Letters

Primary biliary cholangitis and SARS-CoV-2 infection: incidence, susceptibility and outcomes

We read with interest the work by Mansoor *et al*[1] regarding the outcomes of COVID-19 in coeliac disease. The impact of pre-existing chronic liver diseases on COVID-19 outcomes has been largely evaluated,[2–4] and consequently specific recommendations have been made in these patients.[5] However, the relationship between primary biliary cholangitis (PBC) and SARS-CoV-2 remains unknown.[6] We aimed to determine (1) the cumulative incidence of SARS-CoV-2 infection in a population of patients with PBC, comparing with the general Spanish cumulative incidence by the end of April 2021; (2) the baseline factors associated with a higher susceptibility to SARS-CoV-2 infection; and (3) the baseline factors associated with COVID-19-related hospitalisation.

We performed a multicentre retrospective study enrolling 1151 patients from 13 Spanish referral hospitals. We collected information about SARS-CoV-2 infection from medical records of all patients with PBC from January 2020 to April 2021 (online supplemental material 1). Exclusion criteria were patients who died before January 2020, liver transplant before or after the enrolment and patients having received some dose of a vaccine against SARS-CoV-2.

The Spanish government officially publishes the prevalence, incidence and outcomes of SARS-CoV-2 (https://www.mscbs.gob.es/). For this study, data were accessed on 30 April 2021. The cumulative incidence of SARS-CoV-2 infection was 7.3% (85 of 1151) in the PBC population vs 7% in the Spanish global population (p=0.567). In turn, the cumulative hospitalisation rate related to COVID-19 was 0.51% (238 891 of 47 026 208) in the Spanish population vs 1.74% (20 of 1151) (p=0.0001) in the PBC population. In addition, the cumulative mortality rate related to COVID-19 in Spain was 0.10% (48 436 of 47 026 208), while this rate was 0.35% (4 of 1151) in the PBC population (p=0.01). Table 1 summarises the age-specific cumulative incidence and hospitalisation comparing the overall and PBC populations.

The baseline features of the overall cohort are presented in table 2. Albumin levels were decreased in patients with SARS-CoV-2 infection (4.14±0.45 g/dL vs 4.25±0.44 g/dL; p=0.033). Also, both positive anti-mitochondrial autoantibodies (AMA) (6.6% (59 of 898) vs negative 12.6% (22 of 174); p=0.006) and anti-Sp100 (4.1% (7 of 171) vs negative 8.4% (52 of 619); p=0.05) were inversely associated with infection. A higher protection was observed in patients with two positive autoantibodies (1.5%, 2 of 130) compared with those with only one (8%, 45 of 565) or subjects with none (12.6%, 12 of 95) (p=0.005). In the multivariate analysis (logistic regression), albumin levels (OR 0.41 (95% CI 0.23 to 0.75); p=0.003) and positive AMA (OR 0.41 (95% CI 0.22 to 0.77); p=0.006) were independently associated with SARS-CoV-2 infection (table 2). In the case of patients with positive AMA and anti-Sp100, the OR was 0.12 (95% CI 0.03 to 0.57; p=0.007).

The proportion of patients who required hospital admission after SARS-CoV-2 infection was 23.5% (20 of 85), while 3.5% (3 of 85) required intensive care unit admission and 4.7% (4 of 85) died. Male sex, arterial hypertension, older age, and creatinine, alkaline phosphatase (ALP), albumin and platelet levels were associated with COVID-19-related hospitalisation in the univariate analysis. In the multivariate analysis (logistic regression), male sex (OR 13.44 (95% CI 1.92 to 94.13); p=0.009), arterial hypertension (OR 5.24 (95% CI 1.12 to 24.32); p=0.035), ALP levels (OR 1.004 (95% CI 1.00 to 1.01); p=0.05) and older age (OR 1.06 (95% CI 0.99 to 1.12); p=0.07) were

Table 1 Comparison between the general Spanish population and the PBC cohort: age-specific cumulative incidence of SARS-CoV-2 infection and hospitalisation related to COVID-19

