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Characteristic of Hospitalized COVID 19 Patients with Gastrointestinal Manifestation and Liver Injury

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Background: COVID-19 is known to affect the digestive and liver systems. These can occur during the disease, and the prevalence was varied widely.

Objective: This study aimed to investigate the prevalence and characteristics of hospitalized COVID-19 patients with gastrointestinal symptoms and liver injury.

Methods: The data collected from the first 3 months of COVID-19 hospitalized patients (April – June 2020). We analyzed patients with gastrointestinal symptoms (nausea or vomiting, abdominal discomfort or pain, diarrhea, and anorexia) and patients with liver injury (alanine aminotransferase (ALT) (> 45 U/L for men and > 34 U/L for women) or aspartate aminotransferase (AST) level (> 35 U/L for men and > 31 U/L for women) at admission), then compared their clinical features with those who did not show gastrointestinal symptoms and liver injury.

Results: A total of 232 hospitalized COVID-19 patients were included. Gastrointestinal symptoms were found in 16.4% of patients. The symptoms were diarrhea (3.01%), anorexia (1.72%), nausea or vomiting (12.06%), and abdominal pain or discomfort (1.72%). The patients with gastrointestinal symptoms were more likely than those without to be admitted to the intensive ward (13.15% vs. 2.5%; p= 0.012). The elevation of liver aminotransferase levels on admission was found in 40.9% of patients. Longer hospitalization (15 days vs 11 days; p= 0.007) more likely to have liver injury.

Conclusion: Patients with liver injury had a longer hospital stay than patients without liver injury, while gastrointestinal symptoms have no significance on the duration of hospitalization.

Keywords: COVID-19, gastrointestinal symptoms, liver injury.

INTRODUCTION

Nowadays, the world is suffering from an ongoing pandemic disease that was caused by the severe acute respiratory syndrome coronavirus 2 (SARS-COV-2), which for the first time was encountered in Wuhan City, Hubei province of China in December 2019 then abruptly spread around the world.[1] Despite each country making various efforts to decrease the spreading of the viral, the cases continue to rise. The last report showed the total number of confirmed cases worldwide was 767,750,853, with the total death of 6,941,095. However, the case fatality rate of COVID-19 was found to be lower than severe acute respiratory syndrome (SARS) and middle east respiratory syndrome (MERS).[2,3]

SARS-COV-2 is transmitted from human to human through the infectious respiratory vehicle. The respiratory vehicle expelled by infected patients through cough, sneezing, or talking can contaminate surfaces and objects. The viable SARS-COV-2 can be found on those surfaces and objects ranging from hours to days. These explain the contact route of transmission. Airborne transmission of SARS-COV-2 can occur during the medical procedure that generates aerosol. Another study found viable SARS-COV-2 in the urine and stool of infected patients, but there were no published reports about fecal and urine as a transmission route for infections.[4]

The spikes on the outer surface of the coronavirus resembled a crown shape, that's why it was named a coronavirus,[1] and these spike proteins were related to specific cellular receptors of their target cells called angiotensin-converting enzyme 2 (ACE2).[5] These receptors spread mostly in the alveolar epithelial cells of the lung; this explains the major symptom of COVID-19 infection was related to the respiratory tract system. Furthermore, studies

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showed the ACE2 protein was expressed in cholangiocytes, hepatocytes, and enterocytes of the small intestine.[5,6] SARS-CoV-2 may enter the digestive system through the trachea-esophagus-intestine route.[7]

Most cases show mild symptoms and can resolve spontaneously, but some develop into respiratory failure and other complications. The COVID-19 symptomatic patients mostly experienced fever (83-99%), fatigue (44-70%), anorexia (40-84%), and shortness of breath (31-40%). Other symptoms, such as nasal congestion, myalgia, sore throat, and headache, may appear (4). The gastrointestinal symptoms in COVID-19 patients were also reported and had a variety of manifestations, such as nausea/vomiting, abdominal discomfort/pain, anorexia, and diarrhea.[8] A study by Pan et al shows the prevalence of gastrointestinal symptoms in their study was 50,5%, including anorexia (78.6%), diarrhea (34%), vomiting (3.9%), abdominal pain (1.9%), and those patients have a longer time from onset to admission, higher liver enzyme, and longer coagulation compared with patients without gastrointestinal symptoms.[9]

