Abnormal Liver Function Tests in Patients WithCOVID-19

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Abnormal liver function tests in COVID-19 patients: relevance and potential pathogenesis

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ABSTRACT

Abnormal liver function tests (LFTs) are reported frequently in hospitalized coronavirus disease 2019 (COVID-19) patients. A review of the literature shows that 46% of admitted COVID-19 patients had elevated plasma aspartate aminotransferase (AST) and 35% had elevated alanine aminotransferase (ALT) levels on admission. Elevations of both AST and ALT are mostly below 5 times the upper reference limit and are associated with severe disease and increased inflammatory markers. AST and ALT elevations are more frequent in US patients compared to Chinese patients. Mild elevations in gamma-glutamyltransferase (GGT), alkaline phosphatase (ALP) and total bilirubin are also reported, although less frequently.

Significant impairment of liver function or overt liver failure as the cause of death in COVID-19 rarely occur. There is no direct evidence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) hepatic infection, although a subset of hepatocytes and cholangiocytes express the host receptor utilized for cellular entry by SARS-CoV-2. The presence of pre-existing liver disease in patients with elevated LFTs on admission has not been comprehensively assessed in most studies but is unlikely to account for all abnormalities in LFTs. Although abnormal LFTs are already frequently present upon admission before the start of treatment, drug-induced liver injury should be taken into consideration, especially after the use of acetaminophen, lopinavir/ritonavir and remdesivir, which are potentially hepatotoxic.

In conclusion, these initial observations suggest that the prevalence of abnormal LFTs is high in COVID-19 patients, but that the clinical relevance is limited and that treatment is not required. The mechanisms underlying abnormal LFTs in COVID-19 are likely multifactorial and related to a hyper-inflammatory status and thrombotic microangiopathy that are observed in severe COVID-19 disease.

Introduction

The current pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to over 6 million cases and over 370 thousand deaths as of June 1st, 2020 (1). Although the majority of patients infected with SARS-CoV-2 only develop mild symptoms, a minority of patients require hospitalization and intensive care (2). Based on the available clinical data, abnormal liver function tests (LFTs) are frequently observed in coronavirus disease 2019 (COVID-19) patients, of which the underlying pathogenesis is incompletely understood. We reviewed the available information on the prevalence, nature, relevance and the potential pathogenesis of altered LFTs in COVID-19 patients.

Epidemiology of abnormal liver function tests in COVID-19 patients

Liver function tests (LFTs) include measures of hepatocyte injury (AST and ALT), of bile duct injury or cholestasis (alkaline phosphatase, ALP, and gamma-glutamyltransferase, GGT), markers of hepatic clearance/biliary secretion capacity (bilirubin), as well as measures of synthetic capacity (prothrombin time and albumin). LFTs are not necessarily liver-specific. It has been suggested that elevated aminotransferases in COVID-19 could also originate from myositis rather than liver injury (3). In a large descriptive study, the muscle damage marker creatinine kinase (CK) was elevated in 14% of COVID-19 patients (4). Hypoalbuminemia was reported in 55% of hospitalized COVID-19 patients (5) and was associated with disease severity (6). Hypoalbuminemia was an independent predictor of mortality (7). Lower levels of pre-albumin in severe COVID-19 patients were reported, suggesting decreased hepatic synthesis (5). In the context of inflammation, hypoalbuminemia may also reflect albumin extravasation as a consequence of increased capillary permeability (8). Additional factors that could explain the observed hypoalbuminemia in severe COVID-19 are increased catabolism and malnutrition.

The prevalence of ALT elevations among COVID-19 patients ranged between 4-33% in Chinese cohorts (weighted average: 19%), but was as high as 39% in a large cohort from the New York City area (5,9–21) (**Fig. 1**). ALT elevations were generally mild, defined as <5 times the upper reference limit (9,10,14–19,21–34). The prevalence of AST elevations ranged between 4-53% in Chinese cohorts (weighted average: 21%) and was 58% in the US cohort (4,5,18,19,21,22,24,25,29,34,35,9–16) (**Fig. 1**). AST elevations were similarly <5 times the upper reference limit (9,10,14–16,18,19,21–31,34,36). AST and ALT elevations had also been reported in patients with SARS caused by SARS-CoV (37). Several case reports have described severe LFTs abnormalities (18,38,39) or acute on chronic (40,41) liver failure in COVID-19 patients. Zhang *et al.* (33) reported that 1 out of 82 deceased COVID-19 patients had a hepatic cause of death, although it was not clear whether this patient had pre-existing liver disease.

