Archives of the Balkan Medical Union
vol. 58, no. 3, pp. 264-272
September 2023
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ORIGINAL PAPER

DIGESTIVE MANIFESTATIONS IN PATIENTS WITH COVID-19

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Received 26th June 2023, Accepted 15th Aug 2023
https://doi.org/10.31688/ABMU.2023.58.3.05

Abstract

Introduction. The pandemic severe acute respiratory syndrome coronavirus 2 infection significantly marked our lives and still represents a health problem.
The objectives of this study were to assess the most frequent digestive manifestations (DMs) and laboratory changes that may occur in patients with coronavirus disease 2019 (COVID-19).
Materials and methods. A retrospective and analytical study was conducted between January 1st, 2020, and December 31st, 2022, on 120 patients admitted to the medical department of the Bihor County Emergency Clinical Hospital, Oradea, Romania. The patient's data were collected through archived files, and the information was analyzed in an Excel file.
Results. We enrolled 120 patients (72 men) with COVID-19 and DMs over 3 years. A higher incidence was found in patients from urban area (55%) and in the 6th-7th (58%) decades of life. The most frequent symptom was diarrhea (37%), followed by nausea (29%), vomiting (18%), and abdominal pain (12%). Only 4% presented other gastrointestinal (GI) symptoms such as odynophagia or upper GI bleeding. Regarding liver damage, 25.83% of the patients had high levels of alanine aminotransferase, 20.83% of aspartate aminotransferase, 15.18% of total bilirubin, and 10% of

Résumé

Manifestations digestives chez les patients atteints de COVID-19

Introduction. La maladie à coronavirus 2019 (COVID-19), causée par le coronavirus du syndrome respiratoire aigu sévère 2, a marqué nos vies et reste un problème de santé.
Les objectifs de cette étude étaient d'analyser les manifestations digestives (DM) fréquentes et les alterations des testes de laboratoire chez les patients atteints de COVID-19.
Matériels et méthodes. Étude rétrospective analysant 120 patients hospitalisés de janvier 2020 à décembre 2022 dans un service médical à Hôpital clinique d'urgence du comté de Bihor, Oradea, Roumanie.
Résultats. Nous avons inclus 120 patients (72 hommes) atteints de COVID-19 et de DM, sur 3 ans. Une incidence plus élevée a été observée chez les patients urbains (55%) et dans les 6e-7e décennies de vie (58%). Le symptôme le plus fréquent était la diarrhée (37%), suivie des nausées (29%), des vomissements (18%) et des douleurs abdominales (12%). Seuls 4% présentaient d'autres symptômes gastro-intestinaux tels que l'odynophagie ou des saignements

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gamma-glutamyl transferase. The most common comorbidities were high blood pressure (62.5%), obesity (48.3%), and diabetes (35.83%). Based on computed tomography scans, mild (53%), moderate (39%), and severe (8%) forms of disease were observed. The evolution under treatment was favorable in 81 cases (67%). The patients with isolated DMs had a better evolution than those with associated respiratory symptoms.

Conclusions. COVID-19 remains a significant problem due to its rapid spread and the variety of symptoms. Besides respiratory symptoms, DMs are significant and highly correlated with outcomes in COVID-19 patients.

Keywords: SARS-COV2, COVID-19, gastrointestinal symptoms, digestive abnormalities.

List of abbreviations:

ACE2 – angiotensin-converting enzyme 2
ALT – alanine aminotransferase
AST – aspartate aminotransferase
COVID-19 – coronavirus disease 2019
CT – computed tomography
DMs – digestive manifestations
GGT – gamma-glutamyl transferase
GI – gastrointestinal
IL-1 – interleukin-1
IL-6 – interleukin-6
MCP-1 – monocyte chemoattractant protein-1
R – Statistical Software R Project for Statistical Computing
SARS-CoV-2 – severe acute respiratory syndrome coronavirus 2

gastro-intestinaux supérieurs. Concernant les lésions hépatiques, 25,83% des patients avaient des niveaux élevés d'alanine aminotransférase, 20,83% d'aspartate aminotransférase, 15,18% de bilirubine totale et 10% de gamma-glutamyl transférase. Les comorbidités les plus courantes étaient l'hypertension artérielle (62,5%), l'obésité (48,3%) et le diabète (35,83%). Les scanners de tomodensitométrie ont révélé des formes légères (53%), modérées (39%) et sévères (8%) de la maladie. L'évolution sous traitement était favorable dans 81 cas (67%). Les patients présentant uniquement des DM avaient une meilleure évolution que ceux présentant des symptômes respiratoires associés.