Age-specific cumulative incidence of SARS-CoV-2 infection							
	General population			PBC population			
Population age interval (years)	n	SARS-CoV-2 infection	Cumulative incidence (%)	n	SARS-CoV-2 infection	Cumulative incidence (%)	P value
0–39	20 269 831	1 523 897	7.5	33	2	6.1	0.750
40–49	7 813 176	556 259	7.1	113	15	13.3	0.011
50–59	6 974 009	484 805	6.9	287	22	7.7	0.634
60–69	5 281 877	306 533	5.8	326	20	6.1	0.798
>70	8 301 882	388 853	4.7	392	26	6.6	0.068
Overall	47 026 208	3 271 060	6.96	1151	85	7.38	0.567
Global infection ratio (95% CI)				1.07 (0.86 to 1.33)			
Age-specific cumulative incidence of hospitalisation related to COVID-19							
	General population			PBC population			
Population age interval (years)	n	SARS-CoV-2 infection	Cumulative hospitalisation (%)	n	SARS-CoV-2 infection	Cumulative hospitalisation (%)	P value
0–39	20 269 831	23 093	0.11	33	1	3	0.017
40–49	7 813 176	24 040	0.31	113	1	0.88	0.268
50–59	6 974 009	36 363	0.52	287	3	1.05	0.210
60–69	5 281 877	42 653	0.81	326	3	0.92	0.820
>70	8 301 882	112 060	1.35	392	12	3.06	0.003
Overall	47 026 208	238 891	0.51	1151	20	1.74	0.0001
Global hospitalisation ratio (95% CI)				3.46 (2.23 to 5.39)			

PBC, primary biliary cholangitis.

Table 2 Baseline characteristics of the overall population and predictive factors associated with SARS-CoV-2 infection susceptibility in the overall PBC cohort

Characteristics	Overall cohort (n=1151)	Infected patients with PBC (n=85)	Non-infected patients with PBC (n=1066)	Unadjusted OR (95% CI); p value	Adjusted OR (95% CI); p value
Female sex, % (n)	91.1 (1049/1151)	90.6 (77/85)	91.2 (94/1066)	1.07 (0.50 to 2.29); 0.853	0.49 (0.21 to 1.12); 0.092
Age, years ±SD	63.9±12.4	62.5±13.6	64±12.3	0.99 (0.97 to 1.01); 0.282	0.98 (0.96 to 1.00); 0.082
Obesity (BMI ≥30 kg/m^2), % (n)	20.9 (221/1058)	20.3 (16/79)	20.9 (205/979)	0.96 (0.54 to 1.70); 0.885	
Arterial hypertension, % (n)	32.6 (375/1151)	25.9 (22/85)	33.1 (353/1066)	0.71 (0.43 to 1.17); 0.171	
Type 2 diabetes mellitus, % (n)	14.4 (166/1151)	17.6 (15/85)	14.2 (151/1066)	1.30 (0.72 to 2.33); 0.379	
Dyslipidaemia, % (n)	35.1 (404/1151)	29.4 (25/85)	35.6 (379/1066)	0.76 (0.47 to 1.22); 0.254	
AST ±SD (IU/L)	30±17	33±22	29±16	1.01 (1.00 to 1.02); 0.053	
ALT ±SD (IU/L)	29±56	33±26	29±58	1.00 (0.99 to 1.00); 0.611	
GGT ±SD (IU/L)	80±104	106±177	77±98	1.00 (1.00 to 1.00); 0.020	
Alkaline phosphatase ±SD (IU/L)	159±121	180±193	157±113	1.00 (1.00 to 1.00); 0.092	
Bilirubin ±SD (mg/dL)	0.72±0.9	0.72±0.83	0.72±0.92	1.01 (0.80 to 1.27); 0.962	
Albumin ±SD (g/dL)	4.24±0.4	4.14±0.45	4.25±0.44	0.61 (0.39 to 0.97); 0.033	0.41 (0.23 to 0.75); 0.003
Creatinine ±SD (mg/dL)	0.79±0.36	0.83±0.4	0.79±0.36	1.24 (0.76 to 2.01); 0.387	
Platelet count ±SD (×10^9/L)	231±81	225±87	231±81	0.99 (0.99 to 1.00); 0.547	
INR ±SD	1.05±0.3	1.15±0.6	1.04±0.3	1.78 (1.14 to 2.78); 0.011	
IgM ±SD (mg/dL)	1.05±0.3	306±216	265±201	1.00 (1.00 to 1.00); 0.123	
AMA, % (n)	83.8 (898/1072)	72.8 (59/81)	84.7 (839/991)	0.49 (0.29 to 0.82); 0.006	0.41 (0.22 to 0.77); 0.006
Anti-Sp100, % (n)	21.6 (171/790)	11.9 (7/59)	22.4 (164/731)	0.47 (0.21 to 1.04); 0.058	0.47 (0.21 to 1.09); 0.078
Anti-Gp210, % (n)	13.2 (103/779)	11.9 (7/59)	13.3 (96/720)	0.88 (0.39 to 1.98); 0.749	
ANA, % (n)	13.2 (103/779)	59.5 (47/79)	62.3 (611/981)	0.89 (0.56 to 1.42); 0.623	
UDCA therapy, % (n)	97.7 (1124/1151)	96.5 (82/85)	97.7 (1042/1066)	0.63 (0.19 to 2.14); 0.454	
OCA therapy, % (n)	10.3 (119/1151)	12.9 (11/85)	10.1 (108/1066)	1.32 (0.68 to 2.56); 0.413	
Fibrate therapy, % (n)	14.8 (170/1151)	8.2 (7/85)	15.3 (163/1066)	0.50 (0.23 to 1.10); 0.078	
Cirrhosis, % (n)	18.3 (211/1151)	23.5 (20/85)	17.9 (191/1066)	1.41 (0.83 to 2.38); 0.198	