The abnormality in liver aminotransferase enzymes was observed in up to half of COVID-19 patients, although there was no previous history of liver disease.[9] A recent study shows that the raised of serum alanine aminotransferase (ALT) and aspartate aminotransferase was reported to occur in 24.1% and 33.3% of COVID-19 patients, respectively.[10] The frequency and severity of the rise of this aminotransferase were linear to the severity of COVID-19.[11] Available data suggest this virus can replicate in hepatocytes and cause a direct cytopathic effect. Other factors such as sepsis, hypoxemia, hypotension, and the given medication (drug-induced liver injury) can cause liver injury.[10,11,12]

Our hospital is Udayana University Hospital, one of the referred hospitals for COVID-19 in Bali province, Indonesia. The initial observation in our hospital shows that COVID-19 patients mostly come with respiratory symptoms and fever, which this finding was similar to most other studies. Some of our patients also show gastrointestinal symptoms and have liver injury. The prevalence of gastrointestinal symptoms and liver involvement in COVID-19 patients varied between studies. Our study aimed to evaluate the prevalence, clinical features, and outcome of COVID-19 patients with gastrointestinal symptoms and liver injury.

MATERIAL AND METHODS

This study was a retrospective cohort study with data from all hospitalized confirmed COVID-19 patients between April – June 2020 at Udayana University Hospital Bali. The sample size of this study was based on the available retrospective data which came to Udayana University Hospital. This study was approved by the ethics committee of the medical faculty of Udayana University. The diagnosis of confirmed COVID-19 patients was based on criteria by the World Health Organization; patients detected with SARS-CoV-2 nucleic acid by real-time (RT) polymerase chain reaction (PCR) in their nasopharyngeal aspirates. The ribonucleic acid (RNA) was extracted and tested by 2019-nCoV specific primer and probe in our hospital's biosafety level 2 cabinet. A cycle threshold value (Ct-value) less than 40 was defined as positive, and a Ct-value of 40 or more was defined as negative.[4]

The patient's medical records were reviewed. The epidemiology and demographic data, clinical presentation, laboratory measurement, radiological result, treatment, comorbid disease, the severity of the disease, and outcome were gathered. The medication history of the patient was also documented. The laboratory and radiology examinations were obtained on the day of admission. The enrolled patients were designated into separate groups; patients with and without gastrointestinal symptoms and those with liver injury or not. The features were compared between the opposite group.

We defined the positive gastrointestinal symptoms in COVID-19 patients as the patient required to have experienced at least one of the following symptoms: anorexia, nausea/vomiting, abdominal discomfort/pain, and diarrhea. Diarrhea was defined as passing loose stool more than 3 times a day. The liver injury in COVID-19 patients was defined as the value of aspartate transaminase (AST) > 35 U/L for men and > 31 U/L for women or alanine transaminase (ALT) value > 45 U/L for men and > 34 U/L for women respectively. So far, there has been no consensus to classify or define the cut-off value for liver injury related to COVID-19 infections. The exclusion criteria were a known history of chronic liver disease and chronic alcohol drinking.

Data analysis was performed using a statistical package for social science (SPSS). The continuous variables data were presented as mean and standard deviation (SD) or median as appropriate. The categorical variables data were presented as count (percentage). The Mann-Whitney U test was used to compare continuous variables data. The categorical data were compared using Fisher's exact test. A P-value of 0.05 was used to define statistically significant.

