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Acute liver injuryin COVID-19 infection: Report from Field hospital and COVID-19 situation update in Association of Southeast Asian Nations (ASEAN)

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***Abstract: Introduction*: *Emergence of the novel severe acute respiratory syndrome corona virus 2* (*SARS-CoV-2*) *has affectedalmost every country*. *This study aimed to provide the patterns of acute liver injuryof COVID-19 infection from field hospital in Thailand and ASEAN and update situation of COVID-19 infection in ASEAN*.**

Method*: *All patients diagnosed with COVID-19 and admitted toThammasatuniversity field hospital between January 2020 and May 2020 were included*.*ASEAN COVID-19 studies have beensearched by PubMed and Scopus and extensively reviewed.

***Results*:*There were 381 ASEAN COVID-19 studies searched by PubMed and Scopus. However, 3 studies reported the liver function tests and met our inclusion criteria*. *Total of 86 patients* (*52 patients form Thailand, 18 patients from Indonesia and 16 patients from Singapore*) *were included and described liver parameters of COVID-19 infection in ASEAN*. *From our field hospital, total of 412 COVID-19 tests performed and 41 patients were confirmed SARS-CoV-2 infection*.*The abnormal liver function test was detected in 52.6%.The patterns of acute liver injury in COVID-19 patients were transaminitis* (*36.8*%) *and hypoalbuminemia* (*31.6*%)*whichsignificantly associated with severe COVID-19 infection* (*OR 14.50, 95*%*CI 1.14-185.18, p=0.040; OR 31.49, 95*%*CI 1.41-705.47, p=0.030; respectively*).**

***Conclusions*:*Acute liver injury could be found in COVID-19 infectionespecially in ASEAN*. *COVID-19 patients with transaminitis and hypoalbuminemia should raise clinical suspicion for severe disease andbe closely monitoredfor rapid disease progression*.

Keywords*:*COVID-19, ASEAN, Acute liver injury

1. INTRODUCTION

Almost every country in the world has been affected by the pandemic of Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)emerging from Wuhan, China[1].More than 34.1 million confirmed cases and over 1 million deaths have been reported worldwide from the beginning of the pandemic to September 30,2020. Although COVID-19equally affectsmales and females, the male-to-female ratio varies among countries.Many studies reported that men appeared to have higher risk for developing severe COVID-19, worse outcomes, and higher mortality than women[2-5].From the onset of the outbreak to September 2020, Southeast Asian region has continued to report steadily increasing number of new cases and deaths with 6,073,462 cumulative confirmed cases and 101,700 deaths.Thailand has prepared response plans for COVID-19 including promoting health literacy on prevention and personal hygiene, healthcare facility preparedness, encouragingsocial distancing, along with active case detection, prompt isolation, and quarantine of close contacts. The aforementioned actions have resulted in the declineof daily new cases in this country since the end of April 2020.According to the Global COVID-19 Index (GCI), Thailand has been ranked the third place from 184 countries in the global COVID-19 recovery index.

COVID-19 causeswidespectrum of diseaseranging from asymptomatic to very severeassociated with intensive care unit (ICU) admission and high mortality[6].Over 80% of patients had only mild disease[7].Common presenting symptoms are fever and respiratory symptoms[8].However, physicians have paid more attentionto gastrointestinal manifestations of COVID-19after the detection of SARS-CoV-2 ribonucleic acid (RNA) in stool of the first case in the United States of America (USA)[9]. Themost commondigestive symptoms areanorexia, followed by diarrhea, nausea, and vomiting[10-12].On the other hand, COVID-19 patients can also present with liver injury causedby various pathophysiologic mechanisms including direct viral effects on both hepatocytes and cholangiocytes, marked activation of inflammatory markers and innate immune system leading to cytokine dysregulation[13].Previous studies reported varying incidence of liver injury in COVID-19 patients of approximately 16-61% with abnormal alanine aminotransferase (ALT) and aspartate aminotransferase (AST) level[13, 14].A fewstudies revealed the correlation between abnormal liver enzymes and the severity of COVID-19, but the results were still variable and inconsistent[15-17].Until now, the information about the relationship between COVID-19 and liver parameters of Southeast Asian countries has beenscarce due to limited number of studies.

