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Research Article

Outcome of COVID-19 Patients Presented with Gastrointestinal and Hepatic Manifestations

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Background. COVID-19 is rapidly spreading as a global pandemic disease that affects mortality, morbidity, and economic recession worldwide including Myanmar. This study is aimed at investigating the prevalence and temporal nature of gastrointestinal and hepatic manifestations as well as their association with composite clinical endpoints in patients with COVID-19. *Method*. This was a retrospective hospital-based cohort study conducted on confirmed COVID-19 patients who were admitted to two designated COVID-19 hospitals: DSLH and No. (22/100) MH, Yangon, Myanmar, from June 1, 2021, to August 31, 2021. Data related to patients' demographics, clinical characteristics, and clinical outcomes were abstracted manually through individual hospital records. *Results*. Out of the 241 patients recruited, 68 (28.2%) of the patients had GI symptoms. Ageusia/hypogeusia and diarrhea are the most common symptoms at 41.3% and 28.3%, respectively. Abnormal liver chemistries at admission are found in 52.7% of total patients. Mortality is 12.9% (31/241). Patients with abnormal liver chemistry are older ($p < 0.001$), unvaccinated or incompletely vaccinated ($p = 0.04$), associated comorbidities ($p = 0.019$), leukocytosis ($p < 0.001$), lymphopenia ($p = 0.033$), hypoalbuminemia ($p < 0.001$), higher INR ($p < 0.001$), and longer HDU stay ($p < 0.001$) and higher mortality ($p < 0.001$). *Conclusion*. COVID-19-infected patients with abnormal liver chemistry are found to have worse clinical outcomes, although no significant association is found in patients with digestive symptoms. More attention should be given to this group of patients in the next coming wave.

1. Introduction

Coronavirus disease 2019 (COVID-19) is rapidly spreading as a global pandemic disease that results in mortality, morbidity, and economic recession worldwide [1]. As of March 18, 2022, 464,809,377 cases and 6,062,536 deaths were confirmed globally [2]. In Myanmar, 607,399 cases and 19,418 deaths were confirmed as of March 18, 2022 [3], and third wave of COVID-19 was found to hit Myanmar more aggressively than the first and second waves.

COVID-19 infection produces a wide range of symptoms affecting multiple organ systems with varying severity. Patients can present with nonspecific prodromal symptoms, respiratory symptoms, and even gastrointestinal symptoms. Unfortunately, patients with gastrointestinal symptoms had a longer symptom onset, likely related to delayed diagnosis as these symptoms are nonspecific. Liver derangement is noted more in patients with more severe disease upon presentation. It is difficult to identify the independent effect of the virus from various treatment modalities, including antibiotics and the use of new antiviral drugs. Furthermore, these changes could be nonspecific abnormalities related to infection, sepsis, or hypoxia.

The timing, clinical significance, and possible impact of viral spread on GI symptom presentation have not been fully elucidated. Liver function impairment and other laboratory

values have been reported; however, their prognostic significance has not been established. We hypothesize that patients with COVID-19 with gastrointestinal symptoms or abnormal liver function tests might have a worse clinical outcome than those without these clinical features.

This study is aimed at investigating the prevalence and temporal nature of gastrointestinal and hepatic manifestations as well as their association with composite clinical endpoints in patients with COVID-19. Determining the relationship of patients with gastrointestinal and hepatic manifestations and their development of a specific disease outcomes can be helpful in developing a careful management plan in the future COVID-19 pandemics.

2. Materials and Methods

2.1. Study Design. This was a retrospective cohort study conducted on confirmed COVID-19 patients who were admitted to two designated COVID-19 hospitals: Defence Services Liver Hospital, Mingaladon, and No. (22) Military Hospital (100 bedded), Thanlyin, Yangon, Myanmar. Institutional review board approval was obtained from Defence Services Medical Academy before patient identification and data collection.

