Gastrointestinal manifestations in hospitalized patients with chronic liver disease and COVID-19

Eugen Tcaciuc[1], Catalina Olaru-Stavila[2], Zinaida Alexa[2], Angela Tcaciuc[2], Denis Ardeleanu[1]

1) Department of Gastroenterology, Nicolae Testemitanu State University of Medicine and Pharmacy, Chisinau, Republic of Moldova

2) Department of Internal Medicine, Timofei Mosneaga State Republican Hospital, Chisinau, Republic of Moldova

Abstract

Background and aim. Gastrointestinal manifestations in COVID-19 have been frequently acknowledged by clinicians and scientists. However, their clinical significance and potential influence on the disease outcome is not entirely elucidated. In this study we aim to evaluate gastrointestinal involvement, both digestive symptoms and liver-related changes in hospitalized COVID-19 patients in correlation to the presence or absence of underlying liver disease and rate of mortality.

Methods. We performed a retrospective cohort study of COVID-19 patients, consecutively admitted in a hospital from Chisinau, between September 3, 2020 and May 31, 2021. Data on clinical symptoms and laboratory findings were collected from electronic clinical records. The cohort was divided into two groups, with and without pre-existing liver disease. The Fisher exact, Pearson Chi-square tests were used to compare groups.

Results. A total of 1835 patients were included, 108 (5.9%) with pre-existing liver disease and 1727 (94.1%) without this comorbidity. Digestive symptoms were reported by 331(18%) of the patients, diarrhea being the most common symptom 11.8% (217) and being encountered more in patients with underlying chronic liver disease. No statistical difference was identified between the groups in regard to other symptoms, comorbidities and rate of mortality. But patients with chronic liver disease had significant ($P < 0.001$) lower ferritin, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) in comparison with the other group. At admission, 341 (19.2%) had increased aspartate aminotransferase level (AST) and 317 (17.8%) alanine aminotransferase. The enzyme abnormalities were predominantly mild and transitory. Abnormal AST level at admission and during follow up, higher ESR, CRP, ferritin, lactate dehydrogenase (LDH) was found to correlate with higher rates of mortality.

Conclusion. Digestive implications, especially diarrhea in COVID-19 patients is frequent, but do not appear to be associated with mortality. Elevated liver enzymes during hospitalization, age, high ferritin, CRP, LDH might be interpreted as risk factors for mortality in COVID-19 but further studies are needed to address this topic.

Keywords: SARS-CoV-2, COVID-19, chronic liver disease

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Address for correspondence:
colaru38@yahoo.com

Introduction

COVID-19 continues to be considered a serious problem for the entire medical community and global economy, worldwide.

The disease has various manifestations with a predominance of respiratory features causing the majority of morbidity and mortality. However, in addition to pulmonary manifestations, gastrointestinal symptoms such as anorexia, diarrhea, nausea and vomiting, abdominal pain have been reported variably in countless studies (with a prevalence range between 2% and 57%) [1]. As well, patients with or without pre-existing liver disease may present with elevated aminotransferases, reported in 14-58 % of hospitalized patients [2]. A possible explanation of the gastrointestinal involvement is suggested by the presence of converting enzyme type 2 (ACE-2) receptors found in the esophageal, duodenal epithelia and enterocytes of the small intestine, evidence of viral replication in enterocyte on immunohistochemical examinations, as well as determination of viral RNA in the stool [3,4]. The pathophysiological background of liver injury is vague and several mechanisms of action have been proposed, such as direct cytotoxic action via ACE-2 expression in the bile ducts [5], drug hepatotoxicity, distinctively use of acetaminophen, tocilizumab, remdesivir, antibiotics [6,7]. Also, the studies suggest that cytokine storm causing systemic involvement could be a possible cause [8]. And lastly ischemic injury of the virus can lead to hypoxic hepatitis [9].

Although exploration of gastrointestinal involvement in severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) infection has been substantial in the past two years, debates on this subject still exist. It remains uncertain to what extent digestive manifestations influence the disease course and mortality in COVID-19 patients. Moreover, there is lack of clarity, if there is a significant difference between patients with chronic liver disease and without.

