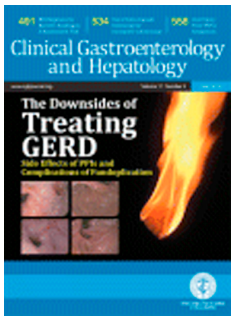

Impact of SARS-CoV-2 pandemic on vascular liver diseases

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Impact of SARS-CoV-2 pandemic on vascular liver diseases

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Abstract

Background and Aims: Vascular liver diseases (VLD) are represented mainly by portosinusoidal vascular disease (PSVD), non-cirrhotic splanchnic vein thrombosis (SVT) and Budd Chiari syndrome (BCS). It is unknown whether patients with VLD constitute a high-risk population for complications and greater COVID-19-related mortality from SARS-CoV-2 infection.

Our objective was to assess the prevalence and severity of SARS-CoV-2 infection among patients with VLD, as well as to assess its impact on hepatic decompensation and survival.

Methods: This is a observational international study analyzing the prevalence and severity of SARS-CoV-2 infection in VLD between March 2020–March 2021 comparing with the general population (GP). Patients from Spain (5 centers, n = 493) and France (1 center, n = 475) were included.

Results: Nine hundred and sixty-eight patients were included: 274 PSVD, 539 SVT and 155 BCS. Among them, 138 (14%) were infected with SARS-CoV-2: 53 PSVD, 77 SVT and 8 BCS. The prevalence of SARS-CoV-2 infection in PSVD (19%) and SVT (14%) was significantly higher than in GP (6.5%, $p < 0.05$), while it was very similar in BCS (5%).

In terms of infection severity, patients with VLD also presented a higher need of hospital admission (14% *vs* 7.3%, $p<0.01$), ICU admission (2% *vs* 0.7%, $p< 0.01$) and mortality (4% *vs* 1.5%, $p < 0.05$) than GP. Previous history of ascites (50% *vs* 8%, $p < 0.05$) and post-COVID-19 hepatic decompensation (50% *vs* 4%, $p < 0.05$) were associated to COVID-19 mortality.

Conclusion: PSVD and SVT patients could be at higher risk of infection by SARS-CoV-2 and at higher risk of severe COVID-19 disease.

Keywords: SARS-CoV-2; COVID-19; vascular liver diseases; portosinusoidal vascular disease; splanchnic vein thrombosis; Budd Chiari syndrome

Introduction

The hasty spread of the global pandemic by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and the resultant coronavirus disease 2019 (COVID-19) has severely impacted global health with devastating effects. Certain populations have been reported as especially vulnerable to COVID-19 disease [1]. Patients with advanced age, male sex and comorbidities including arterial hypertension, obesity, heart disease, diabetes or malignancy have been consistently reported to develop severe COVID19 [2]. Although there is no clear evidence on SARS-CoV-2 hepatotropism, abnormalities in liver tests are present in 15-65% of patients with COVID-19 regardless of the presence of underlying liver disease[3]. Indeed, SARS-CoV-2 is genetically related to Middle East respiratory syndrome Coronavirus (MERS-CoV), which is also known to affect liver tests. Abnormal liver tests in COVID-19 are probably multifactorial, due to a combination of immune-mediated inflammatory response, drug-induced liver injury, hepatic congestion or direct infection of hepatocytes [4]. Several studies have tried to elucidate if patients with chronic liver disease are at higher risk of SARS-CoV-2 infection. It has been shown that cirrhotic patients – specifically with decompensated cirrhosis - have a higher rate of hospitalization and mortality [5,6]. Despite the concern raised by these studies, we currently do not know whether all chronic liver diseases are equally affected by COVID-19 or if there are specific subgroups with increased risk of mortality and morbidity. Immunosuppression does not seem to confer an increased risk for severe COVID-19 in specific subpopulations such as autoimmune hepatitis [7] or liver transplant recipients [8] .

No studies have yet evaluated if patients with vascular liver diseases (VLD) also represent a vulnerable population with higher risk of complications and higher mortality than general population. VLD are a set of diseases that affect young and otherwise healthy patients that usually exhibit a preserved liver function and have a markedly different natural history from cirrhosis. Portosinusoidal vascular disease (PSVD, formerly known as idiopathic portal hypertension), chronic non-cirrhotic splanchnic vein thrombosis (SVT) and Budd Chiari syndrome (BCS) are the most common VLD. Although individually the prevalence of each of these rare diseases is less than 5 per 10,000 inhabitants [9,10], overall they affect a significant proportion of the population. A common feature of these VLD is the presence of non-cirrhotic

portal hypertension and underlying prothrombotic state [11], either *per se* (high incidence of SVT in patients with PSVD regardless of associated thrombophilia) or due to associated underlying diseases (i.e. myeloproliferative disorders, inherited thrombophilia, antiphospholipid syndrome or HIV). As one of the most feared complications of COVID-19 disease is the increased systemic inflammatory response leading to a higher risk of hypercoagulability and thromboembolic disease [12,13], it could be argued that SARS-CoV-2 may further deteriorate the clinical condition of patients with these VLD.

The aim of the present work is to assess the prevalence and severity of SARS-CoV-2 infection among patients with VLD. We provide the first international report detailing the impact of SARS-CoV-2 in VLD and we offer comparison with the corresponding data regarding general population of Spain and France.

Patients and methods

Patients and study design

We conducted an observational multicentric international study including 5 centers in Spain belonging to the REHEVASC network (Hospital Clínic de Barcelona, Hospital Ramón y Cajal, Hospital Universitario Marqués de Valdecilla, Hospital Puerta de Hierro, Hospital de la Santa Creu i Sant Pau) and one center in France (Hôpital Beaujon). The six participating hospitals are the main tertiary referral centers in the field of VLD in Spain and France, thus providing a good description of the VLD population of the two countries. Also, all the participating hospitals prospectively register all patients diagnosed with VLD in their hospitals. The registries offer a comprehensive representation of all the stages of VLD given that both compensated patients (patients diagnosed during an outpatient study of hepatic liver disease) and patients that have required hospitalization are included in the registry. Given the nature of the study, to have a baseline registry was a necessary and limiting factor to participate in the study. The registries included baseline characteristics such as age, gender and associated comorbidities. Using the registries of each hospital as a starting point, we reviewed their clinical records to investigate if they had been infected by SARS-CoV-2 in the period comprised between March 2020 – March 2021 as well as the clinical outcome. Positive cases were also contacted by phone or email and

answered a questionnaire regarding detailed signs and symptoms of presentation. The follow-up period was stopped at March 2021 to avoid interference with the COVID-19 vaccination program. Indeed, no patient was vaccinated during the period of the study. Patients with vascular liver diseases different from PSVD, SVT and BCS were not included in this study due to their extremely low prevalence. The study was performed in accordance with the International Guideline for Ethical Review of Epidemiological studies and principles of the Declaration of Helsinki, and was approved by the local ethics committees.

