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.

supplementary data for Table S1, reviewed data of all previous cases. CMB made a critical revision of the manuscript, helped in the acquisition of data, provided supplementary data for Table S1, reviewed data of all previous cases. All authors revised and gave the approval of the final manuscript.

Supplementary data

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Inflammasome activation and pyroptosis in lymphopenic liver patients with COVID-19

To the Editor:

As has recently been highlighted in the *Journal of Hepatology* and elsewhere, patients with liver diseases such as non-alcoholic fatty liver disease (NAFLD) or cirrhosis, as well as liver transplant recipients, carry a high risk of morbidity and mortality due to coronavirus disease 2019 (COVID-19).[1–3] Many of these patients have additional comorbidities including obesity, diabetes, hypertension, and cardiovascular disease, which are emerging as key predictors of COVID-19 severity.[4,5] Inflammation and T-cell immune dysregulation are also associated with poor COVID-19 outcomes.[6] To what extent these comorbidities cause immune dysregulation in COVID-19 is unknown; but it is known that they are characterized by chronic inflammation involving activation of the inflammasome,[7] which has been shown to play a key role in antiviral immune responses against other coronaviruses.[8] We thus hypothesize that heightened inflammasome activity may drive acute on chronic inflammation, leading to immune dysregulation and ultimately severe disease for these comorbid patients when facing COVID-19. In this letter, we share findings that provide preliminary support for this hypothesis based on data from 8 liver patients with COVID-19 from the MedStar Georgetown Transplant Institute (MGTI), with 8 matched non-liver patients with COVID-19 from SUNY Downstate Medical Center (SUNY).

This study was IRB approved (MGTI: IRB #STUDY00002359, IRB #2017-0365; SUNY: IRB #269846-8; informed consent was obtained). Retrospective and prospective chart review of all hospitalized liver patients with COVID-19 treated by MGTI consecutively in April and early May of 2020 was conducted. Specifically, we analysed data from 4 patients with chronic liver disease and 4 liver transplant recipients. The 8 control patients from SUNY were matched based on age, sex, race, comorbidities, and COVID-19 outcome during the same period.

Keywords: COVID-19; Inflammasome; Pyroptosis; Caspase-1; Lymphopenia; T cells; Liver transplantation; Comorbidities; Chronic liver disease; Liver cirrhosis.
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Table 1. Clinical and immunological characteristics of patients with COVID-19.

