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Original Article

Gastrointestinal and Hepatic manifestations of COVID-19 in patients attending tertiary care hospital.

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Abstract:

Introduction: To evaluate the frequency of Gastrointestinal (GI) symptoms and elucidate the association of GI symptoms and hepatic injury markers with the severity of COVID-19 and mortality.

Methodology: Single-centered observational study recruited 160 confirmed COVID-19 positive patients who were admitted in Medical Unit-1/C1 of Civil hospital Karachi, Pakistan from 21 February to 30 April 2021. Data was analyzed using SPSS version 23.0.

Objective: To evaluate the frequency of GI symptoms and elucidate the association of GI and hepatic abnormalities with the severity of COVID-19 and its mortality.

Results: Among 160 patients, 20% presented with digestive symptoms; abdominal pain (33.1%), and nausea (33.1%) being the most common. GI symptoms and liver injury markers notably ALT, AST, and GGT were significantly associated with severity of disease (p value<0.05), ICU admissions (p value<0.01), and poor outcomes (p value<0.01).

Conclusion: COVID-19 infected patients presenting with GI symptoms and liver dysfunction have a worse prognosis and needs to be addressed on urgent basis to avoid complications and reduce mortality.

Key words: Covid-19, Hepatic injury, Gastrointestinal symptoms, Liver dysfunction.

Introduction:

In December 2019, Severe Acute Respiratory Syndrome Corona virus 2 (SARS-CoV2), a single-stranded enveloped RNA virus, belonging to the Family of Coronaviridae, caused an outbreak of corona virus disease (COVID-19) in Wuhan province of China.[1, 2] On 11th-March2020,outbreak was declared as a pandemic by the World Health Organization due to the massive surge in the number of cases globally. According to the WHO report of 23rd April 2021, globally 144,358,956 cases of COVID-19 have been confirmed, while the death toll from COVID-19 has been around 3,066,113.[3] Furthermore, in the UK, India, South Africa, and other regions around the globe new variants of SARS-CoV-2 have been identified.[4]

Even though, the virus targets primarily the lungs and is mainly transmitted through respiratory droplets,[5] its detection in the stool of the first reported COVID-

19 case in the United States, who presented with gastrointestinal (GI) symptoms prior to respiratory symptoms,[6] implicates early GI involvement and a fecal-oral route of transmission. Moreover, the virus can also be detected in saliva, GI tract, and urine.[7, 8] This could be attributed to Angiotens in-Converting Enzyme 2 (ACE2), the main cellular receptor for the SARS-CoV-2 in humans, which is not only expressed in lungs but also the GI tract, and liver cells.[8] Therefore, throughout the disease, besides the typical respiratory symptoms such as fever, sore throat, cough, and shortness of breath, [9, 10, 11] a wide array of GI symptoms predominantly diarrhea, anorexia, nausea, vomiting, epigastric pain, and liver function abnormalities were commonly reported.[8, 12,13,14] A study by Chen et al, revealed that more than one-third of the patients with Covid-19 had deranged liver function tests (LFTs) including elevated Serum Alanine Aminotransferases (ALT) and/or Serum Aspartate Aminotransferases (AST).[15] A study in China observed that 7 out of 28 patients (25%) with raised AST did not require ICU care however, 8 out of 13 patients (68%) requiring ICU care showed elevated AST.[16]Wang et al also observed raised AST in 19 patients (28%) and raised ALT in 23 patients (33%).[17]A study from Pakistan indicated an association between abnormal liver biochemistry with increased ICU admission and poor outcomes.[18]COVID-19 infected patients presenting with GI symptoms and liver dysfunction may have a worse prognosis. Since there is a paucity of data from previous studies, we conducted this study to evaluate the frequency of GI symptoms and elucidate the association of GI and hepatic abnormalities notably elevated AST, ALT and gamma-glutamyl transferase (GGT) with the severity of COVID-19 and its mortality.

Methodology:

This single-centered, prospective observational study was conducted at a COVID-19 treatment center of tertiary care unit in Pakistan from 21stFebruary till 30th April 2021, after approval from the Institutional Review Board.

The sample size was calculated using PASS 2019 software. Keeping the prevalence of hepatic and GI manifestations of COVID-19 as 15%, a sample size of 139 achieves 95.085% power to detect a difference (P1-P0) of 0.1500 using a two-sided exact test with a significance level (alpha) of 0.050. These results assume that the population proportion under the null hypothesis (P0) is 0.5000.