The current outbreak of COVID-19 has continuedto produce enormous impact on both healthcare and socioeconomic systems. ASEANare currently facingthe upward trend of newly diagnosed cases per day.This study aimed to provide the patterns of acute liver injuryof COVID-19 infection from field hospital in Thailand and ASEAN and update situation of COVID-19 infection in ASEAN.

2. METHODS

Study design

A retrospective cohort study wasconducted in Thammasat university fieldhospital, Thailand between January 1, 2020, and May 31, 2020. Patientsaged15 years or olderwith confirmed COVID-19 test by real-time reverse transcription-polymerase chain reaction (RT-PCR)were included. Patients' data including demographic data, clinical presentation, laboratory results within 24 hours of admission, and treatment outcome were assessed and recorded.ASEAN COVID-19 studies have been searched by PubMed and Scopus and extensively reviewed.

Definitions

Diagnosis of SARS-CoV-2 infection was defined as the detection of SARS-CoV-2 in any specimen from upper respiratory tract or lower respiratory tract by using real-time RT-PCR. Specimens werecollected by nasopharyngeal swab, oropharyngeal swab, tracheal suction, or bronchoalveolar lavage.

Severity of COVID-19 was classified as mild or severe symptomsaccording to Department of Medical Servicesin Thailand[18]. Mild symptoms were defined as patients with normal chest x-raywithout risk factors or comorbidities. Severe symptoms were defined as patients with sign and symptoms of pneumonia or abnormal chest x-ray.

Duration of symptoms was defined as the timefrom the beginning of symptoms to hospital admission.

Reversed albumin-to-globulin ratio was defined ashigher globulin than albumin levels along with normal range of total protein resulting in the albumin-to-globulin ratio of less than 1.

Hypoalbuminemia was defined as serum albumin ≤ 4 mg/dL.Blood sampleswere collected within 24 hours after the admission.

Transaminitis was defined as the levels of liver enzyme exceeding the upper normal limit of AST and ALT levels more than 35 U/L.Blood sampleswere collectedwithin 24 hoursafter admission.

Statistical analysis

Continuous variableswere described as mean and standard deviation. Categorical variables were described as frequency and percentages. Independent Student's t-test was applied to continuous variables. Fisher exact test and Chi-Square tests were used for comparing two groups of categorical variables as appropriate. The univariate and multivariate analyses by binary logistic regression were used to determine the association between liver parameters and severity of symptoms.The p-value less than 0.05 was considered as statistical significance. Statistical analysis was performed using IBM SPSS Statistics software version 26.0 (SPSS Inc., Chicago, IL, USA). This study was approved by the Human Research Ethics Committee of Thammasat University, Thailand and conducted according to the good clinical practice guideline, as well as the Declaration of Helsinki.

3. RESULTS

Patient characteristics

From January 1,2020 to May 31,2020, 412 COVID-19 tests performed. Total of 41 patientswith laboratory confirmedSARS-CoV-2 infectionwere diagnosed and admitted to Thammasat university field hospital, which was established during the large outbreak period in Thailand. The male-to-female ratio was 1:1.3. Eighteen(43.9%) patients weremen, while23 (56.1%) werewomen. The mean age was 30.5 ± 9.3 years. The mean age of males and femaleswas comparable (p = 0.760).There were 5 (12.2%) patients with underlying diseases which were hypertension, dyslipidemia, gout, asthma, andthalassemia. None of them had pre-existing chronic liver disease. From 381 ASEAN COVID-19 studies found by searching from PubMed and Scopus, 3 studies were entry in this study including 52 patients from Thailand, 18 patients from Indonesia, and 16 patients in Singapore. The baseline characteristics of patients with COVID-19 including clinical presentation, laboratory values, treatment, and outcomesare demonstrated in Table 1.Figure 1depictedthe current COVID-19 situation in ASEAN as the geographic distributions of cumulative confirmed COVID-19 casesand deaths since the onset of SARS-CoV-2 pandemic and current situation of COVID-19 with total new cases diagnosed in September 2020. Figure 2 depictedthe bar chart withdaily number of newly diagnosed COVID-19 classified by each country in ASEAN.