	Non-lethal courses of COVID-19					Lethal courses of COVID-19				
	MedStar Georgetown Transplant Institute Liver Patients				SUNY Control Patients	MedStar Georgetown Transplant Institute Liver Patients				SUNY Control Patients
Demographics										
Age, years	49	55	65	65	48–75	70	46	65	61	57–77
Sex, M/F	F	M	F	F	1M, 3F	F	M	F	M	2M, 2F
Race, white (W) or non-white (NW)	NW	NW	W	NW	1W, 3NW	W	W	NW	NW	0W, 4NW
Key comorbidities, n	2	3	3	5	2–3	1	2	3	3	1–3
Diabetes				✓	4 of 4		✓	✓	✓	1 of 4
Obesity	✓	✓	✓	✓	2 of 4			✓		2 of 4
Hypertension		✓		✓	4 of 4			✓	✓	4 of 4
Heart disease	✓		✓	✓	0 of 4				✓	2 of 4
Active liver disease		✓	✓	✓	0 of 4	✓	✓			0 of 4
Transplant/liver disease status										
Transplanted organ type	Liver & Kidney				n.a.		Liver	Liver	Liver & Kidney	n.a.
Underlying liver disease	ETOH cirrhosis	ETOH cirrhosis	NAFLD, ALF	AIH cirrhosis	n.a.	ETOH cirrhosis	HCV, ETOH cirrhosis	PSC cirrhosis	ETOH cirrhosis	n.a.
COVID-19 outcome										
Hospitalization	✓	✓	✓	✓	4 of 4	✓	✓	✓	✓	4 of 4
Supplemental O_2			✓	✓	3 of 4	✓	✓	✓	✓	4 of 4
Intubation/ICU			✓	✓	2 of 4		✓	✓	✓	4 of 4
No discharge by day 14				✓	3 of 4	✓	✓	✓	✓	4 of 4
Death					0 of 4	✓	✓	✓	✓	4 of 4
Liver function tests										
AST (U/L) [3-34], upon presentation	45	86	9654	76	12–88	61	99	19	40	17–175
AST, highest value during hospitalization	45	86	9654	136	18–158	64	233	74	178	117–5147
ALT (U/L) [15-41], upon presentation	73	55	3714	43	21–89	27	77	27	35	9–126
ALT, highest value during hospitalization	73	55	3714	79	21–197	36	111	89	147	87–5,658
Total bilirubin (mg/dl) [0.2-1.3], upon presentation	0.3	5.4	1.8	0.6	0.3–0.6	0.6	26.3	0.8	0.6	0.4–3.7
Total bilirubin, highest value during hospitalization	0.3	5.4	1.8	0.9	0.3–1.3	2.1	30.8	0.8	1.4	1.0–4.3
ALP (U/L) [45-117], upon presentation	254	324	243	254	63–95	182	699	72	80	61–143
ALP, highest value during hospitalization	378	324	319	455	63–156	182	699	102	633	129–195
Inflammatory markers										
LDH (U/L) [84-246], upon presentation	246	337	957	388	603–685	176	352	411	685	217–1,919
LDH, highest value during hospitalization	286	368	957	488	723–746	190	388	411	685	579–1,919
CRP (mg/L) [0.0-3.0], upon presentation	43.0	11.5	53.3	96.2	97–338	3.4	31.4	145	79	100–271
CRP, highest value during hospitalization	43.0	31.9	53.3	296.0	150–461	5.4	101.0	228.0	181.0	100–342
Ferritin (ng/ml) [5.0-148.0], upon presentation	1432	56.8	211.1	258.9	410–2,120	1,527	2,941	2,238	544.2	233–20,956
Ferritin, highest value during hospitalization	1432	113	238	439	1,355–2,120	1,527	4,585	2,754	607	2,707–20,956
D-dimer (μg/ml FEU) [<0.65], upon presentation	4.35	1.44	>20	1.92	0.5–8.0	2.43	5.71	11.55	0.5	n.a.
D-dimer, highest value during hospitalization	4.35	1.44	>20	3.56	1.0–>8.0	2.43	5.71	16.37	7.62	n.a.
Immunomonitoring										
WBC (K/μl) [4.0-10.8], upon presentation	9.9	6.9	17.4	3.7	5.8–13.4	2.7	4.2	8.0	3.6	4.6–16.1
WBC (K/μl), lowest value during hospitalization	2.3	5.2	5.9	3.7	5.1–9.2	2.7	4.2	4.8	3.6	2.3–8.5
Lymphocytes (K/μl) [0.6-4.9], upon presentation	0.8	1.1	0.9	0.9	0.2–2.4	0.9	0.2	0.2	0.5	0.4–1.1
Lymphocytes, lowest value during hospitalization	0.4	1.1	0.9	0.4	0.2–1.6	0.6	0.2	0.2	0.2	0.1–0.5
Days of lymphopenia (total days below 1.0 K/μl)	7	0	2	19	0–4	8	24	7	17	1–13

(*continued on next page*)

Table 1. (*continued*)

