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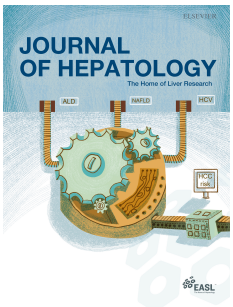

COVID-19 and Liver.

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Title page

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Abstract:

The current pandemic coronavirus labelled as Severe Acute Respiratory Distress Syndrome Coronavirus -2 (SARS -CoV-2) is a significant public health threat over for past few weeks. Overall case fatality rates range between 2-6%; however, the rates are higher in patients with severe disease, advanced age and underlying comorbidities like diabetes, hypertension and heart disease. Recent reports showed about 2-11% of patients with COVID-19 had underlying chronic liver disease. Experience from previous SARS epidemic suggest that 60% of patients developed various degrees of liver damage. In the current pandemic, hepatic dysfunction was seen in 14-53% of patients with COVID-19, particularly in those with severe disease. Cases of acute liver injury have been reported, associated with higher mortality. Hepatic involvement in COVID-19 could be multifactorial related to any of direct cytopathic effect of the virus, uncontrolled immune reaction, sepsis or drug induced liver injury. The postulated mechanism of viral entry is through the host ACE2 receptors that are abundantly present in type 2 alveolar cells. Interestingly, the expression of ACE2 receptors were identified in the gastrointestinal tract, vascular endothelium and cholangiocytes of the liver. Liver transplant recipients with COVID-19 have been reported recently. Effects of COVID-19 on underlying chronic liver disease requires a detailed evaluation and currently data is lacking and further research is warranted in this area. With lack of definitive therapy, patient education, hand hygiene and social distancing appears to be the cornerstone in minimising the disease spread.

Key points:

1. COVID-19 is a pandemic caused by SARS-CoV-2 and this virus has 80% homology with SARS-CoV.
2. In addition to droplets, SARS-CoV-2 also transmits through faeco-oral route.
3. ACE2 present in the alveolar cells (type 2) is the host cell receptor for SARS-CoV-2. ACE2 is abundantly found in gastrointestinal tract and liver.
4. The level of ACE2 expression in cholangiocytes (59.7%) is similar to type 2 alveolar cells.
5. 2-11% of patients with COVID-19 were reported to have underlying chronic liver disease
6. 14-53% of patients with COVID-19 developed hepatic dysfunction.
7. Hepatic dysfunction was significantly higher in critically ill patients and was associated with poor outcome.
8. Cases of acute liver injury have been reported with high mortality,

Introduction

Coronavirus is an enveloped single stranded RNA virus, belonging to the Coronaviridae family and Orthocoronavirinae subfamily. It is one of the largest viruses with size from 27-34 kilobase. Coronavirus infection commonly seen in mammals and birds, ranging from upper respiratory tract infection to diarrhoea. It is a zoonotic infection for humans causing respiratory tract infection. Electron microscopic images shows a 'halo' or 'crown' around the virus and hence the name. Previously, Coronavirus was associated with Severe Acute Respiratory Syndrome (SARS) in 2003 and Middle Eastern Respiratory Syndrome (MERS) in 2012 caused by SARS-CoV and MERS-CoV, respectively.

The current pandemic coronavirus has been labelled as Severe Acute Respiratory Distress Syndrome Coronavirus 2 (SARS-CoV-2) by the International Taxonomy group. Genome sequencing analysis showed SARS-CoV-2 is possibly a chimeric variant of bat coronavirus identified in 2015 by Benvenuto and Colleagues[1]. WHO coined the disease caused by SARS-CoV-2 as Coronavirus Disease-2019 (COVID-19) on 11th February 2020. Recent viral detection studies by Zhou and colleagues[2] showed an 80% homology between SARS-CoV (2003 pandemic) and the current novel coronavirus.

Previously with the SARS epidemic, around 60% of patients developed various degrees of liver damage. Due to phylogenetic resemblance it is possible that SARS-CoV-2 also causes liver injury.

Epidemiology:

Several cases of severe unexplained pneumonia were reported from Wuhan, China in December 2019. Bronchoalveolar lavage from an index case was identified as novel Coronavirus (COVID-19) on 3rd January 2020 by Zhu and colleagues[3] and subsequently WHO announced this disease as an 'epidemic'. With rapid increase in COVID-19 infection across the world, WHO declared this as a 'pandemic' on 11th March 2020, an emergency public health situation. Wuhan was the initial epicentre for COVID-19, where first 41 cases of severe pneumonia were reported following exposure to bats and pangolins at the Huanan Seafood Wholesale market[4]. Subsequent cases were reported from the same locality by Chen and colleagues[5]. However, several patients in the outbreak did not have exposure to animals, indicating person to person droplets spread a high possibility.

WHO report as of 19th May 2020, confirmed 4,731,458 COVID-19 positive cases from 213 countries worldwide of which 1,477,516 cases were reported in United States of America, 231,606 cases in Spain, 225,886 cases in Italy, 246,410 in United kingdom, China the starting point of this pandemic has 84,500 cases and India has recorded 101,139cases [6]. These data indicate the rapid spread of the disease around the world, with a doubling rate of 7.2 days.

Mechanism of injury in COVID-19

Similar to SARS Co-V, Angiotensin Converting Enzyme2 (ACE2) appears to be the susceptible receptor for COVID-19 and is expressed in more than 80% of alveolar cells in the lungs. Invitro Studies from SARS CoV epidemic identified ACE2 as the host receptor for viral entry[7].Immunohistochemistry studies from human tissues during SARS pandemic showed, higher expression of ACE2 receptor protein in vascular endothelium of small and large arteries and veins. In the lungs, type 2 alveolar cells highly expressed ACE2. Interestingly, fibrotic lungs had much higher staining for ACE2; whereas bronchial epithelial cells showed weaker expression. Interestingly, a latest study showed SARS Co-V-2 possessed 10-20-fold higher receptor binding affinity[8]. In addition to respiratory system, ACE2 receptors are expressed in the gastrointestinal tract. Nasal, oral and nasopharyngeal mucosa highly express ACE2 in the basal layer of the squamous epithelium. Smooth muscles of gastric, intestinal colonic mucosa also express ACE2. In addition, brush borders of enterocytes of duodenum, jejunum and ileum abundantly express ACE2[9].

Hepatic expression of ACE2 is peculiar. It is highly expressed in the endothelial layer of small blood vessels. Interestingly sinusoidal endothelium does not express ACE2. A latest study by Chai and colleagues[10] found a higher expression of ACE2 cell surface receptor in cholangiocytes (59.7%) than hepatocytes (2.6%). Interestingly, the level of ACE2 expression in cholangiocytes was similar to type 2 alveolar cells of the lungs, indicating that the liver could be a potential target for SARS-CoV-2. Immunohistochemistry stains were negative on Kupffer cells, T and B lymphocytes.

A recent study from Wuhan showed Asian men had higher expression of ACE2, indicating the possibility of higher susceptibility for COVID-19 in this population[11,12].

Transmission:

SARS CoV-2 started as a zoonotic infection; however, the disease spread rapidly from person to person through coughing and sneezing, particularly amongst close contacts. SARS CoV-2 is resilient and can remain viable for 2 hours to 14 days depending on the fomite and the weather condition[13].

The transmission potential of an infection in the community is based on its basic reproduction rate which is usually denoted as disease transmission ratio (R0). This represents the number of secondary cases occurred from an index case in a susceptible population. The (R0 - R naught) of COVID-19 is 2.2[14].