Clinical features and laboratory values

The mean duration of symptoms was 9.2 ± 5.1 days. Fever (61.5%) was the most common initial symptom, followed by cough (25.6%), and sore throat (5.1%). Twelve (29.3%) patients haddigestive symptoms which were anorexia (17.1%), diarrhea (14.6%), nausea (4.9%), abdominal pain (4.9%), and vomiting (2.4%). The mean duration of symptoms, initial symptoms, and gastrointestinal symptoms were not different between males and females.The mean of white blood cell (WBC) count was more predominantly present in malesthan females (the mean WBC of 5.6 ± 1.8 10^9/L vs. 6.6 ± 2.1 10^9/L, p = 0.042). Similarly, men also had significantly lower mean of absolute lymphocyte count than women (1.8 ± 0.5$10^9$/L vs. 2.5 ± 0.6 10^9/L, p = 0.008). There was no significant difference in liver function test comprising total bilirubin,alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and albumin between males and females. The majority of patients (75.6%) had mild COVID-19 symptoms with the percentages of nasopharyngitis, pharyngitis, andbronchitisof 41.5%, 22.0%, and 12.2%, respectively. The minority of patients (24.4%) had pneumonia. One patient experienced respiratory failure requiringinvasive mechanical ventilator support for 6 days.

Treatment and outcome

Of all patients, 25 (61.0%) patients received medication including lopinavir/ritonavir (LPV/r), darunavir/ritonavir (DRV/r), hydroxychloroquine, favipiravir, and azithromycin. There were 15 patientsdiagnosed with mild COVID-19 requiring medical treatment (36.6% of all patients and 48.4% of mild symptom group).Longer duration of hospitalization was observed in female COVID-19 patients with the average length of hospital stay of 19.9 ± 9.3 days, whereas males were admitted for shorter duration of 14.6 ± 5.4 days (p = 0.038). The proportion of females who had length of hospital stay more than 20 days was significantly higher than males (43.5% vs 11.1%, p = 0.024; OR 6.15, 95%CI 1.14-33.20, p = 0.035). All patients completely recovered from COVID-19 with no mortality in this study.

Acute liver injury and COVID-19

From our field hospital, there were 19 patients whose bloods werecollected for liver function evaluation within 24 hours after admission. Patterns of acute liver injury found in this study were transaminitis and hypoalbuminemia. Seven patients(36.8%) hadtransaminitiswhereas 6 (31.6%) and 4 (21.1%) patientshaving hypoalbuminemia and reversed albumin-to-globulin ratio, respectively. The proportions of patients withtransaminitis, hypoalbuminemia, and reversed albumin-to-globulin ratio were not different between males and females. Meanwhile, hypoalbuminemia was significantly more likely in patients with severe COVID-19thanthose with mild symptoms (71.4% vs. 8.3%, p = 0.010). Similarly, the group of severe symptoms significantly had higher proportion of patients with transaminitis than mild symptom group (71.4% vs. 16.7%, p = 0.045).Table 2 demonstrates hepatic parametersclassified by disease severity with univariate and multivariate analyses. The reversed albumin-to-globulin ratio was not significantlyrelated to disease severity. Interestingly, hypoalbuminemia and transaminitis were independently associated withsevere COVID-19 (OR 31.49; 95%CI 1.41-705.47, p = 0.030, and OR 14.50; 95%CI 1.14-185.18, p = 0.040, respectively).