All cases of laboratory-confirmed SARS-CoV-2 infection with any symptom profile or disease severity were included in the analysis. Positive cases were defined as detection of SARS-CoV-2 by reverse-transcriptase polymerase chain reaction (RT-PCR) on nasopharyngeal swabs, ELISA serological testing for detection of antibodies to SARS-CoV-2 or antigen detection tests. Thirteen patients with conclusive clinical manifestations compatible with COVID-19 infection in which no tests had been performed due to lack of resources at the beginning of the pandemic were also included.

To provide a comparison with general population, we used the data published by both the Spanish (ine.es) and the French government (santepubliquefrance.fr). From these websites we established the general population (GP) prevalence, the stratification of prevalence by age group and the severity of the disease in GP, defined by need of hospital admission, need of ICU admission and COVID-19-related death. Briefly, between March 2020 and March 2021, 3,042,127 people have been diagnosed with SARS-CoV-2 infection in Spain, accounting for 7% of the general population (current Spanish population 46,769,777 people). The proportion of patients needing hospital admission was 7.3%, while 0.7% needed ICU admission and 1.5% died. In France, French population is estimated at 65,273,511 people and between March 2020 and March 2021 there have been 5,498,044 confirmed cases of SARS-CoV2 infection, 8% of French GP, which is similar and comparable to the Spanish data (p=0.6). The French mortality rates were also comparable to that of the Spanish population (1.87% in France *vs* 1.5% in Spain, p= 0.86). We have focused on the Spanish general population data as reference to compare it with our VLD cohort.

Each vascular liver disease (PSVD, PVT and BCS) has been analyzed separately. Additionally, we have performed a subanalysis stratifying patients by age groups (< 40 years old, 40-59 years old, 60-69 years old and >69 years old) to elucidate the possible role of this confounding factor. Supplementary Table 1 lists the points of comparison between GP and our VLD cohort.

Statistical analysis

Continuous variables are reported as mean + SD and categorical variables are reported as absolute and relative frequencies. Groups were compared using the T test or the Mann-Whitney test for continuous variables when appropriate, and the Fisher exact test was used for categorical variables. Logistic regression models were used to study the predictors of COVID-19 infection.

Results

Five-hundred forty-seven patients with VLD were prospectively registered in the 5 Spanish centres (310 in Hospital Clínic de Barcelona, 123 in Hospital Ramon y Cajal, 50 in Hospital de la Santa Creu i Sant Pau, 43 in Hospital Universitario Marqués de Valdecilla and 29 in Hospital Puerta de Hierro), and we obtained data from 493 (90%) **(Supplementary Figure 1).** In Hôpital Beaujoun there were 670 VLD patients registered, and we obtained data from 475 (71%) (**Supplementary Figure 2**). Overall, out of 1217 patients 968 (80%) were included: 274 PSVD, 539 SVT and 155 BCS (Flowchart, **Figure 1**). Among these 968 patients, 138 (14%) were infected with SARS-CoV-2 between March 2020 and March 2021: 53 PSVD (19%), 77 SVT (14%) and 8 BCS (5%).

Table 1 shows that there is a high variability in baseline characteristics. However, most of these differences can be explained by the intrinsic characteristics of each disease (i.e PSVD is usually associated to HIV, IBD or history of neoplasm and chemotherapy; BCS is more frequent in women and usually decompensate as ascites and not as variceal bleeding). **Supplementary Table 2** summarizes the diagnostic method (PCR, serologies, antigen test or clinical signs) used for COVID-19 diagnosis, as well as the reason motivating the diagnostic test. Most patients were diagnosed by PCR (69%) or serologies (11%). The reason prompting the diagnostic test

was only collected in the Spanish cohort, and in most patients it was the presence of symptoms (n= 37, 65%), followed by contact tracing screening program (n= 15, 26%).

Prevalence

- Portosinusoidal vascular disease (PSVD*)*

Out of 274 patients with PSVD, 53 were infected with SARS-CoV-2 (19%), a prevalence significantly higher than in GP (6.5%, $p < 0.05$). This was observed in all age groups (**Figure 2**), except in the > 70 years old group. Indeed, the prevalence reached 15%, 25% and 19% in age groups <40, 40-59 and 60-69 years, respectively.

- Splanchnic vein thrombosis (SVT)

The prevalence of SARS-CoV-2 was also significantly higher in SVT than in GP. Out of 539 patients with SVT, 77 were infected with SARS-CoV-2 (14% vs 6.5% in GP, $p < 0.05$). Regarding age distribution (**Figure 3)**, it was also significantly different from GP ($p < 0.05$): SARS-CoV-2 infection was present in 16% of patients aged < 40 years, in 15% of patients between 40-59 years old and in 13% of patients of among age group 60-69. In patients over 70 years old the prevalence was also higher than in GP (10% *vs* 5.4%) but it did not reach statistical significance.

Importantly, if we exclude the 13 patients that were clinically diagnosed without a confirmation test, the prevalence and severity of SARS-CoV-2 infection in patients with VLD was still higher than in GP (125 of 968, 13% $p < 0.05$, **Supplementary Table 3**). Importantly, this was observed both in the Spanish and in the French cohort (data not shown).

- Budd Chiari Syndrome (BCS)

In our cohort, only 8 patients out of 155 with BCS presented with SARS-CoV-2 (5%). Thus, the global prevalence of SARS-CoV-2 in patients with BCS was very similar to that of GP even stratified by age groups.