As a medical center positioned on the front line in the combat against the pandemic in the Republic of Moldova, we aim to add to the developing knowledge that outline the gastrointestinal manifestations of COVID-19 disease. Also, we intended to evaluate if the presence of liver injury at the time of hospitalization is associated with a higher rate of mortality in patients both with and without underlying chronic liver disease.

Methods

Study design and data collection

We conducted a retrospective cohort study of patients with COVID-19 consecutively admitted to the Republican Clinical Hospital, COVID-19 Department, between September 3, 2020 and May 31, 2021. This institution represents a tertiary care, academic hospital of Chisinau, Republic of Moldova. Diagnosis of COVID-19 patients was performed by reverse transcription polymerase chain reaction (RT-PCR) for SARS CoV-2 of a naso/oropharyngeal swab. Only the patients with a registered RT-PCR test were selected. Patients hospitalized directly in the Intensive Care Unit, with missing data on mortality and outcome were excluded.

Data concerning the demographics, comorbidities, history of symptoms, laboratory tests, disease course and outcome were collected through a survey of electronic clinical records.

Stratification of study cohort

The gastrointestinal manifestations were defined as presence of abdominal pain, nausea, vomiting and diarrhea. Liver injury was defined by alanine aminotransferase (ALT) and aspartate aminotransferase (AST) abnormalities. A borderline increase in liver enzymes was considered <2 times the upper limit of normal (ULN), mild (2–5 times the ULN), moderate to severe (> 5 times the ULN), according to the American College of Gastroenterology Clinical Guidelines, European Association for the Study of the Liver and other studies [10,11].

The study cohort was divided into two groups without and with pre-exiting liver disease, namely viral hepatitis B, C, autoimmune hepatitis, primary biliary cholangitis and cirrhosis.

Statistical analysis

Descriptive statistics of the population are presented as frequencies with percentages for categorical variables, mean and standard deviation (SD) for continuous variables. The Fisher exact test and Pearson Chi-square test were used to compare groups, and a P value less than 0.05 was considered to indicate statistical significance.

Results

A total of 1835 patients were included, mean age 58.3 years, with a slight female predominance - 966 (52.6%). One hundred and eight (5.9%) patients were reported with pre-existing liver disease and 1727 (94.1%) without. Within the 108 total cases, 11 (10.1%) had cirrhosis and 97 (89.9%) had various types of hepatitis. The patients demographics are presented in table I.

Gastrointestinal manifestations were reported by 331 (18%) patients. Most common GI symptom reported was diarrhea with a prevalence of 11.8% in the general cohort, encountered more frequently in patients with chronic liver disease 19.4% vs patients in the second group 11.3% ($P < 0.05$). Other symptoms were nausea or vomiting mentioned by 69 (3.8%) patients and abdominal pain in only 45 (2.4%); they were similarly distributed between the groups.

There was no difference between the two groups on presentation regarding the frequency of dyspnea ($P > 0.05$), cough ($P > 0.05$), comorbidities such as diabetes mellitus ($P > 0.05$). Interestingly, obesity was found more often in patients without liver disease - 52.7% vs. 35.4% ($P < 0.01$) in patients with chronic hepatopathy. Hospital mortality rate was 7.3% in both groups with no significant difference ($P > 0.05$).

Table I. Patients demographics, clinical characteristics and outcome.

