

Frequency and Impact of Preadmission Digestive Symptoms on Outcome in Severe COVID-19: A Prospective Observational Cohort Study

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ABSTRACT

Background: Coronavirus disease-2019 (COVID-19) commonly presents with respiratory symptoms. However, symptoms involving the digestive system may be present, significance of which is not well studied in the Indian scenario.

Methods: This prospective observational cohort study included consecutive patients with severe COVID-19 admitted to intensive care unit of our tertiary care hospital from September 9, 2020, to March 14, 2021. We evaluated the frequency of preadmission digestive symptoms and compared the demographic, clinical, laboratory parameters, and organ failure at admission and during intensive care along with mortality between those with and without digestive symptoms. In the digestive group, we sought to find predictors of mortality.

Results: Digestive symptoms were present in 76/234 (32.4%) with severe COVID-19 infection. In comparison to nondigestive group, digestive patients had higher need for noninvasive ventilation (p 0.028), invasive lines (68%, p 0.003), vasopressors (64%, p 0.01), blood product transfusion (21.1%, p <0.001), and heart failure (55.4%, p 0.041). Confounding factors of alcohol abuse, smoking, sedentary lifestyle as a causative agent for heart failure could not be ruled out. Proportional mortality rate is higher in the digestive group (65.8%, p = 0.015). Mortality is multifactorial with preadmission abdominal pathologies (HR 4.3) or central nervous system (CNS)-related comorbidities (HR 2.829), presentation with multiple digestive symptoms (HR 6.9), higher sequential organ failure assessment score (SOFA) score at admission (HR 1.258) and discharge (HR 1.162), and presence of acute kidney injury (AKI) Grade 3 (HR 2.95) as predictors of mortality. After adjusting for all confounders, need for vasopressor was observed to be associated with 11.58 times higher risk of mortality.

Conclusion: Preadmission digestive symptoms may be associated with a turbulent illness with invasive interventions, heart failure, and greater proportional mortality in severe COVID-19. AKI Grade 3 is identified as a preventable risk factor predicting mortality. CTRI/2021/03/032325.

Keywords: Gastrointestinal complications, Intensive care, Mortality prediction, Severe COVID-19.

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STUDY HIGHLIGHTS

In patients with severe coronavirus disease-2019 (COVID-19) needing intensive care, the frequency of preadmission digestive symptoms is 32.47%, with coexistent respiratory symptoms in most. This patient cohort has a more turbulent hospital course with higher invasive interventions, heart failure, and higher proportional mortality. Severe acute kidney injury is a modifiable factor associated with mortality.

INTRODUCTION

Digestive symptoms have been reported with varied frequency (3–79%) in coronavirus disease-2019 (COVID-19) pandemic.^{1,2} Preadmission digestive symptoms in COVID-19 patients who need intensive care are not studied in the Indian scenario. Moreover, impact of preadmission digestive symptoms on critical care course of patients with severe COVID-19 is not clear. We hypothesized that the presence of preadmission digestive symptoms in patients with severe COVID-19 may be associated with a more severe course of illness and poorer outcomes as compared to those without digestive symptoms.

With this research gap, we conducted a study to find frequency of preadmission digestive symptoms in severe COVID-19 patients who need intensive care with comparison of course of illness and outcomes between those with and without digestive symptoms.

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Conflict of interest: None

MATERIALS AND METHODS

Study Design and Subjects

This prospective cohort study was conducted in an academic Institute in Central India after institutional ethical committee

approval (IHEC-LOP/2020/IM0279) with a waiver of informed consent. We included consecutive patients above 18 years admitted to our intensive care unit (ICU) from September 9, 2020, to March 14, 2021, with confirmed COVID-19 with positive RT-PCR of paired nasopharyngeal and throat swab.

Data Collection

Clinical course of each patient was followed from admission until discharge or mortality.

- **Admission:** We noted demographic details, clinical characteristics, vital signs, laboratory investigations, sequential organ failure assessment score (SOFA score) with detailed history within 15 days of COVID-19-positive testing. Digestive system involvement was defined with the presence of at least one symptom out of loss of appetite, nausea, vomiting, diarrhea (loose stools ≥ 3 per day), abdominal pain, abdominal distension, or gastrointestinal bleeding (hematemesis, melena).
- **During course of ICU stay:** An independent observer blinded about initial symptoms recorded the medications (antiviral, diuretics, tissue plasminogen activator, vasopressors, and antiarrhythmics), invasive vascular lines, renal replacement therapy (RRT), noninvasive (NIMV) or invasive mechanical ventilation (IMV) during treatment along with vitals, and investigations on the third, fifth, and last day of ICU. We noted SOFA score on the last day of ICU stay. New organ injury during the treatment was recorded, including shock, arrhythmias, left ventricular failure, neurological complications, thromboembolic complications, acute respiratory distress syndrome (ARDS) by Berlin definition, acute kidney injury (AKI) by acute kidney injury network (AKIN), and acute liver injury (ALI) [alanine aminotransferase (ALT) more than 50 IU/mL], with 5, 10, >10 times rise graded as mild, moderate, and severe, respectively.
- **Final outcome:** We noted the mortality, duration from symptom onset to hospital admission, discharge, or death along with the total length of ICU and hospital stay.