Signs and symptoms

Among the 138 patients, only 21 (15%) remained completely asymptomatic throughout all the infection period. **Table 2** shows the most frequent symptoms developed in this cohort and

dissects them according to the VLD type. Fever and asthenia were present in 60% of patients, followed by cough in 46%. Cephalea, anosmia, dysgeusia or other symptoms were less frequent.

Risk factors of SARS-CoV-2 infection in VLD

- PSVD

Median age of infected patients was 49.7 ± 17 years and 50% of them were men. There were no statistically significant differences in age and sex distribution among patients infected or not by SARS-CoV-2. We assessed if previous decompensation, variceal bleeding, ascites, hepatic encephalopathy, sex, age, comorbidities (arterial hypertension, diabetes mellitus, obesity, history of neoplasms, inflammatory bowel disease, HIV infection), use of anticoagulation, use of TIPS (transjugular intrahepatic portosystemic shunt), previous SVT in PSVD or baseline liver function were potential risk factors for COVID-19 in VLD population. Only a higher baseline bilirubin was observed in PSVD patients acquiring SARS-CoV-2 (2.5 ± 2.6 *vs* 1.5 ± 1.5 mg/dL, $p < 0.05$) without significant differences in the remaining assessed parameters (**Supplementary Table 4).**

- SVT

Median age of infected patients was 48.3 ± 18 and 38% of them were male. History of arterial hypertension (28% *vs* 16%, $p < 0.05$), inflammatory bowel disease (8% vs 2%, $p<0.01$) higher bilirubin (2.6 **±** 2.8 *vs* 1.5 **±** 1.9 mg/dL, $p<0.01$), higher protrombin time (38% ± 44 vs 55% ± 41, $p <0.05$**)** and use of anticoagulation (79% vs 67%, $p < 0.05$) were associated with SARS-CoV-2 infection, but only inflammatory bowel disease [4.3 (1.1– 17.2); $p < 0.05$) and bilirubin levels [1.2 (1.1-1.4); $p<0.01$] were independently associated to it (**Supplementary Table 5 and Supplementary Table 6)**.

- BCS

No further analysis was performed in patients with BCS given the low number of cases recorded and the similar prevalence to GP.

Severity of COVID-19 disease in VLD

Table 3 summarizes the severity of COVID-19 disease in patients with VLD using the need of hospital admission, need for ICU care and mortality as indicators. The analysis was performed either globally or categorized by age groups (**Supplementary Table 7**). As shown, patients with VLD presented a higher need of hospital admission (14% *vs* 7.3%, p<0.01), ICU admission (2% *vs* 0.7%, p< 0.01) and COVID-19-related mortality (4% *vs* 1.5%, p < 0.05) than GP. However, COVID-19 infection increase in severity was not homogeneously distributed. Indeed, although the low sample size when subanalyzing by age groups reduces the strength of the finding, our results suggest that the increase of COVID-19 severity in VLD patients focuses in those patients below the age of 60.

Regarding BCS, only one patient required hospital admission, which makes it difficult to draw any conclusions from this subpopulation. This single patient presented full recovery afterwards without further complications.

Liver decompensation after SARS-CoV2 infection

Six patients (2 PSVD, 4 SVT) developed hepatic decompensation during COVID-19 disease: splanchnic thrombosis and variceal bleeding in the two patients with PSVD; ascites, variceal bleeding and two episodes of re-thrombosis in the 4 patients with SVT. Noteworthy, according to their clinical characteristics, presence or not of underlying prothrombotic factors or previous development of splanchnic thrombosis in patients with PSVD, at inclusion 89% of patients with BCS, 68% of patients with SVT and 31% of patients with PSVD were on long-term anticoagulation treatment. Based on the local clinical guidelines of each center, 3 of 53 patients with PSVD (5.7%) and 4 of 77 patients with SVT (5.2%) received anticoagulation as part of the treatment of SARS-CoV-2 infection. The 3 episodes of thrombosis were the only post-COVID-19 thrombotic recorded events in our cohort and they were all in the splanchnic territory. The two patients with SVT had associated underlying thrombophilia that conferred them a higher risk of thrombosis and were accordingly under long term anticoagulation.

Given the low number of events, to assess the risk of hepatic decompensation and risk of mortality due to COVID-19 we evaluated the VLD cohort globally. We found that history of diabetes mellitus (12% *vs* 42% p<0.05), previous ascites (8% *vs* 42%, p<0.01) or hepatic

encephalopathy (3% *vs* 28%, p<0.05) were significantly more frequent in patients presenting further hepatic decompensation after SARS-COV-2 infection.

Four patients died due to COVID-19 pneumonia and respiratory insufficiency (n=1 PSVD; n= 3 SVT). Previous history of ascites (50% *vs* 8%, p<0.05) and post-COVID-19 hepatic decompensation (50% *vs* 4%, p<0.05) were more frequent among these patients.

Discussion

The huge daily death toll, fast infection rates and the burden on intensive care units of COVID-19 pandemic rapidly lead to a worldwide crisis with a dramatic impact on global health care systems. This pandemic made it clear that healthcare systems need to be improved and have to be more resilient to emergencies. One of the most important items to improve the approach to the present –and, eventually, future- pandemics is the identification of vulnerable patients at higher risk of adverse outcomes. Several studies have shown that chronic health conditions can increase the risk of presenting severe COVID-19. Liver disease has also been identified as an important risk factor for severe COVID-19, being especially virulent in those patients with cirrhosis and hepatic decompensation. However, the term liver disease encompasses a broad range of pathologies that have few things in common and that require an individualized approach. Among them, VLD deserve special mention. Despite their relatively low prevalence, they represent a significant health problem in the field of liver disease. They usually affect young patients and cause portal hypertension which, in turn, leads to increased morbidity and mortality.

Although fortunately in some countries the current pandemic situation is beginning to improve thanks to the development of vaccines, the emergence of multiple new SARS-CoV-2 strains make it difficult to predict the long-term protective effects of the available shots. It is therefore clear that one of the best existing strategies is the identification of vulnerable populations. Thus, the aim of the present study is to focus on vascular liver diseases and characterize the effects of SARS-CoV-2 infection in this population.