	Non-lethal courses of COVID-19					Lethal courses of COVID-19				
	MedStar Georgetown Transplant Institute Liver Patients				SUNY Control Patients	MedStar Georgetown Transplant Institute Liver Patients				SUNY Control Patients
T-cell counts										
CD3+ (/μl) [510-2607], upon presentation	636	1012	1373	1071	848–1205	592	414	106	273	729–1359
CD3+CD4+ (/μl) [302-1779], upon presentation	415	562	982	668	619–774	404	83	56	206	572–926
CD3+CD8+ (/μl) [101-951], upon presentation	168	401	336	380	199–289	176	311	44	59	55–343
T-cell phenotype										
CD4+CD38+HLA-DR+ % [0.30-1.35]	5.0	11.3	1.3	6.7	2.7–4.8	4.5	13.9	5.8	16.3	3.3–17.8
CD4+CD25+CD127- % [4.64-8.05]	2.3	4.2	16.8	4.1	2.6–4.4	6.5	3.3	0.0	8.8	2.4–18.1
CD4+ICOS+CXCR5+ % [0.64-2.72]	1.7	3.3	1.2	1.4	0.3–1.6	0.1	2.6	1.3	3.8	0.6–2.5
CD4+CD45RO+ % [9.9-37.7]	38.3	37.7	41.7	55.7	39.0–50.0	35.0	18.2	15.7	68.3	15.3–48.1
CD4+CD45RA+ % [3.4-37.9]	16.7	11.5	14.5	2.3	3.5–14.5	19.1	2.7	21.8	1.5	7.5–48.1
CD8+CD38+HLA-DR+ % [0.13-2.68]	31.8	48.6	1.9	24.6	11.5–33.4	35.5	27.2	21.6	20.6	14.7–56.6
CD8+CD45RO+ % [1.0-8.3]	11.0	5.5	4.3	19.5	3.1–13.7	3.3	23.8	2.2	13.1	0.3–7.0
CD8+CD45RA+ % [2.4-23.0]	8.2	18.9	3.8	5.7	6.0–12.3	18.9	31.3	30.2	2.2	11.3–17.3
Inflammasome activity										
Caspase-1 CD45+CD3+ % [2.11-4.90]	22.38	26.41	21.16	19.68	19.54–40.11	20.21	28.44	18.36	16.80	12.79–35.66
Caspase-1 CD45+CD3+CD4+ % [1.87-3.67]	17.61	24.93	21.22	21.54	11.57–38.37	15.63	30.83	16.77	17.38	11.10–31.11
IL-18 (pg/ml) [60-275]	400.0	989.6	304.5	439.2	1376–4496	229.4	162.2	469.2	162.6	610–2425

For the 8 MedStar Georgetown Transplant Institute liver patients, individual patient data are shown. For the 8 SUNY Downstate Medical Center (SUNY) non-liver control patients, summaries or ranges of high and low patient data are shown for the 4 non-lethal and 4 lethal cases, respectively. "Upon presentation" refers to the first data point available upon COVID-19 presentation; "during hospitalization" refers to data points collected during COVID-19 related hospitalization. Numbers in square brackets represent normal reference ranges from MedStar Georgetown Transplant Institute and CLIA-certified tests. Normal reference ranges for SUNY are listed in supplementary materials & methods. AIH, autoimmune hepatitis; ALF, acute liver failure; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; COVID-19, coronavirus disease 2019; CD, cluster of differentiation; CD4+CD25+CD127-, T-regulatory cell; CD4+ICOS+CXCR5+, T follicular helper cell; CLIA, Clinical Laboratory Improvement Amendments; CRP, C-reactive protein; ETOH, ethyl alcohol; HCV, hepatitis C virus; HLA, human leukocyte antigen; ICU, intensive care unit; IL, interleukin; LDH, lactate dehydrogenase; NAFLD, non-alcoholic fatty liver disease; O_2, oxygen; PSC, primary sclerosing cholangitis; WBC, white blood cell count.

As shown in Table 1, data were collected on demographics, comorbidities, liver disease, and COVID-19-related disease courses as well as from chemistry and immunological laboratory results obtained during hospitalization from the central laboratory of MedStar Georgetown University Hospital (liver patients), SUNY Downstate Medical Center (controls), and Amerimmune, a Clinical Laboratory Improvement Amendments (CLIA) certified laboratory. See supplementary materials & methods for details on methods.