Statistical Analysis

Data were entered, cleaned, and coded in Microsoft excel 2013. Data analysis was done using IBM SPSS version 24. Continuous variables were summarized as mean (SD) when normally distributed and as median (IQR) when nonnormally distributed. Chi-square and Fischer exact tests were used for testing the association between categorical variables. We used unpaired *t*-test/Mann-Whitney for continuous variables based on distribution. Factors predicting the digestive symptom at presentation were analyzed using multivariable logistic regression.

For the purpose of analysis, depending on the presence or absence of digestive symptoms, we categorized the cohort into either digestive or nondigestive groups, respectively. Cox proportional regression analysis was run with time to event as the duration of days from ICU admission to death and event as mortality, and the significant predictors of mortality were outlined. Multivariate Cox regression was applied among the significant predictors from univariable Cox analysis. Among the laboratory parameters and severity scores which turned significant, their respective cutoff parameters were determined using receiver-

operating characteristic (ROC) curve, with area under the curve more than 50% and *p* value <0.05 as significant.

RESULTS

Patients Flow and Baseline Characteristics

A total of 1,338 symptomatic patients were admitted to our tertiary care institute with COVID-19 infection during the study period, of which 234 patients with severe COVID-19 infection who needed intensive care were enrolled in our study. The baseline characteristics of these patients are provided in Table 1. The details of the comorbidities and systemic presentations are outlined in Supplementary Table 1. The median (IQR) duration from symptom onset to ICU admission was 5 (3–7) days. ALI was observed in 72 (30.8%) patients with 62 (26.5%), 8 (3.4%), and 2 (0.9%) patients presenting with mild, moderate, and severe ALI, respectively. Median SOFA score at admission was 4 (IQR 3–5).

Frequency and Clinical Spectrum of Digestive Symptoms

Digestive symptoms were present in 76/234 (32.4%) and absent in 158/234 patients (67.5%) with severe COVID-19 infection admitted to ICU. Only 4/234 (1.7%) patients were presented exclusively with digestive symptoms. The clinical spectrum of digestive symptoms is given in Figure 1. Diarrhea was usually not clinically severe.

Characteristics of Patients with Digestive Symptoms

The average age of the patients with digestive symptoms was 59 (± 12) years and the male to female ratio was 1.8:1. Thirty-one (45.6%) patients were overweight, followed by normal, obese, and underweight categories (Table 1). Comorbidities were present in 67 (88.2%) patients and have been listed in Supplementary Table 1. Dyspnea, fever, and cough were the most common nondigestive symptoms in this group (Table 1).

On application of multivariate regression model to identify predictors of digestive symptoms at admission, males had 3.337 times higher odds of presenting with digestive symptoms. Both low body mass index (BMI) (aOR 0.85, *p* 0.019) and fibrinogen levels (aOR 0.997, *p* 0.034) were more associated with gastrointestinal involvement (Table 2).

Comparison of Digestive and Nondigestive Groups Using Univariate Analysis

At Admission

The univariable analysis of demographic, clinical, laboratory parameters at admission is listed in Table 1. Patients with digestive symptoms had a lower diastolic blood pressure (*p* = 0.037) (Table 1). Fever, cough, and shortness of breath were more common in nondigestive group (Supplementary Table 1). Hepatobiliary diseases were exclusively present in the digestive group (*p* = 0.004). The SOFA score was comparable between digestive and nondigestive groups (*p* = 0.517).

At admission, the digestive group had higher lactate and alkaline phosphatase (*p* values 0.01 and 0.034, respectively) and lower platelet and fibrinogen values (*p* values 0.005 and 0.038, respectively). C-reactive protein (CRP) though higher in the digestive group (139.5 vs 93.5) did not achieve statistical significance (*p* = 0.065).