Elevated ALP was reported in 2-5% of patients (5,11,25,42), and elevated GGT was reported in 13-54% of patients (weighted average: 23%) (5,11,19,42). The prevalence of total bilirubin elevations ranged between 1-18% of COVID-19 patients on admission (4,5,15,16,18,25,35,43). It should be realized, however, that pre-existing liver disease was not comprehensively described in any of these studies.

Stratification of COVID-19 patients according to disease severity, including the extent of respiratory distress and the need for ICU admission, indicated that plasma ALT and AST were elevated more frequently and to a greater extent in patients with severe COVID-19 compared to those with mild disease

(4,5,9,14,22,23,29,31,43–47). This was also the case for SARS patients during the 2002-2004 SARS outbreak (37).

The prognostic value of abnormal LFTs in COVID-19 is unclear. Some studies found that abnormal LFTs, particularly elevated AST and (peak) ALT, are associated with increased disease severity and mortality (17,20,46,47), whereas other studies did not find an association with mortality (48), disease progression (5), ICU admission (27,48), or length of hospital stay (11).

Potential pathogenesis of abnormal liver function tests in COVID-19 patients

Hepatic infection with SARS-CoV-2

SARS-CoV-2 utilizes the angiotensin-converting enzyme 2 (ACE2) as docking and entry receptor on host cells (49). Transmembrane serine protease 2 (TMPRSS2) is also involved in its cellular entry (50).

Theoretically, direct virus-induced cytopathic effects could play a role in LFTs abnormalities in COVID-19 (51). To determine whether SARS-CoV-2 is able to infect the liver, ACE2 expression has been studied in liver cells. Single cell RNA-seq approaches indicated that ACE2 mRNA is expressed in a subpopulation of cholangiocytes, not or minimally in hepatocytes, and not in any other liver cell type (52–55). In line with this, at the protein level ACE2 was visualized by immunohistochemistry in a subset of cholangiocytes, but not in hepatocytes (56,57). TMPRSS2 mRNA expression was found in a subset of hepatocytes and cholangiocytes (58). Zhao *et al.* infected human liver ductal organoids with SARS-CoV-2 and showed increased expression of viral mRNA at 24 hours after infection (59). In these organoids, 3% of cells co-expressed ACE2 and biliary markers and of these 68% co-expressed TMPRSS2. ACE2 expression in endothelial cells is debated (56,57).

ACE2 is highly expressed on the brush border of small intestinal enterocytes (56,57). Accordingly, SARS-CoV-2 infection was observed in human small intestine organoids (60) and SARS-CoV-2 nucleocapsid was detected in the cytoplasm of intestinal biopsies of a COVID-19 patient (61). COVID-19 patients with gastrointestinal symptoms were not more likely to have abnormal LFTs (62). In a minority (<15%) of COVID-19 patients, viral RNA was detected in blood by PCR in low amounts (29,63,64). Assuming brisk viral replication in the intestine, it seems plausible that viruses could enter the portal circulation to reach the liver. Hepatic Kupffer cells would attempt to clear the virus and initiate an inflammatory response. It is also possible that inflammatory mediators from the intestine could enter the portal system and sinusoids.

Evidence for direct hepatic infection was provided by showing SARS-CoV-2 particles without membrane-bound vesicles in the cytoplasm of hepatocytes of two COVID-19 patients with LFTs abnormalities (45). However, no confirmatory PCR testing for viral nucleic acids was performed, leaving the possibility that these 'spiked' inclusions could be of different origin (65).

The role of the host inflammatory response to SARS-CoV-2 infection

Following SARS-CoV-2 infection, the host immune response can be rapid and controlled, resulting in disease resolution with no or mild symptoms, or delayed and dysregulated, resulting in host-damaging complications. COVID-19 complications include acute respiratory distress syndrome (ARDS), a coagulopathy reminiscent of disseminated intravascular coagulation (DIC) and thrombotic microangiopathy, multi-organ failure (MOF) and ultimately death (66). An excessive release of early response inflammatory factors, especially IL-6, IL-10, IL-2 and IFN-γ, correlates with disease severity (67) and may reflect cytokine storm syndrome (CSS). CSS is an excessive or uncontrolled release of pro-inflammatory cytokines which is associated with MOF (68). The cascade of events leading to MOF includes an early phase of endothelial damage and extravasation of inflammatory cells and release of mediators, and a later phase that includes amplification of inflammation and cell damage, that could affect various organs including the liver (bystander effect) (68). Additionally, CSS may result in DIC (69). DIC is observed in critical and non-survivor COVID-19 patients as evidenced by raised D-dimer levels and prolonged prothrombin time (70), as well as autopsy findings of pulmonary embolism and thrombotic microangiopathy in multiple organs (71).