2.2. Patients. Adult patients who were admitted with a confirmed diagnosis of COVID-19 with nasopharyngeal polymerase chain reaction testing for SARS-CoV-2 admitted from June 1, 2021, to August 31, 2021, were considered eligible. To ensure an unbiased sample, a consecutive patient collective method was applied at each center. Out of 247 patients, 2 pregnant patients, 3 missing data, and 1 duplicate patient were excluded from the analysis.

2.3. Data Collection. Data related to patients' demographics, vaccination status, comorbidities, clinical symptoms at admission, and which only developed after admission, laboratory investigations, and clinical outcomes were abstracted manually through individual hospital records under the oversight of a designated clinical investigator. For patients who had not been dispositioned at the end of the study period, data were collected within 3 days of study closure.

Demographic variables such as age, sex, BMI, and vaccination status were obtained. Data on preexisting gastrointestinal and liver diseases such as peptic ulcer disease, gastrointestinal malignancy, hepatitis B, hepatitis C, alcohol-related liver disease, metabolic-associated fatty liver disease (MAFLD), and hepatocellular carcinoma and data on other comorbidities such as hypertension, diabetes mellitus, ischemic heart disease, bronchial asthma, chronic obstructive airway disease, chronic kidney disease, pulmonary tuberculosis, and cerebrovascular accident were also obtained. Clinical symptoms were categorized as with or without gastrointestinal symptoms. Furthermore, initial laboratory data such as hemoglobin, total white cell count, lymphocyte count, platelet count, total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, INR, and albumin were also noted. If any laboratory test was not performed at the time of admission, the first laboratory values within 24 hours of admission were recorded.

2.4. Definitions. Gastrointestinal and liver manifestations were divided into gastrointestinal symptoms and liver chemistry abnormalities. The gastrointestinal symptoms of interest in this study were ageusia or hypogeusia, nausea, vomiting, diarrhea (passage of >3 loose stools per day), anorexia, abdominal pain, hematemesis, and melaena. Constipation is not included as it has not been associated with COVID-19. Patterns of liver chemistry test elevations [4] were defined as (1) hepatocellular type: if the hepatocellular-related indices including ALT or AST levels were above ULN, and ALP level was in the normal range; (2) cholestatic type: if ALP levels were increased but with normal AST and ALT levels; (3) mixed type: in the presence of elevation of both ALP and ALT/AST levels; (4) isolated hyperbilirubinemia: elevation of total bilirubin with normal alkaline phosphatase and ALT/AST levels.

2.5. Data Analysis. Descriptive summary statistics are presented as means and SD for continuous variables and frequencies with percentages for categorical variables. Categorical and continuous variables were tested for statistical significance using chi-square test and Student's t-test, respectively. All analyses were conducted using IBM SPSS Software version 24 (SPSS Inc., Armonk, NY, USA).

3. Results

3.1. Demographic and Clinical Characteristics. Demographic and clinical characteristics of the included patients are shown in Table 1. A total of 241 hospitalized patients were collected during the study period. The mean (SD) age of the study population was 53.9 ± 18.3 years. The male to female ratio was nearly 1 : 1 (56.4% vs. 43.6%). The mean BMI of this study was $24.1 \pm 4.4\, kg/m^2$. Thirty-eight study subjects (15.8%) completed COVID-19 vaccination, 4 (1.7%) were partially vaccinated, and 199 (82.6%) subjects were unvaccinated.

3.2. Comorbidities. In the entire cohort, the most frequently observed comorbidities were hypertension and diabetes mellitus (34.9% and 17.8%, respectively). Ischemic heart disease was present in 9.9% of the cases, while 5.8% of the patients had chronic kidney disease, followed by pulmonary tuberculosis (3.7%), cerebrovascular accident (2.9%), bronchial asthma (1.7%), and chronic obstructive pulmonary disease (0.8%).

3.3. Preexisting Gastrointestinal and Liver Diseases. Four (1.7%) patients had a history of benign peptic ulcer while 1 (0.4%) patient had gastrointestinal malignancy. Seven patients (2.9%) had a diagnosis of chronic hepatitis B, but one patient was found to have hepatocellular carcinoma, 2 patients (0.8%) in chronic hepatitis C and alcohol-related liver disease. Only one patient (0.4%) was recorded as metabolic-associated fatty liver disease. None had inflammatory bowel disease (IBD) or liver transplantation.