Table 1: Univariable analysis of clinical, laboratory parameters, and outcomes

	Total	Digestive symptoms present N = 76	Digestive symptoms absent N = 158	p value
Age mean (SD)	57.7 (13.25)	59 (12)	57 (14)	0.218
Gender n (%)				
Male	162 (69.2)	49 (64.5)	113 (71.5)	0.274
Female	72 (30.8)	27 (35.5)	45 (28.5)	
BMI n (%)				
<18.5	12 (5.1)	7 (10)	5 (4)	0.148
18.5–22.9	42 (17.9)	18 (26.5)	24 (19)	
23–27.4	97 (41.5)	31 (45.6)	66 (52.4)	
>27.5	43 (18.4)	12 (17.6)	31 (24.6)	
Comorbidities				
No	38 (16.2)	9 (11.1)	29 (18.4)	0.206
Yes	196 (83.8)	67 (88.2)	121 (81.6)	
Parameters at admission				
<i>Vitals—mean (SD)</i>				
PR	91.4 (19.6)	92 (19)	91 (20)	0.802
SBP	131.4 (20.6)	129 (21)	133 (21)	0.154
DBP	78.7 (13.4)	76 (14)	80 (13)	0.037
RR	29.4 (7.4)	30 (8)	29 (7)	0.764
SOFA median (IQR)	4 (3–5)	3 (3–5)	4 (3–4)	0.517
<i>Blood investigations</i>				
CBC mean (SD)				
Hemoglobin	12.4 (2.31)	12 (2.7)	12.6 (2.1)	0.108
Total leukocyte count	11.3 (5.53)	10.9 (5.5)	11.45 (5.56)	0.481
Platelets	236 (105.1)	207.9 (108.3)	249.46 (101.1)	0.005
<i>Coagulation tests mean (SD)</i>				
INR	1.2 (0.47)	1.3 (0.5)	1.2 (0.5)	0.344
Fibrinogen	566.5 (203.6)	514 (172)	593 (214)	0.038
aPTT	32.54 (13.01)	31.6 (9)	33 (14.6)	0.512
<i>Cytokines test median (IQR)</i>				
D-dimer	1.02 (0.5–1.8)	1.1 (0.6–1.5)	0.9 (0.5–1.9)	0.937
C-reactive protein	107.5 (58.17–194.5)	139.5 (67–200)	93.5 (53–172)	0.065
Neutrophil–lymphocyte ratio	11 (6.8–18.8)	11 (6.8–18.2)	11 (7–18.8)	0.817
<i>Liver function tests median (IQR)</i>				
Total bilirubin	0.65 (0.5–0.9)	0.7 (0.5–1)	0.7 (0.5–0.9)	0.93
Direct bilirubin	0.2 (0.12–0.3)	0.2 (0.1–0.4)	0.2 (0.1–0.3)	0.227
Aspartate aminotransferase	44.85 (29–67.75)	45 (31–66)	43 (29–68)	0.477
Alanine aminotransferase	34 (23–55)	34 (23–56)	34 (23–54)	0.933
Alkaline phosphatase	90.5 (69–123.25)	107 (73–140)	88 (68–119)	0.034
Albumin	3.17 (2.89–3.4)	3.1 (2.8–3.4)	3.2 (2.9–3.4)	0.34
Lactate	1.6 (0.93)	1.9 (1)	1.5 (0.9)	0.01
<i>Kidney function tests</i>				
Urea median (IQR)	46 (29–71)	46 (33–78)	46.5 (28–68)	0.518
Creatinine median (IQR)	0.99 (0.80–1.29)	1 (0.8–1.5)	1 (0.8–1.2)	0.598
Sodium mean (SD)	134 (5.28)	134 (5)	135 (5)	0.51
Potassium mean (SD)	4.2 (0.73)	4.3 (0.7)	4.2 (0.7)	0.712
<i>Organ-specific complications at admission</i>				
Acute liver injury	72 (30.8)	24 (31.6)	48 (30.4)	0.852
<i>Severity of acute liver injury</i>				
Mild	62 (26.5)	20 (26.3)	42 (26.6)	0.944

(Contd...)

Table 1: (Contd...)

	Total	Digestive symptoms present N = 76	Digestive symptoms absent N = 158	p value
Moderate	8 (3.4)	3 (3.9)	5 (3.2)	
Severe	2 (0.9)	1 (1.3)	1 (0.6)	
ARDS				
Mild	53 (22.6)	19 (25)	34 (21.5)	0.747
Moderate	106 (45.3)	35 (46)	71 (44.9)	
Severe	62 (26.5)	17 (22.4)	45 (28.5)	
Absent	13 (5.6)	5 (6.6)	8 (5.1)	
Interventions and therapy during treatment				
Need of antivirals	101 (43.2)	30 (73.2)	71 (75.5)	0.771
Median (IQR) days of oxygen supplementation	7.5 (5–13)	8 (5–15)	7 (5–12)	0.454
Noninvasive ventilation	206 (88)	72 (94.7)	134 (84.8)	0.028
Duration of noninvasive ventilation median (IQR) days	4 (2–6)	5 (3–7)	4 (2–6)	0.160
Invasive mechanical ventilation	131 (55.98%)	35 (46.1%)	96 (60.8%)	0.034
Median (IQR) days of invasive ventilation	5 (3–9)	5 (3–8)	6 (3–9)	0.725
Invasive line	125 (53.4)	51 (68)	74 (47.1)	0.003
Diuretics	71 (30.3)	23 (30.3)	48 (30.4)	0.868
Renal replacement therapy	20 (8.5)	8 (10.7)	12 (7.6)	0.443
Tissue plasminogen activator	28 (12)	8 (14.8)	20 (16.4)	0.792
Need of transfusion n (%)	24 (10.3)	16 (21.1)	8 (5.1)	<0.001
Surgery	10 (4.3)	3 (3.9)	7 (4.4)	0.864
Complications during the course of hospital stay				
Acute kidney injury	105 (44.9)	39 (51.3)	66 (41.8)	0.169
Acute kidney injury network severity grade (n = 105)				
1	67 (28.6)	27 (35.5)	40 (25.3)	0.429
2	15 (6.4)	5 (6.6)	10 (6.3)	
3	23 (9.8)	7 (9.2)	16 (10.1)	
CNS complications	14 (6)	4 (5.3)	10 (96.3)	0.747
Thromboembolic complications	27 (11.5)	8 (10.8)	19 (12)	0.788
Acute liver injury				
Aspartate aminotransferase >50	96 (41)	34 (44.7)	62 (39.2)	0.423
Alanine aminotransferase >50	68 (29.1)	23 (30.3)	45 (28.5)	0.779
Heart failure	105 (44.9)	41 (55.4)	64 (41)	0.041
Arrhythmias n (%)	49 (20.9)	16 (21.3)	33 (20.9)	0.938
Shock	118 (50.4)	37 (48.7)	81 (51.3)	0.711
ARDS at last ICU day				
Mild	31 (13.2)	5 (6.6)	26 (16.5)	0.103
Moderate	60 (25.6)	17 (22)	43 (27.2)	
Severe	50 (21.4)	18 (23.7)	32 (20.3)	
SOFA score at ICU discharge	5 (2–8)	6 (2–9)	4 (2–8)	0.051
Outcome				
Mortality	128 (54.7)	50 (65.8)	78 (49.4)	0.015
Time-based outcomes in hospitalization				
Total ICU stay	8 (5–14)	8 (5–16)	8 (5–13)	0.291
Total hospital stay	12 (7–18)	13 (6.5–18.5)	11 (8–18)	0.893
Symptom onset to ICU admission	5 (3–7)	5 (3–8)	4 (3–7)	0.064
ICU admission to death	3.5 (0–10)	5 (0–10)	1 (0–9)	0.179
ICU admission to hospital discharge	0 (0–10)	0 (0–8)	1 (0–10)	0.876
Symptom onset to discharge/death	15 (11–21)	16 (11–24)	15 (11–21)	0.296