Characteristics	Total	Chronic liver disease	Non chronic liver disease	P value
Number of patients	1835	108	1727	
Age, mean (SD) (years)	58.3 (19-99)	59.3 (9.9)(19-89)	58.2 (12.3)(19-99)	>0.05
Sex (female)	966 (52.6%)	59 (54.6%)	907 (52.5%)	>0.05
Comorbidities				
Cardiovascular disease	1089 (81.4%)	64 (58.7%)	1025 (83.4%)	
Diabetes mellitus	417 (22.7%)	21 (19.4%)	396 (22.9%)	>0.05
Obesity	769 (51.8%)	29 (35.4%)	740 (52.7%)	**<0.01**
Symptoms				
Cough	1447 (78.9%)	86 (79.6%)	1361 (78.8%)	>0.05
Dyspnea	1341 (73.1%)	72 (66.7%)	1269 (73.5%)	>0.05
Abdominal pain	45 (2.4%)	4 (3.7%)	35 (2%)	>0.05
Nausea/vomiting	69 (3.8%)	5 (1.8 %)	64 (3.7%)	>0.05
Diarrhea	217 (11.8%)	21 (19.4%)	196 (11.3%)	**<0.05**
SpO2 at admission, mean (SD) (%)	93.8 (4.23)	94.5 (4)	93.8 (4.2)	>0.05
Mortality	134 (7.3%)	8 (7.4%)	126 (7.3%)	>0.05

Significant at $P < 0.05$ in bold. SD, standard deviation; SpO2, oxygen saturation.

Table II. Laboratory results of cohorts at the time of admission.

	Total mean (SD)	Chronic liver disease	Non chronic liver disease	P value
WBC ($\times 10^3/\mu$ L)	6.9 (4.3)	6.7 (4.2)	7 (4.3)	>0.05
ESR (mm/h)	28 (17.5)	22.2 (14.3)	28.3 (15.6)	**<0.001**
CRP (mg/L)	53.2 (63.5)	30.9 (47.3)	54.6 (64.1)	**<0.001**
Ferritin (ng/ml)	480.5 (419.8)	393.6 (398.3)	486 (420.6)	**<0.001**
LDH (U/L)	269.4 (150.9)	254.1 (161.6)	270.4 (150.2)	>0.05
serum Albumin (g/l)	36.2 (6.3)	37.1 (6.5)	36.1 (6.2)	>0.05
ALT (U/L)	39.4 (38.5)	42.1 (39.8)	39.2 (38.4)	>0.05
AST (U/L)	35.6 (32.8)	39.2 (28.1)	35.3 (33.1)	>0.05
GGT (U/L)	73 (108.1)	72.1 (104)	73 (108.5)	>0.05

Significant at $P < 0.05$ in bold. WBC, white blood count; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; LDH, lactate dehydrogenase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase.

The laboratory data on admission is displayed in table II.

Patients with chronic liver disease had a lower mean C reactive protein [30.9 (47.3) vs. 54.6 (64.1); $P < 0.001$], a lower ferritin level [393.6 (398.3) vs. 486 (420.6); $P < 0.001$] and lastly lower erythrocyte sedimentation rate [22.2 (14.3) vs. 28.3 (15.6); $P < 0.001$] in comparison with the other group.

With reference to liver injury, on admission the mean value of AST level in the general cohort was 35.6 (32.8) U/L. Initial AST level was normal in 1435 (80.2%) patients and 341 (19.2%) had various types of abnormal levels. Specifically, 293 (16.5%) patients had a minimal increase (1–2 times the ULN), 45 (2.5%) had a mild increase (2–5 times the ULN), and only 3 (0.2%) had moderate to severe changes (>5 times the ULN). There was no statistically significant difference of AST values ($P > 0.05$) between patients both with and without underlying chronic liver disease.

The mean ALT on admission was 39.4 (38.5) U/L. The ALT level was higher in patients with chronic liver disease [42.1 (39.8) vs. 39.2 (38.4); $P > 0.05$], but did not reach statistical significance. The overall prevalence of elevated ALT was 317 (17.8%), particularly 220 (12.4%) patients with borderline increase (1-2 times the ULN), 90 (5.1%) had mild elevation (2-5 times the ULN) and 7 (0.4%) had moderate to severe changes (> 5 times the ULN).