From86 COVID-19 patients in ASEAN (52 patients from Thailand, 18 patients from Indonesia, and 16 patients in Singapore),hepatic manifestations were shown in Table 3.There was case series from Thailand reported increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in 1 (9.1%) COVID-19 patient without pre-existing chronic liver disease. On the other hand, the study from Singapore included COVID-19 patientswith chronic liver disease (100%) did not report baseline liver function tests but reported medians of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and serum albumin were 61 (16-518) U/L, 60 (19-367) U/L, 3.2 (1.9-4.2) g/dL, respectively. The higher proportions of increased ALT (55.6%) and AST (55.6%) were observed in the retrospective study from Indonesia compared to our findings.

4. DISCUSSION

This retrospective cohort study of COVID-19 patients in Thailand and literature review in ASEAN provided pattern of acute liver injury in COVID-19 patients. Clinical presentation, liver parameters, and disease severity of men with COVID-19 were similar to women. Men significantly had lower WBC and absolute lymphocyte count than women, while women had significantly longer length of hospital stay than men. Another striking feature of this study wasthat higher proportion of COVID-19 patients with abnormal liver enzymes and hypoalbuminemia was found in the group ofsevere symptoms. Interestingly, transaminitis and hypoalbuminemiamight be predictors for severe COVID-19 infection and raised clinical concerns for aggressive monitoring in this group of patients.

One systematic review of COVID-19, which collected data about length of hospital stay, includedmajority of studies from China. This study reported the median length of hospital stay in China of 14 days(IQR 10-19 days)[18]. The result was comparable to our study with the median length of hospital stay of 15 days (IQR 13.5-21.5 days). Our study also demonstrated longer duration of hospitalization in women. These findingsmight be explained by higher proportion severe COVID-19 in women and longer duration of the positive COVID-19 test turning to negative test.

Although the mean of AST and ALT levels of all patients were in normal range, approximately one-third of patients had transaminitis on admission. All patients included in this study had no pre-existing chronic liver disease. Our study demonstrated that transaminitis was independently associated with severe symptoms of COVID-19. This finding was correlated with prior studies[19-21].Liver injury in patients with SARS-CoV-2 infectionmay be caused byvarious mechanisms[13].The angiotensin-converting enzyme 2 (ACE2) is a specific receptor for SARS-CoV-2 entry into cells[22]. The ACE2 is not only highly expressed in type 2 alveolar cells, but also found abundantlyin cholangiocytes(59.7%) than hepatocytes (2.6%)[23, 24].Therefore, liver could be a potential target for SARS-CoV-2 infection. SARS-CoV-2 might be directly bound to cholangiocytes and hepatocytes with ACE2 receptor and eventually disruptnormal liver function[14].Moreover, the number ofhyperactivated peripheral cluster of differentiation (CD) 4 T cells and CD8 T cells with cytotoxic granules were substantially reduced, while the level of proinflammatory,chemokine receptor 6 (CCR6+) Th (T-helper cell) 17 in CD4 T cells increased detected byperipheral blood evaluation. These findingsmay imply thatCOVID-19 patients might have severe immune dysfunction from these mechanisms[25].Patients with COVID-19 could markedly establishsystemic inflammation including cytokine dysregulation, cytokine storm,and activation of inflammatory mediators whichcontribute to multiple organ injury including liver damage[13, 26, 27].

Hypoalbuminemia was observed in patients with severe COVID-19 and reported as an independent predictive factor for mortality in previous studies conducted in China[28-30].In our study, hypoalbuminemia at admission was an independent factor for predicting severe symptoms of COVID-19. Hypoalbuminemia is also used as one of the tools for predicting worse outcomes and deathsin both acute and chronic settings including sepsis[31-33].Serum albumin is a major component of plasma protein reflecting the nutritional status and prior physical activity of patients[34].Systemic inflammatory process can also lead to hypoalbuminemia by increased vascular permeability, decreased albumin production, and high rate of albumin breakdown[35].One of the major clinical consequences of COVID-19 is cytokine storm resulting in potentially life-threatening outcome[26].Diminished albumin synthesis in liver could be inhibited by proinflammatory markers such as interleukin-6 (IL-6) level, interleukin-1 (IL-1) and tumor necrosis factorproduced during inflammatory response[34].Low serum albumin level might also be related to the severity of COVID-19.