Demographically, the liver patient cohort included patients between the ages of 46 and 70, 5 females and 3 males, and 5 non-white and 3 white patients. Seven patients had liver cirrhosis and 1 had NAFLD. Four had received liver transplantation and 4 were under our care for liver disease. All patients had significant comorbidities that would imply a chronic inflammatory profile. Six patients had severe COVID-19 courses requiring supplemental oxygen and/or ventilator support, and 4 of those patients died, 3 of whom were liver transplant recipients.

Over the course of their COVID-19 hospitalization, all liver patients had elevated levels of transaminases and alkaline phosphatase – consistent with previous reports on liver function in patients with COVID-19 – and high levels of inflammatory markers including CRP, ferritin, and D-dimer, as well as profound lymphopenia (mean length of 7 days and 14 days for the non-lethal and lethal cases, respectively). Specifically, the mean lowest lymphocyte count across the liver cohort was 0.5 K/μl, and for the non-lethal and lethal cases it was 0.7 and 0.3 K/μl, respectively, in line with the controls (overall mean of 0.6, with 0.8 and 0.3 K/μl for non-lethal and lethal, respectively). The mean absolute T-cell count across the liver cohort was low, with 685 /μl, and strikingly lower for lethal cases when compared to non-lethal cases (346 and 1,023 /μl, respectively). In the control cohort, the mean absolute T-cell count was 988 /μl with similar levels in the non-lethal and lethal cases. The relatively higher levels in the control cohort lethal cases *vs.* the liver cohort lethal cases could be explained by the fact that 3 of the 4 lethal liver patients were on post-transplant immunosuppression, indicating that immunosuppression could exacerbate COVID-19 induced T-cell lymphopenia. Moreover, overexpression of both CD38+ and HLA-DR+ in CD4+ and 8+ T cells across the cohorts, with mean values of 8.1% and 26.5% in the liver and 6.2% and 26.7% in the control cohorts, respectively, points to virally induced T-cell activation.

The T-cell lymphopenia caused us to hypothesize that inflammasome activation might be a driver of pyroptosis-induced T-cell death. This led us to study caspase-1 activation, as its upregulation is the hallmark feature of inflammasome activation. Indeed, we found a global increase in caspase-1 activity levels in T cells, with mean values of 20.7% and 21.7% for CD45+CD3+CD4+ and CD45+CD3+, respectively in the liver cohort and 24.9% and 28.0% in the control cohort. Corroborating this finding across both cohorts were high levels of lactate dehydrogenase (LDH) and IL-18, both of which are known to be released upon pyroptotic cell death (LDH mean values of 472 and 968 u/L and IL-18 mean values of 395 and 1,856 pg/mL in liver and control patients, respectively). The relatively higher IL-18 and LDH levels in control patients may be explained by *a priori* reduced lymphocytes in immunocompromised liver disease and transplant patients. Of note, elevated LDH, IL-18, and caspase-1 findings were consistent in the liver cohort irrespective of transplant or liver disease status.

Our patient data corroborate poor COVID-19 outcomes for liver patients, especially for those with inflammatory comorbidities. Furthermore, analysis of lethal cases shows that patients with the lowest T cell counts are more prone to morbid outcomes. The common link between these findings may be the inflammasome, which plays a role in both comorbidities and viral infections. Specifically, our findings suggest that comorbid patients – independent of liver disease – may already have a constitutive chronic activation of the inflammasome, which is further exacerbated by viruses that activate the inflammasome, as has been shown in monocytes and other immune cells in the face of coronaviruses.[9] Strong upregulation of caspase-1 activity in T cells as well as high IL-18 and LDH levels across all patients suggests pyroptosis-mediated programmed cell death occurring downstream of inflammasome activation as a cause of lymphopenia and driver of heightened inflammation in COVID-19, similar to SARS-CoV-1.[10] Pyroptotic T-cell depletion in patients with COVID-19 may not only prevent the adaptive immune system from mounting an effective antiviral immune response but also fuel a lethal inflammatory response through release of proinflammatory cytokines such as IL-1β and IL-18. Our insights into the potentially critical role of the inflammasome in COVID-19 have therapeutic implications beyond liver diseases, as they imply that upstream prevention of pyroptosis in COVID-19 may be beneficial.