Table 1: Demographic and clinical characteristics of entire cohort ($N = 241$).

No.	Characteristics	Mean ± SD	*N* (%)
1.	Mean age (years)	53.9 ± 18.3	
2.	Gender (male)		136/241 (56.4)
3.	Mean BMI (kg/m^2)	24.1 ± 4.4	
4.	COVID-19 vaccination status		
	Complete		38/241 (15.8)
	Incomplete		4/241 (1.7)
	None		199/241 (82.6)
5.	Comorbidities		
	Hypertension		84/241 (34.9)
	Diabetes mellitus		43/241 (17.8)
	Ischemic heart disease		24/241 (9.9)
	Chronic kidney disease		14/241 (5.8)
	Pulmonary tuberculosis		9/241 (3.7)
	Cerebrovascular accident		7/241 (2.9)
	Bronchial asthma		4/241 (1.7)
	COPD		2/241 (0.8)
6.	Preexisting gastrointestinal diseases		
	Peptic ulcers		4/241 (1.7)
	GI carcinoma		1/241 (0.4)
7.	Preexisting liver diseases		
	Chronic hepatitis B		7/241 (2.9)
	Chronic hepatitis C		2/241 (0.8)
	Alcohol-related liver disease		2/241 (0.8)
	MAFLD		1/241 (0.4)
	Hepatocellular carcinoma		1/241 (0.4)
8.	Days of disease onset at the time of admission (days)	5.74 ± 4.74	
9.	Gastrointestinal symptoms		
	No gastrointestinal symptom at admission		195/241 (80.9%)
	Gastrointestinal symptoms at admission		46/241 (19.1%)
	Ageusia/hypogeusia		19/46 (41.3)
	Diarrhea		13/46 (28.3)
	Nausea and vomiting		6/46 (13)
	Anorexia		6/46 (13)
	Abdominal pain		1/46 (2.2)
	Melaena		1/46 (2.2)
	Gastrointestinal symptoms after hospitalization		22/241(9.1%)
	Diarrhea		8/22 (36.4)
	Ageusia/hypogeusia		7/22 (31.8)
	Anorexia		4/22 (18.2)
	Nausea and vomiting		2/22 (9.1)
	Abdominal pain		1/22 (4.5)
	Total cases with GI symptoms in the entire cohort		68/241 (28.2%)
10.	Liver chemistries (mean distributions of individual tests)		
	Total bilirubin (mg/dL)	0.79 ± 0.44	
	ALT (U/L)	49.81 ± 50.30	

Table 1: Continued.

No.	Characteristics	Mean ± SD	*N* (%)
	AST (U/L)	57.26 ± 69.47	
	ALP (U/L)	90.68 ± 45.69	
	INR	1.39 ± 0.40	
	Albumin (g/dL)	37.05 ± 4.01	
11.	Liver chemistries (categorical distribution)		
	Normal liver chemistries		114/241 (47.3%)
	Abnormal liver chemistries		127/241 (52.7%)
	Pattern of abnormal liver chemistries		
	(1) Hepatocellular type		89/127 (70.1)
	(2) Cholestatic type		9/127 (7.1)
	(3) Mixed type		28/127 (22)
	(4) Isolated hyperbilirubinemia		1/127 (0.8)
12.	Laboratory parameters		
	WCC ($\times 10^9$/L)		8.77 ± 4.94
	Lymphocyte ($\times 10^9$/L)		1.21 ± 0.85
	Platelet ($\times 10^9$/L)		239.82 ± 11.66
13.	Outcomes		
	Mortality (number of expired cases)		31/241 (12.9)
	Hospital stay (days)	12.2 ± 5.3	
	HDU stay (days)	0.8 ± 1.9	

Data are expressed as mean (SD) or *n* (%). BMI: body mass index; COPD: chronic obstructive pulmonary disease; MAFLD: metabolic-associated liver disease; SD: standard deviation; WCC: white cell count; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; INR: international normalized ratio; HDU: high-dependency units.