In conclusion,pandemic of COIVD-19 is currently enormous problem in many countries, where has facedthe upward trend of newly diagnosed cases and deaths. Acute liver injury could be found in COVID-19 infection especially in ASEAN. COVID-19 patients with transaminitis and hypoalbuminemia should be closely monitored for rapid disease progression. Prevention of COVID-19 by wearing masks, hand washing and strict adherence to social distancing rules could be effective methods to reduce new cases of COVID-19 worldwide.

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Table 1. Demographic data, clinical presentations, laboratory values, and outcome of COVID-19 patients classified by gender.

	All patients n = 41	**Male n = 18**	**Female n = 23**	**p-value**
Age, year, mean ± SD	30.5 ± 9.3	31.2 ± 10.3	30.3 ± 8.6	0.760
Alcohol drinking, n (%)	2 (4.9%)	2 (11.1%)	0	0.187
Underlying disease	5 (12.2%)	3 (16.7%)	2 (8.7%)	0.638
Initial symptom, n (%)				
Fever	24 (61.5%)	8 (47.3%)	16 (72.7%)	0.102
Cough	10 (25.6%)	6 (35.3%)	4 (18.2%)	0.282
Sore throat	2 (5.1%)	1 (5.9%)	1 (4.5%)	1.000
Duration of symptoms, days, mean ± SD	9.2 ± 5.1	10.1 ± 4.7	8.8 ± 5.4	0.415
Chest radiography				
Normal	31 (75.6%)	14 (77.8%)	17 (73.9%)	1.000
Abnormal	10 (24.4%)	4 (22.2%)	6 (26.1%)	
Severity, n (%)				
Mild	31 (75.6%)	14 (77.8%)	17 (73.9%)	1.000
Severe	10 (24.4%)	4 (22.2%)	6 (26.1%)	
Laboratory values, mean ± SD				
White blood cell, 10^9/L††	**6.6 ± 2.1**	**5.6 ± 1.8**	**7.3 ± 2.1**	**0.042**
Absolute lymphocyte count, 10^9/L††	**2.2 ± 0.7**	**1.8 ± 0.5**	**2.5 ± 0.6**	**0.008**
Total bilirubin, mg/dL†	0.7 ± 0.4	0.9 ± 0.5	0.5 ± 0.3	0.182
ALT, U/L†	31.4 ± 18.7	35.7 ±19.3	29.1 ± 21.8	0.356
AST, U/L†	28.4 ± 16.1	29.4 ± 21.2	27.5 ± 10.7	0.801
ALP, mg/dL†	56.3 ± 26.2	63.7 ± 26.0	51.2 ± 24.9	0.244
Albumin, g/dL†	4.2 ±0.4	4.2 ± 0.5	4.1 ± 0.3	0.496
Elevated liver enzyme†	7 (36.8%)	3 (33.3%)	4 (40.0%)	1.000
Hypoalbuminemia†	6 (31.6%)	2 (22.2%)	4 (40.0%)	0.628
Reverse A/G ratio†	4 (21.1%)	2 (22.2%)	2 (20.0%)	1.000
Medications, n (%)	25 (61.0%)	12 (66.7%)	13 (56.5%)	0.509
LPV/r	3 (8.1%)	2 (11.8%)	1 (5.0%)	0.584
DRV/r	16 (43.2%)	9 (52.9%)	7 (35.0%)	0.272
Hydroxychloroquine	21 (56.8%)	11 (64.7%)	10 (50.0%)	0.368
Favipiravir	8 (21.6%)	3 (17.6%)	5 (25.0%)	0.701
Azithromycin	11 (29.7%)	4 (23.5%)	7 (35.0%)	0.447
Time to negative test, days, mean ± SD	18.9 ± 8.6	18.6 ± 6.1	19.8 ± 9.8	0.643
Length of stay, days, mean ± SD	**17.4 ± 8.2**	**14.6 ± 5.4**	**19.9 ± 9.3**	**0.038**

