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Elevated liver enzymes in hospitalized patients with COVID-19 in Singapore

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Abstract

Liver dysfunction in patients with COVID-19 (coronavirus disease 2019) has been described. However, it is not clear if the presence of abnormal liver function tests at presentation was related to underlying undiagnosed liver disease, or a result of the viral infection.

We retrospectively examined the first 554 consecutive polymerase chain reaction positive SARS-CoV-2 patients admitted from February 2020 to April 2020 to our academic medical centre. We reviewed their clinical data, chest radiography and laboratory studies obtained within 24 hour of admission.

Despite similar hemodynamic parameters, we found significant aspartate transaminase elevation (64 ± 141 vs 35 ± 23 U/L, $P < .001$) in those with pneumonia compared to those without. Elevated liver enzymes were seen in 102 patients (18.4%). They presented with higher temperatures (38.5 ± 0.9 vs 37.5 ± 0.8 degC, $P = .011$), higher total white cell counts (6.95 ± 2.29 vs 6.39 ± 2.19 x10^9/L, $P = .021$), serum ferritin (240 ± 274 vs 165 ± 198 ng/ml, $P = .002$) and lactate dehydrogenase (632 ± 912 vs 389 ± 107 U/L, $P < .001$). These patients were more likely to require intensive care (6.9% vs 2.7% $P = .036$) and mechanical ventilation (5.9% vs 2.2%, $P = .046$). Migrant workers from dormitories had a higher rate of baseline liver function test abnormalities (88/425 vs 14/129, $P = .01$), which were more likely to persist at the time of discharge.

Despite relatively mild COVID-19 disease, there was a significant prevalence of liver dysfunction, particularly amongst migrant workers. Elevated liver enzymes were associated with more severe disease, despite similar haemodynamic characteristics. Future studies should explore whether pre-existing liver disease may predispose to more severe COVID-19 disease.

Abbreviations: ALP = alkaline phosphatase, ALT = alanine transaminase, AST = aspartate transaminase, COVID-19 = coronavirus disease 2019, LDH = lactate dehydrogenase, LFT = liver function test, NAFLD = non-alcoholic fatty liver disease, ULN = upper limit of normal.

Keywords: coronavirus disease 2019, Singapore, transaminitis

1. Introduction

Coronavirus Disease 2019 (COVID-19), caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), is a global public health crisis. Since late 2019, the virus spread globally at an unprecedented rate.[1] The high infectivity, even amongst those who are pre-symptomatic, led to its rapid global spread. Early studies on transmission dynamics suggests rapid human-to-human transmission.[2] Over time, the disease and its

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various manifestations have been studied comprehensively. Whilst COVID-19 was thought to be a predominantly respiratory disease, it has been shown that multi-system organ dysfunction can occur.[3]

Prior studies had demonstrated that liver function test abnormalities seen with COVID-19 may be demonstrated in up to a third of patients. The liver dysfunction that had been described also had varying degrees of severity.[4] The most common abnormalities seen are elevations in the serum aminotransferases such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST).[5] Beyond transient elevations in transaminases, some patients may experience severe liver injury and develop liver failure.[6] However, the mechanisms underpinning these derangements, as well as the long-term sequelae of this liver dysfunction remains to be studied. The role of pre-existing liver dysfunction in patients with SARS-CoV-2 infection has also not been well characterized.

Of interest, there were also significant differences in the reported geographical distribution of liver dysfunction related to COVID-19. The proportion of patients with liver dysfunction were higher in areas that had reported more intense outbreaks of infection. For example, within China, a larger proportion of cases had liver dysfunction within Wuhan province (where the epidemic had been first reported), compared with the cases outside of Wuhan, China.[7,8]

In Singapore, the COVID-19 pandemic began with cases in returning travellers, followed by clusters within the local population and finally, a large and sustained outbreak within migrant worker dormitories, which are comprised predominantly of young, male laborers of Indian or Bangladeshi descent.[9–12] Between February to April 2020, the majority of these patients were hospitalised primarily for isolation, permitting us to examine clinical and biochemical characteristics of those with asymptomatic and mild COVID-19 disease.[13] We describe the prevalence and characteristics of the patients with COVID-19-related liver dysfunction in hospitalised patients with confirmed COVID-19 in Singapore, within the first three months of the pandemic. We followed these patients for clinical outcomes within their hospital stay.