Conclusions. COVID-19 reste un problème majeur avec propagation rapide et symptômes variés. DM, en plus des symptômes respiratoires, sont liées aux résultats chez les patients COVID-19.

Mots-clés: SARS-CoV-2, symptômes gastro-intestinaux, anomalies digestives.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus has rapidly spread globally, causing a significant burden on healthcare systems worldwide. While the primary mode of transmission is through respiratory secretions, recent evidence suggests that the virus can also affect the gastrointestinal tract (GI) in infected individuals, leading to a wide range of digestive manifestations (DMs). The pathophysiological processes of COVID-19 are not completely understood, but variables related to lifestyle and environment may be regarded as risk factors[1].

The virus enters the host cells through the angiotensin-converting enzyme 2 (ACE2) receptor, which is abundantly expressed in many organs, including the respiratory and gastrointestinal tract, liver, and kidneys[2]. SARS-CoV-2 binding to ACE2 induces alteration of the renin-angiotensin axis, which results in down-regulation of ACE2, reduction of angiotensin-(1-7) with anti-inflammatory potential, and increase of angiotensin II, which functions as a pro-inflammatory enzyme[3]. Moreover, the presence of ACE2 receptors in the GI tract raises the possibility that the virus may infect and cause damage to the GI tract, leading to digestive symptoms[4].

Recent studies have reported that up to 50% of COVID-19 patients have experienced some form of digestive symptoms, including diarrhea, nausea, vomiting, and abdominal pain[5–7]. A meta-analysis of 60 studies involving more than 4,000 patients showed that digestive symptoms were present in approximately 17% of patients with COVID-19, with diarrhea being the most common[6]. In addition to digestive symptoms, COVID-19 can also cause liver injury, which has been reported in up to 60% of patients[7].

The intricate underlying mechanisms governing the DMs in COVID-19 patients are still not

completely acknowledged. It has been suggested that the virus can directly infect the GI tract, leading to inflammation, necrosis, and the shedding of virus particles in the feces[8]. Alternatively, the virus may indirectly affect the GI tract by causing systemic inflammation, leading to changes in gut microbiota and release of pro-inflammatory cytokines that may contribute to the development of digestive symptoms[9].

The objective of the study was to investigate the most frequent DMs and primary paraclinical changes that may occur and impact the evolution of the disease in patients with confirmed SARS-CoV-2 infection.

Materials and methods

Study design

This retrospective study was conducted in the Bihor County Emergency Clinical Hospital, Oradea, in the western part of Romania, to compare the clinical features and outcomes of patients with confirmed SARS-CoV-2 infection who presented with digestive symptoms (i.e., the study group) versus those who did not (i.e., the control group). The study group included 120 patients admitted to the hospital between March 2020 and December 2022, all of whom exhibited GI manifestations. The control group consisted of 100 patients who tested positive for SARS-CoV-2 and were admitted to the hospital during the same period. All patients had previously undergone a routine computed tomography (CT) of the thorax. All the clinical files of the patients were carefully studied.

Inclusion criteria

- Confirmed diagnosis of SARS-CoV-2 infection: the diagnosis was established by real-time reverse transcription-polymerase chain reaction testing of respiratory samples.
- Presence of digestive symptoms: patients were included if they exhibited GI manifestations such as abdominal pain, diarrhea, vomiting, nausea, anorexia, etc.
- Availability of admission and discharge records: patients with complete admission and discharge records, including medical history, laboratory findings, and radiological reports, were eligible for inclusion.
- Age ≥ 18 years old.

Exclusion criteria

- Patients with incomplete records, missing essential information, or incomplete laboratory data were excluded from the analysis.
- Patients with a history of GI surgery were excluded from the study as it may have confounded the GI symptoms experienced.
- Female patients who were pregnant at the time of SARS-CoV-2 infection were excluded.
- Unwillingness to participate in the study.

Data collection

Data were collected from admission and discharge records, encompassing medical history, laboratory findings, radiological reports, paraclinical examinations, and specialist consultations.

Statistical analysis

The collected data underwent descriptive statistical analysis to determine the prevalence of digestive symptoms and laboratory results associated with SARS-CoV-2 infection. Categorical variables were presented as frequencies and percentages, while continuous variables were summarized using means and standard deviations. Statistical analysis was performed using the R programming language version 4.2.3[10] utilizing the T-test for continuous variables and the Chi-square test for categorical variables. Significance was determined at a p-value less than 0.05.

Ethical considerations

This study was approved by the Ethics Committee of the hospital (approval no. 36199/11.10.2021) and conducted in accordance with the principles outlined in the Declaration of Helsinki. Patient confidentiality was maintained throughout the study by using de-identified patient information. Written informed consent was obtained from all patients or their legal representatives upon admission to the hospital.