RESULT

Clinical Features

A total of 232 patients were included in this study. The median age was 37 years old (19-76), including male 137 (59.1%) and female 95 (40.9%), with the mean body mass index was 23.69 (18.37-38.57). Based on epidemiological history, 48 patients (20.7%) had a contact history with a confirmed case, 127 (54.7%) patients had unclear contact history but lived in the area with a high number of positive cases, and 57 (24.6%)

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Table 1. Characteristics and Symptoms of 232 COVID-19 Patients

Characteristics	Value
Age (year)	37 (19-76)
Sex	
Male	137 (59.1%)
Female	95 (40.9%)
Epidemiological Information	
Cruise ship worker	57 (24.6%)
Contact with a confirmed case	48 (20.7%)
Unclear contact history	127 (54.7%)
Ward	
ICU	10 (4.3%)
Non ICU	222 (95.7%)
Comorbid	75 (32.3%)
Pregnancy	8 (3.4%)
Obese	50 (21.6%)
Hypertension	34 (14.7%)
Diabetes mellitus	22 (9.5%)
Cardiovascular	8 (3.4%)
Kidney disease	1 (0.4%)
HIV	1 (0.4%)
Respiratory symptoms	133 (57.3%)
Cough	101 (43.5%)
Sputum production	18 (7.8%)
Sore throat	38 (16.4%)
Shortness of breath	25 (10.8%)
Nasal obstruction	24 (10.3%)
Gastrointestinal symptoms	38 (16.4%)
Anorexia	4 (1.72%)
Diarrhea	7 (3.01%)
Nausea/Vomiting	28 (12.06%)
Abdominal Discomfort	4 (1.72%)
Other symptoms	137 (59.05%)
Fever	133 (57.3%)
Headache	4 (1.7%)

Table 2. Laboratory and Radiographic Finding of 232 COVID-19 Patients

Characteristics	Value
Laboratory and radiographic finding	
WBC	7.13 (1.32-17.48)
Neutrophil	3.99 (0.01-16.11)
Lymphocyte	2.01 ± 0.82
Hemoglobin	13.98 ± 1.63
Platelet	249.50 (36-614)
BUN	12.00 (6.00-42.00)
SC	0.66 (0.10-2.92)
Liver injury	95 (40.9%)
AST only	41 (13-213)
ALT only	53 (13-193)
Elevation of AST	
1-2 ULN	56 (24.1%)
2-3 ULN	13 (5.6%)
>3 ULN	6 (2.6%)
Elevation of ALT	
1-2 ULN	52 (22.4%)
2-3 ULN	16 (6.9%)
>3 ULN	5 (2.2%)
Radiology	
Normal	124 (53.4%)
Abnormal	104 (44.8%)
No data due to pregnancy	4 (1.7%)

patients were cruise ship worker without a known history of exposure (imported case). Ten patients (4.3%) had severe conditions and needed to be admitted to the intensive care unit (ICU). There were 75 patients (32.3%) with a known coexisting medical condition or chronic disease, including hypertension (14.7%), diabetes mellitus (9.5%), cardiovascular disease (3.4%), kidney disease 0.4%), human immunodeficiency virus (HIV) infections (0.4%), obesity (21.6%), and pregnancy (3.4%). The most common symptoms in this study were fever (57.3%) and cough (43.5%). An abnormality on the chest x-ray was seen in 14 (44.8%) patients. The characteristic, laboratory and radiologic findings of the included study was showed in Table 1 and Table 2. During hospitalization, there were 99 (42.7%) patients receiving intravenous antibiotics treatment (e.g., levofloxacin, cephalosporin, meropenem), 141 (60.8%) receiving antiviral treatment (e.g., chloroquine, oseltamivir, lopinavir-ritonavir, remdesivir). The median hospital stay was 14 (0-40) days; this large variation was due to changes in discharged criteria. Earlier, the discharge criteria were 2 negative results for RT PCR test from nasopharyngeal aspirates specimens at 24-hour intervals, then changed to 10 days of quarantine plus 3 days free from symptoms or one negative result for RT PCR test. In addition, 229 (98.7%) patients were discharged, and 3 (1.3%) patients died (Table 3).