The strength of our study rests in the approach and methodology used. For this study, a thorough investigation was performed and we were able to contact 80% of our patients, thus

making highly unlikely a selection bias. Estimations of the real prevalence of the disease, also detecting asymptomatic patients, would have required testing of all VLD patients. However, this is not a real option and we consider that our approach is a good surrogate given that the general population underwent the same testing policy. Our results can be summarized in three important messages:

1) The prevalence of SARS-CoV-2 infection among patients with PSVD and SVT seems to be higher than in general population. On the contrary, in patients with BCS the prevalence was very similar to general population. Of note, as detailed in Table 1, the prevalence of arterial hypertension was significantly lower in patients with BCS than in patients with PSVD and SVT, which could confer a lower risk of severe COVID-19 disease. There were no statistically significant differences in other factors such as diabetes, smoking or obesity. The higher prevalence in PSVD and SVT seems to not be influenced by patients' age. Only in age group > 70 years-old the prevalence was similar to GP, probably due to the low representation of older patients in our cohort and to a higher concern of these patients in preventing infection. A similar finding regarding absence of differences in older groups was observed in the study by Marjot et al [5]. This study showed that while patients without cirrhosis display an age-related gradient for mortality, mortality in patients with cirrhosis was higher in patients under 40 years. Higher bilirubin and IBD were the only features identified as risk factors for SARS-CoV-2 infection. However, the clinical relevance of these findings is debatable. Liver function is usually well-preserved in both PSVD and SVT and generally is not a matter of concern in these patients. Indeed, the only slightly higher levels of bilirubin found in patients with SARS-CoV-2 infection have no clinical relevance. Regarding inflammatory bowel disease, recent publications specifically focused on assessing the incidence and severity of COVID-19 in patients with Crohn's disease and ulcerative colitis suggest that IBD patients are not at higher risk of COVID-19 than GP [14]. Thus, currently we are compelled to consider these results cautiously and wait for validation in future cohorts.

2) Our data suggests that patients with SVT and PSVD could have a more severe course of COVID-19 infection than GP. This stronger severity is more evident at younger ages, which could be explained by the fact that VLD predominantly affect younger patients

BCS seems to relate differently to SARS-CoV-2 than the rest of VLD. Noticeably, the severity of SARS-CoV-2 infection in patients with BCS is strictly comparable to that of GP. We hypothesize that the absence of portal hypertension in compensated BCS could explain this important difference with PSVD and SVT. Although BCS entails of course the development of portal hypertension, in chronic compensated stages patients will have either developed collateral circulation that effectively decompresses the splanchnic system or will have required the placement of a transjugular portosystemic shunt. This is also suggested by the fact that 37% of our patients with BCS were asymptomatic for COVID-19, which is a higher frequency than in SVT and PSVD.

3) We carefully assessed if well-known high risk factors such as age, diabetes, arterial hypertension, obesity or malignancy, among others, played a role in the evolution and final outcome of the SARS-CoV-2 infection. We also assessed if other concomitant diseases, especially the association to myeloproliferative diseases (very frequent in patients with SVT and BCS) could interfere in its severity. Of all the parameters evaluated, diabetes mellitus and previous hepatic decompensation were the only factors associated with post-infection liver decompensation and with mortality. Admittedly, due to the low number of deaths in our cohort the strength of these results is reduced. However, these results support and point in the direction that the higher prevalence and higher severity of COVID-19 in patients with PSVD and SVT is due to the VLD *per se* and is not influenced by associated comorbidities (with the exception of diabetes mellitus facilitating hepatic decompensation). Of note, although the interpretation of these results is limited by not having a comparable control group, comorbidities such as obesity, diabetes mellitus or arterial hypertension had a lower prevalence in our cohort than in both the Spanish and French GP (in our cohort prevalence of diabetes mellitus, arterial hypertension and obesity was 10%, 17% and 12% respectively *vs* 13.8%, 42% and 23% in the Spanish population and 8%, 30% and 26% in the French population), which can

explain why metabolic factors known to increase the risk of severe COVID-19 had a low impact in the outcome of our cohort.

Finally, it is remarkable that although most VLD are associated with a hypercoagulable state and COVID-19 is also considered a prothrombotic condition[16], the rate of thromboembolic events was unexpectedly low. Although this is an important finding, in this observational study no systemic imaging tests looking for thrombotic events were performed and thus asymptomatic thrombotic events could have been underdiagnosed. Accordingly, no strong recommendations regarding venous thromboembolism prophylaxis and anticoagulation can be made based on our results.

In conclusion, this international study shows that PSVD and SVT patients could be at higher risk of infection by SARS-CoV-2 and, importantly, point in the direction that they could also be at higher risk of severe COVID-19 disease. Our results have significant implications for the management and risk stratification of patients with VDL, for both the present pandemic and for future hypothetic outbreaks of new SARS-CoV-2 strains. Future research should be directed at vaccination programs, as data regarding duration of protection, tolerability and long-term safety of COVID-19 vaccines in patients with VLD has yet to be generated. In this regard, as it is known that some patients do not mount a strong immune response to the vaccines and taking into consideration the higher risk of severe COVID-19 disease in VLD, it would seem reasonable to recommend checking the anti-SARS-CoV-2 antibody levels after full vaccination in this population and administer a third dose to all patients not showing good antibody response.