Results

The distribution of cases over the years revealed that there were 48 cases (40%) in 2020, 57 cases (47%) in 2021, and 15 cases (13%) in 2022. The analysis revealed an upward trend in the frequency of cases presenting DMs in 2021 compared to preceding and subsequent years.

The distribution by age group revealed that the highest number of cases (39) was observed in the age group of 60-69 years. The age group of 70-79 years had the next highest number of cases (33), followed by the age group of 80-89 years (21). A lower number of cases were found in the age groups of 50-59 years (9), 40-49 years (8), 30-39 years (5), 41-50 years (7), 18-29 years (3), and 90-99 years (2). These findings suggest that the highest incidence of DMs of COVID-19 occurred among individuals in their sixth and seventh decades of life (Figure 1).

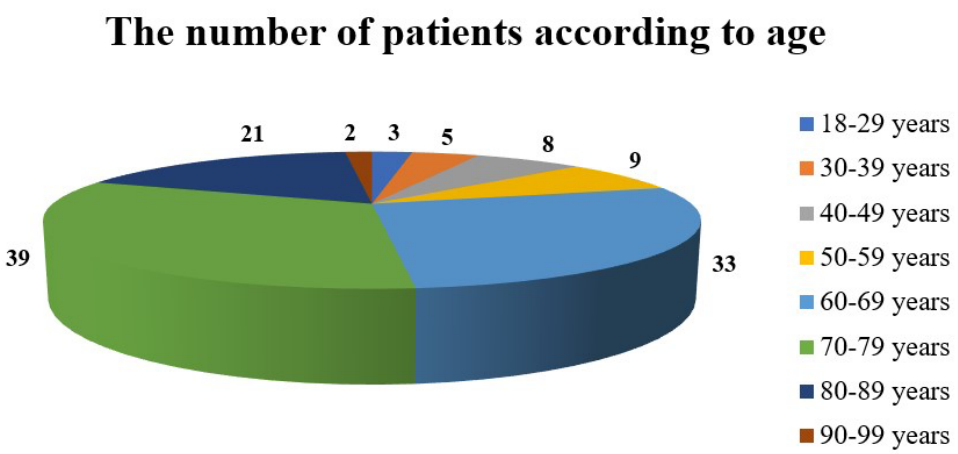


Figure 1. The distribution of patients according to age. Distribution of COVID-19 patients by age groups, highlighting the highest incidence among individuals in their sixth and seventh decades of life.

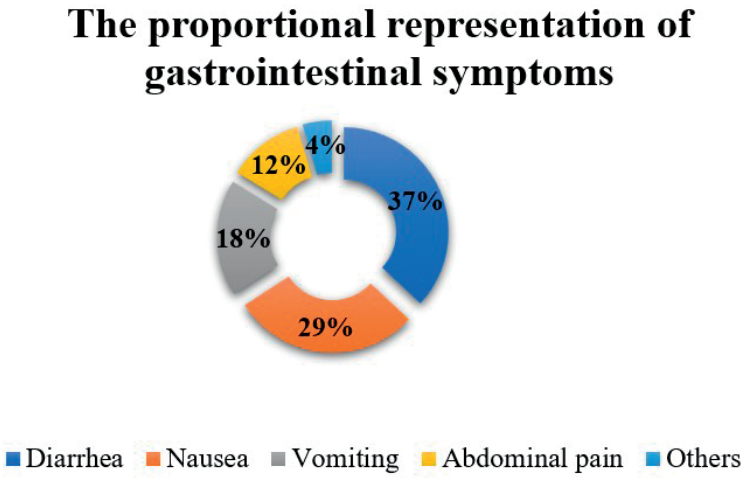


Figure 2. Prevalence of GI symptoms among study participants. Dominant GI symptoms observed in COVID-19 patients include diarrhea, nausea, vomiting, abdominal pain, and infrequent additional manifestations.

The statistical analysis showed no significant difference between the two cohorts in terms of patient age (i.e., the T-test, p = 0.2), confirming their comparability in terms of this demographic characteristic. Furthermore, patients with DMs exhibited a higher mean age across all levels of disease severity. However, a statistically significant difference (i.e., the T-test, p<0.001) was observed only in the case of severe disease when compared to the control group.

The analysis of case incidence stratified by sex demonstrated a perceptible increase in the number of cases among males, with a total of 72 cases, corresponding to 60% of the total study population.