3.4. Gastrointestinal Symptoms. Forty-six (19.1%) patients were suffering from gastrointestinal symptoms at the time of admission, and 22 (9.1%) patients developed gastrointestinal symptoms after admission. The proportion of patients with GI symptoms preceding hospitalization was outnumbered than those with GI symptoms reported only after admission. At admission, ageusia/hypogeusia was the most common symptom (41.3%), followed by diarrhea (28.3%), nausea and vomiting (13%), and anorexia (13%). The most common symptoms after hospitalization were diarrhea (36.4%), followed by ageusia/hypogeusia, and anorexia in 31.8% and 18.2%, respectively. In the entire cohort, ageusia/hypogeusia was the most common GI symptom (38.2%).

3.5. Abnormal Liver Function. In the entire cohort, the mean (SD) bilirubin of the study population was $0.79 \pm 0.44\ mg/dL$, ALT was $49.81 \pm 50.30\ U/L$, AST was $57.26 \pm 69.47\ U/L$, ALP was $90.68 \pm 45.69\ U/L$, and INR was 1.39 ± 0.40. The mean albumin of this study participant was $37.05 \pm 4.01\ g/dL$. One hundred and twenty-seven subjects (52.7%) of the study population had abnormal liver chemistry at admission. Hepatocellular type of abnormal liver elevations was the most common pattern which was detected in 89 patients (70.1%), followed by mixed pattern (22%), cholestatic pattern (7.1%), and isolated total hyperbilirubinemia (0.8%).

3.6. Outcomes of the Study. Among COVID-19 patients with gastrointestinal and hepatic manifestations, 31 patients (12.9%) passed away in hospital while the remainder survived and discharged. The mean length of total hospital stay was 12.2 ± 5.3 days and the mean length of HDU stay was 0.8 ± 1.9 days.

3.7. Demographic and Clinical Characteristics Related to Clinical Outcomes. Apart from days of disease onset at the time of admission, there was no statistical difference between patients with gastrointestinal symptoms and patients without gastrointestinal symptoms in terms of demographics, clinical characteristics, and outcomes, as shown in Tables 2 and 3. Patients with abnormal liver chemistry were significantly older (58.04 ± 16.54 years vs. 49.29 ± 19.11 years; $p < 0.001$), associated comorbidities ($p = 0.019$), a smaller number of complete vaccination status (11.8% vs. 20.2%; $p = 0.04$), leukocytosis (10.09 ± 5.49 vs. 7.29 ± 3.73; $p < 0.001$), lymphopenia (1.10 ± 0.93 vs. 1.33 ± 0.73; $p = 0.033$), hypoalbuminemia (35.22 ± 3.57 vs. 39.08 ± 3.47; $p < 0.001$), and higher INR (1.49 ± 0.38 vs. 1.28 ± 0.39; $p < 0.001$), as shown in Table 4. They also have significantly longer duration of HDU stay (1.23 ± 2.28 vs. 0.27 ± 1.31: $p < 0.001$) and higher mortality (27 (21.3%) vs. 4 (3.5%): $p < 0.001$), as shown in Table 5.

Table 2: Association between demographic characteristics, clinical characteristics, and presence of gastrointestinal symptoms at admission.