2. Methods

2.1. Study population

All consecutive patients (n = 554) who had been admitted to our tertiary healthcare institution from February to April 2020 with confirmed COVID-19 illness based on a positive polymerase chain reaction test from a nasopharyngeal swab were reviewed. There were no patients who were excluded or lost to follow-up. We retrospectively accessed the electronic medical records to collect data for each patient, including each patient's demographic background, past medical history, and clinical presentation. None of our patients had known liver disease prior to admission. All 554 patients had baseline laboratory tests that included liver function tests (LFT), and chest X-rays obtained within 24 h of admission. We followed these patients for clinical outcomes during their hospital admission, tabulating those patients who required intensive care, mechanical ventilation and experienced adverse clinical outcomes such as myocarditis/myocardial injury, kidney injury, and death. Repeat LFTs were not mandated prior to discharge, and had been left to each physician's discretion. A proportion of patients with elevated transaminases had serial LFTs performed during the admission. For these patients, we compared the LFT closest to discharge with the initial LFT obtained within 24 hours of admission.

2.2. Definitions

The presenting day of illness was computed based on the number of days from symptom onset to the day of presentation at the hospital. Symptoms were defined as fever (>38.0 degC), cough, rhinorrhoea or sore throat. Persistent fever was defined as a fever lasting over a 72-hour period. Pneumonia was defined by the presence of radiographic evidence of infiltrates on plain chest radiograph or computed tomography (if performed). For the purpose of this study, severe COVID-19 disease was defined as those who developed COVID-19 pneumonia which required monitoring or mechanical ventilation in an intensive care unit admission. Elevated liver enzymes were defined as any value above the upper limit of normal. Laboratory reference ranges for each of the liver enzymes are as follows; AST: 10–50 U/L, ALT): 10 to 70 U/L, alkaline phosphate (ALP): 40 to 130 U/L, lactate dehydrogenase (LDH): 250 to 580 U/L. Imported cases were defined by those who acquired COVID-19 overseas and returned to Singapore. Locally-transmitted non-dormitory cases were defined as those who acquired COVID-19 in Singapore, having not travelled overseas and who did not live in a foreign worker dormitory. Migrant worker dormitory cases were defined as those with COVID-19 who lived in foreign worker dormitories in Singapore.

2.3. Statistical analyses

We divided the study population based into two groups based on the presence of elevated transaminases on a LFT done on admission. We compared the baseline clinical and laboratory characteristics of those with elevated liver enzyme levels at admission and those normal liver enzyme levels. To compare these groups, Student *t*-tests were used for continuous parameters and the data was presented in the form of means (±standard deviation). Student *t*-tests were carried out only for parameters that followed a normal distribution. Categorical parameters were compared by Chi-squared tests, and the data was presented in frequencies and percentages. A multivariable logistic regression was used to determine which factors were associated with elevated LFTs at presentation. For the proportion of patients with repeat LFTs prior to discharge, we compared the initial LFT on admission and prior to discharge by means of paired t-tests. Characteristics of patients who had resolved LFTs and persistently deranged LFTs prior to discharge were also compared. A *P*-value of less than .05 was considered significant. All data analysis was done on SPSS version 20.0 (SPSS, Inc., IBM Corp, Armonk, NY). This study was approved by the hospital's institutional review board (National Healthcare Group Domain Specific Review Board 2020/00545) prior to the conduct of the study. Data collected was anonymised and a waiver of informed consent had been obtained from the institutional review board.

3. Results

3.1. Baseline characteristics

Of the 554 consecutive patients reviewed, 102 patients (18.4%) had elevated liver enzyme levels based on liver function tests (LFT) on admission. Patients with abnormal LFT were similar to

Table 1

Characteristics of patients with or without elevated liver enzymes on admission.