Previous studies showed 19.6% to 73% of patients with SARS presented with gastrointestinal symptoms [15-17]. Active replication of SARS Co-V was detected in the enterocytes of small intestine [15]. Moreover, SARS Co-V RNA was detected in patients stool samples during the SARS pandemic [15-17], which lead to the possibility of faeco-oral transmission Similar pattern was observed with SARS Co-V-2; between 3% and 79% of patients with COVID-19 developed gastrointestinal symptoms predominantly with nausea, vomiting and diarrhoea. Zhang et al., found 53.3% and 26.7% of oral and anal swabs positive for COVID-19 RNA, respectively. The same study group performed paired samples on a different cohort of COVID-19 patients and found that on day 0, 80%of patients were positive on oral swabs whereas on day 5, 75% of patients were positive on anal swabs, indicating the dynamic changes in the viral tests during the course of the illness[19]. Xiao and colleagues[20] showed patients

with SARS CoV-2 related respiratory illness can continue to shed virus in stool even after a negative respiratory sample. In a series of 73 patients with COVID-19, about 53.42% had detectable RNA in stool sample, of which about 23.29% continued to have positive RT-PCR for SARs -CoV-2 RNA in faecal sample even after they have tested negative for respiratory sample [20]. Yeo and colleagues[21] showed faecal shedding can continue to occur for a longer period after clinical recovery and these patients can potentially infect others. These features illustrate multiple routes of viral entry in a single host and viral persistence in various organ systems and possible faecal-oral transmission of SARS-CoV-2 even during the convalescence period.

Clinical features:

Initial reports from China showed incubation period of SARS-CoV-2 was between 3 to 7 days and occasionally 2 weeks. The longest incubation period identified was 12.5 days [14].

Large studies from Chinese population reported fever ($\geq 38^0$ C), dry cough, fatigue, myalgia, leukopenia and raised liver enzymes as presenting clinical features of COVID-19, as shown in (Table 1). Nausea, vomiting and diarrhoea was seen in 2-10% of patients with COVID-19.

In the latest case series from Wuhan by Wang and colleagues[22], 138 hospitalized patients (including 40 Health care workers and 17 already hospitalised for other conditions) with COVID-19; median age was 56 years (IQR, 22-92 years), with 54.3% males. Clinical features were fever (98.6%), fatigue (69.6%), dry cough (59.4%), lymphopenia $< 0.8 \times 10^9$ /L (70.3%), prolonged prothrombin time (58%), and raised lactate dehydrogenase (LDH) 261 U/L (39.9%). Thirty-six patients (26.1%) received ICU care for ARDS (61.1%), cardiac arrhythmias (44.4%) and shock (30.6%). Onset and the progression of symptoms were dramatic, with a median time from symptoms to ARDS was only 8 days. Patients requiring ICU were older (66 vs 51, years) and with comorbidities (72% vs 32%). ICU patients had higher LDH (435 vs 212, $P<0.001$), AST (52 vs 29, $P<0.001$) and hypersensitive cardiac troponin (11 vs 5.1, $P=0.004$). All 138 patients showed bilateral pneumonia in the thoracic scan. Analysis between the survivors and non-survivors showed higher white blood cell count with severe progressive lymphopenia in the non-survivors. With disease progression, these patients required organ support with progressive deterioration in renal function before death.

In the largest database analysis of 1099 confirmed COVID-19 patients from China, by Guan and colleagues[23] the median age of presentation was 47 years (IQR, 35-58 years) with 58% male. Fever (88.7%), cough (67.8%), nausea or vomiting (5%) and diarrhoea (3.8%). CT chest radiography revealed ground glass opacity (56.4%) and bilateral patchy shadows (51.8%). Of 1099 patients, 5% were admitted in the ICU, 2.3% underwent invasive ventilation and 1.4% died.

Clinical features	Wang et al[22] N =138	Zhou et al[58] N = 191	Guan et al[23] N = 1099
Fever	98.6%	94 %	88.7 %
Cough	59.4 %	79 %	67.8 %
Sputum	NA	23 %	33.7 %
Myalgia	NA	15 %	14.9%
Fatigue	69.6 %	23 %	38.1 %
Diarrhoea	NA	5 %	3.8 %
Nausea/ Vomiting	NA	4 %	5.0 %
Sore throat	NA	NA	13.9 %
Lymphopenia (< $0.8*10^9$ /L)	70.3 %	40 %	NA
Prolonged PT (> 13.5 seconds)	58 %	NA	NA
Raised LDH (> 261U/ L)	39.9 %	NA	NA

Table 1: Spectrum of clinical manifestation and their percentage of occurrence from recent studies on COVID -19 in China. PT: Prothrombin Time, NA: data not available.

COVID-19 disease was classified according to the clinical severity into three groups by the Chinese CDC by Guan and colleagues[23] as shown in Table 2.

Mild Disease (reported in 81% cases)	Fever, dry cough, mild dyspnoea (Respiratory rate<30/min).
Severe Disease (reported in 14% cases)	Dyspnoea, respiratory rate >30 and/or lung infiltrates >50% within 24 to 48 hours.
Critical Disease (reported in 5% cases)	Respiratory failure, septic shock and/or multiple organ dysfunction or failure.

Table 2: Classification of COVID-19 into 3 groups based on severity of clinical manifestations by Chinese Center for Disease Control[23].

COVID-19 and Hepatic dysfunction:

It is intriguing to know the pattern of liver injury in COVID 19. Hepatic involvement in COVID-19 could be multifactorial related to the direct cytopathic effect of the virus, uncontrolled immune reaction, sepsis or drug induced liver injury. Given the higher expression of ACE2 receptors in cholangiocytes, the liver is a potential target for SARS CoV-2. Moreover, COVID-19 may cause worsening of underlying chronic liver disease leading to hepatic decompensation and Acute on Chronic liver failure leading to mortality.

Summary of recently published studies are in described in Table 2 below. Overall, 2-11% of patients with COVID-19 were reported to have underlying chronic liver disease and 14-53% with COVID-19 developed hepatic dysfunction [24] particularly in severe COVID-19. Hepatic dysfunction was significantly higher in critically ill patients and was associated with poor outcome.

In the recent series from Wuhan, by Wang and colleagues[22], 4 patients (2.9%) with COVID-19 had underlying chronic liver disease. Another study from China Medical Treatment Expert group for COVID-19 by Guan and colleagues[23] showed 23 (2.1%) patients were positive for Hepatitis B infection (HBsAg), of which only one had severe COVID-19. Interestingly, a study from outside Wuhan by Xu and colleagues[25] identified 26 patients with COVID-19 in whom 11% had underlying chronic liver disease. In another study, comparing 113 deceased and 161 recovered COVID-19 patients showed 4% had underlying Hepatitis B positive status[26]. Cases of Acute Liver injury has been reported in 13 (5%) out of 274 patients of whom 10 (76.9%) died.[26]

With the knowledge of current evidence, it is clear that elevated liver enzymes are observed predominantly severe and critical cases of COVID-19 compared to mild infection. Raised AST was noted in 8/13 (62%) patients in ICU compared to 7/28 (25%) in the non-ICU setting [24]. The peak ALT and AST levels noted were 7590 U/L and 1445 U/l in severe COVID-19 illness, resepectively[27]. Interestingly, a higher proportion of enzyme elevation was noted in patients receiving Lopinavir/Ritonavir therapy (56.1% vs 25 %).[28]. It is unclear whether the elevated liver enzymes were due to the disease per se or drug induced liver injury. Apart from direct effects, the liver can also be involved in Systemic Inflammatory Response syndrome (SIRS) due to COVID-19 and from the adverse effects of drugs used for viral illness.

