Original paper

Gastrointestinal symptoms in patients with coronavirus disease 2019 (COVID-19) – friend or foe?

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Abstract

Introduction: Gastrointestinal (GI) symptoms can be considered as a manifestation of coronavirus disease 2019 (COVID-19).

Aim: Our study analysed GI symptoms depending on their occurrence, and their possible causes and impact on the course of COVID-19.

Material and methods: A retrospective, single-centre assessment of the frequency, risk factors, and impact of GI symptoms in 441 patients with COVID-19.

Results: A statistically significant reduction in the length of stay (LOS) (15 days vs. 17 days; $p = 0.04$), intensive care unit admission (ICU) (16.9% vs. 26.8%; $p = 0.02$), and need for mechanical ventilation (14.1% vs. 23.4%; $p = 0.02$) in the group who had experienced GI symptoms before hospitalization was noticed. For comparison, patients who developed GI symptoms during hospitalization had statistically significantly longer LOS (21 days vs. 15 days; $p = 0.0001$), were more frequently admitted to the ICU (38.1% vs. 18.6%; $p = 0.0003$), and had a higher need for mechanical ventilation (32.7% vs. 16.2%; $p < 0.001$). Risk factors for GI symptoms during hospitalization in COVID-19 patients included age, *Clostridioides difficile* infection, and receiving certain treatment (antibiotics and lopinavir + ritonavir).

Conclusions: The GI symptoms that developed before admission to hospital correlated with reduced severity of the course of COVID-19. However, in the group of patients who developed GI symptoms during hospitalization, attention should be paid to concomitant treatment. The use of antibiotics should be limited because they are associated with the deterioration of the course of COVID-19; one of the reasons might be changes in the intestinal microbiome.

Introduction

The most common symptoms of the coronavirus disease 2019 (COVID-19) are fever (83–99%), cough (59–82%), and fatigue (44–70%) [1–3]. However, gastrointestinal (GI) symptoms such as nausea, vomiting, diarrhoea, lack of appetite, and abdominal pain are also important features of COVID-19 [4, 5]. The most common is diarrhoea (13%), followed by nausea or vomiting (10%), and abdominal pain [6, 7].

There are many theories regarding the pathogenesis of GI symptoms during COVID-19, which include: affinity of SARS-CoV-2 for the angiotensin-converting enzyme 2 (ACE2) receptor, disturbances in the intestinal microbiome, the theory of cytokine storm, and drug-related complications.

The relationship with the presentation of GI symptoms can be explained by the fact that SARS-CoV-2 has a high affinity for the ACE2 receptor (a significant amount of which is found in the cells of the gastrointestinal tract), and perhaps that is why the genetic material of the virus is present in the stool of COVID-19 patients [7–9]. It was found that the genetic material of SARS-CoV-2 present in the cells of the gastrointestinal epithelium causes impairment of its function or even destruction, which may manifest itself in GI symptoms,

such as diarrhoea [10]. GI symptoms also occurred in the course of the acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV) [11–13]. Finally, the presence of SARS-CoV-2 in human enterocytes was confirmed in *in-vitro* studies, which seems to confirm the above hypothesis [14].

A particular association between GI symptoms with high levels of Interleukin (IL) 6 (IL-6), IL-8, and IL-10 has been reported in patients with poor prognosis, who were admitted to the ICU due to respiratory failure [15–18]. The significantly increased concentration of pro-inflammatory cytokines such as IL-1, IL-6, IL-18, tumor necrosis factor-α (TNF-α), and interferon, which takes place in the "cytokine storm", causes the mobilization of some cells of the immune system. The action of neutrophils, macrophages, and T lymphocytes results in the destruction of the vascular barrier and hence the destruction of the epithelium in the gastrointestinal tract and other organs such as the lungs. Because of time, the whole process leads to multi-organ failure.