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Length of stay 1-10 days	7 (17.1%)	5 (27.8%)	2 (8.7%)	0.209
Length of stay 11-20 days	22 (53.7%)	11(61.1%)	11 (47.8%)	0.397
Length of stay >20 days	**12 (29.3%)**	**2 (11.1%)**	**10 (43.5%)**	**0.024**

†n = 19, ††n = 26

Abbreviations: AGE, acute gastroenteritis; GI, gastrointestinal; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; A/G, albumin to globulin,LPV/r, lopinavir and ritonavir, DTV/r, darunavir and ritonavir.

Table 2**.** Univariate and multivariate analyzes of association between hepatic parameters and disease severity.

Liver parameters	**Mild symptom n = 12**	**Severe symptom n = 7**	**p-value**	**Univariate analysis**		**Multivariate analysis**	
				OR (95%CI)	**p-value**	**OR (95%CI)**	**p-value**
Reversed A/G ratio	1 (8.3%)	3 (42.9%)	0.117	8.25 (0.75-104.20)	0.103		
Hypoalbuminemia	**1 (8.3%)**	**5 (71.4%)**	**0.010**	**27.50 (1.99-378.84)**	**0.013**	**31.49 (1.41-705.47)**	**0.030**
Transaminitis	**2 (16.7%)**	**5 (71.4%)**	**0.045**	**12.50 (1.34-116.80)**	**0.027**	**14.50 (1.14-185.18)**	**0.040**

Abbreviations: OR, odds ratio; 95%CI, 95%confidence interval; A/G, albumin to globulin.

Table 3. Hepatic manifestations of COVID-19 in ASEAN.

Study	Country	Study type	Number	Pre-existing liver disease, n (%)	Liver function test					Notes
					Increased ALT n (%)	Increased AST n (%)	Increased ALP n (%)	Increased TB n (%)	Hypoalbuminemia n (%)	
This study	Thailand	Retrospective study	41	0	4/19 (21.1%)	5/19 (26.3%)	0	0	6/19 (31.6%)	
Pongpirul WA[36]	Thailand	Case series	11	1 (9.1 %)	1 (9.1%)	1 (9.1%)	NA	NA	NA	Onepatient, no pre-existingl liver disease, had elevated liver enzyme with ALT 83 U/L and AST 47 U/L.
Jonathan K[37]	Singapore	Retrospective study	16	16 (100 %)	NA Median (range) 61 (19-518) U/L	NA Median (range) 60 (19-367) U/L	NA Median (range) 86 (45-332)U/L	NA Median (range) 0.9 (0.5-4.3)mg/dL	NA Median (range) 3.2 (1.9-4.2) g/dL	All patients had pre-existing chronic liver disease; 9 patients had NAFLD. Peak ALT was higher

										in NAFLD group (median 84 U/L vs 38 U/L; P = 0.042).
Paramita S[38]	Indonesia	Retrospective study	18	NA	10 (55.6%)	10 (55.6%)	NA	NA	NA	All patients had mild symptoms. AST > 40 U/L and ALT > 41 U/L were defined as abnormal liver enzyme.

Abbreviations:ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; TB, total bilirubin; NAFLD, non-alcoholic fatty liver disease.