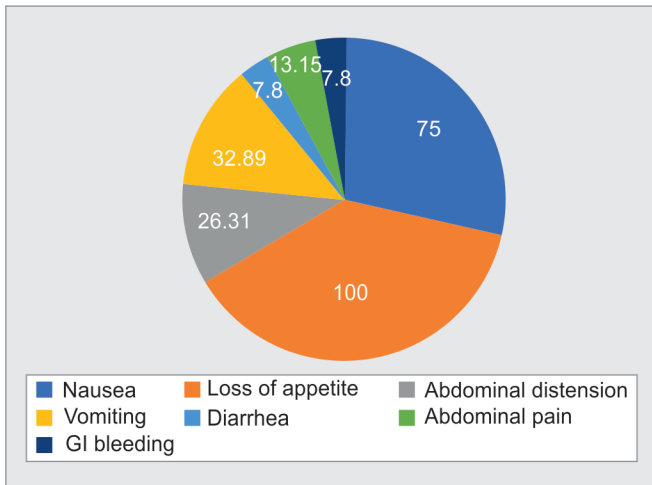


Fig. 1: Digestive symptoms distribution as n (%)

Table 2: Multivariate logistic regression model for identifying predictors of digestive symptom at the time of admission

Variables	Adjustable odd's ratio	p value	95% confidence interval
Age	1.012	0.428	0.977–1.057
Gender	3.337	0.050	0.999–11.153
Male			
Female (Ref)			
BMI	0.850	0.019	0.741–0.973
Presence of comorbidity			
No (ref)	—	—	—
1 comorbidity	2.393	0.374	0.349–16.4
≥2 comorbidity	1.218	0.829	0.204–7.272
At the time of admission			
Platelets	0.998	0.583	0.993–1.004
Total bilirubin	1.235	0.593	0.569–2.682
Aspartate aminotransferase	0.984	0.148	0.964–1.006
Alanine aminotransferase	1.013	0.280	0.990–1.036
C-reactive protein	1.003	0.534	0.998–1.008
Alkaline phosphatase	1.010	0.119	0.997–1.022
Fibrinogen	0.997	0.034	0.995–1.000

Course of Hospital Stay

There was higher need for NIMV in the digestive group ($p = 0.028$) with median duration of 5 days (IQR 3–7). The need for invasive lines (68 vs 47%, $p = 0.003$) and vasopressors (64 vs 45.8%, $p = 0.01$) was more in the digestive group. Nondigestive group had higher need for IMV as expected. Blood product transfusion was higher in the digestive group (21.1 vs 5.1%, $p < 0.001$). More patients with digestive symptoms developed heart failure (55.4 vs 41%, $p = 0.041$). The SOFA score was still statistically higher at ICU discharge with a median value of 6 (IQR 2–9) in digestive group (Table 1).

Supplementary Table 2 provides the changes in the vital signs and laboratory parameters on admission, third, fifth, and last days of ICU. Association was not applied as multiple confounders were present. Digestive group had a higher fall in hemoglobin and albumin levels and a rise in total leukocyte count, neutrophil-lymphocyte ratio (NLR), AST, and ALT during illness. The mean PaO_2/FiO_2 P/F ratio was observed to rise in the nondigestive group.

Outcome

Proportional mortality was higher in digestive as compared to the nondigestive group (65.8 vs 49.4%, $p = 0.015$). The duration of illness from symptom onset to ICU discharge, ICU and hospital stay was similar in both the groups.

Predictors of Mortality in Digestive Group

Table 3 describes the results of Cox proportional hazard used for univariate analysis of predictors of mortality among 76 patients with digestive symptoms. Factors associated with raised risk of mortality were the presence of neurological comorbidity (HR 4.3, $p = 0.02$), hepatobiliary disease (HR 2.89, $p = 0.055$), five preadmission digestive symptoms (HR 6.9, $p = 0.046$), higher SOFA score at admission (HR 1.2) and discharge (HR 1.16), and Grade 3 AKI (HR 2.9) during the treatment. SOFA score of 5.5 at admission predicted mortality with a sensitivity of 36% and specificity of 100% while a SOFA score of 4.5 at discharge predicted mortality with 86% sensitivity and 100% specificity (Fig. 2). The increase in duration of NIMV and IMV was protective against mortality in the digestive group along with duration of ICU and hospital stay.

The need for vasopressor use was associated with 11.53 times increased risk of mortality ($p = 0.016$) on Cox proportional hazard multivariate regression analysis run with all the significant variables from univariate regression along with demographic parameters, number of symptoms at presentation, comorbidities, laboratory tests, organ-specific complications at admission, therapeutic strategies, complications during illness, and days of ICU and hospital stay.