Endothelitis was observed in the liver of COVID-19 patients (72) and fibrin microthrombi were found in liver sinusoids (73). The largest series of liver biopsies taken at autopsy (48 cases) reported massive dilation of portal vein branches, luminal thrombosis, portal tract fibrosis and microthrombi in the sinusoids (74). The altered LFTs observed in critical COVID-19 patients could thus be related to CSS leading to shock and coagulopathy, that affect liver perfusion resulting in cell death. Indeed, several studies reported that patients with severe COVID-19 had higher plasma aminotransferases on admission compared to those with mild disease, concomitantly with higher inflammatory markers (4,5,9,11,14,22,23,29,31,44,46,75).

In patients with mild COVID-19, abnormal LFTs on admission may not be related to general inflammation. Zhao *et al.* (19) compared patients with mild COVID-19 pneumonia with patients with non-COVID-19 pneumonia and comparable disease severity. There were no differences in C-reactive protein and IL-6 between the two groups. While none of the non-COVID-19 pneumonia patients had elevations in AST, ALT

or GGT on admission, elevations were observed in 28%, 28% and 44% of COVID-19 patients, respectively, suggesting that patients with mild COVID-19 may have LFTs abnormalities independently of the inflammatory status. One explanation for these findings is that the specific inflammation caused by SARS-CoV-2 is more likely to cause LFTs abnormalities compared to general inflammation elicited by other pathogens. Whether LFTs abnormalities are present in asymptomatic or paucisymptomatic COVID-19 patients who do not require hospitalization is unknown.

Drug-induced liver injury

Alterations in LFTs in COVID-19 patients have been reported at hospital admission, implying that patients may develop these before starting drug treatment. However, a comprehensive description of pre-existing conditions and prior medication use is lacking.

Many medications used for the symptoms or the management of COVID-19 patients, such as acetaminophen, antivirals, antibiotics, corticosteroids and immune-modulators, are potentially hepatotoxic.

Fan *et al.* (11) retrospectively studied the relationship between medication use and LFTs in 148 COVID-19 patients. Among patients with no LFTs abnormalities on admission, 48% developed them about a week after admission. Whereas 58% of those who developed LFTs abnormalities after admission had received lopinavir-ritonavir, only 31% of those with normal LFTs had received it. However, due to the retrospective nature of this study, lack of treatment randomization should be taken into account. Cai *et al.* reported 7 times higher odds of LFTs alterations after the use of lopinavir-ritonavir (20). In contrast, in a clinical trial including 199 patients with severe COVID-19, AST, ALT and total bilirubin elevations were not more frequent in the lopinavir-ritonavir group compared to those given standard care. Patients with severe liver disease were excluded from the trial.

Remdesivir was recently reported to be superior to placebo in shortening the time to recovery of hospitalized COVID-19 patients (76). In a trial comparing remdesivir treatment for either 5 or 10 days, severe but not immediately life-threatening ALT/AST elevations were reported in 4-6% of patients and life-threatening AST/ALT elevations in 2-3% of patients, necessitating treatment discontinuation (77).

Acetaminophen is frequently used for COVID-19 symptom relief and can cause alterations in aminotransferases even at therapeutic doses (78). However, no studies have assessed its role in COVID-19 management specifically.

Preliminary data did not associate hydroxychloroquine treatment with significant LFTs abnormalities (79,80).

Pre-existing liver diseases and COVID-19

Abnormal LFTs at admission could result from pre-existing (chronic) liver diseases. Reported prevalence rates of pre-existing liver disease in COVID-19 patients vary from 1-11% (42,47,81,82). As most studies reporting LFTs are retrospective, the aforementioned numbers are subject to underreporting, but it seems unlikely that pre-existing liver disease accounts for all observed abnormalities in LFTs.