Gastrointestinal Manifestation

Gastrointestinal symptoms were found in 38 (16.4%) of 232 patients. In our study, one patient can present one or more gastrointestinal symptoms. Of these patients, they also presented with other respiratory symptoms or fever, no one solely presenting only gastrointestinal symptoms. Nausea/vomiting was the most common gastrointestinal manifestation (28/12.06%) found in patients. Seven patients (3.01%) had diarrhea, 4 patients (1.72%) had anorexia, and 4 patients (1.72%) had abdominal discomfort/pain.

For diarrhea cases, these patients presented with watery stool or loose stools, more than 3 times a day. The median duration of diarrhea symptoms was 4 (2-8) days, the cases were mild, and there was no finding of severe dehydration in these patients. Four patients (1.7%) had diarrhea symptoms after more than 7 days of hospitalization after the disappearance of other symptoms. We did not put these patients into the analysis with consideration that these

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symptoms may not cause by COVID-19 infections.

Nausea/vomiting symptoms were mild and the median duration of nausea and vomiting was 2 (1-5) days. Thirteen (5.6%) patients did not report had nausea/vomiting on the day of admission but developed the symptoms after more than 2 days of hospitalization. Aside from a gastrointestinal manifestation of SARS-CoV 2 infections, these symptoms might appear as a result of medication side effects, such as chloroquine, azithromycin, or antiviral agent. Taking this into consideration, we did not include this number in the analysis. If these numbers were included in the analysis, there were 60 (25.9%) total cases with gastrointestinal manifestations in this study.

The gastrointestinal manifestations tended to occur in patients admitted to the intensive ward, patients with a coexisting medical condition or chronic disease, and patients with headache symptoms. The lymphocyte levels were significantly lower than in patients without gastrointestinal

Table 3. Characteristics of Outcome of 232 COVID-19 Patients

Characteristics	Value
Treatment	
Antiviral	157 (67.7%)
Intravenous Antibiotic	99 (42.7%)
Outcome	
Discharge	229 (98.7%)
Death	3 (1.3%)
Length of hospitalization	14 (0-40) days

Table 4. Characteristics of COVID-19 Patients with Gastrointestinal Manifestation

	With GI Manifestation (n=38)	Without GI Manifestation (n=194)	p-value
Age (year)	44.50 (21-73)	36 (19-76)	0.139
Male sex	18/38 (47.36%)	119/194 (61.34%)	0.148
BMI	23.58 (18.73-35.99)	23.69 (18.37-38.57)	0.309
Intensive Ward	5/38 (13.15%)	5/194 (2.5%)	0.012
Any Comorbid	18/38 (47.36%)	57/194 (29.38%)	0.037
Pregnancy	1/20 (5%)	7/75 (9.3%)	1.00
Obese	13/38 (34.21%)	37/194 (19.07%)	0.051
Hypertension	9/38 (23.68%)	25/194 (12.88%)	0.128
Diabetes mellitus	5/38 (13.15%)	17/194 (8.7%)	0.373
Cardiovascular	3/38 (7.89%)	5/194 (2.57%)	0.127
Kidney disease	0/38 (0%)	1/194 (0.51%)	1.00
HIV	0/38 (0%)	1/194 (0.51%)	1.00
Respiratory symptom	27/38 (71.5%)	106/194 (54.64%)	0.073
Cough	23/38 (60.52%)	78/194 (40.20%)	0.031
Sputum production	6/38 (15.78%)	12/194 (6.18%)	0.088
Sore throat	1/38 (2.63%)	37/194 (19.07%)	0.008
Shortness of breath	7/38 (18.42%)	18/194 (9.2%)	0.147
Nasal obstruction	3/38 7.89(%)	21/194 (10.82%)	0.774
Other symptoms			
Fever	20/38 (52.63%)	113/194 (58.24%)	0.592
Headache	3/38 (7.89%)	1/194 (0.51%)	0.015

