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ORIGINAL ARTICLE

Clues from the Pandora's Box: Frequency of Acute Abdominal Symptoms in COVID-19 and Its Association with Inflammatory Markers—a Cross-Sectional Study

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Abstract
Coronavirus disease 2019 (COVID-19) is primarily considered to be a respiratory ailment. Hitherto, abdominal symptoms have been reported with variable frequency in acute COVID-19. The purpose of this study was to estimate the frequency of abdominal symptoms at presentation among patients hospitalised with COVID-19 infection, and to determine their association with disease severity. This was a single-centre cross-sectional observational study conducted at a COVID-19 tertiary care hospital (CTRI/2021/10/037195, registered on 08/10/2021). Consecutive patients hospitalised with acute COVID-19 illness during the study period were included in the study. Their demographic information, abdominal symptoms, comorbidities and category of COVID-19 illness were elicited. All patients had serum inflammatory markers tested on the day of hospitalisation. Among the 685 participants, 214 patients had mild-to-moderate category illness whereas the rest 471 had severe COVID-19 illness. Abdominal complaints were present among 132/685 (18.3%) patients with distension of abdomen (8.03%) being the most common symptom, followed by vomiting (6.72%) and abdominal pain (3.94%). At admission to the hospital, abdominal complaints were commoner among patients with severe disease than in those with mild-to-moderate disease (101/471 vs. 31/214; p=0.029). Abdominal symptoms were associated with a higher neutrophil to lymphocyte ratio (p=0.029). The mortality among COVID-19 patients with abdominal symptoms was higher (9.09 vs. 3.25%; $p = 0.007$). This study demonstrates the spectrum of abdominal symptoms that can be a part of acute COVID-19 at hospitalisation and also highlights their prognostic potential in acute COVID-19 infection.

Keywords COVID-19 severity · Abdominal symptoms · Distension of abdomen · Vomiting · Pain abdomen

Introduction

In the year 2019, the coronavirus disease 2019 (COVID-19) emerged as a pathogen possessing high pathogenicity and transmissibility. This eventually led to the pandemic that has continued to rage on affecting every corner of the globe [1]. COVID-19 illness is chiefly considered to be a respiratory ailment. The primary site of viral attachment and replication is within the respiratory tract epithelial cells. The angiotensin-converting enzyme 2 (ACE2) receptor has been established to be the entry receptor for the virus. This is abundantly expressed on the epithelial cells of the respiratory tract [2]. The mode of transmission is recognised to be primarily via the dispersion of respiratory secretions from infected individuals via droplets and aerosols [3]. The disease is characterised predominantly by respiratory manifestations such as rhinorrhea, cough and breathlessness which may ultimately lead to acute respiratory distress syndrome [4].

Yet, from the outset, extra-pulmonary clinical features have been described among patients infected with COVID-19 including gastrointestinal tract (GIT), ocular, neurological and dermatological manifestations [5–8]. Previous studies on acute COVID-19 have reported abdominal symptoms with variable frequency. Some patients of acute COVID-19 have been seen to present with abdominal complaints in the absence of accompanying respiratory symptoms. Some of the commonly reported bowel symptoms of

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COVID-19 infection include vomiting, anorexia, abdominal pain and diarrhoea. A number of mechanisms have been mooted to explain the occurrence of these abdominal manifestations. The presence of the ACE2 receptors in the epithelial lining of the GIT may facilitate the entry and multiplication of the virus in these sites thereby leading to direct tissue injury. Indeed, the presence of the virus within the gut epithelia has been demonstrated in some studies. Extended viral shedding in the faeces of infected patients has also been reported [5, 9]. In addition, GIT involvement may also be due to CD4+ T cell-mediated inflammation. Hence, these manifestations could occur as part of a systemic immune hyper-response to the virus [10]. Dysfunctional bowel motility may disrupt the composition of the natural gut microbiota which in turn has been proposed to amplify the pro-inflammatory milieu within the GIT [11].