Regarding the area of residence distribution, 64 patients were identified as originating from urban areas, while 56 patients came from rural habitats. The data revealed a slightly higher incidence of cases in urban areas, which can be attributed to the typical lifestyle of socio-economically developed regions with denser human clusters, thereby increasing the risk of infection. There were no statistically significant differences in the source of origin between the cohorts (i.e., the Chi-square test, p = 0.6).

Smoking was identified as a major risk factor, contributing to the development of numerous pathologies. In our study, there were 8 active smokers, 34 individuals with a history of smoking, 70 non-smokers, and 8 who did not provide a response regarding their smoking status. Regarding alcohol consumption, out of the 120 patients analyzed, 10 reported regular alcohol consumption, 6 had consumed it in the past, 90 had only consumed it occasionally in very small quantities, and 14 did not provide a response. No direct correlation was observed between the patients' alcohol and smoking consumption behaviors and the presence of DMs in this cohort of patients.

The most common GI symptoms were diarrhea (37% of patients; n = 41), nausea (29%; n = 32); vomiting (18%; n = 20); and abdominal pain (12%; n=13) (Figure 2). A small proportion of patients (4%)

Table 1. Comorbidities of patients included in the study.

Coexisting medical condition	*Number of patients*	*Percentage ratio (%)*
Obesity	58	48.3%
Diabetes mellitus	43	35.83%
Arterial hypertension	75	62.5%
Cardio-vascular disease	26	21.66%
Respiratory disease	25	20.83%
Cancer	7	5.83%
Compromised immune status	15	12.5%
Gastro-intestinal disease	5	4.16%
Pancreato-biliary disease	3	2.5%
Chronic liver disease	4	3.33%

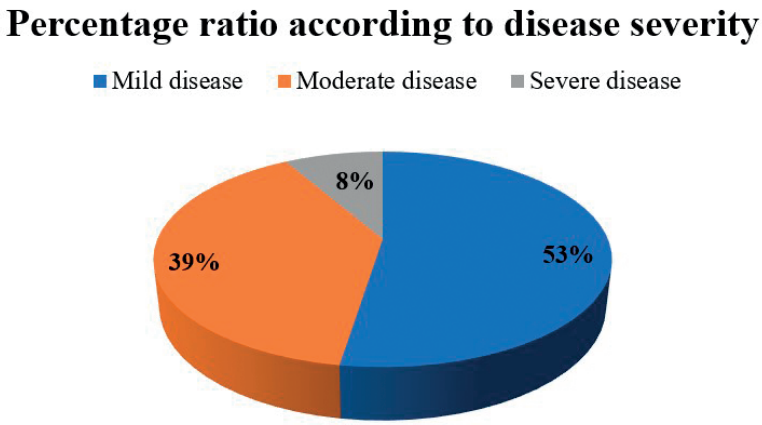


Figure 3. Disease severity breakdown. A significant portion of patients exhibited a mild disease severity, with a subsequent substantial fraction classified as moderate, while a minority displayed a severe disease phenotype.

exhibited additional GI manifestations, including dysphagia, odynophagia, melena, hematochezia, and hematemesis.

The prevalence of comorbidities reached its peak during the 6th, 7th, and 8th decades of life. A noteworthy proportion of patients exhibited a multifaceted comorbidity profile, frequently manifesting with two, three, or even four concurrent medical conditions. Among the most prevalent comorbidities identified in this group of patients there were arterial hypertension (62.5%), obesity (48.3%), and diabetes mellitus (35.83%). Other common comorbidities identified included cardiovascular and respiratory diseases (20.83%), compromised immune status (12.5%), malignancies (5.83%), as well as GI (4.16%), pancreato-biliary (2.5%), and chronic liver disorders (3.33%). The statistical analysis revealed a significant association between obesity and an increased frequency of DMs ($p<0.0001$), implying that individuals with obesity are more likely to present with such symptoms (Table 1).

Considering the severity of SARS-CoV-2 infection, as evidenced by the CT findings, it was observed that the majority of the patients presenting with GI symptoms in the analyzed cohort had mild disease (i.e., 63 patients, accounting for 53% of the total), followed by moderate disease (i.e., 47 patients, accounting for 39% of the total), while severe cases were observed in 10 patients (i.e., accounting for 8% of the total number of patients analyzed) (Figure 3).

The statistical analysis revealed a significant difference between the two groups, indicating that the presence of DMs was associated with a reduced likelihood of severe disease progression in comparison to individuals without such symptoms (i.e., the Chi-square test, $p<0.0001$).