Whether the presence of pre-existing liver disease could affect the course of COVID-19 and *vice versa* is largely unclear. Plasma inflammatory markers were not more elevated in patients with chronic liver diseases (44,47) and no association was found between pre-existing liver disease and COVID-19 severity or mortality (83). However, chronic liver disease comprises a spectrum of conditions that may differentially affect outcomes. Advanced liver disease patients are generally at an increased risk of infection due to cirrhosis-associated immune dysfunction (84). Another patient category that raises concerns is liver transplant recipients and auto-immune liver disease patients receiving immunosuppressant drugs. However, based on currently available data, there is no reason to believe that these patients are at a higher risk of infection or more severe complications compared to the general population (85,86). One study reported high mortality in liver transplant recipients, but these patients also displayed comorbidities (87). It is speculated that immunosuppression could even be beneficial as it might reduce the risk to develop a hyper-inflammatory state and CSS. Conversely, however, it may increase virus-induced injury and the risk for bacterial or fungal superinfection.

Metabolic dysfunction-associated fatty liver disease (MAFLD) and COVID-19 severity

Several studies have identified obesity as a significant risk factor for the severity of COVID-19 disease, independent of associated co-morbidities such as age, type 2 diabetes mellitus and hypertension (51,88–93). Metabolic dysfunction-associated fatty liver disease (MAFLD), also known as NAFLD, is highly associated with obesity but also observed in lean individuals (94). In the initial studies characterizing COVID-19 patients, MAFLD was rarely reported, but as a common (and possibly asymptomatic) hepatic condition, it may account for some of the LFTs alterations observed on admission. Moreover, it could explain the differences in ALT/AST prevalence observed between the large US cohort and the Chinese cohorts (**Fig. 1**). MAFLD prevalence is higher in the US (24%) than in China (15%) (95). MAFLD is closely related to obesity and other lifestyle-related metabolic disorders (e.g. type 2 diabetes). In the US COVID-

19 cohort, 42% of patients were obese and 34% had diabetes (10). In contrast, in the largest Chinese cohort, obesity was not reported, but diabetes prevalence was 15% (4).

Patients with MAFLD displayed more rapid disease progression and longer viral shedding time compared to patients without MAFLD (96). Increased risk for severe disease was observed if MAFLD was present alongside obesity (97), in non-diabetic patients (98), in younger patients (99) and in patients with increased hepatic fibrosis scores (100). While it is unclear how obesity and MAFLD could increase COVID-19 severity, similar pathways relating to alterations in the immune response, macrophage activation and (low-grade) inflammation, often present in both conditions, are thought to play a key role (100–103). MAFLD increases hepatotoxicity of certain drugs including acetaminophen which could also aggravate LFTs alterations in the course of COVID-19 (104,105).

Other causes of LFTs elevations in critically ill patients

In critical COVID-19 patients, hepatic injury may be caused by changes in hemodynamics and oxygen delivery. Hypoxic hepatitis can cause sharp increases in aminotransferases in the setting of respiratory failure, shock, or cardiac failure (106). During acute cardiac failure, which may occur in critical COVID-19 patients (107), the systemic arterial pressure suddenly drops, leading to a reduction in hepatic arterial perfusion and hepatocellular hypoxia. The pathogenesis comprises not only hepatic ischemia, but also hepatic venous congestion due to elevated central venous pressure, which may predispose hepatocytes to even more significant hypoxic injury (108). Similar hemodynamic alterations in the liver may occur in mechanically ventilated patients in response to high positive end-respiratory pressure (PEEP) (109,110). Whether these hemodynamic alterations can alter LFTs is unclear (110). Importantly, the use of high PEEP is usually unnecessary for the respiratory management of COVID-19 patients, as lung compliance is relatively high (111).

Conclusion

Mildly abnormal plasma LFTs, especially AST and ALT, are frequently observed in COVID-19 patients on admission and are associated with severe disease and increased inflammatory markers. In general, abnormal LFTs in COVID-19 patients do not lead to significant liver function impairment or failure, and liver-directed treatment is unnecessary.

The pathogenetic mechanisms for abnormal LFTs in COVID-19 are not fully understood: they are likely multifactorial and, while direct SARS-CoV-2 infection in hepatocytes and/or cholangiocytes seems

unlikely, microthrombotic endothelialitis, immune dysregulation, drug-induced liver injury and hepatic ischemia related to hypoxia and MOF could all play a role.