Some authors have postulated that the presence of abdominal complaints may portend a more ominous course in acute COVID-19 illness. A higher rate of developing complications and even higher mortality has been reported in patients with abdominal symptoms in acute COVID-19 infection [12–15]. Some authors have also claimed that the presence of pre-existing GIT disorder is a risk factor for developing COVID-19 disease [16]. On the other hand, other researchers have claimed that abdominal symptoms do not influence the outcomes in COVID-19 illness [17–21]. Nevertheless, all these articles have been based on very limited study population and many of them had a retrospective study design. There is pertinent need for large-scale prospective studies to investigate the association of abdominal symptoms with COVID-19 disease. The establishment of such an association would warrant COVID-19 patients with abdominal symptoms to be encouraged to seek prompt medical attention and be monitored closely for progression of the disease. It would be prudent to increase awareness regarding abdominal symptoms of COVID-19 within the medical fraternity as well as the general public especially during times of large surge in infections. Hitherto, only a handful of articles from India have described the frequency and relevance of abdominal manifestations in COVID-19. The purpose of the current study was to estimate the frequency of abdominal symptoms at presentation among patients hospitalised with COVID-19 infection and to determine their association with the disease severity.

Patients and Methods

Study Design This was a single-centre cross-sectional observational study conducted at a designated COVID-19 tertiary care hospital from the 1st of April to the 31st of July in 2021. The study protocol was reviewed by the scientific committee and approved by the institutional review board (XXXMC/EC/AP-03/07-2021).

Sample Size It had been observed from the hospital records that the presentation with abdominal symptoms was 44% among patients with elevated inflammatory markers. In the present study, expecting similar results, with 95% confidence level and 10% relative precision, the study required a minimum of 489 subjects.

Data Collection All patients above 18 years of age admitted to the during the study period were enrolled after taking written informed consent. All participants of the study had tested positive on reverse transcriptase polymerase chain reaction (rtPCR) testing for severe acute respiratory syndrome corona virus 2 (SARS-Cov2) performed on nasal and oropharyngeal samples. The rtPCR test was performed on all samples at the National Accreditation Board for Laboratories–accredited laboratory attached to the designated COVID hospital. As the first step, the sample was tested for the presence of the open reading frame (ORF) gene, and if this were to be detected, then the final step to detect the envelop (E) gene was run. Those who had both ORF and the E genes detected in their samples were deemed to have SARSCov2 infection and were classified as COVID-19-positive.

Patients excluded from the study were those who:

- had pre-existing long-term abdominal ailments such as peptic ulcer disease, cholelithiasis, nephrolithiasis, chronic pancreatitis, inflammatory bowel disease, irritable bowel syndrome and disorders of malabsorption.
- had received other medications apart from paracetamol for their acute COVID-19 illness prior to admission.
- were pregnant.

Using a predesigned proforma, the details of their demographic information, abdominal symptoms, medical comorbidities and the category of their COVID-19 illness were documented. Diarrhoea was defined as the passage of watery stools at least three times in a 24-h period [22]. This along with the symptoms of nausea, vomiting, abdominal pain, abdominal distension and constipation was self-reported by the participants. Bleeding per rectum was confirmed by digital rectal examination and proctoscopy.

All patients had their room air peripheral oxygen saturation (SpO2) measured at admission using the Omron CMS50N Contec Pulse Oximeter. The patients were divided into the following categories of COVID-19 illness based on the lowest recorded SpO2 values during their hospital stay [23]:

- Mild-moderate: SpO2 $\geq$ 94%

- Severe: SpO2 < 94%

All patients had their serum inflammatory markers, namely neutrophil to lymphocyte ratio (NLR), C reactive proteins (CRP), lactate dehydrogenase (LDH), ferritin and D-dimer levels tested on the day of admission to the hospital. For patients with moderate and severe category of illness, it was ensured to collect this serum sample prior to the administration of corticosteroids. All patients were managed in accordance with the prevailing standards for treatment of COVID-19 infections.

