[5]*Liver Unit, La Paz University Hospital. CIBERehd. IdiPAZ. Madrid, Spain*
*Corresponding author. Address: Gastroenterology and Hepatology Department, Marqués de Valdecilla University Hospital. Research

Institute Valdecilla (IDIVAL), Avda. de Valdecilla s/n. Santander 39008. Cantabria, Spain; Tel.: +34 942 20 25 20.
E-mail address: javier.crespo@scsalud.es (J. Crespo)

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

To the Editor:

Our understanding of the impact of COVID-19 on liver transplant recipients has recently advanced significantly. In August 2020 Colmenero *et al.* published data on behalf of the Spanish Liver Transplant Society (SETH) in the *Journal of Hepatology*.[1] The authors reported data on 111 LT recipients with SARS-CoV-2 infection and concluded that these patients were at no greater risk of severe COVID-19 than the general population. Furthermore, within LT recipients, comorbidity, male sex, and mycophenolate mofetil (MMF) use were reported as associated with severe disease. We congratulate our Spanish colleagues for rapidly conducting their comprehensive study in the midst of the pandemic.

Helpfully, Colmenero *et al.* provided an extract of their dataset: an important gesture in an era of rapid-fire reports. Having examined this, we feel a number of points would benefit from further exploration. We have also made comparisons with our own analysis of 151 LT recipients with SARS-CoV-2 infection (data extract supplied).[2] A key difference is that Colmenero *et al.* used a composite endpoint of death, intensive care unit (ICU) admission, or mechanical ventilation, whereas we used death alone; neither showed a significant difference between LT and non-LT patients. This is in contrast to the high rates of mortality in patients with cirrhosis.[3]

The first point of note is that only 4/20 (20%) SETH patients who died were admitted to ICU, compared to 22/28 (79%) in our cohort; overall mortality was similar at 18% and 19%, respectively. Although the reasons for this are not apparent, those who died in the SETH cohort without ICU admission were older and had higher Charlson comorbidity index (CCI) scores, which may suggest that ICU admission was thought inappropriate. Within our cohort, 9% of LT recipients deemed in need of ICU due to severe enough disease were not admitted due to this being deemed inappropriate. ICU admission reflects a combination of patient and clinician factors and is therefore an imperfect marker of COVID-19 disease severity.

Second, although Colmenero *et al.* report a univariable association between age and severe COVID-19, their multivariable analysis shows no significant association with age in contrast to the general literature.[4,5] On closer analysis, the authors have included age both alone and as a component of the CCI in their analysis, thus masking age as an independent variable. The

same issue exists for diabetes and renal function, which are both components of the CCI.[6]

Third, Colmenero *et al.* reported a correlation between male sex and severe COVID-19 consistent with findings from other large non-LT datasets.[7] However, comparing their Table 1, Table 2, and the raw dataset demonstrates that the association of poor outcome is in fact with *female* sex [12/79 (15%) men died *vs.* 8/32 (25%) women] and that there has been a transcription error.

Fourth, the multivariable analysis includes a number of variables that change over the disease course of COVID-19, such as immunosuppression withdrawal, and oxygen saturations at diagnosis. Patients were diagnosed with SARS-CoV-2 at varying time points, with time from diagnosis to ICU admission ranging from -1 to 11 days, with ICU admission not being universal as above. Furthermore, patients not hospitalized were excluded. This makes the use of a composite endpoint and time-dependent analysis (*e.g.* Cox regression) more difficult to interpret.

Considering the points above, we re-examined the SETH dataset in relation to the single endpoint of death. We adjusted reported CCI scores to remove age, and only considered baseline variables. To permit comparison, we retrospectively applied the same calculations to our own cohort, using diagnosis as the point-of-entry for both cohorts. We then performed a multivariable logistic regression analysis in each cohort and both cohorts combined, with death as the dependent variable and age, sex, CCI (without age), hypertension, and baseline tacrolimus, azathioprine, ciclosporin, MMF, everolimus, and corticosteroid use as independent variables (Fig. 1A). When analyzed in this way, with backwards selection at *p* <0.1, age and CCI were significantly associated with death whereas no significant associations remained with immunosuppressive regimens (Fig. 1A). A limitation of our registry was that the precise duration from laboratory diagnosis to death was not known, thus preventing the performance of a time-dependent analysis. Our instructions to submitting physicians specified that patients should be followed until mortality or resolution of COVID-19 and both cohorts allowed inclusion of patients presenting at any time point.