During the follow up of the patients on the 10th day of admission, mean ALT value was higher than at the hospitalization, namely 75.6 (137.9). But there wasn't an impactful difference between the groups with and without liver comorbidities [91.9 (203.9) vs. 74.4 (132.2); $P > 0.05$]. Among patients investigated at follow up, 504 (41%) had abnormal ALT, correspondingly borderline changes in 305 (24.8%), mild increase 159 (12.9%) and moderate to severe elevation in 40 (3.3%).

Table III. Association of variables with mortality.

	Deceased mean (SD)	Survivors	P value
Sex, female (%)	48.5%	53%	>0.05
Age	66.4 (10.5)	57.7 (12.1)	**<0.001**
SpO2 at admission (%)	89.8 (7.8)	94.1 (3.6)	**<0.001**
Diarrhea (%)	7.5%	12.2%	>0.05
WBC ($\times 10^3/\mu$ L)	7.7 (5.1)	6.9 (4.2)	>0.05
Ferritin (ng/ml)	690.9 (527.6)	463.8 (405.5)	**<0.001**
LDH (U/L)	364.6 (211)	261.7 (142.3)	**<0.001**
CRP (mg/L)	83.3 (70)	50.8 (62.4)	**<0.001**
serum Albumin (g/l)	33.4 (6.3)	36.4 (6.2)	**<0.001**
Initial ALT (U/L)	42.9 (57.5)	39.1 (36.5)	>0.05
Follow up ALT (U/L)	167.7 (362.4)	64.6 (65.2)	**<0.01**
Initial AST ((U/L)	52 (82.6)	34.2 (24.3)	**<0.05**
Follow up AST (U/L)	237.9 (618.6)	26 (28.8)	**<0.001**
GGT (U/L)	74.9 (95.9)	72.9 (108.8)	>0.05
Follow up GGT	60.2 (65.4)	116.3 (186.6)	>0.05

Significant at $P < 0.05$ in bold.
SD, standard deviation; WBC, white blood count; LDH, lactate dehydrogenase; CRP, C-reactive protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase.

Regarding AST, mean value was 45.8 (253.7) with no differences among the two groups with underlying liver disease and without [44.8 (68.8) vs. 45.8 (205.9); $P > 0.05$]. Contrary to ALT, fewer patients had abnormal AST at repeated exploration 156 (13%), among them 113 (9.3%) with minimal AST elevation, 21 (1.7%) mild and 22 (1.8%) had > 5 times the ULN.

An analysis was then accomplished for a group of chosen laboratory findings to establish their impact on mortality, presented in table III.

An abnormal initial AST level compared with a normal initial AST level was associated with higher rates of mortality ($P < 0.05$). In addition, during the follow up of the patients on the 10th day of admission, elevated liver enzymes were correlated with higher rate of mortality, both AST ($P < 0.001$) and ALT ($P < 0.01$). Besides liver enzyme abnormalities, mortality was associated with age ($P < 0.001$), lower oxygen saturation at admission ($P < 0.001$), ferritin ($P < 0.001$), C-reactive protein ($P < 0.001$), lactate dehydrogenase ($P < 0.001$).

Discussion

In this study, presumably one of the first from Republic of Moldova to address gastrointestinal involvement in COVID-19, we identified a prevalence of digestive manifestations of 18%, with the main reported symptom being diarrhea (11.8%). The results obtained were similar to other studies conducted in United States [12], China [13], Europe [14]. Furthermore, diarrhea had higher rates in patients with chronic liver disease, assumably because SARS CoV-2 exacerbated an already existent intestinal dysfunction in those patients. Regarding mortality, the presence of diarrhea did not impact the clinical course, an opinion consistent with other reports in literature [15,16].

The prevalence of patients with chronic liver disease was 5.7% and did not appear to be over-represented in this cohort compared to other studies [17,18]. The rate of mortality was similar in both groups 7.3%. According to EASL, patients with pre-existing liver disease are at similar risk of infection with SARS CoV-2 and disease course, except for patients with advanced cirrhosis, which are at higher risk of mortality [19]. Unfortunately, as our study included only 11 patients with cirrhosis, we were not able to form an opinion on this matter. Interestingly, patients with chronic liver disease presented statistically significant lower rates of ESR, CRP and ferritin compared with the other group.