Parameter	Elevated liver enzymes (n = 102)	Normal liver enzymes (n = 452)	*P*-value
Age (yr)	35 (±11)	37 (±11)	.088
Male gender	97 (95.1%)	381 (85.0%)	.007
Ethnicity			.419
Chinese	12 (11.8%)	79 (17.5%)	
Malay	5 (4.9%)	29 (6.4%)	
Indian	36 (35.3%)	163 (36.1%)	
Bangladeshi	43 (42.2%)	132 (29.2%)	
Others	6 (5.9%)	49 (10.8%)	
Exposure history			.037
Overseas exposure	4 (3.9%)	25 (5.5%)	
Local non-dormitory transmission	10 (9.8%)	90 (19.9%)	
Dormitory cases	88 (86.3%)	337 (74.6%)	
Hypertension	8 (9.4%)	45 (13.0%)	.370
Hyperlipidaemia	8 (9.5%)	26 (7.7%)	.581
Diabetes mellitus	3 (3.6%)	18 (5.5%)	.483
Temperature (degC)	38.5 (±0.9)	37.5 (±0.8)	.011
Systolic blood pressure (mm Hg)	131 (±14)	130 (±18)	.546
Diastolic blood pressure (mm Hg)	81 (±14)	81 (±12)	.842
Pulse rate (per min)	97 (±19)	94 (±19)	.158
Respiratory rate (per minute)	20 (±7)	19 (±6)	.736
SpO2 (%)	98 (±4)	98 (±2)	.165
Day of illness at presentation	3.7 (±5.4)	3.4 (±4.9)	.551
Laboratory findings			
Total white cell count (x10^9/L)	6.95 (±2.29)	6.39 (±2.19)	.021
Lymphocyte count (x10^9/L)	1.89 (±1.05)	1.90 (±2.18)	.972
Creatinine (μmol/L)	88.4 (±58.2)	77.3 (±17.8)	.001
C-reactive protein (mg/L)	18.3 (±33.8)	12.9 (±25.4)	.080
Ferritin (ng/ml)	240.0 (±273.5)	164.7 (±197.7)	.002
Albumin (g/L)	43.6 (±7.9)	43.2 (±18.5)	.814
Total Bilirubin (μmol/L)	13 (±7)	12 (±8)	.306
Unconjugated Bilirubin (μmol/L)	10 (±4)	9 (±5)	.375
Conjugated Bilirubin (μmol/L)	3 (±4)	2 (±1)	.001
AST (U/L)	75 (±99)	29 (±9)	<.001
ALT (U/L)	101 (±70)	32 (±15)	<.001
ALP (U/L)	91 (±51)	83 (±24)	.020
LDH (U/L)	632 (±912)	389 (±107)	<.001
Medications			
Hydroxychloroquine	2 (2.4%)	1 (0.3%)	.109
Lopinavir/Ritonavir	8 (9.2%)	29 (8.5%)	.844
Remdesivir	2 (2.4%)	16 (4.8%)	.335
Outcomes			
Pneumonia	14 (13.7%)	43 (9.5%)	.206
Acute kidney injury	12 (11.8%)	33 (7.3%)	.136
Requiring oxygen	2 (2.0%)	14 (3.1%)	.536
Required intensive care	7 (6.9%)	12 (2.7%)	.036
Required mechanical ventilation	6 (5.9%)	10 (2.2%)	.046
Persistent fever >72h	10 (9.9%)	30 (6.7%)	.260
Myocarditis/myocardial injury	2 (2.4%)	1 (0.3%)	.048
Death	0 (0.0%)	2 (0.6%)	.474
Length of hospital stay (d)	13.0 (±14.9)	10.0 (±12.5)	.037

AST = aspartate transaminase, ALT = alanine transaminase, ALP = alkaline phosphatase, LDH = Lactate dehydrogenase.

those with normal LFT in terms of age (35 ± 11 vs 37 ± 11 years, $P = .088$), but were more likely to be male (95.1% vs 85.0%, $P = .007$) and more likely to be migrant workers (86.3% vs 74.6%, $P = .037$) (Table 1). Those with elevated liver enzyme levels presented with a higher temperature on admission (38.5 ± 0.9 vs 37.5 ± 0.8 degC, $P = .011$), but otherwise had similar hemodynamics. Patients with elevated liver enzyme levels also had higher total white cell count (6.95 ± 2.29 vs 6.39 ± 2.19 x10^9/L, $P = .021$), higher ferritin (240 ± 274 vs 165 ± 198 ng/ml, $P = .002$), LDH (632 ± 912 vs 389 ± 107 U/L, $P < .001$), and were more likely to require intensive care (6.9% vs 2.7% $P = .036$) and mechanical ventilation (5.9% vs 2.2%, $P = .046$) (Table 1).

Table 2

Migrant workers from dormitories were more likely to have elevated liver enzymes at presentation in a multivariable analysis.