Regarding the hepatic function of these patients, the paraclinical alterations in the observation records were scrutinized, with particular emphasis on the aminotransferases, alanine aminotransferase (ALT) and aspartate aminotransferase (AST), total bilirubin, and gamma-glutamyl transferase (GGT). The analysis detected an elevation in the levels of hepatic enzymes, 31 (25.83%) patients presented with elevated levels of ALT, 25 (20.83%) of the subjects had increased levels of AST, 19 (15.83%) individuals showed an increase

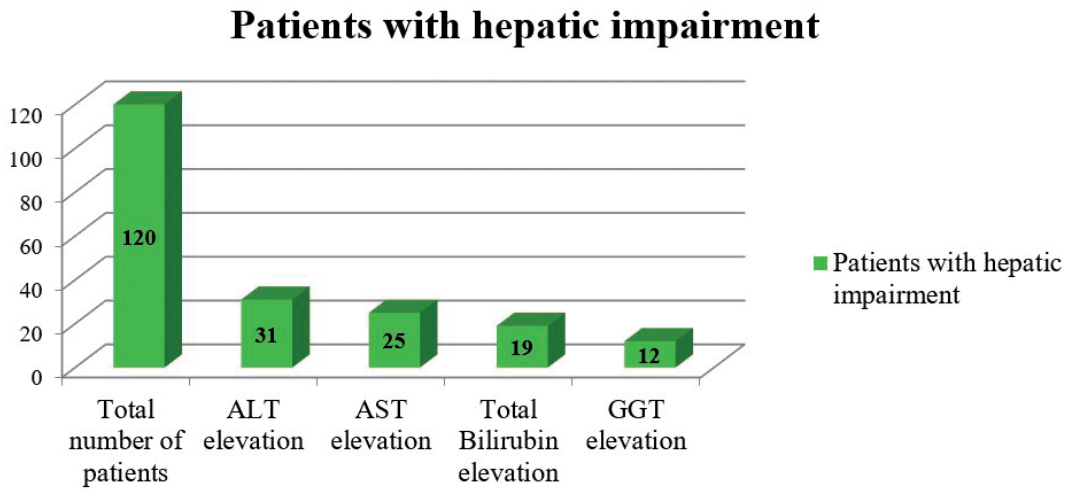


Figure 4. Distribution profile of patients with hepatic impairment**.** COVID-19 patients with digestive symptoms exhibit hepatocellular injury, characterized by elevated levels of alanine aminotransferase, aspartate aminotransferase, bilirubin, and gamma-glutamyl transferase.
Legend. ALT – Alanine aminotransferase; AST – Aspartate aminotransferase; GGT – Gamma-glutamyl transferase.

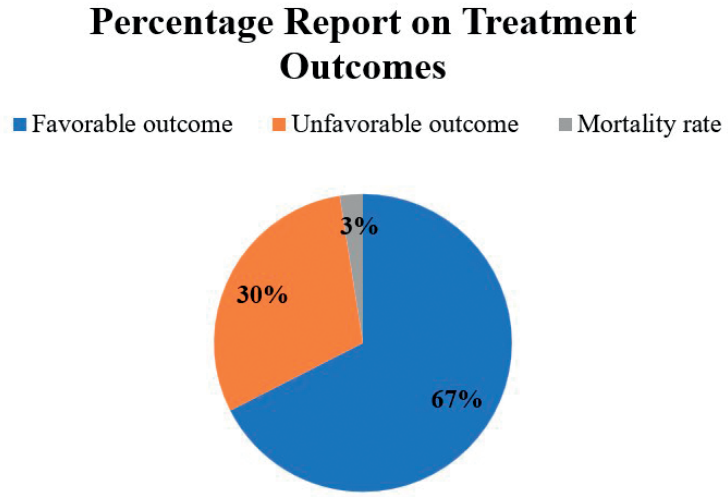


Figure 5. Percentage-based report on treatment outcomes**.** Most patients exhibited favorable course with stable discharge, a subset experienced unfavorable progression, and overall low mortality rate observed.

in the total bilirubin value, and 12 (10%) patients displayed high levels of GGT (Figure 4).

No statistically significant differences in aminotransferases values were observed between the control and test groups, indicating their comparability in terms of this specific biochemical marker (i.e., the Chi-square test, p=0.54).

Patient outcomes were monitored, revealing that a significant proportion (67%) experienced a favorable course of illness, leading to their discharge without any additional pathologies. Conversely, a smaller subset of patients (30%) exhibited an unfavorable progression of illness, requiring extended hospitalization and worsening of pre-existing conditions. The study's findings indicate a low mortality rate (3%) among included patients (Figure 5).

The main characteristics of the patients in our study are summarized in Table 2, providing a comprehensive overview of their key attributes.