Interestingly, despite the presence of ACE2 in cholangiocytes, more patients developed raised transaminases. However, an unpublished data from Wuhan China, by Xu et al showed an increased GGT in severe cases of COVID-19[30]. However, whether COVID_19 aggravates cholestasis in patients with PBC and PSC need further analysis in this subgroup[31]. Larger data is required to ascertain the pattern and the degree of liver injury in patients affected with COVID-19.

Table 3: Studies of COVID-19 and Hepatic manifestations. N; Number of patients, AST; Aspartate aminotransferase, ALT; Alanine aminotransferase, LFT; Liver function test, ICU; Intensive Care Unit, ARDS; Acute Respiratory Distress Syndrome, NAFLD; Non-Alcoholic Fatty Liver Disease, ALD; Alcohol related Liver Disease

<table>
<tr><th>Author</th><th>Country</th><th>Liver abnormalities</th><th>Comments</th></tr>
<tr><td>Chen et al [26]</td><td>China</td><td>
<table>
<tr><td>No. of patients = 274</td><td>Dead (n=113)</td><td>Recovered (n=161)</td></tr>
<tr><td>AST >40 U/L (n=84, 31%)</td><td>59 (52%)</td><td>25 (16%)</td></tr>
<tr><td>ALT >41 U/L (n=60, 22%)</td><td>30 (27%)</td><td>30 (19%)</td></tr>
<tr><td>Acute Liver Injury (n=13, 5%)</td><td>10 (9%)</td><td>3(2%)</td></tr>
<tr><td>Chronic Hepatitis B (n=11, 4%)</td><td>5 (4%)</td><td>6 (4%)</td></tr>
</table>
</td><td>Higher ALT and AST in deceased patients

High mortality in patients with Acute Liver injury (76.9%)</td></tr>
<tr><td>Li et al [32]</td><td>China</td><td>
<table>
<tr><td>No. of patients =85</td><td>Normal ALT (n=52)</td><td>Elevated ALT (n=33) (38.8%)</td></tr>
<tr><td>Chronic liver disease (N=6)</td><td>3 (5.8%)</td><td>3 (9.1%)</td></tr>
</table>
</td><td>7% patients with COVID-19 had underlying chronic liver disease</td></tr>
<tr><td>Wang et al [22]</td><td>China</td><td>
<table>
<tr><td>No. of patients =138</td><td>ICU (n=36)</td><td>Non-ICU (n=102)</td></tr>
<tr><td>ALT (U/L)</td><td>35.0</td><td>23.0</td></tr>
<tr><td>AST (U/L)</td><td>52.0</td><td>29.0</td></tr>
<tr><td>Bilirubin (mmol/L)</td><td>11.5</td><td>9.3</td></tr>
</table>
</td><td>3.9% of patients with COVID 19 had underlying chronic liver disease.

Mortality 4.3%</td></tr>
<tr><td>Guan et al. [23]</td><td>China</td><td>
<table>
<tr><td>No of patients =1099</td><td>Severe (n=173)</td><td>Non-severe (n=926)</td></tr>
<tr><td>AST >40 U/L</td><td>39.4%</td><td>18.2%</td></tr>
<tr><td>ALT >40 U/L</td><td>28.1%</td><td>19.8%</td></tr>
</table>
</td><td>2.1% of COVID-19 patients had Chronic hepatitis B infection

Mortality 1.4%</td></tr>
<tr><td>Huang et al [4]</td><td>China</td><td>
<table>
<tr><td>No. of patients =41</td><td>ICU (n=13)</td><td>Non-ICU (n=28)</td></tr>
<tr><td>ALT (U/L)</td><td>49</td><td>27</td></tr>
<tr><td>AST >40 (n=15)</td><td>8 (62%)</td><td>7 (25%)</td></tr>
</table>
</td><td>Mortality 15%

1 (4%) COVID-19 patient had underlying chronic liver disease</td></tr>
</table>

<table>
<tr><td>Fan et al [28]</td><td>China</td><td><table><tr><td>No. of patients=148</td><td>Abnormal LFT (n=75)</td><td>Normal LFT (n=73)</td></tr><tr><td>Chronic liver disease</td><td>6</td><td>2</td></tr><tr><td>Lopinavir/Ritonavir therapy</td><td>23 (56.1%)</td><td>8 (25%)</td></tr></table></td><td>Patients with abnormal LFT had longer hospital stay (16.4 vs 12.6 days)</td></tr>
<tr><td>Cai Et al [33]</td><td>China</td><td><table><tr><td>No. of patients = 298.</td><td>Severe (n=50)</td><td>Non-severe (n=240)</td></tr><tr><td>Acute Liver injury</td><td>21 (36.2%)</td><td>23 (9.6%)</td></tr><tr><td>NAFLD</td><td>10.3%</td><td>3.3%</td></tr><tr><td>ALD</td><td>3.3%</td><td>1.7%</td></tr><tr><td>Chronic Hepatitis B</td><td>1.7%</td><td>1.7%</td></tr></table></td><td>Higher AST, ALT and GGT in severe disease

Patients with NAFLD had severe disease</td></tr>
<tr><td>Cao W [34].</td><td>China</td><td><table><tr><td>No. of patients= 128</td><td>Severe (n=21)</td><td>Non-severe (n=107)</td></tr><tr><td>ALT (U/L)</td><td>43.8</td><td>28.8</td></tr><tr><td>AST (U/L)</td><td>44.1</td><td>27.9</td></tr></table></td><td>Higher ALT and AST in severe COVID-19</td></tr>
<tr><td>Shi et al [35]</td><td>China</td><td><table><tr><td>No. of patients= 81</td><td>Week 1</td><td>Week 2</td></tr><tr><td>ALT (U/L)</td><td>50.6</td><td>48.7</td></tr><tr><td>Bilirubin (mmol/L)</td><td>14.1</td><td>11.9</td></tr></table></td><td>7 (3%) COVID-19 patients had underlying chronic liver disease</td></tr>
<tr><td>Wu et al[38]</td><td>China</td><td>No of patients: 201<table><tr><td></td><td>No ARDS</td><td>ARDS</td></tr><tr><td>AST (U/L)</td><td>30.0</td><td>38.0</td></tr><tr><td>ALT (U/L)</td><td>27.0</td><td>35.0</td></tr></table></td><td>3% (7) had underlying CLD.

Bilirubin was significantly higher in patients with ARDS related death</td></tr>
<tr><td>Graselli et al[36]</td><td>Italy</td><td>No. of patients=1591
Chronic liver disease= 28(3%) of whom 21 (75%) belonged 50-70 years of age.</td><td>15-30% mortality in patients between 50-70 years of age</td></tr>
</table>

Arentz et al.[37]	USA	No. of patients= 21 Cirrhosis = 1(4.8%) ALT U/L= 108 (11-1414), AST U/L= 273 (14-4432), ALP U/L = 80 (40-164),	3 (14.7 %) patients developed Acute Liver Injury
Zhang et al[24]	China	No. of patients=56 Patients with chronic liver disease=2 (3.6%) Abnormal LFT = 16/56 (28.6%)	Mortality 1.7%

COVID-19 Liver histology

Xu et al reported the first post-mortem findings of a patient succumbed to severe COVID 19. In his study, the liver histology revealed moderate microvesicular steatosis, mild inflammatory infiltrates of hepatic lobule and portal tract. However, at this stage it is unclear whether these changes are related to the viral infection or to the drugs. In addition, peripheral blood examination showed significantly reduced but hyper-reactive CD4 and CD8 cells in a proinflammatory state with increase in CCR6+ Th17 CD4 T cells and cytotoxicity granulations in CD8 cells, which may also contribute to hepatocellular dysfunction [39].