Parameter	Adjusted Odds Ratio (95% Confidence Interval)	*P*-value
Older age (>40 yr old)	1.79 (1.04–3.05)	.034
Fever at presentation	1.05 (0.67–1.64)	.833
Elevated C-reactive protein (>60mg/L)	4.69 (1.91–11.49)	.001
Migrant workers from dormitories	2.11 (1.10–4.00)	.024

3.2. Multivariable analyses

On multivariable analyses, migrant workers from dormitories were found to be independently more likely to have elevated liver enzymes on admission (adjusted odds ratio 2.11, 95% CI 1.10–4.00, $P = .024$) (Table 2), after adjusting for age, fever and whether C-reactive protein levels were elevated on admission. This multivariable model was a good fit to the data (Hosmer and Lemeshow chi-square 4.23, $P = .375$), and correctly classified the outcome 81.2% of the time.

3.3. Subgroup analyses: patients with elevated liver enzymes

Of the 102 patients with raised liver enzymes, 78 patients (76.5%) had elevated AST and 75 patients had elevated ALT (75.5%), and 53 (51.9%) patients had both enzymes elevated. Elevated ALP and bilirubin were seen in 8 (7.8%) and 4 (3.9%) patients respectively. The mean AST, ALT and ALP values were 75 (±99) (upper limit of normal [ULN]: 50), 101 (±70) (ULN: 70) and 91 (±51) (ULN: 130) U/L respectively.

Of the 102 patients with elevated liver enzyme levels on admission, 48 (47.1%) had repeat LFTs prior to discharge. There was a significant decrease in AST from 75 ± 99 to 48 ± 19 U/L ($P = .021$) and LDH from 644 ± 77 to 438 ± 174 U/L ($P = .044$), with no significant change in ALT, ALP or total bilirubin prior to discharge (Fig. 1). 12 out of 48 (25%) had resolved LFTs at time of discharge, while the remaining 75% had persistently abnormal LFTs (Table 3). Patients with pneumonia were more likely to have LFTs which resolved prior to discharge. Patients with persistently abnormal LFTs were younger (36.8 ± 9.7 vs 47.1 ± 15.3 years, $P = .014$), and were more likely to be migrant workers from dormitories (88.9% vs 50.0%, $P = .009$).

Due to cost limitations, only 28 patients underwent viral hepatitis screening. 5 of these patients had a positive Hepatitis B core total antibody and none had a detectable viral load or surface antigen. Hepatitis C total antibody was negative for all tested. 3 patients, all migrant workers, who had persistently raised LFT despite mild COVID-19 disease, underwent ultrasound scans of the liver, all three of which demonstrated hepatic steatosis likely secondary to non-alcoholic fatty liver disease (NAFLD).

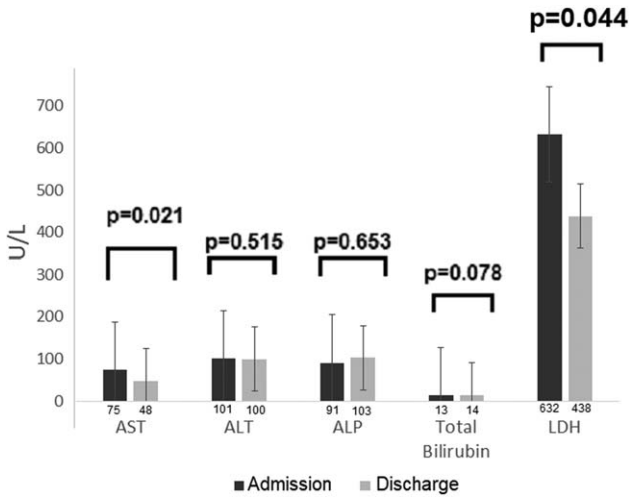

Figure 1. LFT of patients with COVID-19 and elevated liver enzymes at admission and at discharge. COVID-19 = coronavirus disease 2019, LFT = liver function test.

4. Discussion

In a recent review by Jothimani et al, a substantial proportion (starting at 25%) of COVID-19 patients across multiple observational studies had elevated LFT, with transaminase levels increasing as disease severity increased, typically in patients with pneumonia.[14] Following that review, several large meta-analyses have also reported similar trends where elevated liver enzymes correlated with increasing severity of disease in patients with COVID-19.[15–17] Our study population offers unique insight into patients with asymptomatic or mild COVID-19 illness, with only 57 out of 554 patients (10.3%) developing pneumonia. We studied a heterogenous cohort of patients ranging from young and fit migrant workers, to an older local population with a greater number of comorbidities. Amongst this diverse background of our study cohort, we demonstrated that elevated liver enzymes were seen in patients who required intensive care and mechanical ventilation, much as the previous literature has shown. We also showed that younger migrant workers with much milder forms of COVID-19 illness also had elevated liver enzymes on admission to hospital.