One fifth of the patients had liver biochemistry abnormalities on admission (19.2% AST, 17,8% ALT). Our study showed that changes occurred to a similar degree in patients both with and without underlying chronic liver disease. We observed an overall hepatocellular pattern of liver injury, as reported in other studies [20-22], with predominantly mild, transitory elevations of hepatic enzymes. In the general cohort, mean value of liver enzymes and prevalence of ALT abnormalities (41%) was higher at the follow up than at the admission. As the evidence of direct cytotoxic effect of SARS CoV-2 is sparse and yet to be proven [23-25], we consider that the increase is probably due in large part to drug-induced liver damage [26,27].

Increased AST and ALT during the follow up were associated with a higher mortality rate. As AST has a broad representation in various tissues, including skeletal, lung,

cardiac, renal parenchyma, a greater increase and poorer outcomes might be explained by the multiorgan injury seen in severe forms of COVID-19 [11,28].

Though, our study includes a large sample size, it has limitations. Notably the retrospective timeline, the decreased representation of mild COVID-19, as result of reviewing only hospitalized patients. Also, regardless of our best efforts, we suppose that not all the patients with chronic liver pathologies were identified, especially metabolic associated fatty liver disease (MAFLD), due to lack of documentation in electronic data records.

Conclusions

Gastrointestinal manifestations are commonly reported in COVID-19 hospitalized patients, diarrhea being the most frequent, and do not appear to impact mortality. Liver biochemistry deviances are mild, usually transitory. However, an increased AST level at admission and elevated liver enzymes at follow up were associated with a higher rate of mortality. Presence of chronic liver disease has not been associated with a greater risk of mortality in our study. But we strongly believe that further studies should be performed in order to determine disease outcome and management patients with COVID-19 and decompensated liver cirrhosis, MAFLD and alcohol-related liver disease.

