest that SARS-CoV-2 virus can infect the mucosal cells of the stomach, small and large intestines, multiply in these cells and produce infectious virions.[13] In some studies, patients presented with diarrhoea without signs of upper respiratory tract infection, and it was found that diarrhoea lasted for an average of 5 days, and was self-limiting in most patients.[12-15] A meta-analysis of 15 studies published till April 2020 reporting GI symptoms in COVID-19 patients found that the frequency of these symptoms ranged from 3% to 39.6% and the most common symptom was diarrhoea. In addition, it was observed that GI symptoms may precede fever or respiratory symptoms, but no results were found regarding their relationship with the prognosis of the disease.[16] In the current study, the most

common GI symptom was nausea (8.7%). The second most common GI symptom was anorexia (7.4%).

In addition to the disease, drug side effects may also contribute to the frequent occurrence of nausea. The presence of GI symptoms was not found to be associated with the severity of COVID-19 pneumonia or mortality in a study with 521 COVID-19 patients, which examined the relationship of GI symptoms and liver enzyme elevation with the severity of the disease.[17] In a meta-analysis of 47 studies with COVID-19 patients, GI symptoms nausea, vomiting, abdominal pain and diarrhoea were seen in 10% patients.[18] In the current study, when the relationship of GI symptoms with the development of MAS, critical illness and mortality was examined, it was found that anorexia was associated with the development of MAS ($p<0.001$) and mortality ($p<0.001$), while nausea was less common in those who developed critical illness ($p=0.012$). This may be due to the inability to obtain a real history from patients with poor general condition.

When biochemical tests were used to evaluate GI system functions, the most common biochemical abnormality was increased ALT (33.9%). Elevated GGT was the second most common biochemical abnormality (30%). The binding of SARS-CoV-2, which is involved in the pathogenesis of COVID-19, to ACE2 receptors, and the abundance of these receptors in hepatocytes and cholangiocytes may indicate that this cell group, which is the source of GGT, is also affected and infects the GIT. The receptors that SARS-CoV-2 uses for intracellular entry are ACE2 receptors. These receptors are found in gastric, duodenal and rectal epithelium. ACE2 receptors are thought to play a role in faecal-oral transmission. Furthermore, ACE2 receptors can be expressed on hepatic cholangiocytes and hepatocytes. Thus, infection can spread directly to hepatocytes.[19]

In some studies, the presence of hepatic and GI symptoms in COVID-19 patients during hospitalisation was not associated with the severity of COVID-19 pneumonia or overall mortality.[16]

In the current study, anorexia was found to be associated with the development of MAS ($p<0.001$) and mortality ($p<0.001$). This suggests that high cachectin levels lead to anorexia in addition to increased levels of interleukins in MAS and severe disease.

In addition to the respiratory system, a significant proportion of patients infected with COVID-19 show signs of varying degrees of liver damage, suggesting that liver abnormalities in COVID-19 patients may be due to other causes besides hepatocyte damage, such as cholangiocyte dysfunction, drug-induced liver damage and liver damage caused by systemic inflammatory response.[19] In the current study, patients with previously known liver disease were excluded in order to demonstrate this effect more clearly.

In the current study, ALT, AST, amylase, GGT elevation was analysed to explore their relationship with progression to MAS, development of critical illness and mortality.

In a meta-analysis of 36 studies comprising 20,724 patients with COVID-19 infection, LFT abnormality on admission was found to be 46.9% and studies have reported that COVID-19 was associated with increased liver decompensation and mortality.[20] The frequency of ALT and AST elevation was similar to that of general COVID-19 cases, but, interestingly, the frequency of AST elevation was higher than ALT in severe COVID-19 disease.[21] In the current study, ALT elevation was seen 33.9% and 27.1% more frequently than AST elevation. Nevertheless, the relationship of MAS, critical illness and mortality was statistically significant in the group with high AST values. High creatine kinase levels in patients with severe COVID-19 indicate that the disease has muscle involvement in addition to the involvement of many organs. Therefore, the fact that AST elevation was more frequent than ALT elevation in patients who developed MAS, in patients who developed critical illness and in patients who died suggests the presence of more widespread involvement of non-liver cardiac and skeletal muscles. Higher than normal ALT values were associated with the development of MAS and critical illness, but not with mortality. Wang K et al. reported that laboratory abnormalities were better indicators of motility than GI symptoms.[22]

There are studies showing that serum amylase and/or lipase are increased in COVID-19 patients. Pribadi et al. examined 121 COVID-19 patients, and serum amylase was found to be elevated in 12 (17.91%) of 67 severe patients.[23] Similarly, in the current study, elevated amylase levels were found in 46(13.9%) of the patients who developed MAS, and in 32(9.3%) of the patients who died. The association of elevated amylase levels with the development of MAS and mortality was significant ($p<0.002$). This suggests that elevated amylase levels may be due to ACE2 receptor expression in the pancreas, and that pancreatic damage may develop in severe forms of the disease.