Table 5. Laboratory and Radiographic Finding of COVID-19 Patients with Gastrointestinal Manifestation

	With GI Manifestation (n=38)	Without GI Manifestation (n=194)	p-value
WBC	6.45 (1.32-16.70)	7.16 (1.64-17.48)	0.166
Neutrophil	3.64 (0.85-14.38)	4.02 (0.01-16.11)	0.499
Lymphocyte	1.75 ± 0.75	2.06 ± 0.82	0.030
Hemoglobin	13.54 ± 1.73	14.72 ± 1.60	0.068
Platelet	235.50 (36-586)	251.50 (37-614)	0.366
BUN	12.00 (6.00-28.50)	12.00 (6.20-42)	0.378
SC	0.63 (0.30-1.48)	0.67 (0.10-2.92)	0.394
Liver injury	16/38 (42.10%)	56/194 (28.86%)	0.126
Elevated AST only	15/38 (39.47%)	60/194 (30.92%)	0.344
Elevated ALT only	15/38 (39.47%)	58/194 (29.89%)	0.256
Abnormal radiology	22/38 (57.38%)	82/194 (42.26%)	0.603

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Table 6. Characteristics of Outcome of COVID-19 Patients with Gastrointestinal Manifestation

	With GI Manifestation (n=38)	Without GI Manifestation (n=194)	p-value
Treatment			
Antiviral	28/38 (73.68%)	129/194 (66.49%)	0.451
Intravenous antibiotic	14/38 (36.84%)	85/194 (77.98%)	0.476
Discharged	37/38 (97.36%)	192/194 (98.96%)	0.417
Length of hospitalization	15.5 (0-37)	13 (0-40)	0.081

Table 7. Characteristics and Symptoms of COVID-19 Patients with Liver Injury

	With Liver Injury (n=95)	Without Liver Injury (n=137)	p-value
Age (year)	40 (19-73)	36 (19-76)	0.287
Male sex	57/95 (60.0%)	80/137 (58.39%)	0.892
BMI	23.93 (18.37-38.57)	23.30 (18.37-34.53)	0.008
Intensive Ward	6/95 (6.31%)	4/137 (2.91%)	0.324
Any Comorbid	33/95 (34.73%)	42/137 (30.65%)	0.569
Pregnancy	2/95 (2.10%)	6/137 (4.37%)	0.477
Obese	25/95 (26.31%)	25/137 (18.24%)	0.148
Hypertension	16/95 (16.84%)	18/137 (13.13%)	0.455
Diabetes mellitus	7/95 (7.36%)	15/137 (10.94%)	0.495
Cardiovascular	4/95 (4.21%)	4/137 (2.91%)	0.720
Kidney disease	0/95 (0%)	1/137 (0.72%)	1.00
HIV	1/95 (1.05%)	0/137 (0%)	0.409
Respiratory symptom	65/95 (68.42%)	68/137 (49.63%)	0.005
Cough	56/95 (58.94%)	45/137 (32.84%)	0.000
Sputum production	12/95 (12.63%)	6/137 (4.37%	0.025
Sore throat	15/95 (15.78%)	23/137 (16.78%)	1.00
Shortness of breath	15/95 (15.78%)	10/137 (7.29%)	0.052
Nasal obstruction	11/95 (11.57%)	13/137 (9.48%)	0.664
Gastrointestinal Symptom	19/95 (20%)	19/137 (13.86%)	0.279
Anorexia	2/95 (2.10%)	2/137 (1.45%)	1.00
Diarrhea	7/95 (7.36%)	4/137 (2.91%)	0.130
Nausea/Vomiting	15/95 (15.78%)	14/137 (10.21%)	0.230
Abdominal Discomfort	1/95 (1.05%)	6/137 (4.37%)	0.245
Other symptoms			
Fever	56/95 (58.94%)	77/137 (56.20%)	0.688
Headache	4/95 (4.21%)	0/137 (0%)	0.027