Another hypothesis of the occurrence of GI symptoms concerns disturbances of the gut microbiome. In the work of Zuo *et al.* COVID-19 patients showed significant variations in the composition of the gut microbiome, characterized by an increase in opportunistic pathogens and a decrease in the number of beneficial commensals during hospitalization. This probably contributes to an increase in the permeability of the intestinal barrier, generates inflammation, and leads to damage to the epithelium in the gastrointestinal tract, which causes GI symptoms such as abdominal pain and diarrhoea. The number of *Coprobacillus, Clostridium ramosum*, and *Clostridium hathewayi* at the beginning of hospitalization correlated with the severity of COVID-19. On the other hand, *Alistipes onderdonkii, Faecalibacterium prausnitzii, Bacteroides dorei, Bacteroides thetaiotaomicron, Bacteroides massiliensis*, and *Bacteroides ovatus* were the main bacterial species showing a negative correlation with the intensity of COVID-19. In addition, downregulation of ACE2 expression in the intestine of mice showed a significant inverse correlation with the faecal SARS-CoV-2 viraemia in COVID-19 patients [19].

There is no specific antiviral treatment recommended for COVID-19. Therapy is mainly symptomatic, and oxygen is the first step in managing respiratory distress. During the first wave of the pandemic, chloroquine, hydroxychloroquine, and lopinavir + ritonavir were used in COVID-19 treatment. Inflammation inhibitors like tocilizumab, bamlanivimab + etesevimab, casirivimab + imsevimab also appear to be effective [20]. The use of glucocorticosteroids and anticoagulants gained importance after publication of the RECOVERY trial [21, 22]. Moreover, the treatment of bacterial coinfections in the course of COVID-19 involves antibiotics, which were often used in over 70% of patients [23]. The extensive use of antibiotics is a risk factor for the occurrence of *Clostridioides difficile* infection (CDI) [24]. Due to the high use of antibiotics in COVID-19, an increased incidence of CDI has been observed [25].

The impact of GI symptoms in COVID-19 patients on their prognosis is not clearly defined. Currently available data are basically contradictory; GI symptoms may correlate with deterioration or improved patient's prognosis [26–28]. There are no studies available that analyse the prognosis of COVID-19 patients and factors depending on the time of GI symptoms.

On 16 March 2020, the Central Clinical Hospital of the Ministry of Interior and Administration in Warsaw was transformed into a place only for the care of patients with COVID-19. As many as 57.8% of patients presented with GI symptoms, which was an extremely large number compared to other studies. Due to their frequent occurrence, we decided to perform an analysis of those symptoms depending on the time of their presentation, i.e. before admission to hospital and during hospitalization.

Aim

We analysed retrospectively the frequency of gastrointestinal symptoms in the group that presented with these symptoms before admission and during the stay. Both groups were screened for the course of the disease, including length of stay (LOS), need for intensive care unit (ICU) admission, need for mechanical ventilation, and mortality. We analysed potential risk factors for their occurrence, such as drugs used during COVID-19 or CDI.

Material and methods

We conducted a retrospective analysis of risk factors and the impact of gastrointestinal symptoms on a cohort of 441 patients with confirmed SARS-CoV-2 infection, who were hospitalized between 16 March and 15 June 2020 at the Central Clinical Hospital of the Ministry of the Interior and Administration in Warsaw. Patients enrolled in the study were 18 years of age or older. The cohort was divided into 2 groups: patients who had developed GI symptoms before admission and patients who developed GI symptoms during hospitalization. GI symptoms were recorded based on patients' interviews. Glucocorticosteroid use was not analysed because it was introduced into guidelines on the treatment of COVID-19 in Poland after the studied period.

We included all hospitalized patients over the aforementioned period; no patient was excluded from the study.

The main purpose of the article was to assess the incidence, risk factors, and effect of GI symptoms on the course of COVID-19 depending on the time of symptom onset (before and during hospitalization).

Statistical analysis

Statistical analysis was conducted with the use of Statistica software, version 13.0 (https://www.statsoft.pl/). Nominal variables were presented as *n* (% frequency of group), while continuous variables as mean (SD) or median (Q1; Q3), depending on the normality of data distribution. Data normality was verified using the Shapiro-Wilk test and based on visual assessment of histograms. Groups were compared with χ^2 test for dichotomous variables and with *t*-test or Mann-Whitney *U* test for continuous variables, as appropriate. All tests were 2-sided, with $p = 0.05$ considered significant.

Bioethical considerations

The study protocol was approved by the Bioethics Committee of the Central Clinical Hospital of the Ministry of the Interior and Administration in Warsaw. The researchers analysed anonymized data.