Of note, a prior study based on a Chinese cohort had shown that elevated liver enzymes were associated with increased mortality.[18] Our study demonstrated that elevated liver enzymes had been seen in association with the need for mechanical ventilation and intensive care, but did not show this association with mortality. Importantly, the cohorts studied were significantly different. We studied a cohort of predominantly young migrant workers with few medical co-morbidities (mean age of 36 years, compared with 60 years in the prior study).[18] As a result, mortality was too low in our population (2/554, 0.4%) to demonstrate significant trends, compared with the higher mortality (63/2797, 2.3%) in the prior Chinese study.[18]

Those with elevated liver enzymes on admission were indeed at elevated risk of requiring ICU support (23.2% versus 1.2%, $P = .036$). In our cohort only 19/554 (3.4%) patients developed pneumonia requiring ICU support. The co-existing presence of elevated creatinine and ferritin levels in those patients with COVID-19 pneumonia supports the well described systemic inflammation seen in patients with moderate-to-severe forms of COVID-19.[7,8,14] Indeed, as patients with COVID-19 pneumonia improved, liver enzymes elevations were also seen to improve.

Amongst patients with serial liver function tests, AST and LDH were more likely to decrease significantly by the time of discharge, whereas ALT and ALP were unchanged. Amongst liver enzymes, AST and LDH have the shortest half-lives, compared with ALT and ALP.[19] Thus in a patient recovering from acute COVID-19 illness, AST and LDH may be earlier markers of improvement of COVID-19 related hepatic dysfunction compared with ALT and ALP.

Liver injury has been reported in patients with influenza as well as Middle East Respiratory Syndrome, Severe Acute Respiratory Syndrome (SARS), all of which can cause serious pneumonias in the immunocompetent host.[20] Several mechanisms have been postulated to explain liver injury in COVID-19. Since ACE-2 receptors, the main portal of entry of SARS-CoV-2 into cells, have been found more abundantly on cholangiocytes of the bile duct compared with hepatocytes,[21] direct cellular injury by SARS-CoV-2 should result in biliary inflammation and thus an obstructive pattern of liver injury rather than the hepatocellular pattern seen in our cohort and others.[4]

Other mechanisms of injury may be drug induced or cytokine driven injury. In animal models of influenza, even in the absence of viral replication within the liver, the production of inflammatory cytokines resulted in hepatic oxidative stress which leads to hepatocellular injury.[20] Patients with severe disease may also have liver injury secondary to an ischaemic insult, which is classically seen to improve quickly with reperfusion of the organ.[22–25] Only a small proportion of these patients progress to fulminant liver failure, which had not been observed in our cohort.[25] Regardless of the mechanism of injury, data from this study and others suggests that liver injury which occurs as a consequence of moderate to severe COVID-19 disease may be reversible.

More surprising was the finding that younger and fitter migrant workers, who were asymptomatic or had mild COVID-19, had liver enzyme level elevations on admission. Multivariable analysis showed that being a migrant worker from a dormitory was an independent risk factor (adjusted OR 2.11, 95% CI 1.10–4.00, $P = .024$) for liver enzyme elevated levels on admission. This young and otherwise well cohort (largely asymptomatic or with mild COVID-19 illness) were also surprisingly more likely to

Table 3

Characteristics of patients with resolved LFTs compared with those with persistently deranged LFTs at discharge.

Parameter	Resolved LFTs (n = 12)	Persistently deranged LFTs (n = 36)	*P*-value
Clinical profile			
Age	47.1 (±15.3)	36.8 (±9.7)	.014
Male gender	10 (83.3%)	34 (94.4%)	.257
Hypertension	4 (33.3%)	3 (8.3%)	.037
Hyperlipidaemia	4 (33.3%)	3 (8.3%)	.037
Diabetes mellitus	2 (16.6%)	0 (0.0%)	.040
Migrant worker from dormitories	6 (50.0%)	32 (88.9%)	.009
Outcomes			
Pneumonia	7 (58.3%)	4 (11.1%)	.002
Required intensive care	4 (33.3%)	2 (5.6%)	.028
Required mechanical ventilation	4 (33.3%)	2 (5.6%)	.028

LFT = liver function test.

have persistently abnormal LFTs at time of discharge (88.9% vs 16.6%, $P = .009$). The asymptomatic or mild nature of COVID-19 disease at presentation in the cohort of migrant workers, and particularly the failure of the LFT elevations to normalise prior to discharge, suggests that the persistently elevated liver enzymes in this group were unlikely to be from the acute COVID-19 illness alone.