A non-probability convenience sampling technique was used to recruit patients admitted in Medical Unit-1/C1 of Dr. Ruth KM Pfau Civil Hospital Karachi, Pakistan. This study included all consenting adult patients, who were diagnosed by real-time polymerase chain reaction as COVID-19 positive via either nasopharyngeal or oropharyngeal swab. Since the study was aimed at observing the liver enzymes derangements on admission due to COVID-19, and their implications on the course and prognosis of the disease, therefore, patients with a known history of pre-existing chronic liver disease, hepatitis B, and hepatitis C were excluded from the study to eliminate a confounding factor. Moreover, patients who didn't meet the inclusion criteria were also excluded. After detailed history and examination blood samples were sent for complete blood count, urea, creatinine, potassium, arterial blood gases, blood sugar fasting, C-reactive protein, lactic dehydrogenase, ferritin, procalcitonin, liver function test, total protein albumin globulin ratio, Prothrombin Time and International Normalized Ratio (PT/INR). Microsoft Excel database was used to record demographics data, comorbidities (i.e. hypertension, diabetes, chronic obstructive pulmonary disease, and cardiovascular disease), vitals, clinical characteristics constituting both respiratory and digestive symptoms, laboratory data, treatment programs, and outcome measures (i.e. survived and died).

Data was imported into Statistical Package for the Social Sciences (SPSS version 23.0) software from Microsoft Excel for analysis. The Shapiro Wilk test was used to find out the normality of the data. Continuous variables were presented as median with interquartile range whereas categorical variables were presented as frequency and percentages. Moreover, the routine test results were evaluated to check if they were in the normal range. Chi-square test was used to assess the association between digestive symptoms, severity, and mortality. Mann-Whitney U test was used to assess associations between laboratory findings, severity, and mortality. P-value<0.05 considered significant.

Results:

Hundred and sixty hospitalized patients with confirmed COVID-19 infection participated in this study. The majority of them were men (n=107, 66.9%), the median age was 55 (38-65) years and the median oxy-

gen saturation at the time of arrival was 94.5% (93-94.5). Approximately half of the patients had some coexisting disease with hypertension n=65 (40.6%) and diabetes n=62(38.8%) being the most common of them as shown in Table-I. Even though, majority of the patients presented initially with typical COVID-19 symptoms namely fever (85.0%), dyspnea (80.0%), and dry cough (77.5%); a third of the patients presented initially with digestive symptoms, such as abdominal pain (33.1%) and nausea (33.1%). The incidence of GI symptoms amongst patients was 20%.

About one-fourth patients required ICU care (n=43, 26.8%) while approximately one-sixth patients died (n=27, 16.9%). Patients reporting GI symptoms notably abdominal pain, nausea, vomiting, and diarrhea, and elevated ALT, AST, and GGT levels were significantly associated with increased ICU admissions (p-value <0.01) and poorer outcomes (p-value <0.01). Moreover, significantly higher median ALT, AST, and GGT levels were noted in both critical patients and non-survivors (p-value<0.01) as shown in Table-II.Elevated severity markers of COVID-19 were noted in most of the patients however, only around one-fourth of the patients displayed raised neutrophil to lymphocyte ratio (NLR) (n=44, 27.5%). Patients who presented with digestive symptoms displayed significantly raised NLR, CRP, and Procalcitonin levels (p-value<0.05). Additionally, those with liver injury (elevated ALT, AST, and GGT levels) displayed significantly raised NLR, Ferritin, LDH, and Procalcitonin levels (p-value<0.05). Pneumonia (n=116, 72.5%) followed by shock (n=51, 31.9%) were the most commonly noted complications. Symptomatic treatment with multivitamins and antibiotics (n=136, 85%) was received by most isolated patients followed by steroids (n=119, 74.4%) as shown in Table-III.

Discussion:

To our knowledge, this is the first and largest observational study from Pakistan of 160 hospitalized and isolated patients infected with COVID-19 especially those presenting with GI symptoms and hepatic injury. In this study, median age of patients was 55 (38-65) years; mostly men (66.9%); having underlying comorbidity notably hypertension (40.6%) and diabetes (38.8%); and presented initially with typical COVID -19 symptoms notably fever (85.0%), dyspnea (80.0%), and dry cough (77.5%) which is comparable with numerous studies.[9,10,11,16,17,19] However, 20% of the patients presented with gastrointestinal symptoms with abdominal pain (33.1%), and nausea (33.1%) being the most common among them. A finding which is inconsistent with Wang et al. that reported diarrhea and nausea as the most common GI symptoms with an incidence of 10.1% each, while the incidence of abdominal pain was as low as 2.2% .[19] Importantly, 26.9% of the patients in our study required ICU care, while the fatality rate was 16.9%. Digestive symptoms and elevated liver injury markers portend a poor prognosis as they were associated with an increased likelihood of ICU admission and death (p-value<0.05). Moreover, significantly raised severity markers of COVID-19 notably NLR, CRP and Procalcitonin were found in our patients with digestive symptoms (p-value<0.05). This finding is consistent with a meta-analysis that revealed GI symptoms to be associated with the severity of the disease.[20] Additionally, those with elevated ALT, AST, and GGT levels displayed significantly raised NLR, Ferritin, LDH, and Procalcitonin levels (p-value<0.05) which is similar to other studies.[18, 21, 22] This could potentially be due to activation of inflammatory cytokine storm, viral infection in liver cells or pneumonia induced hypoxia.[21]