Kumar et al. reviewed 128 studies analysing liver enzyme levels of COVID-19 patients between 2019 and 2020, and found that liver function abnormalities, such as GGT,

aminotransferase and bilirubin elevations, were common. They also found that elevations in GGT were similar to elevations in aminotransferase levels and were higher than elevations in ALP levels.[21] In a meta-analysis of 159 studies, which examined the liver enzyme levels of COVID-19 patients, high GGT levels were found in severe cases, prolonged LOS was observed, and it was found to be associated with disease severity.[24] Similarly, elevated GGT was observed more frequently than elevated ALP in the current study. In addition, the association of higher than normal GGT values with development of MAS, development of critical illness and mortality was found to be significant. In a study analysing GGT elevation in COVID-19 patients, it was shown that GGT was secreted from somatic cells infected by the virus, and that the dominant type of GGT was GGT1.[25] In terms of limittaions, the current retrospective study excluded those with known elevated liver enzymes before COVID-19, but hepatotoxicity due to the drugs used for treatment could not be clearly ruled out.

Conclusion

ALT values higher than normal were associated with the development of MAS and critical illness, but not with mortality. AST values higher than normal were associated with the development of MAS, critical illness and mortality. The association of higher than normal GGT value with development of MAS, development of critical illness and mortality was significant. Higher than normal amylase levels were significant in the development of MAS and mortality, but not in the development of critical illness. Among GI symptoms and complaints, a significant association was observed between anorexia and development of MAS, and between nausea and development of critical illness. A significant association was observed between the development of MAS and mortality. Advanced age was found to be a significant predictor of mortality.

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References

1. WHO Director-General's remarks at the media briefing on 2019-nCoV on 11 February 2020. [Online] [Cited 2022 April 17]. Available from: URL: https://www.who.int/directorgeneral/speeches/detail/who-director-general-s-remarks-at-the-media-briefing-on2019-ncov-on-11-february-2020.
2. WHO Coronavirus (COVID-19) Dashboard | WHO Coronavirus (COVID-19) Dashboard With Vaccination Data. [Online] [Cited 2022 May 18]. Available from: URL: https://covid19.who.int/
3. Bozkurt D. Ivıg therapy ın clınıcal practıce Palmiye. Izmir: Palmiye publishing house. [Online] [Cited 2022 June 10]. Available from: URL: https://palmeyayinevi.com/klinik-pratikte-ivig-tedavisi
4. Pan L, Mu M, Yang P, Sun Y, Runsheng W, Junhong Y, et al. 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. doi: 10. 14309/ajg. 0000000000000620.
5. McIntosh K, Dees JH, Becker WB, Kapikian AZ, Chanock RM. Recovery in tracheal organ cultures of novel viruses from patients with respiratory disease. Proc Natl Acad Sci USA. 1967; 57:933-40. doi: 10.1073/pnas.57.4.933.
6. Zhou Y, Yang Y, Huang J, Jiang S, Du L. Advances in MERS-CoV Vaccines and Therapeutics Based on the Receptor-Binding Domain. Viruses. 2019; 11:60. doi: 10.3390/v11010060.
7. Masters PS, Kuo L, Ye R, Hurst KR, Koetzner CA, Hsue B. Genetic and molecular biological analysis of protein-protein interactions in coronavirus assembly. Adv Exp Med Biol. 2006; 581:163-73. doi: 10.1007/978-0-387-33012-9_29.
8. Ravelli A, Davì S, Minoia F, Martini A, Cron RQ. Macrophage Activation Syndrome. Hematol Oncol Clin North Am. 2015; 29:927-41. doi: 10.1016/j.hoc.2015.06.010.
9. McGonagle D, Donnell JSO. Sharif K, Emery P, Bridgewood C. Immune mechanisms of pulmonary intravascular coagulopathy in COVID-19 pneumonia. Lancet Rheumatol.2020; 2: e437-45.doi: 10.1016/S2665-9913(20)30121-1
10. Al-Moshary M, Imtiaz N, Al-Mussaed E, Khan A, Ahmad S, Albqami S, et al. Clinical and biochemical assessment of liver function test and its correlation with serum ferritin levels in transfusion-dependent thalassemia patients. Cureus. 2020; 12:e7574. doi: 10.7759/cureus.7574.
11. Wilson MP, Katlariwala P, Low G. Potential implications of novel coronavirus disease(COVID-19) related gastrointestinal symptoms for abdominal imaging. Radiography.2020; 26:274. doi:10.1016/j.radi.2020.04.016
12. Cai Q, Huang D, Yu H, Zhu Z, Xia Z, Su Y, et al. COVID-19: Abnormal liver function tests. J Hepatol. 2020; 73:566-74. doi: 10.1016/j.jhep.2020.04.006.
13. Uno Y. Why Does SARS-CoV-2 Invade the Gastrointestinal Epithelium? Gastroenterology. 2020; 159:1622-3. doi:10.1053/j.gastro.2020.04.006.
14. Jin X, Lian JS, Hu JH, Gao J, Zheng L, Zhang YM, et al. Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. Gut. 2020; 69:1002-9. doi: 10.1136/gutjnl-2020-320926.
15. Uraz S, Şentürk Ö. Gastroenterohepatology symptoms and recommendations in COVID-19. Çelebi A, Uraz S, Şentürk Ö, eds. Gastroenterohepatology and COVID-19. 1st edition. Ankara: Türkiye Klinikleri, 2020; 12-6.
16. Sultan S, Altayar O, Siddique SM, Davitkov P, Feuerstein JD, Lim JK, et al. AGA Institute Rapid Review of the Gastrointestinal and Liver Manifestations of COVID-19, Meta-Analysis of International Data, and Recommendations for the Consultative Management of Patients with COVID-19. Gastroenterology. 2020; 159:320-34.e27. doi:10.1053/j.gastro.2020.05.001
17. Kaiyasah H, Fardan H, Bashir O, Hussein M, Alsubbah H, Dabal LA. Hepatic and gastrointestinal manifestations in patients with COVID-19 and relationship with disease severity: a single-centre experience. IJID Reg. 2022; 3:143-9. doi:10.1016/j.ijregi.2022.03.025
18. Schmulson M, Dávalos MF, Berumen J. Beware: Gastrointestinal symptoms can be a manifestation of COVID-19. Rev Gastroenterol Mex. 2020; 85: 282-7. doi: 10.1016/j.rgmx.2020.04.001.
19. Xiaoqiang Chai, Longfei Hu, Yan Zhang, W Han, Z Lu, A Ke, et al. Specific ACE2 Expression in Cholangiocytes May Cause Liver