Results

A total of 441 hospitalized patients with COVID-19 were included. Among them, 255 (57.8%) presented GI symptoms. The most common symptom was lack of appetite, which was reported in 124 (48.6%) cases. Other GI symptoms like diarrhoea were observed in 109 (42.7%), abdominal pain in 95 (37.3%), vomiting in 37 (14.5%), and nausea in 32 (12.5%) cases. The distribution of sex was similar in both groups: 49.4% females in the group with GI symptoms (cases) vs. 48.4% in the group without GI symptoms (controls); $p = 0.083$. Patients were significantly older: 68.44 years vs. 64.45 years in controls; $p = 0.02$ and had significantly more comorbidities: 91.0% vs. 82.3%; $p = 0.007$, respectively (Tables I and II).

Table I. Prevalence of individual GI symptoms in the COVID-19 patients (cases); general population (*n* = 441)

Parameter	*N* (%)
Gastrointestinal symptoms:	255 (57.8)
Abdominal pain	95 (37.3)
Diarrhoea	109 (42.7)
Nausea	32 (12.5)
Vomiting	37 (14.5)
Lack of appetite	124 (48.6)
No gastrointestinal symptoms	186 (42.2)

The cohort was divided into 2 groups: 142 (32.2%) patients who had developed GI symptoms before admission and 113 (25.62%) patients who developed GI symptoms during hospitalization (Table III).

In the group of 142 (32.2%) patients who had developed GI symptoms prior to admission to hospital vs.

Table II. Study cohort, presence of GI symptoms, and risk analysis

Characteristics	All (*n* = 441)	No abdominal symptoms (*n* = 186)	Abdominal symptoms (*n* = 255)	*P*-value
Sex, female, *n* (%)	216 (49.0)	90 (48.4)	126 (49.4)	0.83
Age [years] mean (SD)	66.76 (18.4)	64.45 (20.48)	68.44 (16.62)	0.02
Hospitalization [days] median (Q1; Q3)	18 (10.00; 24.00)	15.00 (9.00; 22.00)	17.00 (10.00; 25.00)	0.1
Comorbid diseases, *n* (%)	385 (87.3)	153 (82.3)	232 (91.0)	0.007
Need for mechanical ventilation, *n* (%)	90 (20.4)	33 (17.7)	57 (22.4)	0.24
Stay in the ICU, *n* (%)	104 (23.6)	37 (19.9)	67 (26.3)	0.11
Mortality, *n* (%)	148 (33.6)	49 (26.3)	99 (38.8)	0.006
CDI, *n* (%)	48 (10.9)	6 (3.2)	42 (16.5)	< 0.001
PPI use, *n* (%)	197 (44.7)	66 (35.5)	131 (51.3)	< 0.001
Any antibiotic used, *n* (%)	354 (80.3)	133 (71.5)	221 (86.7)	< 0.001
Azithromycin use, *n* (%)	214 (48.5)	83 (44.6)	131 (51.4)	0.16
Other antibiotic than azithromycin used, *n* (%)	300 (68.0)	111 (59.7)	189 (74.1)	0.001
Chloroquine use, *n* (%)	321 (72.8)	132 (71.0)	189 (74.1)	0.46
Lopinavir and ritonavir use, *n* (%)	60 (13.6)	19 (10.2)	41 (9.3)	0.08

Table III. Onset of abdominal symptoms before hospitalizations vs. no abdominal symptoms

Characteristic	All (*n* = 441)	Start of abdominal symptoms before hospitalization (*n* = 142)	No abdominal symptoms before hospitalization (*n* = 299)	*P*-value
Sex, female, *n* (%)	216 (49.0)	69 (48.6)	147 (49.2)	0.91
Age [years] mean (SD)	66.76 (18.4)	67.13 (17.6)	66.58 (18.84)	0.77
Comorbid disease, *n* (%)	385 (87.3)	129 (90.8)	256 (85.6)	0.12
Hospitalization [days] median (Q1; Q3)	18 (10.00; 24.00)	15.00 (10:00; 20.00)	17.00 (10.00; 25.00)	0.04
ICU stay, *n* (%)	104 (23.6)	24 (16.9)	80 (26.8)	0.02
Need for mechanical ventilation, *n* (%)	90 (20.4)	20 (14.1)	70 (23.4)	0.02
Mortality, *n* (%)	148 (33.6)	53 (37.3)	95 (31.8)	0.24
CDI, *n* (%)	48 (10.9)	17 (12.0)	31 (10.4)	0.61
PPI use, *n* (%)	197 (44.7)	72 (50.7)	125 (41.8)	0.08