Statistical Analysis Continuous variables were analysed and summarised in terms of mean and standard deviation. Shapiro-Wilk test was used to determine the normality of distribution of quantitative data. Student *T* tests and Mann-Whitney *U* test were used to compare the means for normally distributed and non-normally distributed data. Acute abdominal symptoms were summarised in terms of percentage. Chi-square test of independence was used to find the association of inflammatory markers with acute abdominal symptoms.

Table 1 List and frequency of abdominal symptoms among patients hospitalised with COVID-19 infection

Abdominal manifestations among hospitalised COVID-19 patients $n = 132/685$	Frequency	%
Abdominal distension	55	8.03
Vomiting	46	6.72
Abdominal pain	27	3.94
Diarrhoea	25	3.64
Constipation	8	1.1
Bleeding per rectum	1	0.14

Results

A total of 685 consecutive patients hospitalised with acute COVID-19 illness were included in the study. Male patients made up 426 from this total. The average age of the patients in this study was 51.3 SD18.05 years. A total of 365 of these patients in the study had at least one pre-existing medical comorbid condition. The most common accompanying comorbidity was type 2 diabetes mellitus in 251/685 (36.64%) followed by systemic hypertension in 186/685 patients (27.15%). The distribution of the patients according to the categories of COVID-19 infection severity was as follows—214 patients had mild-to-moderate while the rest 471 had severe illness.

Abdominal complaints were noted to be present among 132/685 (18.3%) patients in the study (Table 1). The most common of these symptoms was distension of abdomen in 55 (8.03%) patients followed by vomiting and abdominal pain as seen in 46 (6.72%) and 27 (3.94%) patients.

The comparison of the baseline characteristics between those with and without abdominal complaints is summarised below (Table 2). The presence of abdominal complaints at admission among patients with severe disease (101/471) was significantly higher than in those with mild-to-moderate (31/214) disease (p=0.029). When the category of COVID-19 illness was compared against each of the individual abdominal symptoms, it was seen that a significantly higher number of patients with severe COVID-19 disease had experienced nausea and vomiting. This was not observed with the other abdominal complaints (Table 3).

The number of deaths among patients with abdominal symptoms was significantly higher than in those without (9.09 vs. 3.25%; $p = 0.007$). On comparing the survivors vs. the non-survivors in the study with respect to abdominal symptoms, it was revealed that a significantly greater proportion of the non-survivors had at least one abdominal complaint (12/30 (40%) vs. 120/655 (18.32%); p=0.007).

Table 2 Comparison of various characteristics between those with and without abdominal symptoms

Parameter	1 ≤ abdominal symptoms $n = 132$	No abdominal symptoms $n = 553$	p value
Age	52.37 SD16.36	51.10 SD18.41	0.437
Male gender	84 (63.64)	342 (61.84)	0.703
1 ≤ comorbidity	71 ()	294 ()	0.897
Type 2 DM	48 (36.71)	203 (36.36)	0.941
Hypertension	40 (30.3)	146 (26.4)	0.361
CAD	2 (1.52)	18 (3.25)	0.250
HRCT severity score at admission	13.66 SD6.30	14.28 SD5.15	0.62
Final severe COVID-19 illness	101 (76.52)	370 (66.91)	**0.029**

Statistically significant p values have been marked in bold.