DISCUSSION

To the best of our knowledge, this is the first study from India in patients with severe COVID-19 illness requiring intensive care, which showed the following:

- Digestive symptoms are present in 32.47% of patients with association with male gender, low BMI, and low fibrinogen.
- Digestive group has higher need for invasive lines, vasopressor use, blood transfusion, and noninvasive ventilation; higher incidence of heart failure; and raised mean SOFA score at last ICU day with a higher proportional mortality.
- Mortality in digestive group was multifactorial in digestive group with preadmission abdominal pathologies or central nervous system (CNS) comorbidities, multiple (five or more) digestive symptoms, higher SOFA score at admission and discharge, and severe AKI during illness. There was no significant association with days of respiratory support (NIMV or IMV). On multivariate analysis, the need for vasopressors had 11.53 times higher risk of mortality.

Digestive symptoms in COVID-19 have been reported earlier in the community-based survey or hospitalized inpatients.^{1,3-5} An earlier study in North India done on follow-up of initial COVID-19 diagnosis found that among 44 symptomatic patients with COVID-19, 25% had only gastrointestinal symptoms while combined nongastrointestinal symptom was present in 34.1% of patients.⁶ Though digestive symptoms may seem trivial, they have been noted to be associated with increased severity of illness.⁴ However, the frequency of digestive symptoms in patients with severe COVID-19 is not reported in an Indian context.

Regional variation in the digestive symptoms in COVID-19 is seen with a higher prevalence in North America followed by

Table 3: Univariable analysis of predictors of mortality among patients presenting with digestive symptoms: (Cox regression)

	Survived (n = 26)	Died (n = 50)	Hazard ratio	p value	95% CI
Age mean (SD)	57 (13.7)	60.3 (11.5)	0.989	0.438	0.96–1.02
Gender n (%)					
Male	15 (57.7)	34 (68)	0.886	0.699	0.47–1.64
Female (ref)	11 (42.3)	16 (32)	—	—	—
Body mass index n (%) #					
<18.5 (ref)	2 (8.3)	5 (11.4)	—	—	—
18.5–22.9	7 (29.2)	11 (25)	0.874	0.809	0.29–2.60
23–27.4	10 (41.7)	21 (47.7)	0.525	0.208	0.19–1.43
>27.5	5 (20.8)	7 (15.9)	0.828	0.753	0.26–2.68
Preadmission digestive symptoms					
Only 1 symptom	3 (11.5)	2 (4)	—	—	—
2 symptoms	12 (46.2)	19 (38)	0.955	0.950	0.22–4.14
3 symptoms	9 (34.6)	17 (34)	1.180	0.827	0.27–5.19
4 symptoms	2 (7.7)	9 (18)	1.092	0.911	0.23–5.10
5 symptoms	0	3 (6)	6.953	0.046	1.03–46.8
Comorbidities					
No (ref)	2 (7.7)	7 (14)	—	—	—
Yes	24 (92.3)	43 (86)	0.469	0.075	0.20–1.08
Type of comorbidity					
Diabetes	13 (50)	31 (62)	0.734	0.298	0.41–1.31
Hypertension	13 (50)	31 (62)	0.734	0.298	0.41–1.31
Coronary artery disease	4 (15.4)	5 (10)	0.491	0.179	0.17–1.38
Neurological	2 (7.7)	3 (6)	4.310	0.020	1.26–14.73
Chronic kidney disease	0	5 (10)	1.40	0.479	0.55–3.56
Hepatobiliary	0	4 (8)	2.829	0.055	0.97–8.19
Endocrine	5 (19.2)	5 (10)	0.594	0.328	0.21–1.68
Respiratory	0	6 (12)	1.184	0.701	0.49–2.18
Obstructive sleep apnea	0	1 (2)	2.86	0.310	0.37–21.68
Malignancy	0	2 (4)	3.505	0.093	0.81–15.16
Laboratory parameters at admission					
Hemoglobin	12.8 (11.3–14)	12.2 (10.5–13.5)	0.984	0.750	0.888–1.089
Total leukocyte count	8.96 (6.88–11.38)	9.95 (7.3–13.5)	0.629	1.012	0.965–1.061
Platelets	218.5 (196.5–264)	180 (117–239)	0.999	0.416	0.996–1.002
Aspartate aminotransferase	44 (26–58)	49 (33–84)	1.000	0.508	0.999–1.001
Alanine aminotransferase	28 (23–45)	37.3 (24–65)	1.000	0.477	0.999–1.002
Alkaline phosphatase	98 (72.5–140.5)	108 (76–128)	1.000	0.580	0.998–1.004
Fibrinogen	499 (351–650)	482 (408–584)	1.000	0.998	0.998–1.002
C-reactive protein	111 (76–192)	144 (67–200)	1.001	0.676	0.998–1.004
Lactate	2 (1.2–2.2)	1.8 (1.1–2.5)	1.038	0.815	0.761–1.415
Creatinine	0.9 (0.8–1)	1.1 (0.8–1.5)	1.128	0.427	0.838–1.517
Complications					
Arrhythmias* n (%)					
Absent (ref)	24 (96)	35 (70)	—	—	—