In another report by Tian S et al., post mortem liver biopsy in 4 COVID-19 patients showed mild sinusoidal dilatation and focal macro vesicular steatosis. There was mild lobular lymphocytic infiltration, which was not significant in portal areas. SARS-CoV-2 RNA was isolated from liver tissue through RT-PCR in one of the patients. Though the bile duct epithelium happens to express higher ACE2 receptors, there was not much of evidence to point towards bile duct damage[40].

During SARS-CoV outbreak in 2002, 23% to 60% patients had hepatic dysfunction and few patients underwent liver biopsy. This revealed mild to moderate lobular lymphocytic inflammation, ballooning of hepatocytes and apoptosis. The most prominent feature was high mitotic figures indicative of rapidly proliferative state (positive Ki-67). The Ki proliferative index for chronic hepatitis C is around 0.45 to 1% suggestive of high replicative phase of hepatocytes in chronic hepatitis C infection. Immuno histochemistry studies showed that Ki proliferative index of hepatocytes in SARS CoV was much higher than Chronic hepatitis C Infection and liver regeneration. The mitotic index was probably due to cell cycle arrest following SARC CoV. It is possible that similar pathogenesis can occur in COVID -19.[41]

Liver abnormality in SARS: SARS was a major pandemic in 2003. Hepatic dysfunction was described in patients with SARS. Up to 10% of patients had underlying chronic liver disease, particularly, chronic Hepatitis B probably due to the geographic location where SARS primarily occurred. Over 50% patients developed abnormal liver function tests, mostly mild and majority recovered. However, in some studies, elevated liver function tests were associated with severe disease and in particular high ALT predicted ICU and death. This raised the possibility of SARS causing liver dysfunction rather than a simple association [(42-48

Liver abnormality in MERS: Middle Eastern Respiratory Syndrome (MERS) is caused by Middle Eastern Respiratory Syndrome Corona Virus (MERS CoV). The first case was reported in 2012 in Saudi Arabia[49]. Unlike SARS CoV and SARS CoV-2, MERS CoV utilises dipeptidyl peptidase -4 (DPP-4) as the cell entry receptor[50] abundantly found in liver. Low albumin was found to be an independent predictor of severe MERS CoV infection [51]. The liver biopsy in MERs patients showed lobular lymphocytic infiltration, mild hydropic degeneration of hepatocytes.[52,53]. MERS non survivors had higher incidence of liver injury than Survivors. 91.3% Vs 77.9% respectively.[54,55]. Mortality was higher in patients with comorbidities [56,57]

Clinical outcome:

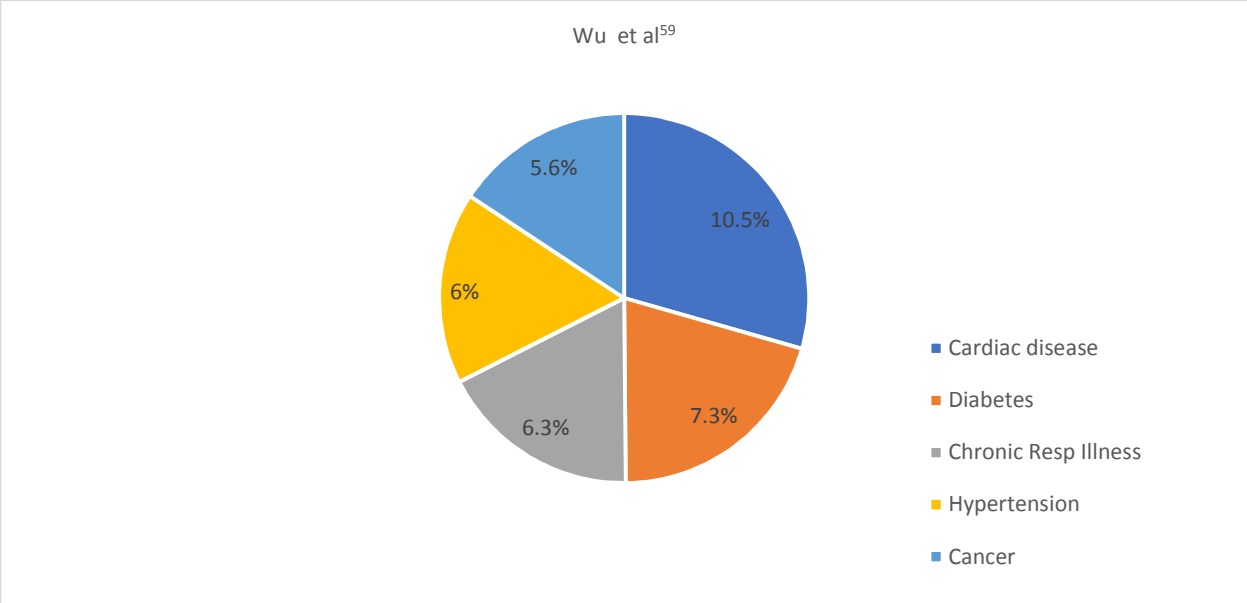
According to Wang and colleagues[22] the disease progression manifested with increasing respiratory distress leading to pneumonia. In these patients CT showed bilateral ground-glass appearance and patchy pneumonia in almost 100% of patients. Majority of patients recovered with no sequalae. Overall, 19.6% of patients developed Acute Respiratory Distress Syndrome (ARDS),16.7% had myocarditis which manifested as arrhythmias and 8.7% developed septic shock in severe COVID-19 illness. However, this number was higher with patients in ICU; ARDS 61%, arrhythmias 44.4%, and shock 30.6%. These patients required mechanical ventilation and Extracorporeal Membrane Oxygenation (ECMO).

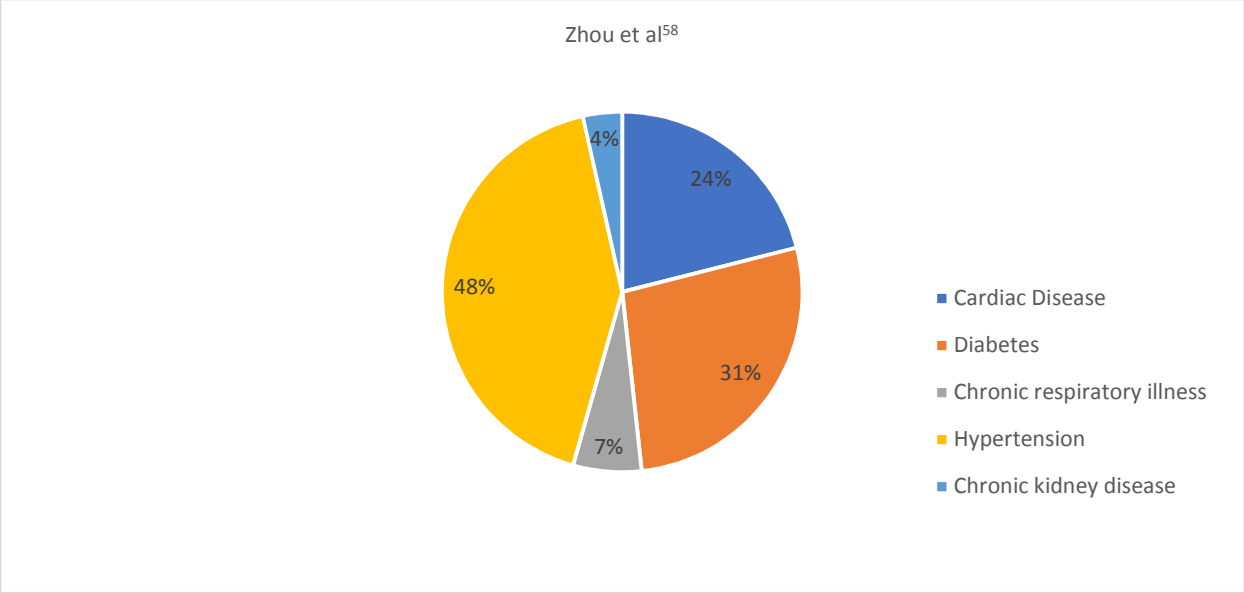
Case fatality with COVID-19 reported in 4292 Chinese patients, with an overall mortality of 3.6-15%. Mortality was higher in men (3.25:1) with a median age 75 years and with comorbidities (Diabetes mellitus, Hypertension and cardiovascular disease). These comorbidities were noted in 48% of patients in a study by Zhou and colleagues[58]. In his publications of 191 patients with COVID-19, 54 died (28.2% mortality) in whom 36 (66.6%) had underlying chronic disease. Figure 1., illustrates the distribution of comorbidities in deceased patients. In the largest case series by Wu and colleagues[59], the overall mortality was 2.3%; however, in patients with critical disease the mortality was 49%. In a recent report from Italy by Remuzzi and colleagues[60], mortality related to COVID-19 was 6% (827 patients) with Male: Female ratio 4:1 and a mean age 81 years. More than 60% of these patients had comorbidities. The median time from presentation to death was 14 days.[4,22]. Age adjusted mortality in these two large series is shown in Figure 2.