Table IV. Group of patients with GI symptoms before admission to hospital vs. no GI symptoms; general population (*n* = 441)

Parameter	*N* (%)
Gastrointestinal symptoms before admission:	151 (34.2)
Abdominal pain	70 (15.9)
Diarrhoea	60 (13.6)
Nausea	10 (2.2)
Vomiting	11 (2.5)
Lack of appetite	84 (19.9)
No gastrointestinal symptoms before admission	290 (65.8)

patients without GI symptoms, we observed a statistically significant reduction in the LOS: 15 days vs. 17 days; $p = 0.04$, a reduction in the frequency of stays in the ICU: 16.9% vs. 26.8%; $p = 0.02$, and a lower need for mechanical ventilation: 14.1% vs. 23.4%; $p = 0.02$, respectively. No statistical significance was noted for mortality among patients with GI symptoms prior to admission to hospital, i.e. 53 (37.3%) vs. asymptomatic groups, i.e. 95 (31.8%); $p = 0.24$. Sex distribution, age, comorbid diseases, proton pump inhibitors (PPI) used, and frequency of CDI were not risk factors for the presentation of GI symptoms before hospitalization (Table III). In the group of patients with GI symptoms before admission to hospital, the most common symptom was lack of appetite in 84 (19.9%), followed by abdominal pain in 70 (15.9%), diarrhoea in 60 (13.6%), vomiting in 11 (2.5%), and nausea in 10 (2.2%) cases (Table IV).

As many as 113 (25.62%) patients who developed GI symptoms during their hospital stay (vs. patients without GI symptoms) had statistically significantly longer LOS, i.e. 21 days vs. 15 days; $p = 0.0001$, more frequent ICU stays, i.e. 38.1% vs. 18.6%; $p = 0.0003$, a higher need for mechanical ventilation, i.e. 32.7% vs. 16.2%; $p < 0.001$, and a more frequent incidence of CDI, i.e. 22.1% vs. 7.0%; $p = 0.0001$, respectively. No statistical significance was noted for mortality among patients with GI symptoms during their stay vs. asymptomatic groups, i.e. 46 (40.1%) vs. 102 (31.1%), respectively; $p = 0.06$. Age, frequency of CDI, and some specific drugs for COVID-19 treatment (any antibiotics, azithromycin, antibiotics other than azithromycin and lopinavir + ritonavir) were risk factors for the presentation of GI symptoms during hospitalization. Sex, comorbid diseases, PPI, and chloroquine use were not risk factors for presenting with GI symptoms during hospitalization (Table V). In the group of patients with GI symptoms during hospitalization, the most common was diarrhoea, present in 49 (11.1%) cases, followed by lack of appetite in 40 (9.1%), vomiting in 26 (5.9%), abdominal pain in 25 (5.7%), and nausea in 22 (5.0%) (Table VI).

Discussion

As a COVID-dedicated hospital with the highest level of reference, we dealt with a group of patients who were in advanced age and had many comorbidities. In the other analysed studies, the cohorts were younger, which makes our analysis much more difficult, because advanced age is an independent deteriorating prognostic factor in COVID-19 [28]. The mean age of our group of patients was 66.76 years, compared to the mean age in the study by Cheung *et al.* at 45.1 years, Livanos *et al.* at 60.5 years, and Pan *et al.* at 52.9 years [6, 28, 29].

Another unfavourable prognostic factor in COVID-19 is the presence of comorbidities [30, 31]. In our study, over 87.3% of patients had at least 1 comorbid disease, which is quite typical for elderly patients. In more than half of the younger cohort from the study of Cheung *et al.*, comorbidities were not analysed, which could be

Table V. Onset of abdominal symptoms during hospitalizations vs. no abdominal symptoms