Digestive Symptoms in COVID-19

Present	1 (4)	15 (30)	0.799	0.472	0.43–1.47
Heart failure**					
Absent (ref)	7 (28)	26 (53.1)	—	—	—
Present	18 (72)	23 (46.9)	0.868	0.628	0.49–1.54
Acute liver injury at admission					
Absent (ref)	21 (80.8)	31 (62)	—	—	—
Present	5 (19.2)	19 (28)	0.686	0.205	0.38–1.23
Severity of acute liver injury (n = 72)					
Absent (ref)	21 (80.8)	31 (62)	—	—	—
Mild	5 (19.2)	15 (30)	0.730	0.327	0.39–1.37
Moderate	0	3 (6)	0.442	0.188	0.13–1.49
Severe	0	1 (2)	1.755	0.585	0.23–13.2
Acute respiratory distress syndrome at admission					
Absent (ref)	4 (15.4)	1 (2)	—	—	—
Mild	6 (23.1)	13 (26)	1.46	0.718	0.19–11.33
Moderate	13 (50)	22 (44)	0.98	0.987	0.13–7.38
Severe	3 (11.5)	14 (28)	1.48	0.707	0.19–11.39
Acute respiratory distress syndrome at last day in ICU					
Absent (ref)	2 (7.7)	34 (68)	—	—	—
Mild	4 (15.4)	1 (2)	1.331	0.780	0.18–9.92
Moderate	14 (53.8)	3 (6)	2.166	0.215	0.64–7.35
Severe	6 (23.1)	12 (24)	0.623	0.203	0.30–1.29
AKI during treatment					
Absent (ref)	18 (69.2)	19 (38)	—	—	—
Present	8 (30.8)	31 (62)	1.838	0.052	0.99–3.40
Severity of AKI					
0 (ref)	18 (69.2)	19 (38)	—	—	—
Grade 1	7 (26.9)	20 (40)	1.589	0.173	0.82–3.09
Grade 2	1 (3.8)	4 (8)	2.252	0.156	0.74–6.90
Grade 3	0	7 (14)	2.952	0.020	1.19–7.32
Shock					
Absent (ref)	13 (50)	26 (52)	—	—	—
Present	13 (50)	24 (48)	1.22	0.49	0.69–2.16
CNS complications					
Absent (ref)	26 (100)	46 (92)	—	—	—
Present	0	4 (8)	1.565	0.390	0.56–4.34
Thromboembolic complications					
Absent (ref)	24 (92.3)	46 (92)	—	—	—
Present	2 (7.7)	4 (8)	1.565	0.390	0.56–4.34
Severity–median (IQR)					
SOFA score on admission*	3 (3–4)	4 (3–7)	1.258	<0.001	1.15–1.38
SOFA score on last day in ICU*	2 (2–3)	8 (6–11)	1.162	0.001	1.07–1.27

(Contd...)

Table 3: (Contd...)

	Survived (n = 26)	Died (n = 50)	Hazard ratio	p value	95% CI
Treatment					
Antivirals					
No (ref)	16 (61.5)	33 (66)	—	—	—
Yes	10 (38.5)	17 (34)	0.755	0.365	0.41–1.38
Need of vasopressors n (%)*					
No (ref)	23 (92)	4 (8)	—	—	—
Yes	2 (8)	46 (92)	0.362	0.068	0.12–1.08
Oxygen supplementation and mechanical ventilation					
Median (IQR) days of oxygen supplementation	8 (5–15)	7 (5–15)	0.773	<0.001	0.71–0.841
Noninvasive ventilation					
No (ref)	3 (11.5)	1 (2)	—	—	—
Yes	23 (88.5)	49 (98)	1.631	0.630	0.22–11.94
Median (IQR) days of noninvasive ventilation	3 (3–7)	3 (1–6)	0.808	<0.001	0.73–0.90
Invasive mechanical ventilation duration	6 (4–10)	6 (3–22)	6 (4–8)	0.62	0.92–1.98
Invasive line*					
No (ref)	18 (72)	6 (12)	—	—	—
Yes	7 (28)	44 (88)	0.679	0.383	0.28–1.62
Diuretics*					
No (ref)	20 (76.9)	32 (64)	—	—	—
Yes	5 (19.2)	18 (36)	0.750	0.337	0.42–1.35
Renal replacement therapy*					
No (ref)	25 (100)	42 (84)	—	—	—
Yes	0	8 (16)	1.639	0.209	0.76–3.54
Tissue plasminogen activator					
No (ref)	22 (84.6)	45 (90)	—	—	—
Yes	4 (15.4)	5 (10)	1.771	0.238	0.69–4.57
Need of transfusion n (%)					
No (ref)	24 (92.3)	36 (72)	—	—	—
Yes	2 (7.7)	14 (28)	1.276	0.453	0.68–2.41
Surgery					
No (ref)	26 (100)	47 (94)	—	—	—
Yes	0	3 (6)	1.711	0.375	0.523–5.60
Outcome					
Total ICU stay	9 (6–16)	8 (5–15)	0.235	<0.001	0.15–0.367
Total hospital stay	15 (10–20)	10.5 (6–17)	0.682	<0.001	0.60–0.776

*1 data missing; **2 data missing; ***5 data missing; #8 data missing

Europe and Asia.⁷ Further, non-Chinese patients have a higher frequency of diarrhea, nausea/vomiting, and abdominal pain as compared to Chinese patients.⁸ Cultural differences, dietary habits, innate immunity, and various other factors may influence clinical presentation and extrapolating data from Europe, America, Australia, or China may not be appropriate in the Indian scenario.