Table 8. Laboratory and Radiographic Finding of COVID-19 Patients with Liver Injury

	With Liver Injury (n=95)	Without Liver Injury (n=137)	p-value
WBC	6.50 (1.32-17.25)	7.26 (1.64-17.48)	0.156
Neutrophil	3.94 (0.26-15.57)	4.02 (0.01-16.11)	0.474
Lymphocyte	1.83 (0.08-4.65)	2.04 (0.00-5.92)	0.025
Hemoglobin	14.10 (9.00-18.40)	14.10 (10.20-17.10)	0.523
Platelet	256 (36-614)	244 (91-470)	0.213
BUN	12.00 (7.00-42.00)	12.00 (6.00-30.00)	0.957
SC	0.68 (0.27-2.92)	0.65 (0.10-1.47)	0.550
Abnormal radiology	54/95 (56.84%)	50/137 (36.49%)	0.012

symptoms, and no significant differences were found in other parameters. Table 4, Table 5, and Table 6 shows the characteristic of patients with and without gastrointestinal symptoms.

Liver Injury

Of 232 patients with COVID-19, 95 (40.9%) patients had elevated aminotransferase levels on admission, including 73 (31.46%) patients had an elevation of ALT and 72 (32.32%)

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Table 9. Characteristics of Outcome of COVID-19 Patients with Liver Injury

	With Liver Injury (n=95)	Without Liver Injury (n=137)	p-value
Treatment			
Antiviral	63/95 (66.31%)	94/137 (68.61%)	0.776
Intravenous Antibiotic	51/95 (53.68%)	48/137 (35.03%)	0.007
Discharged	94/95 (98.94%)	135/137 (98.54%)	1.00
Length of hospitalization	15 (3-37)	11 (0-40)	0.007

had an elevation of AST, with median values of AST and ALT were 41 (13-213) and 53 (13-193) respectively. This shows that the aminotransferase elevations were mild, and none developed acute liver failure.

There was no patient with known chronic liver disease and chronic alcohol consumption. 7 (3.01%) patients had taken prescribed medication for chronic disease that known can affect liver aminotransferase (12), including 5 (2.1%) had statins, 1 (0.4%) patient had allopurinol, and 1 (0.4%) patient had phenytoin. Seventy-seven (33.2%) patients had taken acetaminophen as pre-hospitalized medication, with an average dosage of 1-2 gr daily. None of the patients receive more than 3 g of acetaminophen per day. Seventeen patients (7.3%) with an elevation of aminotransferase more than twice from the normal upper limit were tested for HBsAg and Anti HCV, but none showed a reactive result.

The median age of patients with and without a liver injury was 40 (19-73) and 36 (19-76), respectively. Patients with liver injury were more likely than those with normal aminotransferase to be had a higher BMI level, more likely to present respiratory symptoms and headache, had an abnormal finding on chest x-ray, had a lower lymphocyte level, had a longer duration of hospitalization, and more to receive intravenous antibiotic treatment. The patients admitted to the intensive ward tended to have an elevation of liver aminotransferase, but it was not statistically significant compared with non-intensive ward patients (8.3% vs. 2.5%; p = 0.074). There was no difference between the groups in terms of age, male sex, pre-existing medical conditions, the presence of gastrointestinal symptoms, and other laboratory measurements. The group's characteristics were summarized in Table 7, Table 8, and Table 9.

DISCUSSION

COVID-19 spread rapidly throughout Bali-Indonesia after the first case was confirmed in March 2020. The disease shows diversity in symptoms with varying degrees of illness. The majority of identified presentations of COVID-19 were fever and respiratory symptoms, but other symptoms such as anorexia, myalgia, nausea/vomiting, diarrhea, headache, fatigue, and skin rash can be presented. In accordance with other studies, respiratory symptoms and fever were the most common presentation of COVID-19 infections in our study, and the most common laboratory finding was lymphopenia.[13,14,15] Our study's patients with gastrointestinal symptoms and liver injury show evidence of lymphopenia.