To explore the relationship between age, co-morbidity and death we plotted age against CCI according for both LT cohorts (Fig. 1B,C). Notably, no patient from either cohort with a CCI of 0 died. Conversely, patients who died were older with higher CCI scores. For the SETH cohort, the CCI threshold for death was <3. In our cohort, 6 patients died with a CCI <3 however in 4 cases an additional important cofactor not captured by CCI was identified (Fig. 1C). The pattern of increasing mortality

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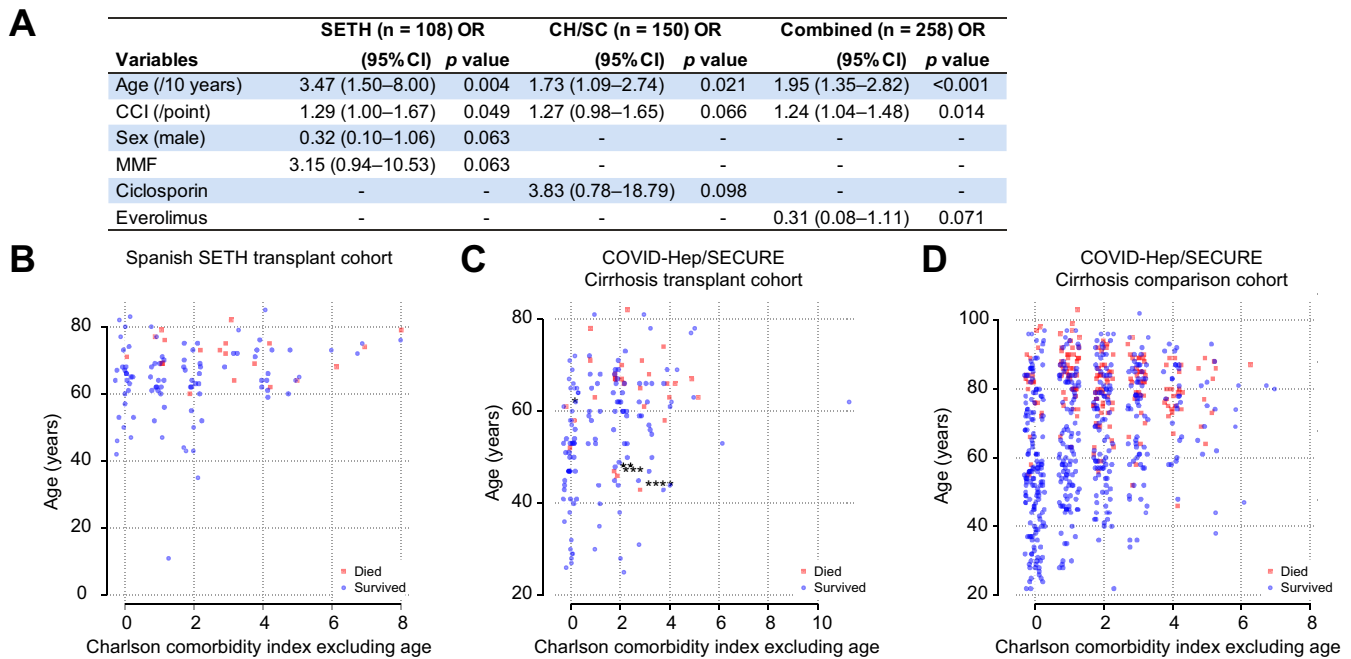| Variables	SETH (n = 108) OR (95% CI)	p value	CH/SC (n = 150) OR (95% CI)	p value	Combined (n = 258) OR (95% CI)	p value
Age (/10 years)	3.47 (1.50–8.00)	0.004	1.73 (1.09–2.74)	0.021	1.95 (1.35–2.82)	<0.001
CCI (/point)	1.29 (1.00–1.67)	0.049	1.27 (0.98–1.65)	0.066	1.24 (1.04–1.48)	0.014
Sex (male)	0.32 (0.10–1.06)	0.063	-	-	-	-
MMF	3.15 (0.94–10.53)	0.063	-	-	-	-
Ciclosporin	-	-	3.83 (0.78–18.79)	0.098	-	-
Everolimus	-	-	-	-	0.31 (0.08–1.11)	0.071