Jin et al. reported gastrointestinal symptoms in 22.97% of patients with severe COVID-19 illness.⁹ Ghoshal et al. observed that severe/critical disease was present in 13/44 patients with digestive symptoms.⁶ In our study, both digestive and nondigestive symptoms were present in 30.34% of patients. Frequency of digestive symptoms in our study was higher as compared to the literature from Asia.⁷ This may be attributed to increased



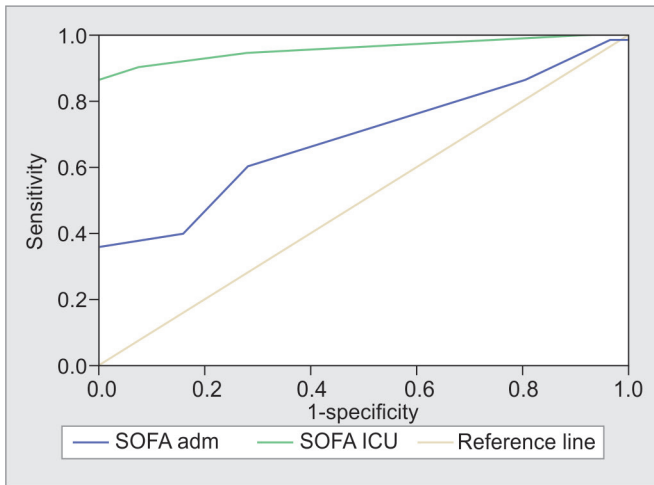


Fig. 2: ROC curve analysis

Table 4: Receiver-operating curve of SOFA score as a predictor of mortality

	Area under the curve	p value	95% confidence interval
SOFA on admission	0.685	0.010	0.57–0.80
SOFA on last day ICU	0.954	0.000	0.91–1.00

awareness of nonrespiratory symptoms and not asking specific history of each digestive symptom. Further, we studied only severe COVID-19 patients, where frequency of digestive symptoms may be higher. High density and virulence of the virus may damage the digestive system.³ As the severity of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) increases, the digestive symptoms are reported to be more pronounced.¹⁰ Digestive symptoms indicate viral load and replication within the gastrointestinal tract, increasing disease severity.³

Pan et al. reported the loss of appetite, diarrhea, vomiting, and abdominal pain in severe illness with frequency of 100, 21.4, 7.14, and 0%, respectively with higher abdominal pain in critical patients (8.70%).³ We noted a similar frequency of loss of appetite (100%), less frequent diarrhea (7.8%) though higher frequency of nausea (75%), vomiting (32.89%), abdominal distension (26.3%), abdominal pain (13.15%), and gastrointestinal bleeding (7.8%) was present. Abdominal pain is associated with increased severity of COVID-19 illness.¹¹ In two patients with nausea, vomiting, loss of appetite, and acute abdominal pain, acute abdomen was diagnosed necessitating emergency laparotomy.

Male gender, low BMI, and low fibrinogen were observed to be predictors of digestive symptoms. Low fibrinogen and low platelet count may reflect a coagulation disorder in severe COVID-19, which can lead to microthrombosis in different organ systems. Loss of intestinal barrier integrity and gut microbes can activate the release of proinflammatory cytokines, leading to systemic inflammation.¹² Gastrointestinal symptoms have previously been associated with younger age and multiple comorbidities.^{13,14}

We did not study the mechanistic pathways for involvement of the digestive system in COVID-19. With the presence of both respiratory and digestive symptoms in 71 patients, the vital cross-talk between lung and gut cannot be overemphasized. Lung–gut

axis is bidirectional as microbial metabolites and endotoxins can modulate the lung through blood and lung inflammation can in turn alter the gut microbiota.³ Angiotensin-converting enzyme-2 (ACE-2) receptors in endothelium and smooth muscle cells of the colon and surface cells of small intestine may serve as an entry pathway for direct cytopathic attack.¹⁵ Further, hypoxemia may exacerbate gastrointestinal mucosal injury, leading to ulceration and bleeding.¹ Secondary damage due to inflammation and hypercoagulation state may further increase cell injury and endotoxemia, causing poor outcomes.¹⁶ New onset symptoms of gastrointestinal tract heralding severe COVID-19 can be part of systemic hyperinflammation seen during the second phase of COVID-19 illness.¹⁷

Frequency of liver injury at admission was 30.8% similar to that reported previously (7.6–39%).¹⁵ Mild liver injury was most frequent (26.5%). The liver may be targeted in COVID-19 by the immune system activation, triggering of a cytokine, besides direct viral attack through portal circulation and drug-induced hepatotoxicity.^{18–21}

Impact of Digestive Symptoms on Course of Hospital Stay

Shorter time from symptom onset to hospital admission (5 vs 4 days) in our study as compared to published literature in COVID-19 (9.0 vs 7.3 days) may be due to increased awareness and subsequent earlier admission.³

In our study, COVID-19 patients with digestive symptoms did not have severe inflammation (D-dimers, NLR) at admission. Similar lower inflammatory biomarkers in patients with gastrointestinal symptoms were present in a retrospective study from China and the United States of America.^{9,18} They hypothesized that lower degree of inflammation may modulate rates of adverse outcomes, but impaired immune response may lead to inability to clear the virus, resulting in prolonged duration of illness. The change in gut microbiota has been associated with changes in the immune system and susceptibility to suffer more severe clinical consequences of COVID-19.¹² So, the digestive group needed more interventions with a higher need for blood transfusion, exploratory laparotomy, and noninvasive ventilation. The mean hemoglobin and albumin tended to decrease over time.