Mortality of COVID-19 is higher in patients with underlying comorbidities. According to a metanalysis of eight studies with 46248 patients in total, which analysed the prevalence of co morbidities in COVID-19, the most common is hypertension with a prevalence of 14-22%, followed by diabetes 6-11%, cardiovascular diseases 4-7% and respiratory disease 1-3 % [61]. The mortality rate was higher in patients with hypertension 48%, followed by 21% in diabetics, 14% in patients with cardiovascular illness, 10 % in chronic Lung disease, 4% each for malignancy, chronic kidney disease and cerebro vascular diseases[26]. However, the mortality in patients with underlying Chronic Liver disease was 0-2 % [62]. In this analysis, HT (48% vs 24%, diabetes (21% vs 14%), and Cardiovascular disease (14% vs 4%) were more common in the deceased patients. Fatty liver is likely seen in this group patient as part of metabolic syndrome which can complicate the issue.

Characteristic features of deceased patients (n=113) was reported from Wuhan. AST, ALT, ALP, GGT and bilirubin levels were significantly higher in non-survivor patients compared to survivors. Elevated AST (>40 U/L) was observed in 59 (52%) expired and 25(16%) recovered patients and likewise ALT (>41 U/L) was found in 30 (27%) and 30 (19%) deceased and recovered patients, respectively. Similarly, hypoalbuminemia (<32 g/L) was found in 74 (65%) of expired patients as compared to 22 (14%) recovered patients. Serum bilirubin was 12.6 mmol and 8.4 mmol in the deceased and recovered patients, respectively. In a recent report by Chen et al 13 (5%) of COVID-19 patients developed acute liver injury during the course of the illness of whom 10 (76.9%) died [26]. Although the numbers are small, but this conveys an important message on COVI-19 patients with hepatic dysfunction.

Figure 1: Distribution of comorbidities in deceased COVID-19 patients.





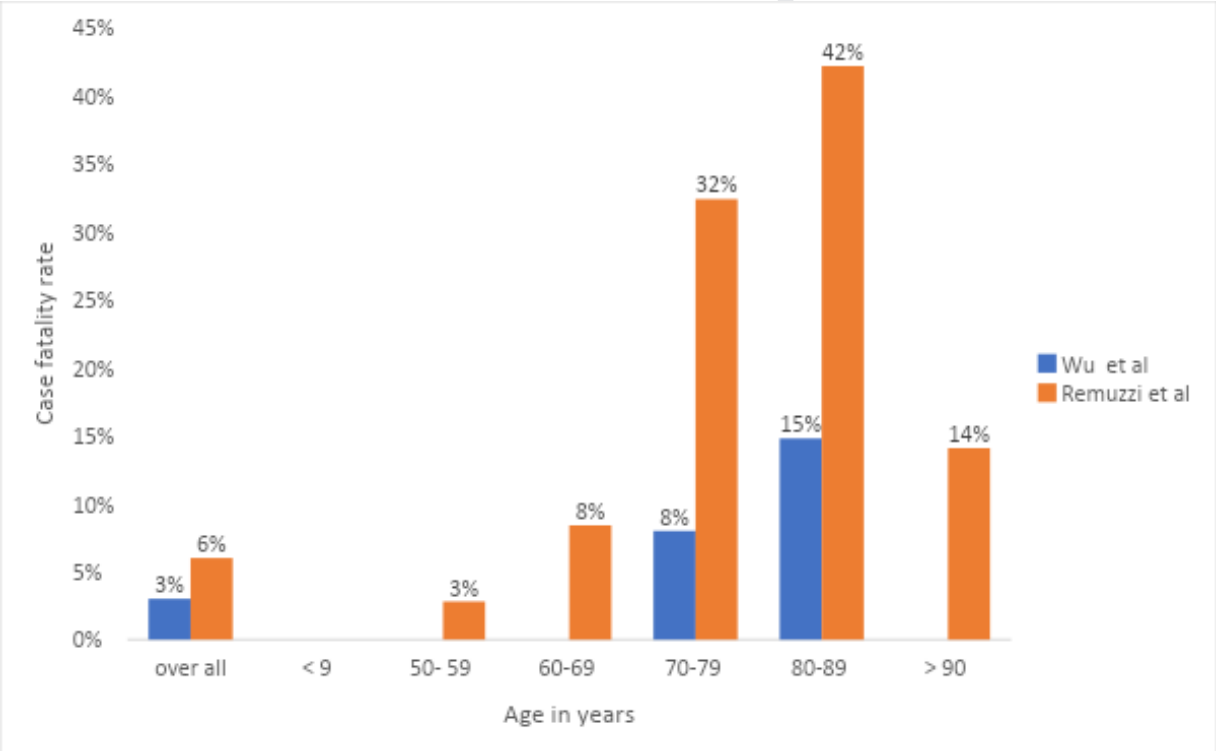


Figure 2: Comparison of the case fatality rates of COVID-19 based on respective age groups in two large cohorts from China[59] and Italy[60]. NA: No data were available for age groups 50-59,60-69, >90 years in Chinese cohort.

Diagnosis:

Diagnosis of COVID-19 was based on Real time reverse transcription polymerase chain reaction (RT-PCR). In the case series described by Wang and colleagues[22] centrifuged throat swab samples were used for testing. The total viral RNA was extracted within 2 hours using an RNA isolation kit. RT-PCR of the suspension was performed and amplification of Open reading frame (ORIF) and nucleocapsid protein were carried out using respective forward, reverse primers and the probe. Diagnosis were also obtained using nasal swabs, oral and rectal swabs. Interestingly, Xiao and colleagues[20] showed patients with SARS CoV-2 related respiratory illness can continue to shed virus in stool even after a negative respiratory sample.