We postulate that an underlying, pre-existing liver disease coupled with acute COVID-19 infection, resulted in the elevated liver enzyme levels seen in this cohort of otherwise well migrant workers. 82 (80.4%) of patients with raised liver enzyme levels had an AST/ALT ratio of <1 which supports the possibility that they may have had underlying NAFLD as contributory factor to the elevated liver enzyme seen.[26–28] Migrant workers, who are of East Asian and South Asian descent (n = 125, 22.6%; n = 374, 67.5% respectively in our cohort), are at increased risk of NAFLD (30–40% prevalence based on epidemiologic studies).[26] Even though the migrant workers were non-obese with a low prevalence of diabetes mellitus (n = 3, 2.9%), non-obese NAFLD has been reported to occur in up to 19% of Asians[26,29] making underlying NAFLD in our cohort of migrant workers a possibility. Indeed, all three migrant workers who had ultrasound examinations of the liver to investigate persistently elevated LFT levels demonstrated fatty infiltration on sonography.

Alternative aetiologies of raised liver enzyme levels in this group were not found when sought: whilst 5 patients had a positive Hepatitis B Core Total antibody, none had any detectable Hepatitis B viral load on polymerase chain reaction. None were found to have hepatitis C. The finding of persistently elevated liver enzymes could have been confounded by the fact that these healthier dormitory workers were discharged to community isolation facilities earlier and thus, normalisation of LFTs, if it did occur, could not be captured. This is in contrast with patients with more severe disease and co-morbidities had longer hospital stays and thus we were more likely to be able to observe the normalization of elevated liver enzyme levels over time.[14]

4.1. Limitations

We examined a single-centre, but moderately-sized cohort of patients. The study was observational and retrospective, including consecutive patients diagnosed and hospitalised with COVID-19. Patients who were managed in community care facilities outside of tertiary hospitals could not therefore be included. We only followed the clinical progress of patients within the initial hospital admission, and were not able to longitudinally examine patients for long-term sequelae of the disease. Only a minority of patients could afford ultrasound examinations of the liver and screening for viral hepatitis which could have further elucidated the cause of raised LFT in the migrant worker population. Body mass index (BMI) was also not routinely assessed for each patient which if done could have added to our hypothesis that NAFLD was contributory to raised LFT in this group. Finally, a prospective observational study which examines medications used prior to admission, BMI and waist-circumference, presence of viral hepatitis, quantification of alcohol use, further longitudinal LFT measurements and liver imaging would have allowed us to better delineate causality, clinical course and associations of liver enzymes changes in the acute course of COVID-19.

5. Conclusions

There was a significant prevalence of liver dysfunction in hospitalised patients with COVID-19 illness in Singapore. A higher proportion of patients with liver dysfunction on admission required intensive care and mechanical ventilation. Liver enzyme elevations were generally found to occur in two separate groups. The first was a more unwell cohort with pneumonia, where LFT elevated normalised as pneumonia resolved. The second group comprised of relatively well migrant worker population. We postulate that underlying undiagnosed liver disease in the second group may account for this. Future prospective studies of COVID-19 in this specific population should be done to investigate this, particularly in the event of a future dormitory outbreak.

Author contributions

JNN, NC, SMT, ZYL, TL, SYC and CHS contributed to the acquisition of data, statistical analysis, drafting and critical revision of the manuscript. PAT, AS, MM and GBC contributed to the study concept and design, statistical analysis, and critical revision of the manuscript.

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References

[1] Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020;382:727–33.
[2] Li Q, Guan X, Wu P, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med 2020;382:1199–207.
[3] Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507–13.
[4] Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. Lancet Gastroenterol Hepatol 2020;395:428–30.
[5] Liu C, Jiang ZC, Shao CX, et al. Preliminary study of the relationship between novel coronavirus pneumonia and liver function damage: a multicenter study. Zhonghua Gan Zang Bing Za Zhi 2020;28:148–52.
[6] Wu Y, Ma Z, Guo X, et al. Characteristics and in-hospital outcomes of COVID-19 patients with abnormal liver biochemical tests [published online ahead of print, 2021 Apr 20]. Ann Hepatol 2021;24:100349.