Higher incidence of acute renal insufficiency is reported in COVID-19 patients with gastrointestinal symptoms (9.3 vs 3.1%).²² The incidence of AKI, ALL, and ARDS in our digestive cohort was much higher as compared to published literature.³ This may be attributed to inclusion of only severe COVID-19 illness in our study. Heart failure was indeed higher, though no difference was found in the incidence of any other organ-specific complication as compared to the nondigestive group. Impaired intestinal functional barriers and increased inflammatory cytokine activation may promote cardiac involvement in COVID-19 patients.²³ Endotoxemia, increased gut permeability, and systemic sepsis may have been higher in our digestive patients, though we did not study sepsis-related parameters as they could have multiple contributory confounders.

Gastrointestinal symptoms have been associated with a longer indolent illness with lower mortality (0.0 vs 5%).^{5,14} In contrast to these, we observed a significantly higher mortality in patients with digestive symptoms, though time-based parameters remained similar between the groups. So, while initial inflammatory markers were not significantly raised in the digestive group, course of illness was turbulent with higher proportional mortality rate.

Predictors of Mortality in Digestive Group

In past studies in patients admitted with COVID-19, diarrhea, liver injury at presentation, older age, number of comorbidities, tachypnea, and severe hypoxia have been identified as independent predictors of mortality.^{7,24,25}

We observed a higher risk (aHR 4.3, $p < 0.02$) of mortality in patients with digestive symptoms with chronic neurological disorders than patients presenting with only chronic neurological disease (HR 2.129).²⁶ The presence of multiple digestive symptoms may support the presence of both upper and lower gastrointestinal inflammation with activation of a sepsis-like state.²⁷ We hypothesize that compromised nutritional status, decreased immunity, and predisposition to infection may be responsible for mortality in patients with both digestive symptoms and neurological disorders. Furthermore, patients with hepatobiliary diseases and chronic liver disease are already in a precarious balance, which is easily decompensated in the presence of COVID-19 (aHR 2.829, $p < 0.05$). The presence of severe AKI as a predictor of mortality has been seen in earlier studies in COVID-19 patients also.²⁸

SOFA score is often used for prognostication in critical care patients. In a study exploring effectiveness of SOFA score, a value of 3 was used to predict inhospital mortality in critically ill COVID-19 patients with a sensitivity and specificity of 90.00 and 83.18%, respectively.²⁹ We observed that in nonsurvivors with preadmission digestive symptoms, a SOFA score of 5.5 at admission and 4.5 at discharge was present with a sensitivity of 36 and 86% and specificity of 100%, respectively Table 4.

We found that as the duration of noninvasive or invasive ventilation and ICU or hospital stay increased, there was less association with mortality. This resonates with earlier studies where patients who were discharged alive had longer length of stay than those who died.^{30,31} It is not surprising, as patients who are critical may pass away soon after hospital/ICU admission, automatically leading to a decrease in duration of any intervention or hospital/ICU stay.

As time progresses, patients within the digestive group may be more vulnerable to endotoxemia and subsequent sepsis with the need for vasopressors to maintain perfusion. After adjusting for all confounders, vasopressor use was associated with 11.58 times higher risk of mortality. It is prudent to identify predictors of mortality at admission and during illness for triage, timely intervention, prognostication, and optimum resource allocation in patients with preadmission digestive symptoms with severe COVID-19.

Strength of Our Study

- Our data collection was prospective with specific history of digestive symptoms taken at admission, hence ensuring that no patient was missed.
- We included preadmission digestive symptoms only to negate the influence of polypharmacy, change in diet, and nosocomial infection on the gastrointestinal system.
- Team which collected data during the course of hospital stay and final outcome was blinded to the group allocation of the patient thus removing investigator bias.
- We have holistically studied the clinical parameters, laboratory investigations, organ-specific complications, and invasive interventions in medical course in each patient with and without digestive symptoms in COVID-19.

- We have summarized risk factors of digestive symptoms in severe COVID-19 as well as predictors of mortality found in these patients, which may help in better prognostication, optimization, and resource allocation.

Limitations

- It is a single-center study which may decrease the external validation of our results. However, our institute is the main referral center for patients from Madhya Pradesh and neighboring states. Hence, the results may be generalized to central India till there is availability of more data.
- Since we studied only severe COVID-19 illness needing intensive care, organ-specific complications and overall mortality were more than reported previously.
- We did not study interleukin-6 and serial D-dimers to study the cytokine response due to institutional policy. However, we used NLR, CRP, and fibrinogen to study the same.
- Our study finding of higher incidence of heart failure in COVID-19 associated with digestive symptoms is confined by limitation of difficulty in removing confounders in observational studies of alcohol abuse, smoking, and sedentary lifestyle, though we did assess for age, gender distribution, BMI, comorbidities like hypertension, preexisting coronary artery disease, and diabetes between the survivors and nonsurvivors in the digestive group.

CONCLUSION

This study demonstrates that patients with preadmission digestive symptoms in severe COVID-19 may have less inflammation at admission, but need more invasive interventions with higher incidence of heart failure and proportional mortality rate. Possibility of confounding factors for heart failure exists.

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