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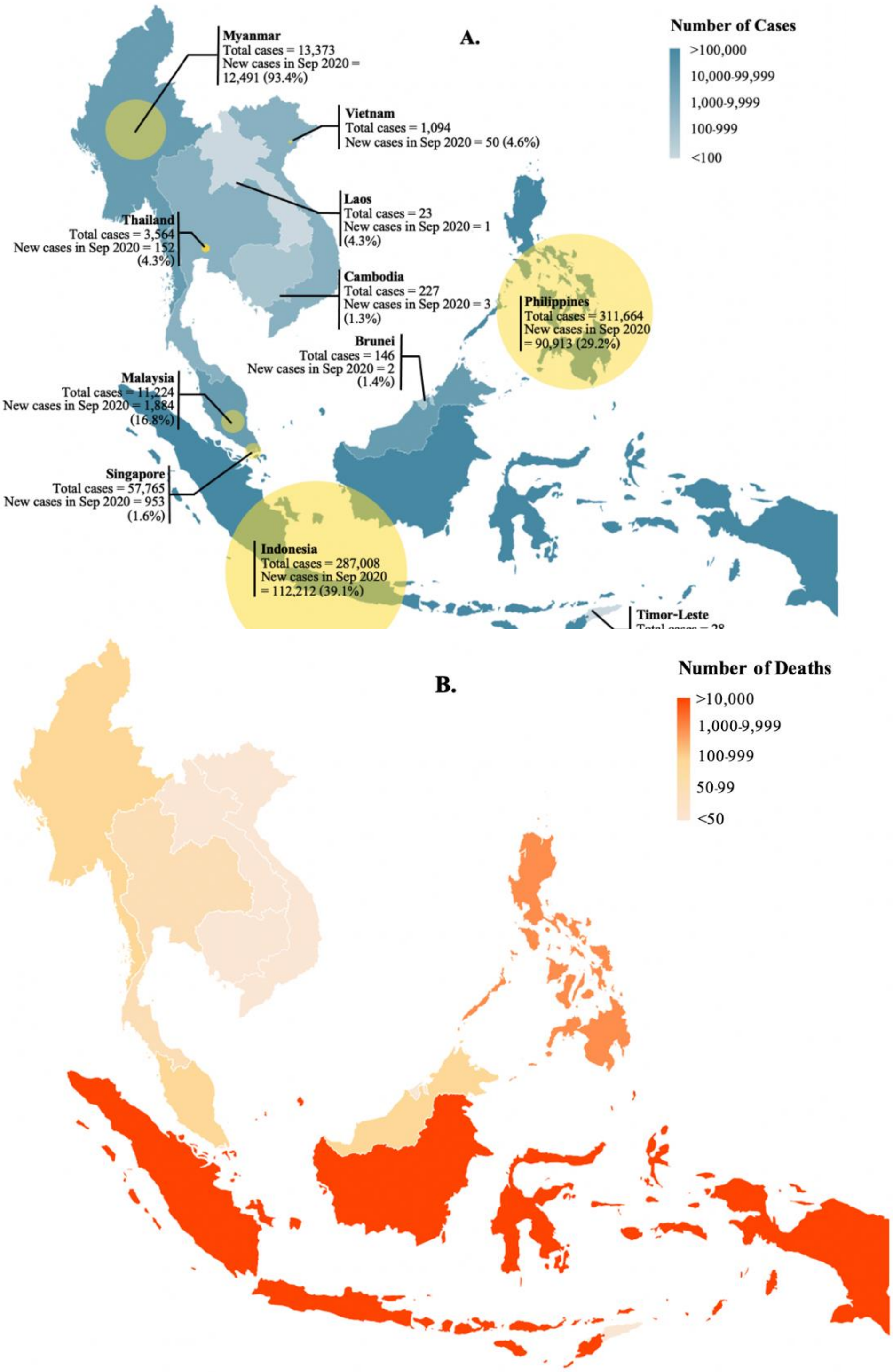
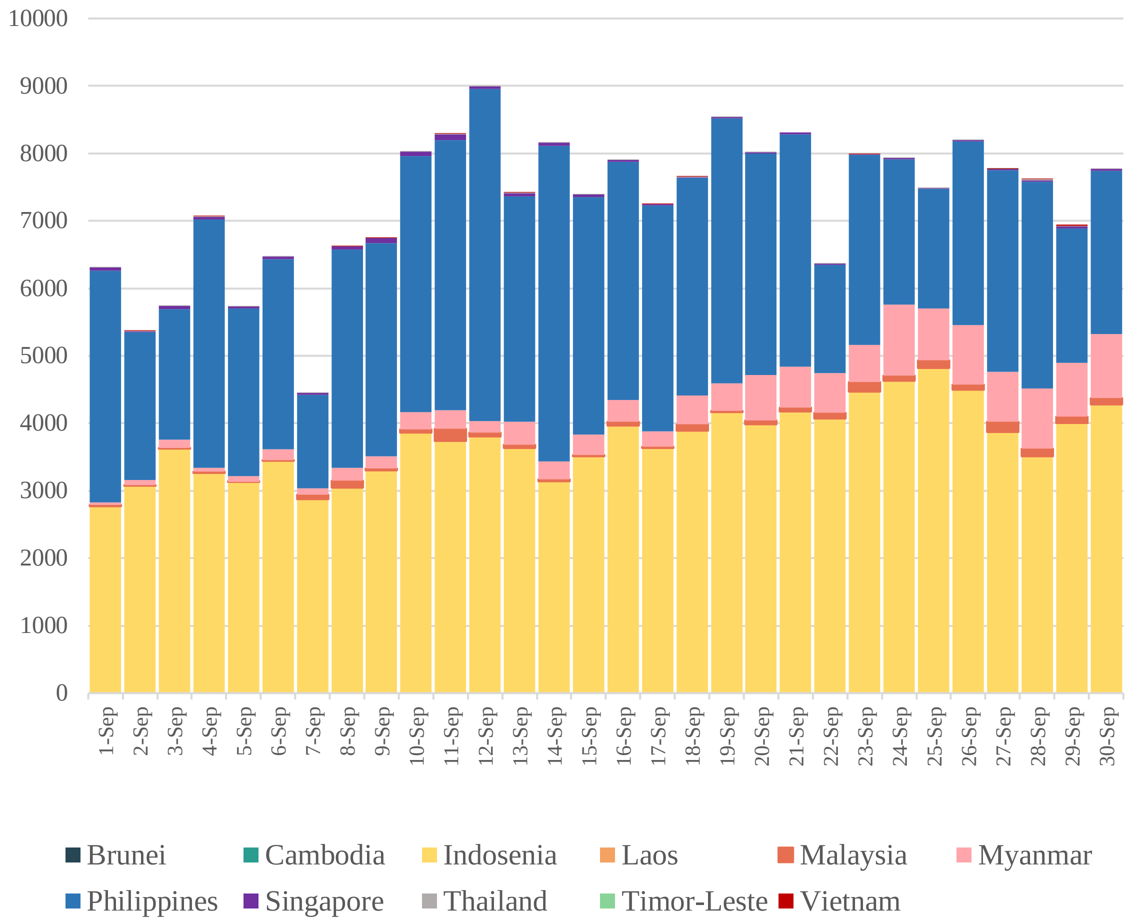
Figure 1**.** The geographic distribution of COVID-19 in Southeast Asia.