Table 1. Baseline characteristics of vascular liver diseases cohort

	PSVD n=274	SVT n= 539	BCS n=155	p value
Age	53.2±15.4	52.5 ± 15.1	50.5 ± 14.5	0.22
Sex (male)	155 (57%)	301 (56%)	51 (33%)	**<0.01**
Excessive alcohol consumption*	25 (9%)	65 (12%)	13 (9%)	0.25
Smoking	25 (9%)	68 (13%)	12 (8%)	0.48
Obesity	19 (7%)	81 (15%)	19 (12%)	**<0.01**
Arterial hypertension	48 (17%)	98 (18%)	14 (9%)	**0.02**
Diabetes mellitus	32 (12%)	51 (10%)	10 (6.5%)	0.21
HIV	29 (11%)	0	0	**<0.01**
Neoplasm	16 (6%)	7 (1%)	2 (1%)	**<0.01**
MPN	12 (4%)	116 (22%)	73 (47%)	**<0.01**
IBD	15 (6%)	13 (2%)	0	**<0.01**
Any comorbidity	149 (54%)	218 (40%)	62 (40%)	**<0.01**
Any previous PH complication	71 (26%)	129 (24%)	62 (40%)	**<0.01**
Previous variceal bleeding	52 (19%)	77 (14%)	12 (8%)	0.06
Previous ascites	32 (12%)	73 (14%)	51 (33%)	**<0.01**
Previous HE	7 (3%)	9 (2%)	7 (4.5%)	0.23
TIPS	22 (8%)	13 (2%)	59 (38%)	**<0.01**

*PSVD Portosinusoidal vascular liver disorder; SVT splanchnic vein thrombosis; BCS Budd Chiari Syndrome; HIV human immunodeficiency virus; MPN myeloproliferative neoplasm; IBD Inflammatory bowel disease; PH portal hypertension, HE Hepatic Encephalopathy; Excessive alcohol consumption is defined as more than 4 units of alcohol per day; TIPS transjugular intrahepatic portosystemic shunt

Table 2. Symptoms associated to SARS-CoV-2 infection

Symptoms	All VLD n= 138	SVT n= 77	BCS n= 8	PSVD n=53	p value
Fever	84 (61%)	48 (62%)	4 (50%)	32 (60%)	0.87
Asthenia	83 (60%)	48 (62%)	4 (50%)	31 (58%)	0.81
Cough	64 (46%)	32 (41%)	3 (37%)	29(54%)	0.34
Cephalea	47 (34%)	28 (36%)	2 (25%)	17 (32%)	0.80
Anosmia	44 (32%)	25 (32%)	2 (25%)	17 (32%)	1
Dysgeusia	37 (27%)	23 (30%)	2 (25%)	12 (22%)	0.67
Dyspnea	26 (18%)	15 (19%)	1 (12%)	10 (18%)	1
Diarrhea	21 (15%)	11(14%)	0	10 (18%)	0.42
Asymptomatic	21 (15%)	8 (10%)	3 (37%)	10 (18%)	0.07

* VLD Vascular Liver diseases; SVT splanchnic vein thrombosis; BCS Budd Chiari Syndrome; PSVD Portosinusoidal vascular liver disorder

Table 3. Severity of SARS-CoV-2 infection and need of hospital admission, ICU admission and Mortality

	GP N=3.042.127	**VLD** **N=138**	p	**PSVD** **N=53**	p	**BCS** **N=8**	p	**SVT** **N=77**	p
Admission	221.118 (7.3%)	20(14%)	**0.01**	5 (9%)	0.57	1 (12%)	0.60	14(18%)	**0.01**
ICU	20.362 (0.7%)	4 (2%)	**0.01**	2 (4%)	**0.01**	0	0.81	2 (3%)	**0.04**
Mortality	45.797 (1.5%)	4 (4%)	**0.04**	1(2%)	0.8	0	0.72	3 (6%)	**0.01**

*GP General population, VLD Vascular Liver diseases, PSVD Portosinusoidal vascular liver disorder; BCS Budd Chiari Syndrome; SVT splanchnic vein thrombosis

Figure 1. Flowchart

Figure 2. Age distribution of SARS-CoV-2 infection among patients with VLD compared to GP

Supplementary Figure 1. Vascular liver diseases Spanish cohort

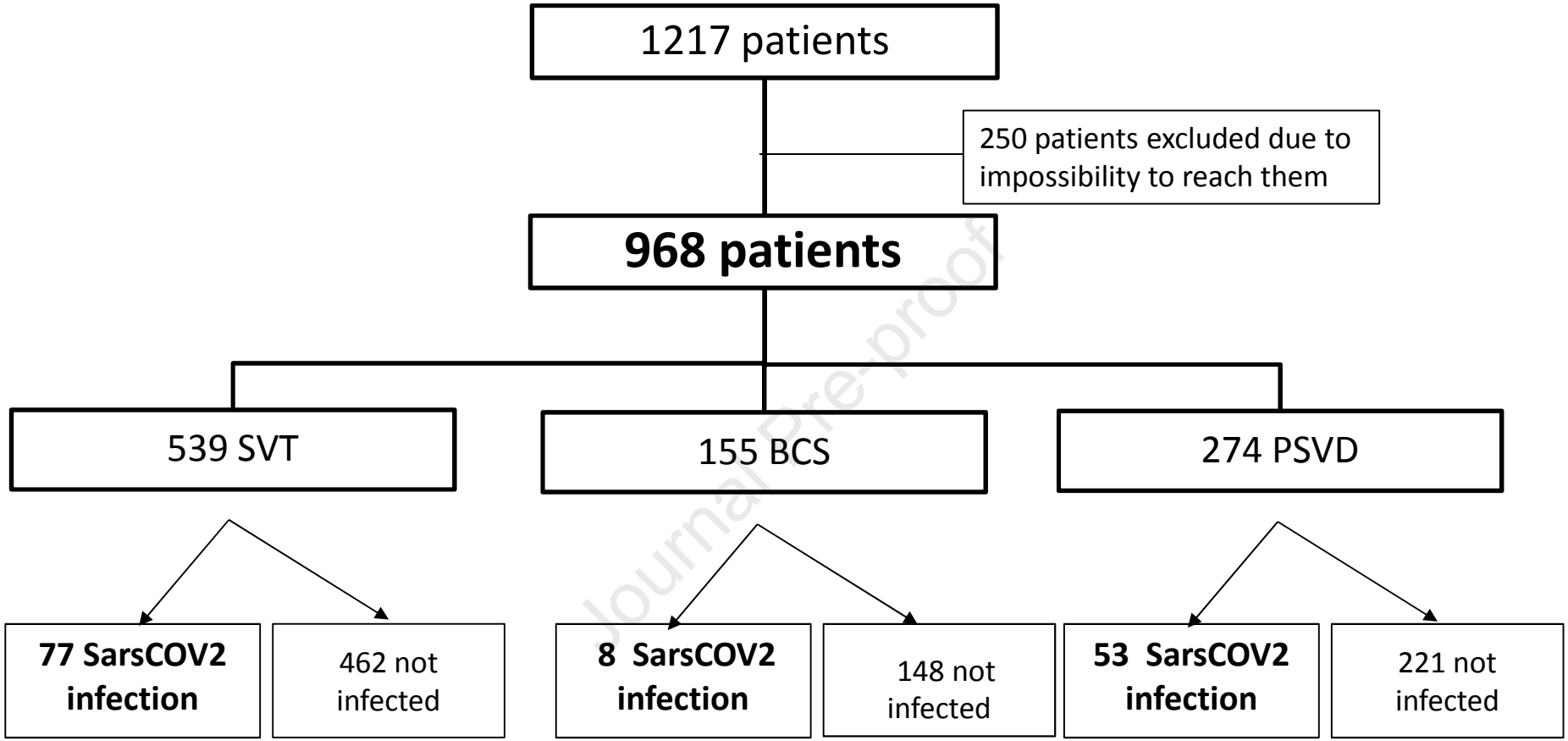
Supplementary Figure 2. Vascular liver diseases French cohort