[7] Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497–506.
[8] Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. JAMA 2020;323:1061–9.
[9] Lim RJ, Lee TH, Lye DCB. From SARS to COVID-19: the Singapore journey. Medical Journal of Australia 2012;212:497–502.
[10] Ngiam JN, Tham SM, Vasoo S, Poh KK. COVID-19: Local lessons from a global pandemic. Singapore Med J 2020;61:341–2.
[11] Koh D. Migrant workers and COVID-19. Occup Environ Med 2002; 77:634–6.
[12] Bagdasarian N, Fisher D. Heterogenous COVID-19 transmission dynamics within Singapore: a clearer picture of future national responses. BMC Med 2020;18:164.
[13] Ngiam JN, Chew N, Tham SM, et al. Demographic shift in COVID-19 patients in Singapore from an aged, at-risk population to young, migrant workers with reduced risk of severe disease. Int J Infect Dis 2021; 103:329–35.
[14] Jothimani D, Venugopal R, Abedin MF, Kaliamoorthy I, Rela M. COVID-19 and the liver. J Hepatol 2020;73:1231–40.
[15] Del Zompo F, De Siena M, Ianiro G, Gasbarrini A, Pompili M, Ponziani FR. Prevalence of liver injury and correlation with clinical outcomes in patients with COVID-19: systematic review with meta-analysis. Eur Rev Med Pharmacol Sci 2020;24:13072–88.
[16] Sharma A, Jaiswal P, Kerakhan Y, et al. Liver disease and outcomes among COVID-19 hospitalized patients - A systematic review and meta-analysis. Ann Hepatol 2021;21:100273.
[17] Wu ZH, Yang DL. A meta-analysis of the impact of COVID-19 on liver dysfunction. Eur J Med Res 2020;25:54.
[18] Wu Y, Ma Z, Guo X, et al. Characteristics and in-hospital outcomes of COVID-19 patients with abnormal liver biochemical tests. Ann Hepatol 2021;24:100349.
[19] Giannini EG, Testa R, Savarino V. Liver enzymes alteration: a guide for clinicians. CMAJ 2005;172:367–79.
[20] Papic N, Pangercic A, Vargovic M, Barsic B, Vince A, Kuzman I. Liver involvement during influenza infection: perspective on the 2009 influenza pandemic. Influenza Other Respir Viruses 2012;6:e2–5.
[21] Kukla M, Skonieczna-Zydecka K, Kotfis K, et al. COVID-19, MERS and SARS with concomitant liver injury—systematic review of the existing literature. J Clin Med 2020;9:1420.
[22] Botta M, Tsonas AM, Pillay J, et al. PRoVENT-COVID Collaborative GroupVentilation management and clinical outcomes in invasively ventilated patients with COVID-19 (PRoVENT-COVID): a national, multicentre, observational cohort study. Lancet Respir Med 2020;9: 139–48.
[23] Cai Q, Huang D, Ou P, et al. COVID-19 in a designated infectious diseases hospital outside Hubei Province, China. Allergy 2020;75: 1742–52.
[24] Waseem N, Chen PH. Hypoxic hepatitis: a review and clinical update. J Clin Transl Hepatol 2016;4:263–8.
[25] Wu Y, Ma Z, Guo X, et al. Clinical characteristics and outcomes of COVID-19 patients with hypoxic hepatitis. Clin Res Hepatol Gastroenterol 2021;45:101665.
[26] Fan GJ, Kim SU, Wong VWS. New trends on obesity and NAFLD in Asia. J Hepatol 2017;67:862–73.
[27] Sattar N, Forrest E, Preiss D. Non-alcoholic fatty liver disease. BMJ 2014;349:g4596.
[28] Ji D, Qin E, Xu J, et al. Non-alcoholic fatty liver diseases in patients with COVID-19: a retrospective stdudy. J Hepatol 2020; 73:451–3.
[29] Huang R, Zhu L, Wang J, et al. Clinical features of patients with COVID-19 with nonalcoholic fatty liver disease. Hepatol Commun 2020; 4:1758–68.