ALT, alanine aminotransferase; AMA, anti-mitochondrial autoantibodies; ANA, antinuclear antibodies; AST, aspartate aminotransferase; BMI, body mass index; GGT, gamma glutamyl transferase; INR, internacional normalised ratio; OCA, obeticholic acid; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid.

independently associated with COVID-19-related hospitalisation in SARS-CoV-2-infected patients with PBC.

This nationwide study is the first to characterise the incidence and outcomes of SARS-CoV-2 in patients with PBC. First, we observed that both cumulative incidences of hospitalisation and mortality were greater in patients with PBC than in the general Spanish population, although the lack of adjustment for other comorbidities could be a limitation. Second, we found some factors associated with lower rates of SARS-CoV-2 infection, notably higher albumin levels and positive AMA antibodies. Third, ALP levels were independently associated with severe SARS-CoV-2 infection and requirement for hospital admission, beyond other known variables such as older age, male sex and arterial hypertension. Our study showed novel and relevant findings that could result in additional therapeutic decisions and preventive strategies in patients with PBC.

Javier Ampuero [1,2,3,4] **Ana Lucena,**[1] **Manuel Hernández-Guerra,**[5] **Isabel Moreno-Moraleda,**[6] **Juan Arenas,**[7] **Isabel Conde,**[8] **Laura Muñoz,**[9] **Lidia Canillas,**[10] **Edgar Fernandez,**[11] **Raisa Quiñones,**[12] **Miguel Angel Simon,**[13] **Elena Gómez-Dominguez,**[14] **Maria Luisa Gutierrez,**[15] **Conrado Fernandez-Rodriguez,**[15] **Maria Jose Domper-Arnal,**[13] **Francisco Jorquera,**[4,12] **Maria Luisa Garcia-Buey,**[11] **Montserrat Garcia-Retortillo,**[10] **Rosa Morillas,**[4,9] **Marina Berenguer,**[4,8] **Marta Casado,**[6] **Dalia Morales-Arraez,**[5] **José Manuel Sousa,**[1] **Esther Molina**[16]