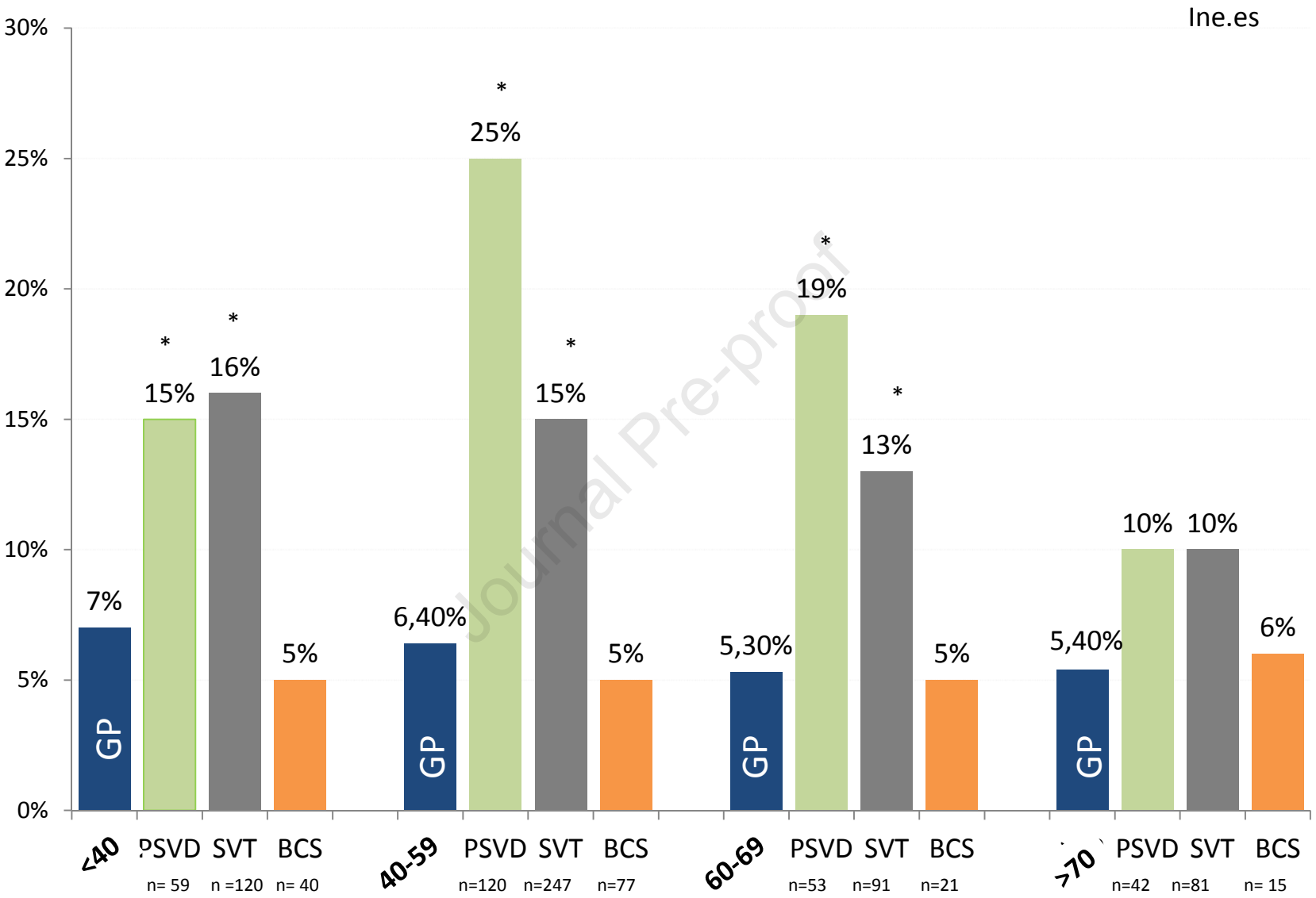
REFERENCES

1. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet (London, England) 2020;395:1054-1062.
2. Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature 2020;584:430-436.
3. Sultan S, Altayar O, Siddique SM, et al. AGA Institute Rapid review of the gastrointestinal and liver manifestations of COVID-19, meta-analysis of international data, and recommendations for the consultative management of patients with COVID-19. Gastroenterology 2020;159:320-334.e27.
4. Jothimani D, Venugopal R, Abedin MF, et al. COVID-19 and the liver. J Hepatol 2020;73:1231-1240.
5. Marjot T, Moon AM, Cook JA, et al. Outcomes following SARS-CoV-2 infection in patients with chronic liver disease: An international registry study. J Hepatol 2021;74:567-577.
6. Marjot T, Webb GJ, Barritt AS, et al. COVID-19 and liver disease: mechanistic and clinical perspectives. Nat Rev Gastroenterol Hepatol 2021;18:348-364.
7. Marjot T, Buescher G, Sebode M, et al. SARS-CoV-2 infection in patients with autoimmune hepatitis. J Hepatol 2021;74:1335-1343.
8. Linares L, Cofan F, Diekmann F, et al. A propensity score-matched analysis of mortality in solid organ transplant patients with COVID-19 compared to non-solid organ transplant patients. PLoS One 2021;16:1-13.
9. Valla DC, Cazals-Hatem D. Vascular liver diseases on the clinical side: definitions and diagnosis, new concepts. Virchows Arch 2018;473:3-13.
10. Hernández-Gea V, De Gottardi A, Leebeek FWG, et al. Current knowledge in pathophysiology and management of Budd-Chiari syndrome and non-cirrhotic non-tumoral splanchnic vein thrombosis. J Hepatol 2019;71:175-199.
11. Hernández-Gea V, Baiges A, Turon F, et al. Idiopathic portal hypertension. Hepatology 2018;68:2413-2423.
12. Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med 2020;46:1089-1098.
13. Spiezia L, Boscolo A, Poletto F, et al. COVID-19-Related severe hypercoagulability in patients admitted to intensive care unit for acute respiratory failure. Thromb Haemost 2020;120:998-

1000.