DM diabetes mellitus, *CAD* coronary artery disease, *SD* standard deviation

Table 3 Comparison of the different categories of COVID-19 illness with respect to abdominal symptoms

Parameter	Mild-to-moderate COVID-19 illness $n = 214$	Severe COVID-19 illness $n = 471$	p value
Abdominal symptoms	31 (14.49)	101 (21.44)	**0.029**
Abdominal distension	18 (8.41)	37 (7.86)	0.804
Vomiting	6 (2.8)	40 (8.49)	**0.003**
Abdominal pain	5 (2.34)	22 (4.67)	0.127
Diarrhoea	5 (2.34)	19 (4.03)	0.245

Statistically significant p values have been marked in bold

Table 4 Comparison of abdominal complaints among survivors vs. non-survivors

Parameters	Survivors $n = 655(\%)$	Non-survivors $n = 30(\%)$	p value
Abdominal symptoms	12 (40)	120 (18.32)	**0.007**
Abdominal distension	4 (13.3)	51 (7.79)	0.312
Vomiting	7 (23.33)	39 (5.95)	**0.002**
Abdominal pain	5 (16.67)	22 (3.26)	**0.004**
Diarrhoea	0 (0)	24 (3.6)	0.139

Statistically significant p values have been marked in bold

Table 5 Comparison of serum prognostic markers of COVID-19 with the severity of COVID-19 illness in the study

Category of COVID-19 Prognostic marker	Mild-to-moderate	Severe	p value
NLR	6.32 SD6.52	8.47 SD8.93	**<0.001**
CRP	12.92 SD25.65	15.00 SD30.68	0.365
LDH	361.17 SD197.11	477.31 SD260.28	**<0.001**
Ferritin	345.53 SD302.30	424.41 SD304.46	**0.003**
D-dimer	0.928 SD1.35	2.61 SD1.93	**0.045**
IL-6	33.42 SD35.06	81.90 SD107.58	**0.014**

Statistically significant p values have been marked in bold.

NLR neutrophil to lymphocyte ratio, *CRP* C reactive protein, *LDH* lactate dehydrogenase, *IL-6* interleukin 6, *SD* standard deviation

On analysing the individual complaints, only nausea and vomiting (23.33 vs. 5.95%; p=0.002) as well as abdominal pain (16.67 vs. 3.26%; p=0.004) were seen to be present in significantly greater numbers among the non-survivors (Table 4).

It was observed that an elevation in all the serum prognostic markers measured at admission except CRP and D-dimer correlated well with the category of COVID-19 illness among the patients in this study (Table 5). The presence of abdominal symptoms also correlated with higher NLR values at admission in the study participants but this was not true for any of the remaining serum prognostic markers of disease severity (Table 6).

Table 6 Comparison of prognostic markers between patients with and without abdominal complaints

Parameters	1 ≤ abdominal symptoms $n = 132$	No abdominal symptoms $n = 553$	p value
NLR	8.06 SD8.78	6.79 SD5.92	**0.029**
CRP	12.33 SD22.2	14.82 SD30.61	0.287
LDH	428.33 SD261.93	445.47 SD245.24	0.526
Ferritin	417.83 SD332.15	394.27 SD299.25	0.482
D-dimer	1.444 SD2.28	2.223 SD17.69	0.185
IL-6	87.01 SD125.30	72.24 SD97.04	0.521

Statistically significant p values have been marked in bold.

NLR neutrophil to lymphocyte ratio, *CRP* C reactive protein, *LDH* lactate dehydrogenase, *IL-6* interleukin 6, *SD* standard deviation

Discussion

The estimated prevalence of abdominal symptoms at presentation among patients getting hospitalised with acute COVID-19 in this study was 18.3%. This is in agreement with some studies including a meta-analysis of 125 articles which found that 20.3% of the 25,252 COVID-19 patients overall had GIT manifestations [12, 13]. The estimates of GIT symptoms in some studies involving COVID-19 patients, such as the ones by Redd WD et al. (61% among 318 patients) and Nobel YR et al. (35% among 278 patients), were higher [20, 21, 23]. Chen R et al. also found that 29.8% of 1113 COVID-19-infected patients in their retrospective study had GIT symptoms at admission to the hospital [18]. The lower rates in the present study may be owing to multiple reasons. This was a prospective study with a greater sample size compared to many of these preceding trials. Unlike many of these previous studies, anorexia was not included as an abdominal symptom since it is a nonspecific feature that accompanies any acute illness. Another reason for the lower prevalence may be due to patients with pre-existing chronic abdominal disorders being excluded from the study. Medications that have been used in pre-hospital treatment of acute COVID-19 such as azithromycin and hydroxychloroquine (HCQ) may also lead to drug-related abdominal complaints, but in this study, such patients were also excluded [24, 25].