In the current study, more than half of the patients were men (59.1%). The other studies also demonstrated a similar result.[16] But we found no difference in male sex between the group with and without gastrointestinal symptoms nor between those with and without liver injury.

Approximately 48 (20.7%) patients had close contact with confirmed COVID-19 patients or suspects, whereas 127 (54.7%) had no clear contact history, but they either lived or visited the area with a high number of cases (red zone area). About 57 (24.6%) patients were cruise ship workers who just arrived home. They disembarked from several cruise ships. The operation of the cruise industry was suspended because of the COVID-19 pandemic, and the crew member was sent back to their home. The cruise ship posed a greater risk for spreading SARs CoV 2 because the cruise ship worker was living and working in a nearly circumscribed environment with numerous ship passengers on board, making the social distancing challenging. The asymptomatic person may spread the infection among crew ship members or to other passengers. The infection may spread to other ships or communities if the infected individual travels on a cruise ship between countries.[17]

Thirty-eight (16.4%) patients presented gastrointestinal symptoms, including 12.06% nausea/vomiting, 3.01% diarrhea, 1.72% anorexia, and abdominal discomfort. Jin et al. reported 11.4%, Cheung et al. reported 25.4%, and Pan et al. reported 50.5% of the prevalence of gastrointestinal symptoms in their study.[9,18,19] The diarrhea estimates were similar to other studies.[13,20] Nausea/vomiting estimates were higher than the study by Wang et al. (10.1%) but lower than the study by Zhang et al. (17.3%).[21,22] A close estimate of abdominal pain was found in the study by Wang et al. (2.2%) and Pan et al. (0.98%).[21,22] Nonetheless, the incidence of gastrointestinal manifestation between studies was varied, implying that the diagnostic criteria used to define gastrointestinal symptoms differed. Besides the different criteria used, in this study, participant was recruited on the first 3 after the beginning of the disease outbreak in Bali, so the clinicians might miss the presentation of the symptoms other than the respiratory

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symptom. Therefore the RNA analyses were not conducted and the patients will be treated as common patients with gastrointestinal disease in other hospitals.[8]

A study by Jin et al. found that about 28.38% of patients show only gastrointestinal without respiratory symptoms.[23] But in our study, 71% of patients with gastrointestinal symptoms also had respiratory symptoms, and 52% also presented fever. None patients in our study presented only gastrointestinal symptoms.

Patients with gastrointestinal symptoms in our study were likely to have headache symptoms, have a co-existing chronic disease, and be admitted to the intensive ward. To support our finding, a study by Jin et al. identified a significantly increased complication of acute respiratory syndrome (ARDS), intensive ward admission, and the use of mechanical ventilation in patients with gastrointestinal symptoms compared with those without the symptoms. This finding shows that the disease severity of COVID-19 patients presenting with gastrointestinal symptoms was more severe than those without.[23]

SARS-CoV-2 enters the host cell through the ACE-2 receptors expressed mainly in the distal and proximal of the small intestine, but also expressed in the distal esophagus and colon. Another study shows the transmembrane protease serine-2 (TMPRSS-2) was also required for entry of the virus into the host cells. Despite the precise mechanism of how SARS-CoV-2 causes gastrointestinal symptoms, the virus might cause the alteration of intestinal permeability, change in protein expression, and enzyme modification.[24,25,26]

Several studies reported liver injury in COVID-19 patients. The prevalence varied from 14% to 53%, and ALT was predominantly increased.[13,16,27,20] The elevation of liver aminotransferase in our study was mild; the increase of 1-2 times from the upper limit of normal (ULN) value occurred in 24.1% of patients. Only 2.6% of patients had elevation more than 3 times from ULN. These findings were consistent with other studies.[15,16]

