Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Reply to: "Age and comorbidity are central to the risk of death from COVID-19 in liver transplant recipients"

To the Editor:

We read with great interest the letter by G. J. Webb *et al.*[1] regarding our recent nationwide study promoted by the Spanish Society of Liver Transplantation (SETH), which evaluated the incidence and outcomes of coronavirus disease 2019 (COVID-19) in liver transplant (LT) patients.[2] The authors merged the SETH data with their own international cohort (COVID-Hep/SECURE-Cirrhosis)[3] resulting in 258 LT patients with COVID-19. The combined data analysis allowed them to highlight the importance of age and comorbidities as key factors influencing outcomes. We completely agree with this conclusion, which may also be true for non-transplant patients with COVID-19. However, some statements require further clarification.

Firstly, Webb *et al.* used overall mortality as the only outcome in the analysis. Although mortality is the true hard outcome, there are some patients with severe acute respiratory distress syndrome who will not ultimately die but who will require mechanical ventilation and prolonged stay in the intensive care unit, with important physical and cognitive sequelae.[4] As these survivors are mostly young individuals without previous comorbidities, neglecting them in the primary outcome would increase the relative weight of older age and comorbidities as prognostic factors in the multivariate analysis. A composite endpoint including mechanical ventilation, admission to the intensive care unit and/or death (whatever occurred first) would be more appropriate to capture the true severity of COVID-19, independently of age and comorbidities. This composite endpoint has been used in large cohort studies evaluating clinical features and outcomes in COVID-19.[5]

An important limitation of the COVID-Hep/SECURE-Cirrhosis study[3] was that the interval from diagnosis to outcome was not recorded. This is why the authors had to use multivariate logistic regression for the merged database analysis. Since both mortality and the composite event are time-dependent outcomes, this statistical approach may not be optimal, particularly in clinical situations in which the time of follow-up varies among patients, as in this case. As a consequence, and also influenced by the reduction in statistical power associated with the outcome modification, the statistical significance of mycophenolate mofetil to increase the risk of severe COVID-19 found in our study (relative risk [RR] 3.94; 95% CI 1.59–9.74; $p = 0.003$)[2] was lost in the analysis by Webb *et al.* regarding mortality[3] (odds ratio [OR] 3.15; 95% CI 0.94–10.53; $p = 0.063$). However, the deleterious effect of mycophenolate mofetil on COVID-19 severity seems consistent and clinically relevant with a similar RR and OR, respectively, in both analyses, and it is a matter of sample size and statistical approach to obtain significant results. In our study using Kaplan-Meier curves and Cox's regression analysis, we showed a dose-dependent relationship between mycophenolate mofetil at baseline and development of severe COVID-19 during follow-up ($p = 0.003$). In addition, among those patients receiving the full dose of mycophenolate (*i.e.* 2,000 mg per day), a complete drug withdrawal upon admission had a trend towards reduced severity of COVID-19.[2] Indeed, there is a plausible physiopathological mechanism underlying these clinical observations consisting of a synergic and deleterious effect of mycophenolate and SARS-CoV-2 on depleting lymphocytes, which ultimately results in worse outcomes.[5,6] Regarding other immunosuppressants, we found a protective role of tacrolimus against severe COVID-19 in the initial multivariate model (RR 0.19; 95% CI 0.05–0.68; $p = 0.011$), but its significance was lost in the final model. In a more recent international cohort including data from 243 LT patients with COVID-19 from 9

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European countries, tacrolimus was found to reduce the risk of mortality after controlling for age and comorbidities in the multivariate analysis (hazard ratio 0.55; 95% CI 0.31–0.99; p = 0.049).[7] The role of mTOR inhibitors could not be adequately analyzed in these studies since they were seldom used in the included patients but the merged database analysis of Webb *et al.* again provided interesting results with a trend towards reduced risk of mortality in patients receiving everolimus after controlling for age and comorbidities (OR 0.31; 95% CI 0.08–1.11; p = 0.071).[1] Finally, corticosteroids have been demonstrated to improve survival in immunocompetent patients with COVID-19 in well-designed randomized controlled trials.[8]

In conclusion, age and comorbidities are crucial determinants of the severity of COVID-19 infection (and of mortality) among LT patients. However, the immunosuppression protocol may be the only true modifiable risk factor. Taken together, the available series, each with inherent strengths and limitations, point in the same direction: modifications of baseline immunosuppression could be helpful to ameliorate the severity COVID-19. In the absence of randomized controlled trials in LT patients, the current evidence calls for the consideration of a dose reduction or withdrawal of mycophenolate and maintenance or initiation of other immunosuppressants, such as corticosteroids, tacrolimus or everolimus, in LT patients with confirmed COVID-19.

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Conflict of interest
JC has received lecture fees from Chiesi, Astellas and Novartis. Advisory to Chiesi. MR-P has received lecture fees from Astellas, Novartis and Intercept Pharma. MS has received lecture fees from Astellas, Novartis, and Chiesi. Advisory to Jazz and Novartis. JP has received lecture fees by Astellas, Chiesi, and Gilead.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions
All authors contributed equally to this work.

Supplementary data
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IgG, a novel predictor for acute-on-chronic liver failure and survival in patients with decompensated cirrhosis?

To the Editor:

With great interest we read the article of Basho and colleagues.[1] Patients with liver cirrhosis often present with hypergammaglobulinemia (HGG),[2] most likely as a response to an increase in gut-derived endotoxins in the course of

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