Characteristics	All (*n* = 441)	Start of abdominal symptoms during hospitalization (*n* = 113)	No abdominal symptoms during hospitalization (*n* = 328)	*P*-value
Sex, female, *n* (%)	216 (49.0)	57 (50.4)	159 (48.5)	0.72
Age [years] mean (SD)	66.76 (18.4)	70 (15.25)	65.61 (19.3)	0.03
Hospitalization [days] median (Q1; Q3)	18 (10.00; 24.00)	21.00 (10.0; 32.00)	15.00 (9.00; 21.25)	0.0001
Need for mechanical ventilation, *n* (%)	90 (20.4)	37 (32.7)	53 (16.2)	< 0.001
ICU stay, *n* (%)	104 (23.6)	43 (38,1)	61 (18.6)	0.0003
Mortality, *n* (%)	148 (33.6)	46 (40.1)	102 (31.1)	0.06
CDI, *n* (%)	48 (10.9)	25 (22.1)	23 (7.0)	0.0001
Comorbid disease, *n* (%)	385 (87.3)	103 (91.2)	282 (86.0)	0.15
PPI use, *n* (%)	197 (44.7)	59 (52.2)	138 (42.1)	0.06
Any antibiotic used, *n* (%)	354 (80.3)	104 (92.0)	250 (76.2)	0.0002
Azithromycin use, *n* (%)	214 (48.5)	68 (60.2)	146 (44.5)	0.004
Other antibiotic used, *n* (%)	300 (68.0)	92 (81.4)	208 (63.4)	0.0004
Chloroquine, *n* (%)	321 (72.8)	90 (79.6)	231 (70.4)	0.06
Lopinavir and ritonavir, *n* (%)	60 (13.6)	24 (21.2)	36 (11.0)	0.006

due to the fact that patients of such a young age were not burdened with typical chronic diseases, e.g. diseases of the cardiovascular and respiratory systems. In other analysed studies, the number of comorbidities was clearly lower. In the study by Livanos *et al.*, only 16.3% of patients had comorbidities, and in the study by Pan *et al.* it was almost half (49.99%) of the cohort [6, 28, 29].

Lack of appetite was the most common GI symptom in our study, which occurred in 124 (48.6%) cases. As a highly non-specific symptom, it was not analysed in the study by Livanos *et al.* or Pan *et al.* Cheung *et al.* also found that anorexia was the most common symptom in the cohort with GI symptoms. It was present in 26.8%, which is almost half the frequency found in our cohort. The evidently greater lack of appetite in our cohort could be associated with a significantly higher age of patients and a greater number of comorbidities [6, 28, 29]. These factors, along with severe COVID-19 course that required hospitalization, could reduce appetite, especially considering the mechanism of inflammation and the so-called "cytokine storm", with a high number of inflammatory mediators inversely correlating with appetite [31].

Diarrhoea, which is defined as more than 3 bowel movements a day, was also a common symptom among COVID-19 patients. Our study found it in 42.7% of patients. A much lower rate of diarrhoea in the Cheun *et al.* study, i.e. 12.5% of patients, may suggest that the symptom was overlooked in the early stages of the pandemic. When the battle against COVID-19 began, doctors focused primarily on fighting acute respiratory failure. This was also cited as a limitation in this work. A similar number of patients with diarrhoea was reported on by Livanos *et al.* (39%) and Pan *et al.* (34%), where the cohort patients were of relatively similar age and had fewer comorbidities [6, 28, 29]. The occurrence of diarrhoea in patients with COVID-19 may be related to the use of the ACE2 receptor by SARS-CoV-2. The entry of SARS-CoV-2 into the host cell is mediated by the interaction between the encapsulated viral spike protein and the host receptor, consisting of ACE2. Mouse models show that the presence of ACE2 alterations is associated with colitis, suggesting that virus activity may cause enzyme modifications, increasing the susceptibility to intestinal inflammation and diarrhoea [32].

Table VI. Group of patients with GI symptoms during hospitalization vs. no GI symptoms; general population (*n* = 441)

Parameter	*N* (%)
Gastrointestinal symptoms during hospitalization	162 (36.7)
Abdominal pain	25 (5.7)
Diarrhoea	49 (11.1)
Nausea	22 (5.0)
Vomiting	26 (5.9)
Lack of appetite	40 (9.1)
No gastrointestinal symptoms before admission	279 (63.3)

Moreover, the aspect of disturbing the intestinal microbiota in the formation of diarrhoea is emphasized. In the publication of Zuo *et al.*, patients with SARS-CoV-2 infection were found to have significant changes in their gut microbiome compared with controls, characterized by enrichment of opportunistic pathogens and depletion of beneficial commensals [19].

Abdominal pain, defined as a non-specific subjective symptom characterized by pain localized in the abdominal cavity, occurred in 37.3% of patients in our study. In a study by Livanos *et al.* abdominal pain was not reported. This symptom was a rare occurrence in the study by Pan *et al.*, being present in 1.9% of patients, but was more frequent, i.e. present in 9.2% of patients, in the study by Cheung *et al.* [6, 28, 29].