Fig. 1. **Associations between age and comorbidity with death following SARS-CoV-2 infection in liver transplant patients.** (A) Outcomes of multivariable logistic regression with backwards stepwise selection for retention in the model at p <0.1 with death as the dependent variable and the following independent variables: age, sex, Charlson comorbidity index (CCI; without age), hypertension, and baseline tacrolimus, ciclosporin, mycophenolate mofetil (MMF), everolimus, and corticosteroid use. SETH = cohort described by Colmenero *et al*; CH/SC = COVID-Hep/SECURE-Cirrhosis; combined represents the 2 cohorts combined. Within the SETH cohort, factors remaining significantly associated with death were age (odds ratio [OR] 3.47/10 years; 95% CI 1.50–8.00; p = 0.004) and CCI without age (1.29/point; 95% CI 1.00–1.67; p = 0.049). Within the COVID-Hep/SECURE-Cirrhosis cohort only age (OR 1.73/10 years; 95% CI 1.09–2.74; p = 0.02) remained significant. Within the combined cohort, age (1.95/10 years; 1.35–2.82; p <0.001) and CCI (OR 1.24; 95% CI 1.04–1.48; p = 0.014) remained significant. (B–D) Plots of age in years against CCI adjusted to exclude age and split by whether patients survived (blue circles) or died (red squares) following SARS-CoV-2 infection in (B) Spanish SETH cohort (n = 108 with complete data); (C) COVID-Hep/SECURE-Cirrhosis international cohort (n = 150); (D) COVID-Hep/SECURE-Cirrhosis comparison non-LT cohort from a single UK hospital network (n = 627). A single Spanish patient from the COVID-Hep/SECURE-Cirrhosis registries who could potentially have been included in the Spanish SETH registry was not included in the analysis. Asterisks for patients who died with CCI <3 (including points for age) in panel B denote additional at-risk cofactors: *concurrent influenza; **second liver transplant; ***recurrent primary sclerosing cholangitis with jaundice at baseline; ****baseline jaundice of unknown cause. Horizontal jitter has been added to the X axis. (This figure appears in color on the web.)

with age and CCI in both cohorts was similar to that observed in our non-LT comparison cohort (Fig. 1D).

Considering the above, age and comorbidity appear key in determining outcome from SARS-CoV-2 infection in the LT population. The fact that both published datasets have similar findings supports their generalizability. Although immunosuppressive regimens may be of additional importance, it appears unlikely to confer more risk than 10 years of additional age. Further formal work with larger/combined datasets is required before medication changes can be recommended.

Conflict of interest

The authors have no other conflicts of interest.

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

Authors' contributions

All authors contributed equally.

Data availability statement

An extract from the COVID-Hep.net and SECURE-Cirrhosis registries representing the data used to produce this analysis is provided alongside the manuscript. Additional data may be available on request to the corresponding author.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2021.01.036.

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Author names in bold designate shared co-first authorship

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Gwilym J. Webb[1,*]
Andrew M. Moon[2]
Eleanor Barnes[3]
A. Sidney Barritt IV[2]
Thomas Marjot[3]

[1]Cambridge Liver Unit, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK
[2]Division of Gastroenterology and Hepatology, University of North Carolina, Chapel Hill, NC, USA
[3]Oxford Liver Unit, Translational Gastroenterology Unit, Oxford University Hospitals NHS Foundation Trust, University of Oxford, Oxford, UK

[*]Corresponding author. Address: Cambridge Liver Unit, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK.
E-mail address: gjwebb@protonmail.com (G.J. Webb)

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