Pneumonia (72.5%), shock (32.9%), acute hypoxic failure (27.5%), and acute respiratory distress syndrome (27.5%) constituted the major complications in our study sample which is similar to the results of other studies[8, 16, 19] Since supportive care is recommended for COVID-19 infection as no specific treatment is available, most of the patients received antibiotics and multivitamins (85.0%) for covering secondary bacterial infections followed by steroids (74.4%) and Tocilizumab (27.5%) for reducing the pro-inflammatory cytokine storm induced by SARS-CoV2 implicating increased severity of the disease.[23] For critically ill patients(16.3%) CPAP continuous positive airway pressure (CPAP) and mechanical ventilation (10.6%) were used. There are some notable limitations of our study. Firstly, nasopharyngeal or oropharyngeal swabs were taken to confirm COVID-19 diagnosis using RT-PCR rather than stool, urine, or tissue specimens therefore we can't correlate the prevalence of digestive symptoms in other GI samples. Secondly, the viremia in the specimen was not evaluated

so the severity of the GI symptoms couldn't be correlated with viral load in the sample. Thirdly, the efficacy of different supportive treatment options was not assessed in our study which could help in quantifying the best practice management in COVID-19 patients presenting with extra pulmonary manifestations.

Conclusion:

In this single-center case series of 160 laboratory-confirmed COVID-19 positive patients in Karachi, Pakistan, 20% presented initially with GI symptoms, and 26.9% were admitted to the ICU while the mortality rate was 16.9%. The severity and poor outcomes were noticed in patients with digestive symptoms and deranged liver injury markers notably ALT, AST, and GGT therefore, early recognition of GI symptoms and liver injury markers is pivotal in decreasing the severity and mortality due to COVID-19.

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Table I: Baseline characteristics of patients infected with COVID-19 n=160

Variable	n (%)
Age, median (IQR) years	55 (38-65)
Sex	
Female	53 (33.1)
Male	107 (66.9)
Comorbidities	89 (55.6)
Hypertension	65 (40.6)
Cardiovascular disease	42 (26.3)
Diabetes	62 (38.8)
COPD	27 (16.9)
HIV infection	13 (8.1)
Heart rate, median (IQR), bpm	85 (75-95)
Mean arterial pressure, median (IQR), mm Hg	90 (87-100)
PaO_2, median (IQR), mm Hg	78 (68-85)
SpO_2, median (IQR), %	94.5(93-94.5)
$PaCO_2$, median (IQR), mm Hg	35 (30-40)

Table III: Severity markers, complications, and treatment of patients infected with COVID-19 (n=160)

	No. (%)
Severity markers	
Raised NLR	44 (27.5)
Raised Ferritin levels	135 (84.4)
Raised C-Reactive Protein	157 (98.1)
Raised Lactate Dehydrogenase	140 (87.5)
Raised Procalcitonin	131 (81.9)
Complications	
Pneumonia	116 (72.5)
Shock	51 (31.9)
Acute Heart Failure (AHF)	44 (27.5)
Arrhythmia	39 (24.4)
Acute Respiratory Distress Syndrome (ARDS)	44 (27.5)
Treatment	
Antibiotics and Multivitamins	136 (85)
Steroids	119 (74.4)
Biological agent	44 (27.5)
CPAP	26 (16.3)
Mechanical Ventilation	17 (10.6)

Table II: Severity and outcome of patients presenting with GI symptoms and liver injury							
	Total (N=160)	ICU (N=43)	Non-ICU (N=117)	P-value	Survived (N=133)	Died (N=27)	P-value
GI symptoms							
Abdominal pain	53 (33.1)	26 (49.1)	27 (50.9)	0.000	32 (60.4)	21 (39.6)	0.000
Vomiting	46 (28.7)	26 (56.5)	20 (43.5)	0.000	25 (54.3)	21 (45.7)	0.000
Nausea	53 (33.1)	26 (49.1)	27 (50.9)	0.000	32 (60.4)	21 (39.6)	0.000
Diarrhea	41(25.6)	21 (51.2)	20 (48.8)	0.000	23 (56.1)	18 (43.9)	0.000
Liver injury markers							
Elevated ALT	129 (80.6)	43 (33.3)	86 (66.7)	0.000	102 (79.1)	27 (20.9)	0.005
Elevated AST	126 (78.8)	43 (34.1)	83 (65.9)	0.000	99 (78.6)	27 (21.4)	0.003
Elevated GGT	67 (41.7)	28 (41.8)	39 (58.2)	0.000	47 (70.1)	20 (29.2)	0.000
Laboratory findings							
ALT, median (IQR),U/L	80 (55-110)	110 (85-150)	75 (40-87)	0.000	75 (55-98)	150 (90-180)	0.000
AST, median (IQR), U/L	65 (40-95)	95 (65-140)	65 (35-85)	0.000	65 (40-85)	140 (75-170)	0.000
GGT, median (IQR), U/L	55 (40-85)	85 (55-95)	55 (40-60)	0.000	55 (40-65)	90 (55-110)	0.000
Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Gamma-Glutamyl Transferase (GGT)							