To the Editor:

We would like to thank Ryan et al. for taking keen interest in our recently published manuscript wherein we show that serum ferritin is a predictor of early mortality in patients with decompensated cirrhosis (DC) [1]. We completely agree with their comments that serum ferritin in patients with DC is a marker of both inflammation and iron overload. Ferritin is an established marker of secondary iron overload in these patients. We in our study, therefore excluded patients with secondary iron overload to demonstrate the role of ferritin primarily as a marker of systemic inflammation and macrophage activation in the absence of iron overload. We looked at the correlation of ferritin with leucocyte counts (TLC) to elucidate its role as a marker of systemic inflammation. In the CANONIC study both leucocytosis and C-reactive protein (CRP) were shown as markers of the systemic inflammatory response syndrome [2]. Of these, the utility of adding leucocyte counts and not CRP was also proposed in a new prognostic score for patients with cirrhosis and liver failure [3]. We do not routinely measure CRP levels in our patients and therefore the association of ferritin with CRP could not be determined and was not shown in this study. As expected, serum ferritin also correlated with markers of iron overload i.e. serum iron (p < 0.001, r = 0.33), TIBC (p < 0.001, r = −0.64) and transferrin saturation (TS) (p < 0.001, r = 0.58).

Because we had excluded patients with secondary iron overload in this study, obviously raising a potential for selection bias, we also looked at serum ferritin in a separate cohort of DC, irrespective of the iron overload state (n = 377, 77% males). Here, again we explored the relationship of ferritin with TLC (as a marker of inflammation) and transferrin saturation (TS) (as a marker of iron overload). Log transformation of ferritin, TS and TLC was done for analysis. Interestingly, a significant and direct linear association was noted between serum ferritin and TLC (r² = 0.71, p < 0.0001) as well as TS (r² = 0.96, p < 0.0001) (Fig. 1A and B). However, this relationship was stronger for TS as compared to TLC (Fig. 1B). Ferritin levels were maximally elevated for patients with both high TS and TLC (Fig. 1C). On univariate analysis ferritin (Fig. 1D), TLC and TS were significantly associated with mortality. On multivariate analysis (after excluding ferritin), both TLC (HR 1.53, 95% CI 1.01–2.48) and TS (HR 1.8, 95% CI 1.02–3.1) significantly predicted mortality, highlighting the prognostic significance of both systemic inflammation and iron overload in patients with DC. Also, ferritin as a single biomarker could reflect both inflammation and iron overload in these patients.

Serum hepcidin is influenced both by inflammation and iron overload and a positive correlation of hepcidin with ferritin and TS has been reported in patients with cirrhosis [4,5]. We have already reported a decrease in serum hepcidin along with increased serum iron and ferritin in patients with ACLF as compared to cirrhosis and healthy controls. The levels also correlated with the severity of the disease [4]. Hepcidin is synthesized in hepatocytes, and in states of iron excess it maintains iron homeostasis by preventing iron absorption from the gut and its release by macrophages. Therefore, reduced levels of hepcidin in patients with severe liver disease perpetuate the state of iron overload. However, as stated by Ryan et al. we could not unveil the role of hepcidin in this study as it was a retrospective study. Because excess iron is toxic as it potentiates oxidative stress, removal of excess iron could be beneficial, however, future prospective studies are needed to provide definite answers to these interesting observations.
Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

References


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Fig. 1. Association of serum ferritin with iron, inflammation and mortality. (A) Correlation of ferritin with leucocyte count, (B) transferrin saturation, (C) with both leucocyte count and transferrin saturation and (D) with mortality.