Damage After 2019- nCoV Infection. [Online] [Cited 2020 February 4]. Available from: URL: https://doi.org/10.1101/2020.02.03.931766
20. Del Zompo F, De Siena M, Ianiro G, Gasbarrini A, Pompili M, Ponziani FR. Prevalence of liver injury and correlation with clinical outcomes in patients with COVID-19: systematic review with meta-analysis. Eur Rev Med Pharmacol Sci. 2020; 24:13072-88.doi: 10.26355/eurrev_202012_24215.
21. Kumar-MP, Mishra S, Jha DK, Shukla J, Choudhury A, Mohindra R, et al. Coronavirus disease (COVID-19) and the liver: a comprehensive systematic review and meta-analysis. Hepatol Int. 2020; 14:711-22.doi: 10.1007/s12072-020-10071-9.
22. Wang K, Zuo P, Liu Y, Zhang M, Zhao X, Xie S, et al. Clinical and Laboratory Predictors of In-hospital Mortality in Patients With Coronavirus Disease-2019: A Cohort Studyin Wuhan, China. Clin Infect Dis. 2020; 71:2079-88.doi: 10.1093/cid/ciaa538.
23. Pribadi RR, Simadibrata M. Increased serum amylase and/or lipase in coronavirus disease 2019 (COVID-19) patients: Is it really pancreatic injury? JGH Open. 2020; 5:190-2.doi: 10.1002/jgh3.12436.
24. McGrowder, DA, Miller F, Anderson Cross M, Anderson-Jackson L, Bryan S, Dilworth L. Abnormal liver biochemistry tests and acute liver injury in COVID-19 patients: current evidence and potential pathogenesis. Diseases, 2021. 9(3), 50.
25. Liu J, Yu C, Yang Q, Yuan X, Yang F, Li P, et al. The clinical implication of gamma-glutamyl transpeptidase in COVID-19. Liver Res. 2021; 5:209-16.doi: 10.1016/j.livres.2021.09.001.

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HA: Concept, design, data acquisition, interpretation and final approval.
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