Discussion

Because of the complex pathophysiological mechanisms of COVID-19, patients with chronic GI disease may be at greater risk of developing serious health conditions. In addition, there is evidence that the occurrence of DMs may be a predictor of an increased risk of developing respiratory issues[11].

A retrospective study in Wuhan, China, involving 651 COVID-19 patients, reported GI symptoms in 15.8% of cases[12]. Similarly, an Italian retrospective study found that at least one GI symptom was present

Table 2. The main characteristics of patients included in the study.

Variables	*COVID-19 patients with DM*				*COVID-19 patients without DM*			
Age (mean)	*66.41*				*63.75*			
Gender, n (%)	*F= 48(40%)*		*M=72(60%)*		*F=51(51%)*		*M=49(49%)*	
Env, n (%)	U=64(53.33%)		R=56(46.67%)		U=58(58%)		R=42(42%)	
Relevant comorbidities, n (%)	DM=43 (35.83%)	HBP=75 (62.5%)	OB=58 (48.3%)		DM=33 (33%)	HBP=55 (55%)	OB=9 (9%)	
Severity, n (%)	Mild=63 (53%)	Moderate=47 (39%)	Severe=10 (8%)		Mild=40 (40%)	Moderate=18 (18%)	Severe=42 (42%)	
Liver impairment, n (%)	AST=25 (20.83%)	ALT=31 (25.83%)	GGT=12 (10%)	BI=19 (15.83)	AST=50 (50%)	ALT=47 (47%)	GGT=20 (20%)	BI=16 (16%)
Outcome, n (%)	Fav=80 (67%)	Unfav=36 (30%)	D=4 (3%)		Fav=45 (45%)	Unfav=21 (21%)	D=34 (34%)	

Abbreviations: ALT – alanine transaminase; AST – aspartate aminotransferase; BI – indirect bilirubin; D – death; DM – diabetes mellitus; Env – environment; F – female; Fav – favorable; GGT – gamma-glutamyl transferase; HBP – high blood pressure; M – male; OB – obesity; R – rural; U – urban; Unfav – unfavorable.

in 34% of patients[13]. Another retrospective study conducted in New York City revealed GI symptoms in 36.6% of COVID-19 patients[14]. These findings highlight the variation in the prevalence of GI symptoms across different populations and regions, emphasizing the need for further research to elucidate the epidemiology and pathophysiology of DMs in COVID-19 patients.

Our findings demonstrate a heightened prevalence of DMs among COVID-19 patients, with a particular emphasis on the elderly population, specifically those in their sixth and seventh decades of life. These observations align with a recent study conducted by Huang et al.[15], which reported a higher incidence of digestive symptoms in patients infected with SARS-CoV-2 virus in 2021 compared to previous years, particularly among older individuals, further supporting our findings.

In terms of gender-based differences, our results showed a higher prevalence of digestive symptoms in male patients, which is consistent with the study by Mao et al.[5] and also in line with some previous studies that have reported a male predominance in COVID-19 patients with GI symptoms[4,16]. However, the study by Huang et al.[15] reported no significant difference in the incidence of these symptoms between male and female patients. Further research is needed to better understand the underlying reasons for this gender difference in COVID-19-related DM.

In our study, we found that diarrhea was the most frequent GI symptom (37%), followed by nausea (29%), vomiting (18%), and abdominal pain (12%). These findings were consistent with previous studies that reported GI symptoms as common manifestations of COVID-19[8,12] and further emphasized the importance of considering DMs in the evaluation and management of COVID-19 patients. A study conducted on GI symptoms in COVID-19 reviewed 15 articles and found that the frequency of GI symptoms varied from 3% to 39.6%[17]. Like other viral infections, COVID-19 exhibited diverse clinical manifestations. Diarrhea was consistently reported as the most common symptom across all the reviewed articles, and our findings were consistent with this trend, with 41 patients (37%) in our study also exhibiting this symptom[17]. Another study found a heightened frequency of diarrhea in patients who were admitted to intensive care units. Furthermore, this study documented that 10% of patients reported experiencing nausea, 4% vomiting, and 2% abdominal pain[18].