Characteristics	Patients with GI symptoms ($n = 46$)	Patients without GI symptoms ($n = 195$)	Overall ($n = 241$)	p value
Demographic characteristics				
Age in yrs (mean ± SD)	53.37 ± 16.72	54.03 ± 18.69		0.827
Sex: female %	21 (45.7%)	84 (43.1%)		0.751
BMI (mean ± SD)	24.07 ± 3.55	24.05 ± 4.57		0.970
Preexisting GI diseases - %	1 (2.2%)	4 (2%)	5 (2.1%)	0.849
Preexisting liver diseases-%	3 (6.6%)	10 (5.1%)	13 (5.4%)	0.691
Other comorbidities - %	24 (52.2%)	103 (52.8%)	127 (52.7%)	0.937
Complete vaccination - %	9 (19.6%)	29 (14.9%)	38 (15.8%)	0.691
Days of disease onset at the time admission (mean ± SD)	7.20 ± 6.57	5.42 ± 4.18		0.023
Clinical characteristics (mean ± SD)				
WCC ($\times 10^9$/L)	8.75 ± 4.99	8.77 ± 4.94	8.77 ± 4.94	0.978
Lymphocyte ($\times 10^9$/L)	1.18 ± 0.63	1.21 ± 0.89	1.21 ± 0.85	0.801
Platelet ($\times 10^9$/L)	219.83 ± 113.53	244.53 ± 110.99	239.82 ± 111.66	0.178
Total bilirubin (mg/dL)	0.89 ± 0.53	0.76 ± 0.41	0.79 ± 0.44	0.063
ALT (U/L)	58.94 ± 63.04	47.66 ± 46.74	49.81 ± 50.30	0.172
AST (U/L)	68.02 ± 89.38	54.72 ± 63.90	57.26 ± 69.47	0.244
ALP (U/L)	95.17 ± 40.83	89.62 ± 46.79	90.68 ± 45.69	0.460
Albumin (mg/dL)	36.54 ± 3.67	37.16 ± 4.09	37.05 ± 4.01	0.346
INR	1.36 ± 0.33	1.39 ± 0.42	1.39 ± 0.40	0.595
Treatment at hospital: n (%)				
AV alone	4 (8.7%)	15 (7.7%)		
CS alone	10 (21.7%)	40 (20.5%)		
AV and CS combined	15 (32.6%)	44 (22.6%)		
CS and IM combined	NIL	2 (1%)		
AV, CS, and IM combined	NIL	3 (1.5%)		

Data are expressed as mean (SD) or n (%). BMI: body mass index; GI: gastrointestinal; WCC: white cell count; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; INR: international normalized ratio; SD: standard deviation; AV: antiviral; CS: corticosteroid; IM: immunomodulator.

Table 3: Association between hospital outcomes and presence of gastrointestinal symptoms at admission.

Hospital outcomes	Patients with GI symptoms ($n = 46$)	Patients without GI symptoms ($n = 195$)	Overall ($n = 241$)	p value
Hospital stay- days (mean ± SD)	12.48 ± 5.72	12.16 ± 5.16	12.2 ± 5.3	0.712
HDU stay- days (mean ± SD)	0.69 ± 1.99	0.79 ± 1.94	0.8 ± 1.9	0.756
Mortality: expiry - %	3 (6.5%)	28 (14.4%)	31 (12.9%)	0.153

Data are expressed as mean (SD) or n (%). HDU: high-dependency units; SD: standard deviation.

4. Discussion

A total of 247 COVID-19 patients were admitted to two hospitals dedicated to COVID-19 inpatients during the study period. Six patients were excluded based on exclusion criteria and incompleteness in data entry, and therefore, 241 patients were included in this study.

Out of 241 patients, 68 (28.2%) of the patients had GI symptoms (at least one symptom such as diarrhea, nausea or vomiting, and abdominal pain) in the entire cohort, and this finding is agreeable with the theory of SARS-CoV2 GI entry and infection via ACE2 receptor [5]. Digestive manifestations may be common in patients with COVID-19, although reports have been conflicting, and the true prevalence remains uncertain. Several studies conducted in China suggested that gastrointestinal symptoms occur in less than 10% of patients [6, 7, 8, 9] whereas other studies done in China [10–11] and United States [12], have suggested

Table 4: Association between demographic characteristics, clinical characteristics, and patients with abnormal liver chemistries at admission.