14. Singh AK, Jena A, Kumar-M P, et al. Risk and outcomes of coronavirus disease in patients with inflammatory bowel disease: A systematic review and meta-analysis. United Eur Gastroenterol J 2021;9:159-176.
15. Https://www.euro.who.int/en/health-topics/noncommunicable-diseases/obesity/data-and-statistics. World Health Organization, Europe.
16. Buso G, Becchetti C, Berzigotti A. Acute splanchnic vein thrombosis in patients with COVID-19: A systematic review. Dig Liver Dis 2021;53:937-949.





* $P < .05$

Supplementary Table 1. Variables compared between general population and vascular liver disease cohort.

Variable	General population	Vascular Liver cohort	p
Prevalence of SARS-CoV-2 infection	6.5%	14%	<0.05
Need of hospital admission	7.3%	14%	<0.05
Need for ICU care	0.7%	2%	<0.05
Mortality	1.5%	4%	<0.05
Prevalence of diabetes mellitus	13.8%	10%	0.4
Prevalence of obesity	23%	12%	<0.05
Prevalence of arterial hypertension	42%	17%	<0.05

Supplementary Table 2. SARS-CoV-2 infection diagnostic method and reason leading to test

Diagnostic method (all cohort, n = 138)	**n (%)**
PCR	96 (69%)
Serology	15 (11%)
Antigens test	14 (10%)
Clinical	13 (10%)
Reason for diagnosis (Spanish cohort, n = 57)	
Symptoms	37 (65%)
High risk contact	15 (26%)
Screening	5 (8%)

Supplementary Table 3. Severity of SARS-CoV-2 infection and need of hospital admission, ICU admission and mortality excluding the 13 patients that were diagnosed clinically without SARS-CoV-2 diagnostic test.

	GP **N=**3.042.127	**VLD** **N=125**	P	**PSVD** **N=46**	p	**BCS** **N=8**	p	**SVT** **N=71**	p
Admission	221.118 (7.3%)	18(14%)	**0.01**	4 (9%)	0.57	1 (12%)	0.60	13 (18%)	**0.01**
ICU	20.362 (0.7%)	4 (3%)	**0.01**	2 (4%)	**0.01**	0	0.81	2 (3%)	**0.04**
Mortality	45.797 (1.5%)	4 (3%)	**0.04**	1(2%)	0.8	0	0.72	3 (8%)	**0.01**

Supplementary Table 4. Risk Factors for SARS-COV-2 infection in portosinusoidal vascular disorder

PSVD	No infection N=221 N ± SD	Infection N=53 N ± SD	p		No infection N=221 N ± SD	Infection N=53 N ± SD	p
Age	53 ± 18	50 ± 17	0.27	Anticoagulation	72	13	0.25
Sex (male)	128	27	0.36	TIPS	18	4	1
Alcohol	18	7	0.58	IBD	11	4	0.5
Tobacco	21	2	0.07	**Bilirubin (mg/dL)**	**1.5 ± 1.5**	**2.5 ±2.6**	**0.02**
Decompensation	57	14	1	Albumin (mg/dL)	38 ± 4.7	39 ± 5.5	0.30
Variceal bleeding	39	13	0.33	PT (%)	39 ± 36	62 ± 34	0.85
Ascites	28	4	0.35	ASAT U/L	38 ± 30	39 ± 16	0.44
HE	5	2	1	ALAT U/L	39 ± 32	33 ± 19	0.15
Thrombosis	59	12	0.60	AP U/L	146 ± 119	97 ± 60	0.99
Comorbidities	119	30	0.76	GGT U/L	73 ± 72	57 ±48	0.35
Art. Hypertension	38	10	0.81	Platelets	116 ± 67	113 ± 89	0.32
DM	24	8	0.47	Cr mg/dL)	0.95 ± 0.3	1.1 ± 1	0.35
Obesity	15	4	1	Leucocytes	5.2 ± 2.1	4.2 ± 1.9	0.01
Neoplasm	13	3	1	Hb (mg/dL)	131 ± 20	128± 18	0.37
HIV	23	6	1				

*****PSVD Portosinusoidal vascular disorder; HE Hepatic encephalopathy; Art. Arterial; DM Diabetes Mellitus; HIV Human immunodeficiency virus; TIPS Transjugular intrahepatic portosystemic shunt; IBD inflammatory bowel disease; PT Protrombine time; Cr Creatinine; Hb Hemoglobine; ASAT aspartate aminotransferase; ALT alanine aminotransferase, AP alkaline phosphatase; GGT gamma glutamil transpeptidasa

Supplementary Table 5. Risk Factors for SARS-COV-2 infection in splanchnic vein thrombosis