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LIST OF ABBREVIATIONS

LFTs: liver function tests

COVID-19: coronavirus disease 2019

AST: aspartate transferase

ALT: alanine transferase

US: United States

GGT: gamma-glutamyltransferase

ALP: alkaline phosphatase

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

CK: creatinine kinase

SARS-CoV: severe acute respiratory syndrome coronavirus

ICU: intensive care unit

ACE2: angiotensin-converting enzyme 2

TMPRSS2: transmembrane serine protease 2

PCR: polymerase chain reaction

ARDS: acute respiratory distress syndrome

DIC: disseminated intravascular coagulation

MOF: multi-organ failure

IL: interleukin

IFN-γ: interferon gamma

CSS: cytokine storm syndrome

MAFLD: metabolic dysfunction-associated fatty liver disease

NAFLD: non-alcoholic fatty liver disease

PEEP: positive end-respiratory pressure

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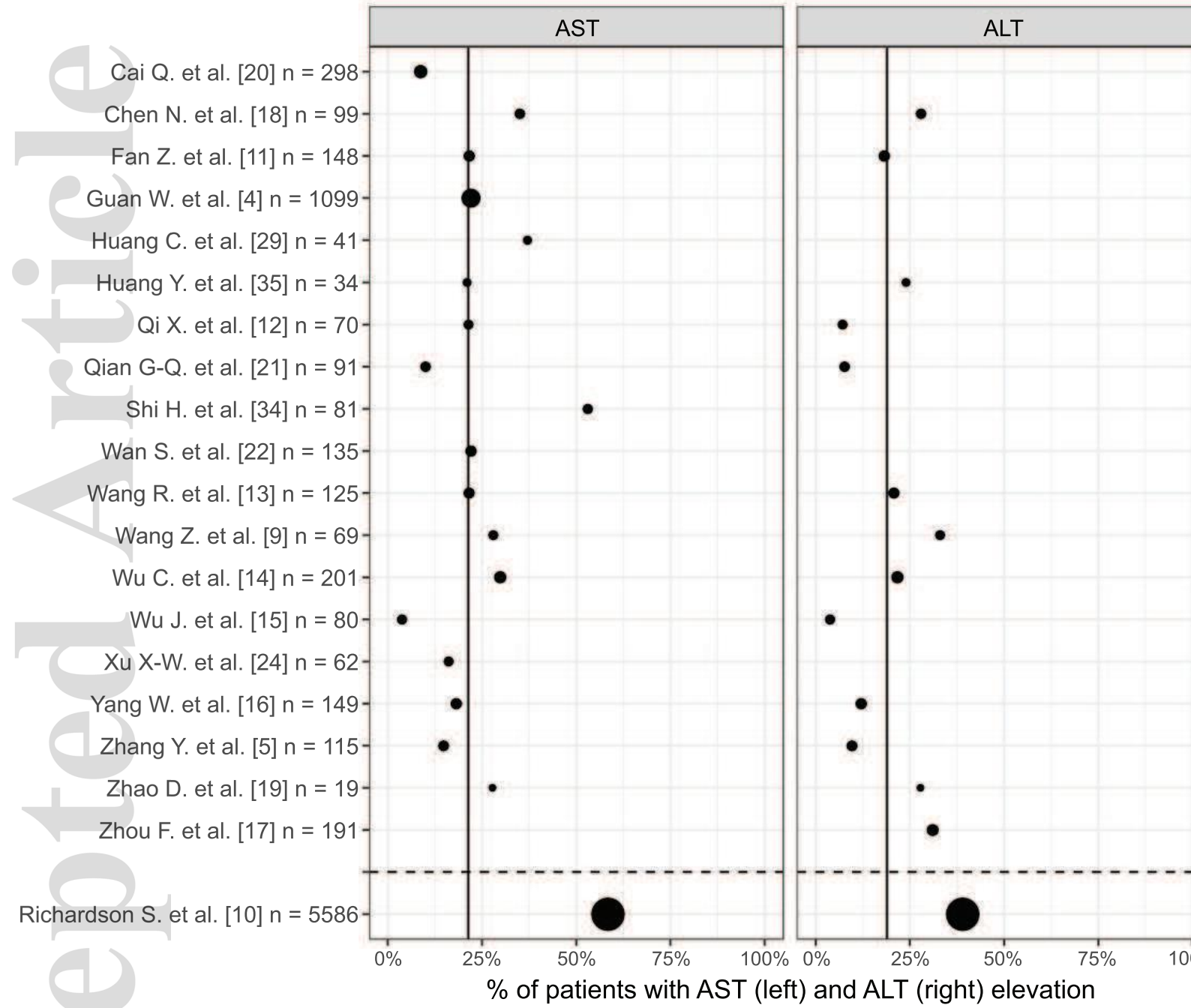

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