Characteristics	Patients with normal liver chemistry ($n = 114$)	Patients with abnormal liver chemistry ($n = 127$)	Overall ($n = 241$)	p value
Demographic characteristics				
Age in yrs (mean ± SD)	49.29 ± 19.11	58.04 ± 16.54		**<0.001**
Sex: female %	57 (50%)	48 (37.8%)		0.056
BMI (mean ± SD)	24.06 ± 4.52	24.05 ± 4.29		0.985
Preexisting GI diseases - %	4 (3.5%)	1 (0.8%)	5(2.1%)	0.303
Preexisting liver diseases -%	6 (5.3%)	7 (5.6%)	13(5.4%)	0.537
Other comorbidities - %	51 (44.7%)	76 (59.8%)	127(52.7%)	**0.019**
Complete vaccination - %	23 (20.2%)	15 (11.8%)	38(15.8%)	**0.040**
Days of disease onset at the time of admission (mean ± SD)	5.47 ± 5.19	5.98 ± 4.33		0.408
Presenting symptoms at onset (GI vs. non-GI) (n) (%)	16 (14%) vs. 98 (86%)	30 (23.6%) vs. 97 (76.4%)		0.059
Clinical characteristics (mean ± SD)				
WCC ($\times 10^9$/L)	7.29 ± 3.73	10.09 ± 5.49	8.77 ± 4.94	**<0.001**
Lymphocyte ($\times 10^9$/L)	1.33 ± 0.73	1.10 ± 0.93	1.21 ± 0.85	**0.033**
Platelet ($\times 10^9$/L)	235.17 ± 100.67	243.99 ± 120.93	239.82 ± 111.66	0.541
Albumin (mg/dL)	39.08 ± 3.47	35.22 ± 3.57	37.05 ± 4.01	**<0.001**
INR	1.28 ± 0.39	1.49 ± 0.38	1.39 ± 0.40	**<0.001**
Treatment at hospital: n (%)				
AV alone	10 (8.8%)	9 (7.1%)		
CS alone	19 (16.7%)	31 (24.4%)		
AV and CS combined	10 (8.8%)	49 (38.6%)		
CS and IM combined	NIL	2 (1.6%)		
AV, CS, and IM combined	1 (0.9%)	2 (1.6%)		

Data are expressed as mean (SD) or n (%). BMI: body mass index; GI: gastrointestinal; WCC: white cell count; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; INR: international normalized ratio; SD: standard deviation; AV: antiviral; CS: corticosteroid; IM: immunomodulator.

Table 5: Association between hospital outcomes and patients with abnormal liver chemistries at admission.

Hospital outcomes	Patients with normal liver chemistry ($n = 114$)	Patients with abnormal liver chemistry ($n = 127$)	Overall ($n = 241$)	p value
Hospital stay- days (mean ± SD)	11.70 ± 3.69	12.68 ± 6.32	12.2 ± 5.3	0.148
HDU stay- days (mean ± SD)	0.27 ± 1.31	1.23 ± 2.28	0.8 ± 1.9	**<0.001**
Mortality: expiry - %	4 (3.5%)	27 (21.3%)	31 (12.9%)	**<0.001**

Data are expressed as mean (SD) or n (%). HDU: high-dependency units; SD: standard deviation.

proportions in the range of 30% to 60%. Nonetheless, only 25% of patients admitted to a tertiary medical center in Brooklyn, New York [13], had GI symptoms which is comparable to the present study.

Studies from different countries have also been reported a variety of gastrointestinal symptoms in COVID-19 patients. Most of the studies showed diarrhea is the commonest GI manifestation. A meta-analysis by Parasa et al. [9] showed that about 12% of 4805 COVID-19 patients presented with GI symptoms, comprising 7.4% of diarrhea (4.3%-12.2%), and 4.6% of nausea or vomiting (2.6-8%). Similarly, among 25% of the study population presented with GI symptoms in the study of Ferm et al. [13], the most common was diarrhea (19.8%). Likewise, in 4243 COVID-19 patients in the meta-analysis of Cheung et al. [14], 17.6% of patients presented with GI symptoms, of which 12.5% with diarrhea, 10.2% with nausea and/or vomiting, and 9.2% abdominal pain were demonstrated.