Management

Although the evidence is less clear, the current treatment recommendations include anti-viral drugs, antibiotics, intravenous fluids and corticosteroids. Oseltamivir was utilized in 89.9% of patients in the Wuhan series this current pandemic situation. Remdisivir has shown good results with COVID-19[63]. Being an RNA virus, one would expect broad spectrum Ribavirin to work; unfortunately, during SARS outbreak ribavirin was associated with significant toxicity including severe haemolysis. Interestingly, Omrani and colleagues[64] found interferon alpha 2A in combination with ribavirin showed higher initial survival (70% vs 17%, P=0.004) by day 14 but not in 28 days (30% vs 17%, p=0.054) in MERS CoV outbreak.

Lopinavir/Ritonavir, approved for HIV infection showed invitro activity against Coronavirus and was beneficial in MERS Co-V[65]. These drugs are being tried in COVID-19. Lopinavir, a protease inhibitor has been shown effective in controlling SARS. Ritonavir was added to increase Lopinavir trough level through CYP 450 enzyme inhibition in liver. A recently published open labelled, randomised controlled trial on 199 patients with severe COVID-19 showed no benefit of Lopinavir and Ritonavir (99 patients). It was debated whether the trial

should have been conducted in less sick patient and treatment should have been initiated early phase of COVID-19. In this study, 20.5% and 41% of patients had elevated AST and ALT prior to randomisation, respectively; however, presence of cirrhosis, ALT or AST >5 times upper limit normal were exclusion criteria in this trial. Increased bilirubin and elevated AST were noted in 3.2% and 2.1%, respectively in the treatment group[66]. Usage of this drug Inhibition of CYP450 will increase the trough levels of CNI, the most commonly used immunosuppression in solid organ transplant recipients. This can lead to potential drug toxicity.

Antibiotics such as fluoroquinolones, third generation cephalosporins were used to reduce secondary infection. Corticosteroids was used in 44.9% of COVID-19 patients to curtail inflammation[22]. Chronic Hepatitis B can reactivate with the use of corticosteroids. HBsAg positive patients should be covered with antiviral therapy. We recommend to check Hepatitis B core antibody status and positive should be treated with antivirals for the duration of steroid therapy.

Recently, Chen et al, constructed a 3-dimensional crystal structure model of SARS-Co V 2 proteases. Virtual screening inhibition of the active viral site as a therapeutic measure identified Hepatitis C NS5A inhibitor to be effective in controlling SARS Co V2 virus. Ledipasvir and Velpatasvir readily inhibited SARS Co V proteases in their model. However, this requires more evidence [67].

COVID 19 and HCC: Patients with underlying cancer are immunosuppressed by nature of the disease and due to chemotherapy. A preliminary report from China, COVID 19 patients with underlying cancer were investigated. In a nationwide study of 1590 cancer patients with COVID-19 across 575 hospitals in China, it was observed that patients with cancer had higher risk of contracting SARS-CoV-2 infection and severe illness. They also had and poorer outcomes as against those without cancer[68]. Most patients with HCC have underlying chronic liver disease and therefore, they fall under this high-risk category and likely to have worse outcome. AASLD currently recommends to possibly delay HCC surveillance by 2 months; however, HCC related treatments should be carried out without much delay[31]. EASL recommends to avoid HCC surveillance in COVID 19 positive patients, also to postpone locoregional therapy and to temporarily withhold immune check point inhibitor theray[69].

COVID-19 and Deceased donor transplantation:

There has been a significant decline in cadaveric organ donation during COVID-19 pandemic [69]. This can affect patients awaiting liver or other solid organ transplantation leading to death. There has been a recent debate on harvesting organs from SARS-Co-V-2 positive donors, similar to the utility of HCV positive donors [70]. However, the risk of disease transmission to the transplant team remains a major concern [71]. This may be an interesting option in future following effective vaccination.

Post-Liver transplant COVID 19:

COVID 19 leaves no stone unturned, including liver transplant recipients. A recent case report from Wuhan described a 37-year-old gentleman with Hepatitis B and HCC, who developed fever on 3rd day post Trans

arterial chemoembolization. He was treated initially with antibiotics and subsequently liver transplantation on day 7. His fever continued on day 9, and a CT chest showed hypostatic changes in both lung fields. A repeat CT chest on the third week showed bilateral ground glass appearance. His nasopharyngeal swab confirmed COVID-19. His tacrolimus was dose reduced to maintain under 10 ng/ml. His liver enzymes increased by 4th week but settled gradually. His PCR remained positive for nearly 2 months and subsequently cleared [72].

Another case of post-transplant COVID 19 was described recently. Patient underwent cadaver liver transplantation in July 2017. He presented recently with high fever and developed severe COVID-19. His tacrolimus was discontinued for a month but received corticosteroids therapy. His allograft function remained normal[73].

Some immunosuppressive drugs possess antiviral activity by virtue of their mechanism of actions. Studies from SARS, identified interaction of SARS CoV non-structural proteins with cyclophilins, resulting in modulation of T cell immune response. In vitro studies showed cyclosporine to inhibit SARS Co V at higher doses. However, clinical utility was limited by its profound immunosuppressive effects [74]. Similarly, Mycophenolic acid, an active component of MMF exhibited potent antiviral properties against MERS CoV invitro[75]. Interestingly, mTOR inhibitors (Everolimus) showed effectiveness against SARS and MERS Co V viral infections by blocking early viral entry and post-entry consequences[76,77.] Although invitro studies, the antiviral properties of these drugs may offer some protection against COVID-19 in transplant recipients, particularly to ameliorate disease severity.

Literature from SARS-CoV and MERS show that post liver transplant patients on immunosuppression were not at risk for high mortality. The data for the same with SARS-CoV-2 is very limited.[78]
The rapid clinical deterioration in COVID-19 is due to cytokine storm associated with elevated interleukins IL-6, IL-8 and TNF alpha levels. The effects of SARS-CoV-2 infection in immunosuppression is not well established. However, stopping immunosuppressive medications in transplant patients may lead to rejection. In COVID patients on high dose steroids the dose needs to be brought down and maintained at 10 mg/day. When there is lymphopenia, fever and worsening lung condition, azathioprine and Mycophenolate and Calcineurin inhibitors dose needs to be reduced but not stopped. Caution needs to be exercised when considering initiation of steroids or other immunosuppressive therapy in liver disease patients e.g.; Severe alcoholic hepatitis, Auto immune hepatitis etc[31]. Patients on immunosuppression may be more infectious as they have higher viral titres.[79].

The American Society of Transplantation has provided few recommendations for COVID-19 specifically for those awaiting liver transplantation and transplant recipients. The recommendations include patient education, hand hygiene and social distancing, provision for patients to contact the transplant centre via telephone if they develop fever, cough or flu like symptoms. Each hospital should provide layout protocols for managing these high-risk patients. Careful monitoring of allograft function and drug interactions should be excised in transplant recipients with COVID-19, because Ritonavir can potentially inhibit CYP34A enzyme leading to increasing trough levels of mTOR and calcineurin inhibitors, and drug toxicity. In addition, they have recommended

postponing elective surgeries including living donor transplantation and non-urgent deceased donor transplantations in areas of high COVID-19. In addition, potential deceased donors should be adequately tested for SARS-CoV-2 with nucleic acid assay [79].