A, the geographic distribution of COVID-19 cumulative cases in Southeast Asia as of September 30, 2020 and area of the yellowish circles representedhigh rate of new cases diagnosed in September 2020. The data were attained from World Health Organization; B, the geographic distribution of COVID-19 deaths in Southeast Asia as of September 30, 2020. The data were attained from World Health Organization.

Figure 2.Bar charts shows the daily new cases diagnosed with COVID-19 in Southeast Asian countries in September 2020.



Research highlight

Coronavirus disease 19 (COVID-19) has caused over 1.6 million deaths worldwide. Thailand announced the first confirmed case outside mainland China in January 2020. ASEAN is composed of 11 countries with a total population of more than 655 million people ranking third among all subregions in the world. The disease also spread widely across ASEAN. The current outbreak of COVID-19 has continuedto produce enormous impact on both healthcare and socioeconomic systems. ASEANare currently facingthe upward trend of newly diagnosed cases per day.

Our study indicated that acute liver injury could be found in COVID-19 infection especially in ASEAN. COVID-19 patients with transaminitis and hypoalbuminemia should raise clinical suspicion for severe disease andbe closely monitoredfor rapid disease progression.This information will be raised concerns and awareness to improve Covid 19 diagnosis and management lead to reduce morbidity and mortality of this group of patients worldwide.