

# Prognostic value of bilirubin and drug interactions

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Dear Editor:

I read with interest the results presented by Weber and colleagues,<sup>1</sup> regarding the correlations between at-admission liver function parameters, and severity of COVID-19 infection. The authors reported that over half (57.6%) of the cohort presented with any liver function abnormality on admission. Adjusted for age, gender, and comorbidities, hypoalbuminaemia was the most predictive of severe COVID-19 (OR 9.95,  $p<0.001$ ). This was followed by AST elevation (OR 2.54,  $p=0.005$ ), and ALT elevation (OR 2.10,  $p=0.030$ ). Total bilirubin elevation was the most predictive singular factor of COVID-19-related death (OR 4.80,  $p=0.032$ ). The predictive value was doubled when combined with hypoalbuminaemia (OR 9.64,  $p=0.024$ ).

However, there are concerns as to whether the predictive value of bilirubin in COVID-19 is fully explored in the study. Total bilirubin comprises direct (conjugated) bilirubin, and indirect (unconjugated) bilirubin. The normal values for total bilirubin and direct bilirubin are, respectively, at 1.2 mg/dL, and 0.3 mg/dL.<sup>2</sup> Direct bilirubin indicates the presence of cholestasis. Yet, from the study, only 4.6% of the cohort experienced total bilirubin elevation at admission. The figure rose to 19.8% at peak level. This formed a contrast with the much higher prevalence gamma-glutamyltransferase (GGT) elevation (At admission: 36.9%; peak level: 59.9%), which is another marker for biliary disease. Furthermore, the least

patients experienced total bilirubin elevation both at admission, and at peak, relative to other recorded liver parameters.

COVID-19 infection entails a hyperinflammatory response. The increase in inflammatory activity may impact on indirect bilirubin levels. According to pre-clinical models, inflammation decreases UGT1A1, UGT1A9, and UGT2B5 mRNA expression.<sup>3</sup> This might be related to specific cytokine changes. Glucuronidation was inhibited 51% by IL-6 expression at 24 hours in porcine hepatocytes.<sup>4</sup> As COVID-19 is associated with increased IL-6 levels,<sup>5</sup> glucuronidation in COVID-19 patients is expected to be further dampened. Hence, by logic, indirect bilirubin levels increase with disease severity. There is also evidence of cholangiocyte injury due to higher ACE2 expression - a key target of SARS-CoV-2.<sup>6</sup> In addition to that a substantial proportion of patients experienced GGT elevation, direct bilirubin should also increase. It is therefore interesting why only a small proportion of the cohort experienced total bilirubin elevation. An even more surprising note is that only total bilirubin elevation and hypoalbuminaemia were significantly correlated with COVID-19-related mortality. Total bilirubin elevation was not significantly associated with severe COVID-19.

Such interesting correlations can be explored further by elucidating the changes of direct and indirect bilirubin levels in patients with

COVID-19. There is a possibility that the increase of either is compensated by the decrease of the other, via different mechanisms. Another point of interest is the role of drugs. The authors have commented that since at-admission (baseline) parameters were used for prognostication, drug-induced liver injury is unlikely. Adjustment was also made for comorbidities. However, since many patients have chronic diseases (arterial hypertension: 53.0%; diabetes mellitus type II: 23.5%; coronary artery disease: 19.8%), it is likely that chronic medication is taken. Such medications can introduce variations to the study findings by interacting with COVID-19-related medication, and/or causing liver injury. Moreover, drug regimens can lead to fluctuations in bilirubin levels. The importance of investigating direct and indirect bilirubin levels separately is augmented by recent studies showing that direct bilirubin, and indirect bilirubin/direct bilirubin ratio are predictive of disease severity.<sup>7,8</sup>

There is thus an attraction to clarify the prognostic value of bilirubin levels in COVID-19 infection, preferably by analysing direct and indirect bilirubin levels separately.

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