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Conflicts of interest
The authors declare no conflicts of interest that pertain to this work.

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

Authors' contributions
AK, KK, and TMF designed the study. AK and KK performed clinical data analysis at MedStar Georgetown Transplant Institute. MAH and RG performed clinical data analysis at SUNY Downstate Medical Center. MP and OA conducted the clinical immunology studies done at Amerimmune. AK, KK, and TMF wrote the manuscript.

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SARS-CoV-2 in patients on antiviral HBV and HCV therapy in Spain

To the Editor:

The impact of SARS-CoV2 in patients with underlying chronic liver disease is still a matter of analysis within the Hepatology community.[1] We read with great interest several studies suggesting that antivirals against HCV or HBV could be evaluated as COVID-19 therapeutics. A study virtually screening usable therapeutics against SARS-CoV-2 showed that velpatasvir and ledipasvir (inhibitors of the NS5A protein of the HCV) were among the 16 candidates which gave promising binding models.[2] The polymerase of SARS-CoV-2 has been modeled and then targeted using different anti-polymerase drugs currently on the market that have been approved for use against various viruses. The structural superposition of the HCV and SARS-CoV-2 polymerase shows that the residues that bind to the drug are present in the latter, suggesting the potential use of sofosbuvir.[3,4] In addition to ribavirin and remdesivir, the HBV nucleotide analog tenofovir has appeared as a candidate drug against SARS-CoV-2 due to its tight binding to its polymerase.[4,5] However, information on COVID-19 in patients with HCV infection under active direct-acting antivirals (DAAs) or with HBV infection under tenofovir is scarce.

It is not clear if chronic HBV or HCV *per se* could impact on susceptibility to SARS-CoV-2 infection. In the preliminary report of 2 international registries, 152 cases of laboratory-confirmed COVID-19 were reported in patients with chronic liver disease (CLD). HBV and HCV accounted for 11.8% and 10.5% of the underlying causes of CLD, but there was no information regarding antiviral therapy or active disease. In a study including 5,700 patients hospitalized in New York, 0.1% of patients had HBV infection and 0.1% HCV infection, but as in the previous report, no information on the antiviral therapy status was available.[6] Due to the higher prevalence of HBV in China, we focused on the main reports from this country to study the correlation between HBV and COVID-19 diagnosis. A large hospitalized patient series from Wuhan, China, observed that 2.1% (23/1,099) of patients were HBV infected, although this was defined by the sole presence of HBsAg and no data on antiviral therapy or disease phase was provided.[7] An unpublished single-center retrospective study from China specifically analyzed the association between COVID-19 and HBV infection. This study found that 12.2% (15/123) of patients with COVID-19 had HBV infection, and reported that HBV infection was associated with a more severe course and higher mortality rate (13.3% *vs.* 2.8%), but no information on antiviral therapy was provided.[8] Finally, a recent letter suggested an inverse association between HBV and COVID-19, considering the HBV prevalence in several regions. While the HBV rates of those with COVID-19 remained between 0–1.3%, the corresponding HBV rates among the same age groups ranged from 7–11%.[9] According to these data, one might speculate about a low incidence of HCV and HBV infection in hospitalized patients with COVID-19. Nevertheless, no studies to date have reported the effect of HCV/HBV antiviral therapy on COVID-19 incidence and outcomes.

Spain has been one of the countries severely hit by the COVID-19 pandemic, with up to 239,638 reported confirmed cases so far (1 June 2020). In the most affected regions (Madrid and Catalonia) the infection rate ranged between 771–1,045 cases/100,000 habitants. The prevalence of HCV and HBV infection in these regions is 1.02% (95% CI 0.65–1.39) and 0.52% (0.26–0.77), respectively.[10]

We aimed to evaluate the incidence of SARS-CoV-2 in patients under 'active' antiviral therapy with tenofovir and DAAs

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