With limited therapeutic options, prevention by social distancing appears to be the corner stone of to minimise COVID-19 spread. Virus transmission can be reduced in various methods described in the WHO protocol[6]. This includes, maintaining safe social distance, regular hand washing for 20 seconds, using 60% alcohol hand rub, not to touch face, nostrils or mouth, avoiding crowded places and public events. Countries have taken different measures to reduce viral transmission and most of the countries in the world have gone into 'Lockdown' in order to stop viral transmission. Being a large virus particle, a surgical face mask should provide adequate protection against viral inhalation. N-95 masks should be reserved to the treating team. Personal Protective Equipment (PPE) should be worn according to the institutional policy. All patients with a history of travel to affected regions should be screened for SARS-CoV-2 even if they are asymptomatic. People with high temperature, dry cough, profound tiredness, diarrhoea or other unusual symptoms with recent travel history should be tested for COVID-19. Nations need to make and modify their prevention, testing and treatment strategies time to time based on Guidelines issued by WHO.

Conclusion

COVID-19 caused by SARS-CoV-2 is currently a pandemic. Overall mortality is 2-6% but higher in patients with advanced age and comorbidities. COVID-19 causes pneumonia, but hepatic dysfunction can occur in severe cases and were associated with fatal outcome. Cases of severe acute liver injury has been reported with higher mortality Larger studies with long term follow up are required to characterize the extent of liver damage in COVID-19. Effects of COVID-19 on underlying chronic liver disease requires a detailed evaluation and currently data is lacking and further research is warranted in this area.

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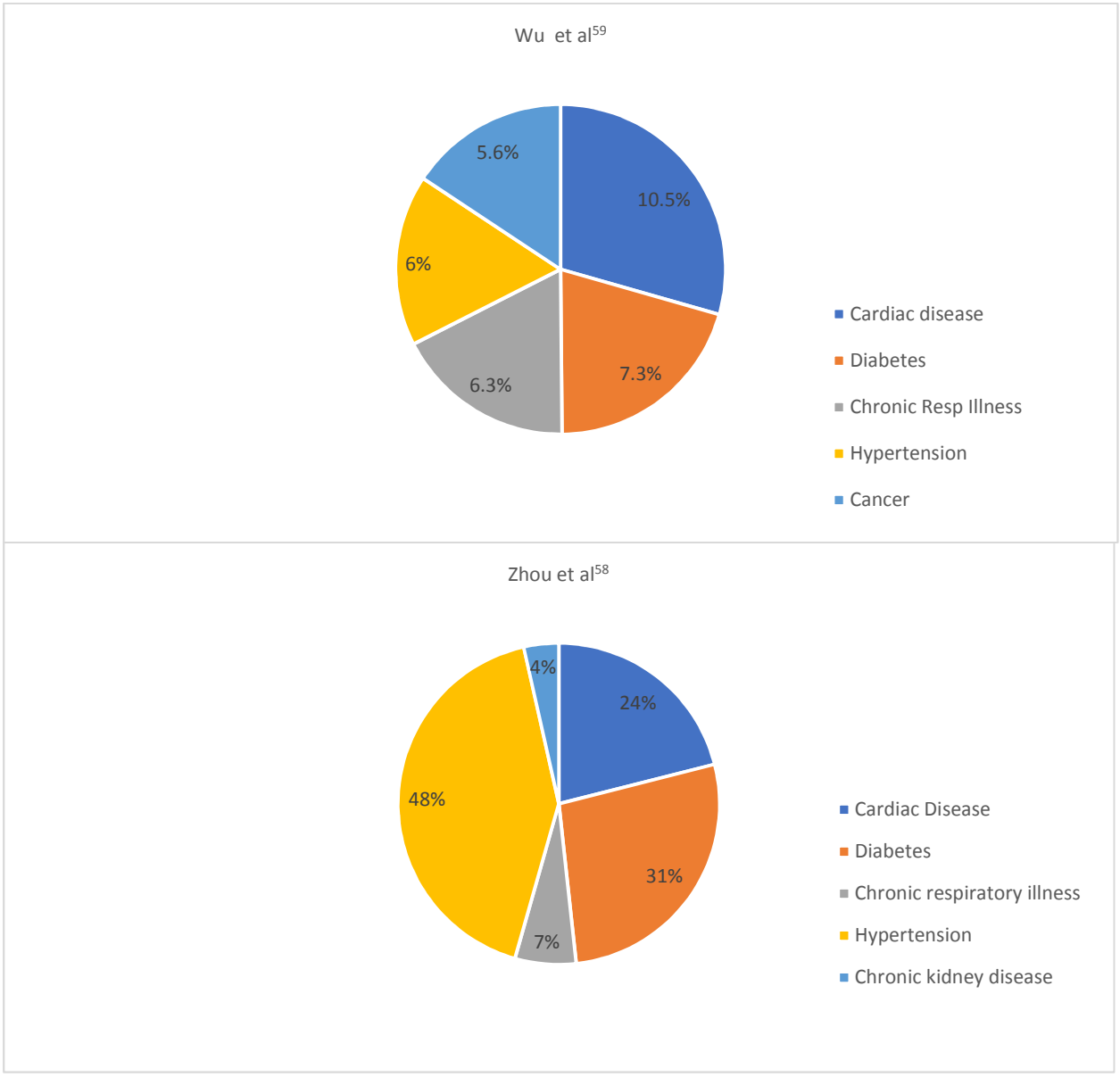
Figure 1: Distribution of comorbidities in deceased COVID-19 patients.



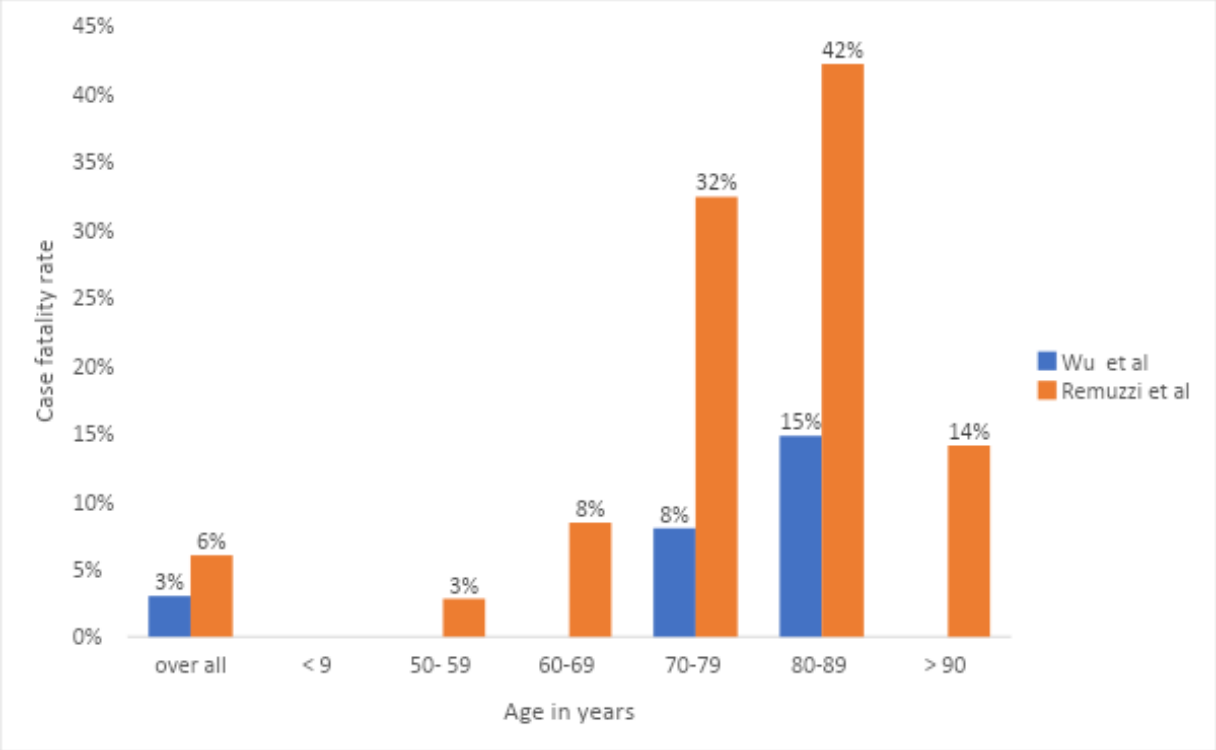


Figure 2: Comparison of the case fatality rates of COVID-19 based on respective age groups in two large cohorts from China[59] and Italy[60]. NA: No data were available for age groups 50-59,60-69, >90 years in Chinese cohort.