The present study's findings on the prevalence of digestive symptoms in COVID-19 patients suggest a potential correlation between diarrhea and the underlying mechanism associated with rapid T cell activation by SARS-CoV-2. Rapid T cell activation by SARS-CoV-2 triggers the release of inflammatory cytokines, such as interleukin-1 (IL-1), interleukin-6 (IL-6), granulocyte-macrophage colony-stimulating factor, monocyte chemoattractant protein-1 (MCP-1), and interferon gamma, initiating an inflammatory cascade and tissue damage[19]. ACE2-expressing cells produce pro-inflammatory cytokines including tumour necrosis factor-alpha, MCP-1, IL-6, IL-1, and tumour growth factor, contributing to the inflammatory response[20]. Reduced ACE2 expression in the colon in murine models leads to increased susceptibility to inflammation and colitis, potentially due to decreased antimicrobial peptides and alterations in gut microbiota, resulting in diarrhea[21]. Further investigations are necessary to confirm the applicability of these mechanisms in humans.

Our results also revealed that liver damage was present in some patients, as evidenced by increased levels of aminotransferases, total bilirubin, and GGT. This finding is consistent with previous studies that have reported liver damage in COVID-19 patients[7,22]. However, one of the studies found no significant association between liver damage and digestive symptoms[15]. Another study aimed to systematically compare the results of laboratory tests between COVID-19 patients who exhibited GI symptoms and those who did not. Specifically, the focus was on ALT and AST, two biomarkers widely used to monitor liver function. ALT, which is mainly distributed in hepatocytes, serves as an indicator of hepatocellular integrity, while AST, which is predominantly present in the mitochondria of hepatocytes, reflects mitochondrial dysfunction. The authors observed significantly elevated levels of ALT in patients with GI symptoms, suggesting a potential SARS-CoV-2-mediated injury to the liver[20].

Furthermore, a meta-analysis of 14 studies showed a trend towards increased levels of total bilirubin in the GI group, though statistical significance was not achieved. These results imply that COVID-19 patients with GI symptoms are at greater risk of hepatic injury and may require closer monitoring of liver function. In the context of hepatic impairment, ACE2 plays a crucial role in the mechanism of the virus's pathogenesis and propagation. Our study supports this notion by demonstrating that liver damage was present in some patients, as indicated by elevated levels of aminotransferases, total bilirubin, and GGT. ACE2 expression in the cholangiocytes of the liver suggests that the virus may directly affect liver cells, leading to hepatic impairment. These findings highlight the importance of ACE2-mediated viral attachment and entry in the liver, which can result in alterations in corresponding laboratory indices[23].

The medication for COVID-19 may also be the cause of a variety of dysfunctions. GI manifestations, alterations in kidney functioning, allergic reactions, and blood dyscrasias are the most frequently reported side effects of lopinavir/ritonavir administration in COVID-19 patients, according to a retrospective study[24].

It is important to acknowledge certain limitations in our study, which encompass selection bias from the retrospective design, potentially excluding asymptomatic or mildly symptomatic cases, and limited generalization due to the single healthcare system used. While our results are consistent with previous studies, further research is needed to fully understand the mechanisms underlying these symptoms and their potential long-term effects.

Conclusions

This study provides valuable insights into the prevalence, characteristics, and management of digestive symptoms in individuals infected with SARS-CoV-2 in our geographical area. The findings emphasize the crucial importance of promptly recognizing and addressing these symptoms, particularly in vulnerable populations such as the elderly. Additionally, the study brings attention to the broader effects of COVID-19, emphasizing the presence of liver damage among certain individuals. These insights have implications for clinical decision-making and improving patient outcomes.

Author Contributions:

Conceptualization, C.M.M. and O.C.F.; methodology, C.M.M. and E.C.P.; software, C.H. and S.D.M.; validation, A.I.M and O.C.F..; formal analysis, C.M.M. and I.L.P.; investigation, C.M.M. and S.D.M..; resources, O.C.F.; data curation C.M.M and C.H.; writing–original draft preparation, C.M.M. and E.C.P; writing–review and editing, C.M.M and E.C.P; visualization, I.L.P. and A.I.M.; supervision, O.C.F.; project administration, C.J. and C.D.P.

All the authors have read and agreed with the final version of the article.

Compliance with Ethics Requirements:

"The authors declare no conflict of interest regarding this article"

"This study was approved by the Ethics Committee of the hospital and was conducted in accordance with the principles outlined in the Declaration of Helsinki. Patient confidentiality was maintained throughout the study by using de-identified patient information. Written informed consent was obtained from all patients or their legal representatives upon admission to the hospital"

"There was no funding for this study".

Acknowledgements:

Our gratitude extends to Professor Dr. Habil Fratila Ovidiu, our supervisor, for his invaluable guidance and unwavering support throughout the research process, shaping the direction and focus of our study. We extend our sincere appreciation to Dr. Ilea Codrin for his invaluable contributions in conducting the statistical analysis for this study.