Vomiting and nausea are other important, although non-specific gastrointestinal symptoms. In our study, vomiting occurred in 14.5% and nausea in 12.5% of cases. A similar rate of nausea and vomiting, i.e. 10.2%, was found in the study by Cheung *et al.* In the study by Pan *et al.* only vomiting was analysed, with the rate of 3.9%, which was relatively small. A similar rate of vomiting was found in the study by Livanos *et al.*, i.e. 13%, while nausea was found in more than 25% [6, 28, 29].

The results of our study on the occurrence of GI symptoms before hospitalization confirm the conclusions of the study by Livanos *et al.* because it is evident that the presence of GI symptoms before hospitalization correlates with improved course of the disease, particularly shown by shorter LOS, and reduced need for mechanical ventilation or stay in the ICU. In the study by Livanos *et al.*, 47% of patients reported GI symptoms. In our study, GI symptoms occurred much more often, i.e. in 57.8% of the entire cohort. The researchers did not take into consideration symptoms such as abdominal pain and lack of appetite, which may have contributed to the lower incidence of GI symptoms. The presence of diarrhoea (39% vs. 42.7%, respectively) and vomiting (13% vs. 12.5%, respectively) was similar. There was a difference in the incidence of nausea (25% vs. 12.5%, respectively); in the study by Livanos *et al.*, it occurred twice as often. The group presenting the GI symptoms was younger than ours, i.e. 61 years vs. 68.44 years, respectively. The biggest difference between the cohorts was in the distribution of comorbidities. In the study by Livanos *et al.* only 16.3% of patients with GI symptoms had comorbidities, as compared to 91% of patients in our study. It is worth emphasizing that the Central Clinical Hospital of the Ministry of the Interior and Administration in Warsaw had the highest referential degree, so it hospitalized the most difficult cases with the highest number of comorbidities, which required the most specialized care. In the study by Livanos *et al.*, the group with GI symptoms had a significantly lower mortality as compared to the group from our study, i.e. 15.7% vs. 38.8%, respectively. The authors concluded that GI symptoms remain significantly correlated with better COVID-19 outcomes. The lower mortality in their study certainly resulted from the younger age of the patients, and above all from the fact that they had significantly fewer comorbidities. An external validation cohort further confirmed decreased mortality in COVID-19 patients with GI symptoms. In the second validation cohort, the presence of GI symptoms was used to predict reduced disease severity and mortality. During short-term follow-up there was a significantly lower rate of death. The inclusion of 3 independent cohorts totalling 1163 patients enhanced the strength and validity of their findings. Furthermore, their model to predict COVID-19 severity and mortality was improved by the inclusion of GI symptoms suggesting that intestinal parameters should be considered in initial assessments and stratification of COVID-19 patients. These data suggest the potential for tissue-specific response to SARS-CoV-2 and the potential for attenuation of viral pathogenicity by the GI tract. Compared to our study, the 3 cohorts from the Livanos *et al.* study were younger and had fewer comorbidities, which contributed to a significant reduction in the severity of the disease, and thus mortality. It was also emphasized that the attenuation of SARS-CoV-2 by the GI tract could significantly improve the disease course and reduce mortality. The findings from our study are similar for the group who presented with GI symptoms before admission to hospital [28].

On the other hand, our results concerning the occurrence of GI symptoms during hospitalization show an evidently worse course of the disease, defined by prolonged LOS, and increased need for mechanical ventilation and for ICU stay. The presence of those GI symptoms significantly correlates with some drugs used during COVID-19 treatment (antibiotics and lopinavir + ritonavir) and with the frequency of CDI, which is significantly associated with the widespread use of antibiotics [24, 25]