In contrast, in the present study, loss of taste (ageusia/hypogeusia) was found to have the most common GI symptoms constituting 38.2% (26/68 patients) of those having GI manifestations in the entire cohort and 41.3% (19/46 patients) of those who had preceding GI manifestations before admission. This was followed by diarrhea (28.3%),

nausea or vomiting (13%), and abdominal pain (2.2%) in patients who had preceding GI manifestations before admission. However, during hospitalization, 36.4% of patients had developed diarrhea followed by ageusia/hypogeusia (31.8%), loss of appetite (18.2%), nausea or vomiting (9.1%), and abdominal pain (4.5%).

Generally, gustatory and olfactory dysfunction is a widespread presentation in COVID infection. Gustatory dysfunction was found to be as high as 88.0% in a set of 417 mild-to-moderate COVID-19 patients in a European study. In addition, gustatory dysfunction was also significantly associated with olfactory dysfunction, which was identified with a high prevalence of 85.6% and may further exacerbate the loss of appetite [15]. It was also stated in a systematic meta-analysis that patients who reported a loss of smell and taste had sixfold higher odds of being COVID-19 positive [16]. In the study of Vaira et al. [17], within the first 4 days of COVID-19 symptoms, 40.6% of patients had gustatory disorders like ageusia or severe hypogeusia, but significantly, it was increased; improvement occurred within the first 10 days. Comparable to that study, although 41.3% of patients had symptoms of ageusia or hypogeusia before hospitalization, the prevalence of that symptom was found to be reduced after hospitalization in the present study.

In this study, the prevalence of diarrhea symptoms described as more than 3 loose stools per day in the entire cohort was 21 patients (21/241, 8.7%), which was similar to the prevalence of diarrhea reported by earlier studies conducted in Wuhan in the range of 3%-10% [6, 7, 18] but lower than that of a study conducted in Singapore as 17% [19].

Among patients having GI symptoms before admission, the prevalence of diarrhea was 28.3% (13/46 patients), but its prevalence became rising to 36.4% (8/22 patients) after admission. Similarly, findings as shown in Sultan et al. [20], only 5.2% of patients had diarrhea on admission, but most patients developed diarrhea during hospitalization. Perhaps, that finding may have been attributed to treatment with medications or concomitant GI pathogens during hospitalization.

Between the two groups as shown in Table 2, there was no significant difference in terms of demographic, clinical, and laboratory findings and comorbidities as described. Transaminitis, total WBC, and lymphocytes did not differ in both groups, suggesting that GI symptoms in COVID-19 patients might not be associated with inflammatory reaction and organ dysfunction.

In an earlier meta-analysis, it was suggested that GI symptoms are more common in the severe form of disease [14]. However, one meta-analysis [21], consisting of 78,798 patients with COVID-19 found no association between the presence of GI symptoms/elevated liver enzymes and mortality or ICU admission which is also in line with the finding of other studies [22, 23]. Again, in the present study, the length of hospital stay, HDU stay, and mortality were not significantly associated with the presence or absence of GI manifestation, showing that it did not lead to a more severe course.

In addition to digestive symptoms, patients with COVID-19 are also at risk of developing liver injury and abnormal LFT, especially in severe cases, but the results have been inconsistent, and the exact magnitude remains uncertain. In the present study, out of a total of 241 patients admitted to the hospital, 52.7% presented with abnormal liver transaminases on admission, which is in line with 56% in the study of Kumer et al. [24] and 58.5% in the study of Saini et al. [25] showing that significant portion of the study population may be affected. Unlike the present study, Bender & Worman [26] stated that the pattern of laboratory abnormalities was most often cholestatic (58.2%) and then (35.2%) in mixed, and (6.6%) in hepatocellular pattern. It was already identified that SARS-CoV virus binds the ACE receptors in the host cells, and its expression was found in cholangiocytes and hepatocytes [27]. However, the possible mechanisms of liver injury in COVID-19 are quite complex and usually explained by direct injury of the virus, cytokine storm as a result of severe disease course, ischemic injury following cardiac, circulatory or respiratory failure, and drug-induced liver injury with the use of antiviral agents and antipyretics [28]. Chen et al. [29] described in their retrospective analyses of 830 cases of COVID-19 infection that age and comorbidities are risk factors for COVID-19-associated liver injury. We also found a statistically significant association between age and comorbidities, and the presence of abnormal liver function ($p < 0.001$, $p = 0.019$, respectively).