[1]Hepatology Unit, Virgen del Rocio University Hospital, Sevilla, Spain
[2]Instituto de Biomedicina de Sevilla, Sevilla, Spain
[3]Facultad de Medicina, Universidad de Sevilla, Sevilla, Spain
[4](CIBERehd) Instituto de Salud Carlos III, Centro de Investigación Biomédica en Red Enfermedades Hepáticas y Digestivas, Madrid, Spain
[5]Gastroenterology and Hepatology, Hospital Universitario de Canarias, La Laguna, Spain
[6]Digestive Department, Complejo Hospitalario Torrecardenas, Almeria, Spain
[7]Digestive Department, Donostia Ospitalea, San Sebastian, Spain
[8]Liver Transplantation and Hepatology Unit, Hospital Universitari i Politècnic La Fe de Valencia, Valencia, Spain
[9]Digestive Department, Hospital Germans Trias i Pujol, Badalona, Spain
[10]Digestive Department, Hospital del Mar, Barcelona, Spain
[11]Digestive Department, Hospital Universitario de la Princesa, Madrid, Spain
[12]Gastroenterology, IBIOMED, Complejo Asistencial Universitario de Leon, Leon, Spain
[13]Digestive Department, Hospital Clinico Zaragoza, Zaragoza, Spain
[14]Servicio de Aparato Digestivo, Hospital Universitario 12 de Octubre, Madrid, Spain
[15]Digestive Diseases Unit, Alcorcón University Hospital, Alcorcon, Spain
[16]Digestive Department, Hospital Clinico Universitario Santiago Compostela, Santiago de Compostela, Spain

Correspondence to Dr Javier Ampuero, Virgen del Rocio University Hospital, Sevilla, Andalucía, Spain; javi.ampuero@gmail.com

Twitter Maria Jose Domper-Arnal @MJosDomperArnal

Contributors Guarantor of the article: JAm. Study design: JAm. Drafting the manuscript: JAm, CF-R, MB. Statistical analyses and interpretation: JAm. Data acquisition and critical review of the manuscript: all authors. All authors approved the final version of the article, including the authorship list.

Funding This project has been partially funded by the 'Consejería de Salud de la Junta de Andalucía' (PI-0075-2014) and the 'Spanish Ministry of Economy, Innovation and Competition, Instituto de Salud Carlos III' (PI19/01404, PI16/01842, PI17/00535 and GLD19/00100).

Disclaimer The funders have not had any role in the design, analysis, writing or interpretation of this project.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/gutjnl-2021-325700).

To cite Ampuero J, Lucena A, Hernández-Guerra M, *et al*. *Gut* 2022;**71**:2138–2140.

Received 21 July 2021
Accepted 29 November 2021
Published Online First 7 December 2021

Gut 2022;**71**:2138–2140. doi:10.1136/gutjnl-2021-325700

ORCID iD
Javier Ampuero http://orcid.org/0000-0002-8332-2122

REFERENCES

1 Mansoor E, Alikhan MM, Perez JA, *et al*. Clinical characteristics, hospitalisation and mortality rates of COVID-19 among patients with coeliac disease in the USA: a multicentre network study. *Gut* 2022;71:1691–2.
2 Iavarone M, D'Ambrosio R, Soria A, *et al*. High rates of 30-day mortality in patients with cirrhosis and COVID-19. *J Hepatol* 2020;73:1063–71.
3 Ampuero J, Sánchez Y, García-Lozano MR, *et al*. Impact of liver injury on the severity of COVID-19: a systematic review with meta-analysis. *Rev Esp Enferm Dig* 2021;113:125–35.
4 Belli LS, Duvoux C, Cortesi PA, *et al*. COVID-19 in liver transplant candidates: pretransplant and post-transplant outcomes - an ELITA/ELTR multicentre cohort study. *Gut* 2021;70:1914–24.
5 Bollipo S, Kapuria D, Rabiee A, *et al*. One world, one pandemic, many guidelines: management of liver diseases during COVID-19. *Gut* 2020;69:1369–72.
6 Trivedi PJ, Hirschfield GM. Recent advances in clinical practice: epidemiology of autoimmune liver diseases. *Gut* 2021;70:1989–2003.