In the study by Pan *et al.*, 204 patients with COVID-19 from 3 hospitals in Hubei were enrolled. The mean age was 52.9 years, which is much lower than in our cohort (68.44 years). As many as 50.5% of their patients had GI symptoms, vs. 57.8% according to our results. Lack of appetite occurred in 78.6% of cases, which was higher than in our cohort (48.6%). Diarrhoea was reported less frequently than in our study, i.e. in 34% vs. 42.7% of cases, respectively. Abdominal pain (1.9% vs. 37.3%, respectively) and vomiting (3.9% vs. 14.5%, respectively) were reported less frequently as compared to our study. The authors excluded the lack of

appetite in analysis, because according to them it was not specific for the GI tract. There were 18.6% of cases with GI symptoms after the lack of appetite was excluded. As compared to our study, the lack of appetite was also the most common symptom. Its exclusion seems justified because the reason for its occurrence may be related to the "cytokine storm", patient's age, or number of comorbidities. In their study, Pan *et al.* analysed contact history, comorbidities (respiratory, digestive, cardiovascular, nervous, endocrine system diseases, and malignant tumour), medical treatment after admission (antibiotic, antifungal, antiviral treatment, glucocorticosteroids, nebulized interferon, and intravenous immunoglobulin), and clinical outcome (duration of hospitalization, stay in the ICU, discharge from hospital, or death). The study group was younger compared to our cohort and had fewer comorbidities. No statistical significance was demonstrated in the GI symptoms group for comorbidities, medical treatment, or clinical outcome. In our study, the outcome of COVID-19 infection varied in both groups, and significant differences were noted in LOS, stay in the ICU, and need for mechanical ventilation. Mortality was higher in our study (38.8%) as compared to the study by Pan *et al.* (18.45%), which could be related to the lower age of their cohort and fewer comorbidities. There was more widespread antibiotic treatment in our group than in the Pan *et al.* study, but they did not analyse the incidence of CDI due to the high rate of antibiotic use [29].

In the meta-analysis by Cheung *et al.*, among 4243 patients with COVID-19 from 6 countries, all GI symptoms (including loss of appetite, nausea and vomiting, diarrhoea, or abdominal pain) were observed in 17.6% of patients, which is much less when compared to our results. Loss of appetite was the most common GI symptom (26.8%), followed by diarrhoea (12.5%), nausea and vomiting (10.2%), and abdominal pain or discomfort (9.2%). The GI symptoms may have been overlooked at the beginning of the outbreak, especially in the study from Wuhan, because China was the first country to develop COVID-19, and this may have contributed to underestimated GI symptoms in previous studies. Cheung *et al.* concluded that patients with GI symptoms had a more severe disease course compared to the asymptomatic group (17.1% vs. 11.8%, respectively). In our study, there were 57.8% of GI symptoms compared to 17.6% in the meta-analysis by Cheung, who admits in his study's limitations that these symptoms may have been underreported in some studies, which may lead to a lower pooled prevalence rate [6].

The strength of our study is a cohort treated in a uniform way from one centre and one geographical region. Another important feature is the analysis of drugs used during hospitalization based on electronic patient charts. Our study has also several limitations. First, the study is retrospective in nature, and risk factors for the severe/critical type of COVID-19 were identified according to patients' data on admission. Second, we did not look for SARS-CoV-2 RNA in stool samples, despite over 50% of viral RNA being detected in the faeces according to another study. Third, we analysed only hospitalized patients; therefore, mostly patients with severe COVID-19 were included in the analysis.

The data published until now on the presentation of GI symptoms in COVID-19 are very interesting. There are many discrepancies concerning their impact on the course of the disease, with most studies showing a negative impact on COVID-19 course and mortality. So far, these studies have not analysed other possible factors related to GI symptoms. Our work confirms GI symptoms as a manifestation of COVID-19. We analysed GI symptoms depending on the time of their onset and tried to elucidate risk factors for the development of GI symptoms during hospitalization. It turned out that antibiotics and lopinavir-ritonavir significantly correlated with symptoms during hospitalization and a worsened course of the disease. We understand that correlation does not mean causation, but we think that the fact that the time of occurrence of GI symptoms correlates with COVID-19 severity requires further research on the mechanisms behind it and can be useful for patient stratification. The fact that certain medications correlate with GI symptoms during hospitalization is also thought- and hypothesis-provoking and requires further elucidation.

Conclusions

The GI symptoms that developed prior to admission to hospital correlate with a reduced severity of the disease course; conversely, GI symptoms that develop during hospitalization correlate with a more sever COVID-19 course. Certainly, more in-depth research is required. However, inclusion of GI symptoms (before and during hospitalization) in disease severity prediction models seems promising. On the other hand, in the group of patients who develop GI symptoms during their stay, attention should be paid to concomitant medication.

Conflict of interest

The authors declare no conflict of interest.

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