Table 1: Spectrum of clinical manifestation and their percentage of occurrence from recent studies on COVID -19 in China. PT: Prothrombin Time, NA: data not available.

Clinical features	Wang et al[22] N =138	Zhou et al[58] N = 191	Guan et al[23] N = 1099
Fever	98.6%	94 %	88.7 %
Cough	59.4 %	79 %	67.8 %
Sputum	NA	23 %	33.7 %
Myalgia	NA	15 %	14.9%
Fatigue	69.6 %	23 %	38.1 %
Diarrhoea	NA	5 %	3.8 %
Nausea/ Vomiting	NA	4 %	5.0 %
Sore throat	NA	NA	13.9 %
Lymphopenia (< $0.8*10^9$ /L)	70.3 %	40 %	NA
Prolonged PT (> 13.5 seconds)	58 %	NA	NA
Raised LDH (> 261U/ L)	39.9 %	NA	NA

Table 2: Classification of COVID-19 into 3 groups based on severity of clinical manifestations by Chinese Center for Disease Control[23].

Mild Disease (reported in 81% cases)	Fever, dry cough, mild dyspnoea (Respiratory rate<30/min).
Severe Disease (reported in 14% cases)	Dyspnoea, respiratory rate >30 and/or lung infiltrates >50% within 24 to 48 hours.
Critical Disease (reported in 5% cases)	Respiratory failure, septic shock and/or multiple organ dysfunction or failure.

Table 3: Studies of COVID-19 and Hepatic manifestations. N; Number of patients, AST; Aspartate aminotransferase, ALT; Alanine aminotransferase, LFT; Liver function test, ICU; Intensive Care Unit, ARDS; Acute Respiratory Distress Syndrome, NAFLD; Non-Alcoholic Fatty Liver Disease, ALD; Alcohol related Liver Disease

Author	Country	Liver abnormalities	Comments
Chen et al [26]	China	No. of patients = 274 / Dead (n=113) / Recovered (n=161) AST >40 U/L (n=84, 31%) / 59 (52%) / 25 (16%) ALT >41 U/L (n=60, 22%) / 30 (27%) / 30 (19%) Acute Liver Injury (n=13, 5%) / 10 (9%) / 3(2%) Chronic Hepatitis B (n=11, 4%) / 5 (4%) / 6 (4%)	Higher ALT and AST in deceased patients High mortality in patients with Acute Liver injury (76.9%)
Li et al [32]	China	No. of patients =85 / Normal ALT (n=52) / Elevated ALT (n=33) (38.8%) Chronic liver disease (N=6) / 3 (5.8%) / 3 (9.1%)	7% patients with COVID-19 had underlying chronic liver disease
Wang et al [22]	China	No. of patients =138 / ICU (n=36) / Non-ICU (n=102) ALT (U/L) / 35.0 / 23.0 AST (U/L) / 52.0 / 29.0 Bilirubin (mmol/L) / 11.5 / 9.3	3.9% of patients with COVID 19 had underlying chronic liver disease. Mortality 4.3%
Guan et al. [23]	China	No of patients =1099 / Severe (n=173) / Non-severe (n=926) AST >40 U/L / 39.4% / 18.2% ALT >40 U/L / 28.1% / 19.8%	2.1% of COVID-19 patients had Chronic hepatitis B infection Mortality 1.4%
Huang et al [4]	China	No. of patients =41 / ICU (n=13) / Non-ICU (n=28) ALT (U/L) / 49 / 27 AST >40 (n=15) / 8 (62%) / 7 (25%)	Mortality 15% 1 (4%) COVID-19 patient had underlying chronic liver disease

<table>
<tr><td>Fan et al [28]</td><td>China</td><td><table><tr><td>No. of patients=148</td><td>Abnormal LFT (n=75)</td><td>Normal LFT (n=73)</td></tr><tr><td>Chronic liver disease</td><td>6</td><td>2</td></tr><tr><td>Lopinavir/Ritonavir therapy</td><td>23 (56.1%)</td><td>8 (25%)</td></tr></table></td><td>Patients with abnormal LFT had longer hospital stay (16.4 vs 12.6 days)</td></tr>
<tr><td>Cai Et al [33]</td><td>China</td><td><table><tr><td>No. of patients = 298.</td><td>Severe (n=50)</td><td>Non-severe (n=240)</td></tr><tr><td>Acute Liver injury</td><td>21 (36.2%)</td><td>23 (9.6%)</td></tr><tr><td>NAFLD</td><td>10.3%</td><td>3.3%</td></tr><tr><td>ALD</td><td>3.3%</td><td>1.7%</td></tr><tr><td>Chronic Hepatitis B</td><td>1.7%</td><td>1.7%</td></tr></table></td><td>Higher AST, ALT and GGT in severe disease

Patients with NAFLD had severe disease</td></tr>
<tr><td>Cao W [34].</td><td>China</td><td><table><tr><td>No. of patients= 128</td><td>Severe (n=21)</td><td>Non-severe (n=107)</td></tr><tr><td>ALT (U/L)</td><td>43.8</td><td>28.8</td></tr><tr><td>AST (U/L)</td><td>44.1</td><td>27.9</td></tr></table></td><td>Higher ALT and AST in severe COVID-19</td></tr>
<tr><td>Shi et al [35]</td><td>China</td><td><table><tr><td>No. of patients= 81</td><td>Week 1</td><td>Week 2</td></tr><tr><td>ALT (U/L)</td><td>50.6</td><td>48.7</td></tr><tr><td>Bilirubin (mmol/L)</td><td>14.1</td><td>11.9</td></tr></table></td><td>7 (3%) COVID-19 patients had underlying chronic liver disease</td></tr>
<tr><td>Wu et al[38]</td><td>China</td><td>No of patients: 201<table><tr><td></td><td>No ARDS</td><td>ARDS</td></tr><tr><td>AST (U/L)</td><td>30.0</td><td>38.0</td></tr><tr><td>ALT (U/L)</td><td>27.0</td><td>35.0</td></tr></table></td><td>3% (7) had underlying CLD.

Bilirubin was significantly higher in patients with ARDS related death</td></tr>
<tr><td>Graselli et al[36]</td><td>Italy</td><td>No. of patients=1591
Chronic liver disease= 28(3%) of whom 21 (75%) belonged 50-70 years of age.</td><td>15-30% mortality in patients between 50-70 years of age</td></tr>
<tr><td>Arentz et al.[37]</td><td>USA</td><td>No. of patients= 21
Cirrhosis = 1(4.8%)
ALT U/L= 108 (11-1414),
AST U/L= 273 (14-4432),
ALP U/L = 80 (40-164),</td><td>3 (14.7 %) patients developed Acute Liver Injury</td></tr>
</table>

Zhang et al[24]	China	No. of patients=56 Patients with chronic liver disease=2 (3.6%) Abnormal LFT = 16/56 (28.6%)	Mortality 1.7%