References

1. Negru PA, Radu AF, Vesa CM, et al. Therapeutic dilemmas in addressing SARS-CoV-2 infection: Favipiravir versus Remdesivir. *Biomedicine & Pharmacotherapy* 2022;147:112700.

2. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 2020;181(2):271-280.
3. Al-Kuraishy HM, Al-Gareeb AI, Gabriela Bungau S, Radu AF, El-Saber Batiha G. The potential molecular implications of adiponectin in the evolution of SARS-CoV-2: Inbuilt tendency. *Journal of King Saud University – Science* 2022;34(8):102347.
4. Cheung KS, Hung IFN, Chan PPY, 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(1):81–95.
5. Mao R, Qiu Y, He J-S, et al. Manifestations and prognosis of gastrointestinal and liver involvement in patients with COVID-19: a systematic review and meta-analysis. *The Lancet Gastroenterology and Hepatology* 2020;5(7):667–678.
6. Sultan S, Altayar O, Siddique SM, 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(1):320–334.
7. Zhang C, Shi L, Wang F-S. Liver injury in COVID-19: management and challenges. *The Lancet Gastroenterology and Hepatology* 2020;5(5):428–430.
8. Xiao F, Tang M, Zheng X, Liu Y, Li X, Shan H. Evidence for gastrointestinal infection of SARS-CoV-2. *Gastroenterology* 2020;158(6):1831–1833.
9. Gu S, Chen Y, Wu Z, et al. Alterations of the gut microbiota in patients with coronavirus disease 2019 or H1N1 influenza. *Clinical Infectious Diseases* 2020;71(10):2669–2678.
10. The R Project for Statistical Computing. https://www.r-project.org/ (Accessed on March 3, 2023).
11. Fitero A, Bungau SG, Tit DM, et al. Comorbidities, associated diseases, and risk assessment in COVID-19—a systematic review. *International Journal of Clinical Practice* 2022;2022:1–24.
12. Pan L, Mu M, Yang P, et al. Clinical characteristics of COVID-19 patients with digestive symptoms in Hubei, China: a descriptive, cross-sectional, multicenter study. *The American Journal of Gastroenterology* 2020;115(5):766–773.
13. Norsa L, Indriolo A, Sansotta N, Cosimo P, Greco S, D'Antiga L. Uneventful course in patients with inflammatory bowel disease during the severe acute respiratory syndrome coronavirus 2 outbreak in Northern Italy. *Gastroenterology* 2020;159(1):371–372.
14. Hajifathalian K, Krisko T, Mehta A, et al. Gastrointestinal and hepatic manifestations of 2019 novel coronavirus disease in a large cohort of infected patients from New York: clinical implications. *Gastroenterology* 2020;159(3):1137–1140.
15. Huang L, Shi Y, Gong B, Jiang L, Liu M, Yang J. Digestive system involvement in COVID-19: a retrospective study of 214 cases. *Scientific Reports* 2022;12(1):1316.
16. Nasr A, Mahmoud AB, Salah S, et al. Prevalence and impact of gastrointestinal symptoms in COVID-19 patients: a multicenter study in Egypt. *The American Journal of Gastroenterology* 2020;115(12):2058–2065.
17. Schmulson M, Dávalos MF, Berumen J. Beware: Gastrointestinal symptoms can be a manifestation of COVID-19. *Mexican Journal of Gastroenterology* 2020;85(3):282–287.
18. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA* 2020;323(11):1061–1069.
19. Zhang Y, Geng X, Tan Y, et al. New understanding of the damage of SARS-CoV-2 infection outside the respiratory system. *Biomedicine & Pharmacotherapy* 2020;127:110195.
20. Wong SH, Lui RN, Sung JJ. Covid-19 and the digestive system. *Journal of Gastroenterology and Hepatology* 2020;35(5):744–748.
21. Yu W, Ou X, Liu X, et al. ACE2 contributes to the maintenance of mouse epithelial barrier function. *Biochemical and Biophysical Research Communications* 2020;533(4):1276–1282.
22. Cai Q, Huang D, Ou P, et al. COVID-19 in a designated infectious diseases hospital outside Hubei Province, China. *Allergy* 2020;75(7):1742–1752.
23. Zhao R, Shi J, Song Y, Zhang R. Comparison of laboratory characteristics of gastrointestinal symptoms and nongastrointestinal symptoms in patients infected with COVID-19: a systematic review and meta-analysis. *Therapeutic Advances in Gastroenterology* 2022;15:17562848221116264.
24. Negrut N, Codrean A, Hodisan I, et al. Efficiency of antiviral treatment in COVID-19. *Experimental and Therapeutic Medicine* 2021;21(6):648.