Bilirubin levels in patients with mild and severe Covid-19: A pooled analysis

Dear editor,

We read with interest the commentary by Sun et al regarding the impact of coronavirus disease 19 (Covid-19) on liver function; the authors gave a brief insight of the alterations in several liver function biomarkers described in the current literature. Bilirubin levels have been found altered in patients with Covid-19, but the dynamics of such alteration are not clear, especially in relation to the severity of the disease. To understand this, we performed a pooled analysis of studies retrieved in Medline (Pubmed), Scopus, and Web of Science databases from January 1, 2020 to April 11, 2020, reporting bilirubin levels in patients with and without severe Covid-19. The keywords used were ‘bilirubin’ and ‘coronavirus’ or ‘bilirubin’ and ‘Covid-19’. In all, 19 articles were initially detected, but 12 were excluded as duplicates and three because of lacking data; two further articles were retrieved from reviewing the reference lists, and therefore, six articles were enrolled for analysis.

Standardized mean differences (SMD) were used to build forest plots of continuous data and to evaluate differences in bilirubin levels. \( P < .05 \) was considered statistically significant, and 95% confidence intervals (CIs) were reported. In five studies, the mean and standard deviation values were extrapolated from median and interquartile range (IQR). Heterogeneity of SMD was tested with Q statistic (significance level at \( P < .10 \)), and the \( I^2 \) was calculated. In analyses with high heterogeneity, a random-effects model was applied. Sensitivity was tested by sequentially excluding one study in each turn. Statistical analyses were performed using Stata 14 (STATA Corp.).

The mean difference in serum bilirubin between Covid-19 patients with or without severe disease is shown in Figure 1. In five studies, patients with severe Covid-19 displayed higher bilirubin levels compared to those with milder forms (mean difference ranging between 0.27 and 0.95 \( \mu \text{mol/L} \)), while in the remaining study the bilirubin concentration was found to be higher in patients with non-severe Covid-19 (mean difference \(-0.25 \mu \text{mol/L}\)). The pooled results revealed that bilirubin concentration was significantly higher in patients with severe Covid-19 (mean difference \(0.25 \mu \text{mol/L}\)). The pooled results showed that the effect size was not modified when every single study was in turn removed (effect size ranged between 0.36 \( \mu \text{mol/L} \) and 0.62 \( \mu \text{mol/L} \)). Bilirubin concentration remained significantly higher (SMD: 0.53 \( \mu \text{mol/L} \); 95% CI, 0.04 to 1.03 \( \mu \text{mol/L} \), \( P = .034 \); \( I^2 = 76.7\% \)) in patients with severe COVID-19 also after excluding the large study of Zhang et al, which accounted for nearly 51% of the overall sample size. The results of this pooled analysis show that bilirubin levels are significantly increased in patients with severe Covid-19.

**KEYWORDS**
liver, bilirubin, coronavirus, Covid-19, Infection

**CONFLICTS OF INTEREST**
None.

---

**FIGURE 1** Forest plot of SMD differences of serum albumin between COVID-19 patients with or without severe disease

**Abbreviations:** CIs, confidence intervals; Covid-19, coronavirus disease 19; IQR, interquartile range; SMD, standardized mean difference.
AB0, von Willebrand factor/factor VIII and portal vein thrombosis in decompensated cirrhosis: Too late to unmask the culprit?

To the Editor,

We read with interest the paper from Scheiner et al, who investigated the influence of AB0 blood group on the risk of portal vein thrombosis (PVT) in patients with cirrhosis and wish to make comments.1 In the general population, the venous thrombosis risk is 2-4 fold increased in non-0 individuals, likely because of their higher von Willebrand factor (VWF) and factor VIII (FVIII) levels.2 In cirrhotics, VWF and FVIII are markedly increased.3 However, Scheiner et al could not find association between non-0 group and PVT in 84 947 cirrhotics listed for liver transplantation in the USA. In a second independent cohort of 411 cirrhotics (Child B/C: 84%), they found that the contribution of non-0 blood group on VWF variation was substantially smaller than in the general population and limited to patients with early stage cirrhosis, without further effect on FVIII, thus justifying the lack of association between non-0 blood group and PVT. To further explore this issue, we evaluated VWF:Ag, FVIII-activity, protein C and endogenous thrombin potential with/without thrombomodulin ratio (ETPr) in 69 patients with stable cirrhosis (age 61 ± 12, 70% male, Child A: 41%, Child B/C: 59%). VWF:Ag increased with cirrhosis severity, without further effect on FVIII. Non-0 vs 0 blood group had higher VWF:Ag (+49%, P < .05) in Child A patients, but not in Child B/C (+9%, P = .486) (Table 1). Interestingly, FVIII/VWF:Ag linear correlation was stronger in non-0 blood-group (Pearson correlation R = .621, P < .001) than in 0-blood group (R = .110, P = .481). These data confirm that the influence of blood-group on VWF:Ag/FVIII, observed in the general population, is maintained only in the early stages of cirrhosis, and suggest a disease-gradient effect from Child A to Child B/C cirrhosis that overcomes genetics and modifies the correlation VWF/FVIII. FVIII levels, though increased, reached a plateau and did not parallel the further rises of VWF with cirrhosis severity.

Abbreviations: ETPr, thrombin potential with/without thrombomodulin ratio; FVIII, factor VIII; PVT, portal vein thrombosis; VWF, von Willebrand factor.

References
1. Sun J, Aghemo A, Forner A, Valentì L. COVID-19 and liver disease. Liver Int. 2020.http://doi.org/10.1111/liv.14470. 2. Qian ZP, Mei X, Zhang YY, et al. Analysis of baseline liver biochemical parameters in 324 cases with novel coronavirus pneumonia in Shanghai area. Zhonghua Gan Zang Bing Za Zhi. 2020.http://doi.org/10.3760/cma.j.cn501113-20200229-00076. 3. Xie H, Zhao J, Lian N, et al. Clinical characteristics of non-ICU hospitalized patients with coronavirus disease 2019 and liver injury: a retrospective study. Liver International. 2020.http://doi.org/10.1111/liv.14449. 4. Zhang X, Cai H, Hu J, et al. Epidemiological, clinical characteristics of cases of SARS-CoV-2 infection with abnormal imaging findings. Int J Infect Dis. 2020; 94:81-87 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(2:148-152 6. 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. 7. Wang D, Hu BO, Hu C, et al. novel coronavirus-infected pneumonia in Wuhan. China. JAMA. 2019;2020: https://doi.org/10.1001/jama.2020.1585.