Evidence of chronic liver disease in our study was excluded by careful history taking and physical examination by the attending physicians. Data show not all patients were tested for HBsAg and anti-HCV. This limitation may masking liver injury related to COVID-19. Previous studies by Qun Li et al. and Fan et al. show the proportion of elevation of liver aminotransferase in a group with chronic liver disease compared with a group without chronic liver disease was not statistically significant.[28] Another study shows a different result; the proportion of preexisting chronic liver disease was higher in the liver injury group. Within these groups, only up to 6.8% had chronic liver disease, so the preexisting chronic liver disease was not entirely responsible for liver injury in COVID-19 patients.[6]

Our study found a higher BMI level in the group with liver injury. This finding was probably related to nonalcoholic fatty liver disease (NAFLD). A study by Huang et al. shows that NAFLD is the risk factor for liver injury in COVID-19 patients. Their study found the patients had a higher BMI level, the aminotransferase elevation was mild, predominantly ALT, and no severe liver injury nor liver failure was observed.[15]

We found that patients with liver injury were more likely to receive antibiotics treatment. These may be related to disease severity and secondary bacterial infections, but not all of our's patients who received intravenous antibiotics treatment were tested for procalcitonin. Because of the limited resources, our clinician may rely on clinical findings. A study by Hao Sha-Rui et al. shows the increase in procalcitonin levels was related to liver injury in COVID-19 patients.[6]

The level of aminotransferase abnormality increased with COVID-19 disease severity.[29] The abnormal finding on the chest x-ray and respiratory symptoms were found more to occur in the patient with liver injury. The proportion of patients with liver injury was higher in the intensive ward compared with the regular isolation room, although it was not statistically significant because of the minimal number of patients.

Although the mechanism is not fully understood yet, several studies have been proposed about the mechanism of COVID-19-related liver injury, such as direct liver injury as the cytopathic effect of SARS-CoV-2 to hepatocyte and cholangiocyte through ACE2 receptors, immune-mediated inflammations, the hepatotoxic effect of the given medications, hypoxia, circulatory failure, and preexisting chronic liver disease.[30,31,32] According to many studies, liver injury in COVID-19 patients generally was mild. Only a few studies reported evidence of acute liver failure. Caution is still needed when using any therapeutic agent known to be hepatotoxic.[16,32]

In this study, two hundred ninety-two patients (98.7%) were discharged from the hospital, including 94 patients with a liver injury and 37 with gastrointestinal symptoms. Three patients (1.3%) died during hospitalization, including 1 patient who had both gastrointestinal symptoms and liver injury, and 2 patients were in the normal group who had no gastrointestinal symptoms or liver injury. No significant association was found between gastrointestinal symptoms and liver injury with patients' outcomes in this study, but we found the length of hospital stay was longer in patients with elevated liver aminotransferase. To support our findings, another study also found a similar result.[16]

The limitation of our study was incomplete some of the patient data because of secondary data gathering after the patient's discharged. The direct association of causality between COVID-19 and the risk of gastrointestinal symptoms

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or liver injury can not be revealed by our study. In addition, we did not exclude patients with hepatitis B, hepatitis C, fatty liver, and drug induce liver injury condition. This issue may serve as major limitation in our study, hindering the validity of this study results. Our study focused on the variables that were discovered in the first identification of liver injury and gastrointestinal symptoms.

CONCLUSION

Among COVID-19 patients, patients admitted to the intensive ward, with a coexisting medical condition, and had headache commonly present with gastrointestinal manifestations. Furthermore, patients with higher BMI, abnormality in chest x-ray, and presented with respiratory symptoms tend to have liver injury. Patients with an elevation of liver aminotransferase also had a longer duration of hospitalization and were more likely to receive intravenous antibiotic treatment when compared to those who did not.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest to disclose.

ETHICS CONSIDERATION

This research has been approved by ethical committee of Udayana University Hospital Bali.

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AUTHOR CONTRIBUTIONS

All authors equally contribute to the study from the conceptual framework, data gathering, and analysis.

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