There have been many studies focusing on how preexisting liver diseases might influence the clinical course of COVID-19. While many aspects remain poorly understood, Boettler et al. [30] pointed out as it has become increasingly evident that preexisting liver diseases and liver injury during the disease course must be kept in mind when caring for patients with COVID-19. Surprisingly, presence of preexisting liver diseases, including chronic hepatitis B in 2.9% of the entire cohort, chronic hepatitis C in 0.8%, alcoholic liver disease in 0.8%, and MAFLD in 0.4%, did not significantly affect the liver function in the present finding. In fact, fibrosis status should have been assessed for all patients with preexisting liver disease for more detail analysis.

Many studies showed that increased INR and decreased albumin levels in severe COVID-19 patients indicate a damage of liver synthetic function [31–33]. The present study found out that patients with abnormal liver chemistry had lower albumin levels and higher INR than those with normal liver chemistry at admission ($p < 0.001$ for both), which was similar to the studies conducted by Kumar et al. [24] and Phipps et al. [34]. These findings could also be attributed to the systemic inflammatory response resulting in increased vascular permeability and extracellular migration of albumin, which may be responsible for the decrease in albumin.

Lymphopenia was significantly found out in patients with abnormal LFT group ($p = 0.033$). It could be partially explained by the strong host immune response to SARCoV-2 infection with NK cells and T cells, which became exhausted and simultaneous attack to hepatocyte by inflammatory cytokine [35].

Several studies have shown that abnormalities in liver biochemistry tests are more frequent in severe cases of COVID-19, and it was associated with the worse prognosis

and mortality [23, 36]. It was agreeable with the present finding which also showed that patients with abnormal liver function has longer duration of HDU stay and higher mortality ($p < 0.001$ for both). In contrast, some studies showed liver abnormalities on admission were not associated independently with ICU care such as mechanical ventilation or mortality [37, 38].

Nevertheless, regarding the aforementioned data and interpretation of the results, it was suggested that medical staff should pay much attention to the patients with COVID-19, especially with liver injury, early monitoring and management, and, if necessary, switch treatment modes to further improve prognosis and increase the survival of COVID-19 patients.

5. Limitations

The levels of liver enzymatic parameters were recorded only at admission as baseline in this study, so consecutive measurements were warranted to know the pattern of liver enzyme elevation during hospitalization. Moreover, if inflammatory markers could be evaluated and related to the elevation of liver enzymes in the present study, it could be more explainable for the relationship between the elevation of liver enzymes, inflammatory parameters, and their changes as a reflection of the ongoing dynamics between viral infection and the immune response. Besides, to understand the relationship between preexisting liver diseases and abnormal liver function test, detailed liver status assessments like fibroscan test should be performed. However, there were some limitations to do this test in our two study areas because of strict COVID precautions over transferring patients from one unit to another.

Although liver function abnormalities are objective, GI symptom attribution was governed by several factors related to conducting this research, such as retrospective data collection from medical records rather than direct patient interview.

6. Conclusion

This study was done to determine the GI and liver manifestations and their associations with clinical outcome among patients infected with SARS-CoV-2 delta variant during the 3rd wave of the pandemic in Myanmar. Exploring the presence of gastrointestinal symptoms, it did not tend to associate with clinical outcome, while patients with abnormal liver chemistry were found to have a worse clinical outcome. Currently, there are increasing numbers of new SARS-CoV-2 variants, Omicron infection in Myanmar, and established studies regarding new variants are needed.

Nevertheless, we hope this study will provide requiring knowledge regarding GI and liver manifestations among patients with SARS-CoV-2 infection.

Abbreviations

DSLH: Defence Services Liver Hospital, Mingalardon, Yangon

No. (22/100) MH: No. (22) Military Hospital, Thanlyin, Yangon.

Data Availability

The data used to support the findings of this study are included within the article.

Ethical Approval

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to, and ethical approval was taken from the Ethics Review Committee of Defence Services Medical Academy.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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