The most common abdominal manifestation among the participants in the current study was seen to be abdominal distension (8.03%), followed by vomiting (6.72%),

abdominal pain (3.94%) and diarrhoea (3.64%). This is in contrast to most published studies on abdominal manifestations in COVID-19 where the reported rates of abdominal distension have been far lower [18]. A systematic review of 29 studies based on COVID-19 also reported a 6% (5–9; range 1–19; I^2=87%) combined prevalence of vomiting. A pooled prevalence of 7.8% (95% CI, 7.1–8.5%) of nausea or vomiting was calculated by a review of 26 studies [26]. Some studies have reported abdominal pain and diarrhoea to be the commonest abdominal symptoms of COVID-19 infection [18, 26].

The present study also demonstrated the association between abdominal manifestations and severe COVID-19 illness. Abdominal symptoms correlated well with the NLR which is an early marker of disease severity. When individual manifestations were analysed, only nausea and vomiting were seen to correlate significantly with severe COVID-19 illness. Patients with abdominal symptoms in the study were also seen to have a greater mortality. Again on comparing individual abdominal symptoms among the participants, nausea and vomiting along with abdominal pain were significantly more among the non-survivors. A large retrospective study had also found that the presence of abdominal symptoms were associated with a higher risk of acute respiratory distress syndrome and the need for non-invasive ventilation as well as tracheal intubation in COVID-19 patients [18]. But this was disputed by the findings from another recent meta-analysis that was also based on multiple retrospective studies [17].

This study highlights the prognostic potential of abdominal symptoms in acute COVID-19 infection. The presence of nausea and vomiting as well as abdominal pain should draw greater attention towards such patients, warranting early hospitalisation and closer monitoring. Awareness about these abdominal manifestations should be promulgated especially among the general public. During surges in the infection when the health infrastructure can come under tremendous strain, screening for these abdominal symptoms among patients of COVID-19 can help in early triaging of patients.

Although several mechanisms have been put forward to explain the mechanism behind the abdominal manifestations of COVID-19, the exact pathways remain yet to be elucidated. Stimulation of the central and autonomic nervous systems by direct cytopathic effects as well as cytokine-mediated damage may result in gastrointestinal dysmotility. These may be the reasons behind nausea, vomiting, abdominal pain and constipation in acute COVID-19 infection [27]. There have been reports of acute pancreatitis and hepatitis in COVID-19 which may contribute to abdominal symptoms. The abdominal distension may be a part of dyspepsia as well as constipation that commonly accompany any acute illness. Alteration in the intestinal ACE2 following entry of the virus into the cells may disrupt the synthesis of antimicrobial peptides and also trigger malabsorption that may contribute to diarrhoea [30].

This study had its strengths and limitations. This was a statistically well-powered prospective study that employed vigorous exclusion criteria unlike many of the previous studies on this topic. Since abdominal symptoms were considered only if reported at presentation to the hospital and not if they developed during the hospital stay, this might have been a limitation of the study. In addition, the severity of COVID-19 illness in this study was determined only using clinical parameters and serum inflammatory markers. A computed tomography of thorax could not be performed for all patients to determine the extent of lung involvement and this may also be a drawback of this study.

Conclusion

Despite being a primary respiratory disorder, COVID-19 infection may be characterised by varied abdominal manifestations. The presence of these abdominal manifestations may indicate a greater risk of progression to severe form of COVID-19 disease and warrant closer observation.

Declarations

Conflict of Interest The authors declare no competing interests.

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