References

1. Mao R, Qiu Y, He JS, Tan JY, Li XH, Liang J, et al. Manifestations and prognosis of gastrointestinal and liver involvement in patients with COVID-19: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2020;5:667-678.
2. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497-506.
3. Chen Y, Chen L, Deng Q, Zhang G, Wu K, Ni L, et al. The presence of SARS-CoV-2 RNA in the feces of COVID-19 patients. J Med Virol. 2020;92:833-840.
4. 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.e3.
5. Chai X, Hu L, Zhang Y, Han W, Lu Z, Ke A et al. bioRxiv 2020.02.03.931766; doi: https://doi.org/10.1101/2020.02.03.931766
6. Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet. 2020;395:1569–1578.
7. Anger F, Wiegering A, Wagner J, Lock J, Baur J, Haug L, et al. Toxic drug-induced liver failure during therapy of rheumatoid arthritis with tocilizumab subcutaneously: a case report. Rheumatology (Oxford). 2017;56:1628–1629.
8. 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 Gastrointest Liver Physiol. 2020;319:G245-G252.
9. Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. Lancet Gastroenterol Hepatol. 2020;5:428-430.
10. Sharma A, Jaiswal P, Kerakhan Y, Saravanan L, Murtaza Z, Zergham A, et al. Liver disease and outcomes among COVID-19 hospitalized patients - A systematic review and meta-analysis. Ann Hepatol. 2021;21:100273.
11. Ferm S, Fisher C, Pakala T, Tong M, Shah D, Schwarzbaum D, et al. Analysis of Gastrointestinal and Hepatic Manifestations of SARS-CoV-2 Infection in 892 Patients in Queens, NY. Clin Gastroenterol Hepatol. 2020;18:2378-2379.e1.
12. Stokes EK, Zambrano LD, Anderson KN, Marder EP, Raz KM, El Burai Felix S, et al. Coronavirus Disease 2019 Case Surveillance - United States, January 22-May 30, 2020. MMWR Morb Mortal Wkly Rep. 2020;69:759-765.
13. Cheung KS, Hung IFN, Chan PPY, Lung KC, Tso E, Liu R, et al. Gastrointestinal Manifestations of SARS-CoV-2 Infection and Virus Load in Fecal Samples From a Hong Kong Cohort: Systematic Review and Meta-analysis. Gastroenterology. 2020;159:81-95.
14. Leal T, Costa E, Arroja B, Gonçalves R, Alves J. Gastrointestinal manifestations of COVID-19: results from a European centre. Eur J Gastroenterol Hepatol. 2021;33:691-694.
15. Redd WD, Zhou JC, Hathorn KE, McCarty TR, Bazarbashi AN, Thompson CC, et al. Prevalence and Characteristics of Gastrointestinal Symptoms in Patients With Severe Acute Respiratory Syndrome Coronavirus 2 Infection in the United States: A Multicenter Cohort Study. Gastroenterology. 2020;159:765-767.e2.
16. Cao C, Chen M, He L, Xie J, Chen X. Clinical features and outcomes of COVID-19 patients with gastrointestinal symptoms. Crit Care. 2020;24:340.
17. Marjot T, Moon AM, Cook JA, Abd-Elsalam S, Aloman C, Armstrong MJ, et al. Outcomes following SARS-CoV-2 infection in patients with chronic liver disease: An international registry study. J Hepatol. 2021;74:567-577.
18. Kovalic AJ, Satapathy SK, Thuluvath PJ. Prevalence of chronic liver disease in patients with COVID-19 and their clinical outcomes: a systematic review and meta-analysis. Hepatol Int. 2020;14:612-620.
19. Boettler T, Marjot T, Newsome PN, Mondelli MU, Maticic M, Cordero E, et al. Impact of COVID-19 on the care of patients with liver disease: EASL-ESCMID position paper after 6 months of the pandemic. JHEP Rep. 2020;2:100169.
20. Bloom PP, Meyerowitz EA, Reinus Z, Daidone M, Gustafson J, Kim AY, et al. Liver Biochemistries in Hospitalized Patients With COVID-19. Hepatology. 2021;73:890-900.
21. Cai Q, Huang D, Yu H, Zhu Z, Xia Z, Su Y, et al. COVID-19: Abnormal liver function tests. J Hepatol. 2020;73:566-574.
22. Qi X, Liu C, Jiang Z, Gu Y, Zhang G, Shao C, et al. Multicenter analysis of clinical characteristics and outcomes in patients with COVID-19 who develop liver injury. J Hepatol. 2020;73:455-458.
23. Yao XH, Li TY, He ZC, Ping YF, Liu HW, Yu SC, et al. A pathological report of three COVID-19 cases by minimal

invasive autopsies. Zhonghua Bing Li Xue Za Zhi. 2020;49:411-417.

24. Galanopoulos M, Gkeros F, Doukatas A, Karianakis G, Pontas C, Tsoukalas N, et al. COVID-19 pandemic: Pathophysiology and manifestations from the gastrointestinal tract. World J Gastroenterol. 2020;26:4579-4588.
25. De Smet V, Verhulst S, van Grunsven LA. Single cell RNA sequencing analysis did not predict hepatocyte infection by SARS-CoV-2. J Hepatol. 2020;73:993-995.
26. Fan Z, Chen L, Li J, Cheng X, Yang J, Tian C, et al. Clinical Features of COVID-19-Related Liver Functional Abnormality. Clin Gastroenterol Hepatol. 2020;18:1561-1566.
27. Li Y, Xie Z, Lin W, Cai W, Wen C, Guan Y, et al. Efficacy and Safety of Lopinavir/Ritonavir or Arbidol in Adult Patients with Mild/Moderate COVID-19: An Exploratory Randomized Controlled Trial. Med (N Y). 2020;1:105-113.e4.
28. Kim D, Adeniji N, Latt N, Kumar S, Bloom PP, Aby ES, et al. Predictors of Outcomes of COVID-19 in Patients With Chronic Liver Disease: US Multi-center Study. Clin Gastroenterol Hepatol. 2021;19:1469-1479.e19.