SVT	**No infection N=462** N ± SD	**Infection N=77** N ± SD	**p**		**No infection N=462** N ± SD	**Infection N=77** N ± SD	**p**
Age	52 ± 16	48 ± 19	0.6	**Anticoagulation**	**310 (67%)**	**61 (79%)**	**0.03**
Sex (male)	208	30	0.38	TIPS	10	3	0.41
Alcohol	52	13	0.29	**IBD**	**7**	**6**	**0.01**
Tobacco	59	9	0.07	**Bilirubin (mg/dL)**	**1.5 ± 1.9**	**2.6 ±2.8**	**0.01**
Decompensation	115	14	0.19	Albumin (mg/dL)	40 ± 4.7	39 ± 5	0.06
Variceal bleeding	66	11	1	**PT (%)**	**38 ± 44**	**55 ± 41**	**0.04**
Ascites	67	6	0.11	ASAT U/L	26 ± 12	27 ± 13	0.78
HE	7	2	1	ALAT U/L	29 ± 17	29 ± 16	0.43
Comorbidities	180	38	0.16	AF U/L	146 ± 119	97 ± 60	0.47
Art. Hypertension	**76**	**22**	**0.02**	GGT U/L	57 ± 99	62 ± 77	0.75
DM	40	11	0.21	Platelets	184 ± 97	210 ± 110	0.06
Obesity	64	17	0.08	Cr (mg/dL)	0.95 ± 0.30	1.1 ± 1.0	0.72
Neoplasm	7	0	0.60	Leucocytes	5.5 ± 2.3	5.1 ± 2.7	0.21
Myeloproliferative neoplasm	101	15	0.68	Hb (mg/dL)	138 ± 20.8	130 ± 26	0.37
HIV	0	0	1	APS	6	0	0.59
				Thrombophilia	64	11	0.59

*****SVT Splanchnic vein thrombosis; HE Hepatic encephalopathy; Art. Arterial; DM Diabetes Mellitus; HIV Human immunodeficiency virus; TIPS Transjugular intrahepatic portosystemic shunt; IBD inflammatory bowel disease; PT Protrombine time; Cr Creatinine; Hb Hemoglobine; APS Antiphospholipid syndrome; ASAT aspartate aminotransferase; ALT alanine aminotransferase, AP alkaline phosphatase; GGT gamma glutamil transpeptidasa

Supplementary Table 6. Multivariate analysis of risk factors for SARS-CoV-2 infection in splanchnic vein thrombosis

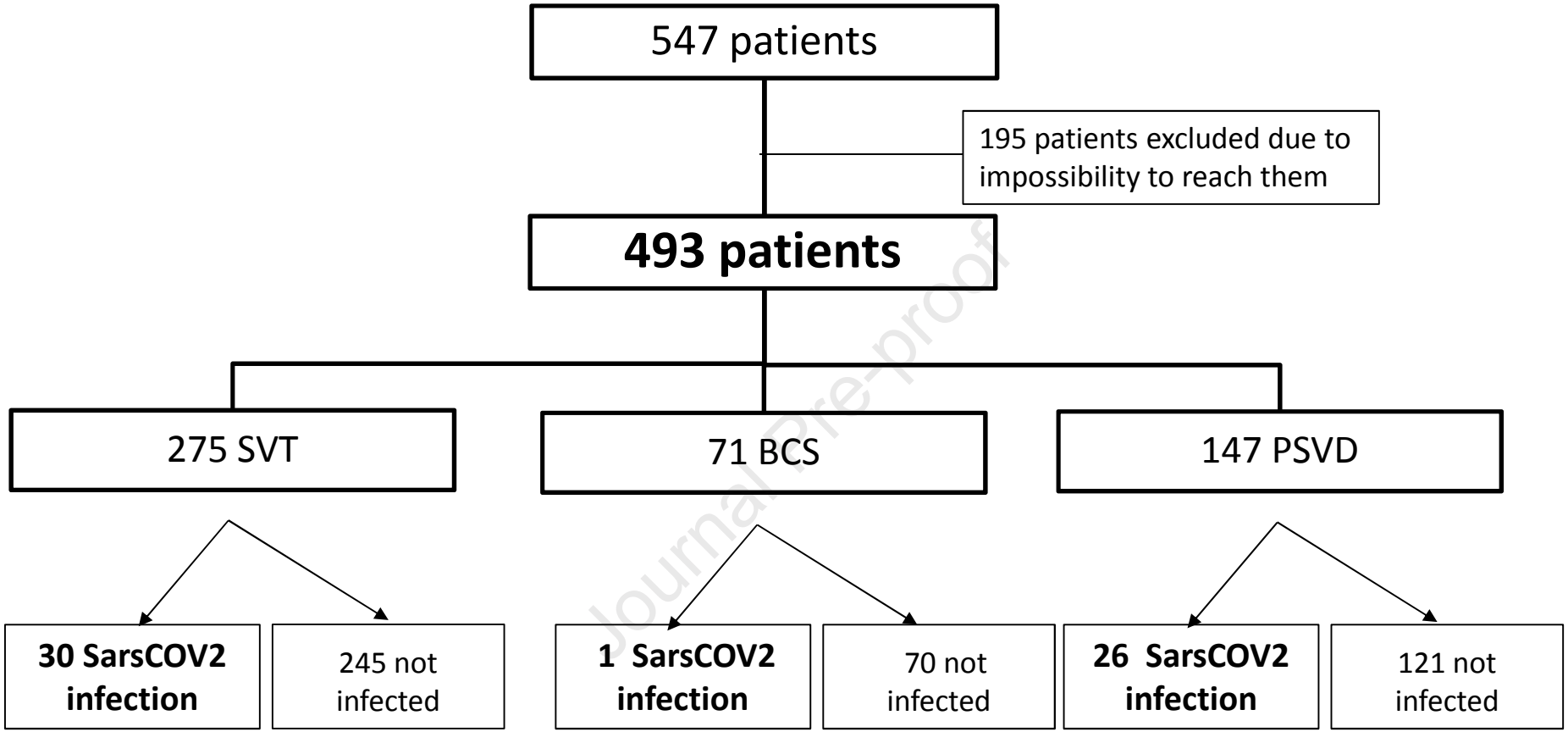
Variables	Univariate analysis		Multivariate analysis	
	HR (CI 95%)	p	HR (CI 95%)	p
Arterial hypertension	2.0 (1.2 – 3.5)	0.02		
Anticoagulation	1.87 (1.0 – 3.3)	0.03		
Inflammatory bowel disease	5.5 (1.8 – 16.8)	0.01	4.3 (1.1 – 17.2)	0.04
Bilirubin (mg/dL)	1.2 (1.1 – 1.4)	0.01	1.2 (1.1 – 1.4)	<0.01
Protrombin time (%)	1.0 (1.0-1.0)	0.01		

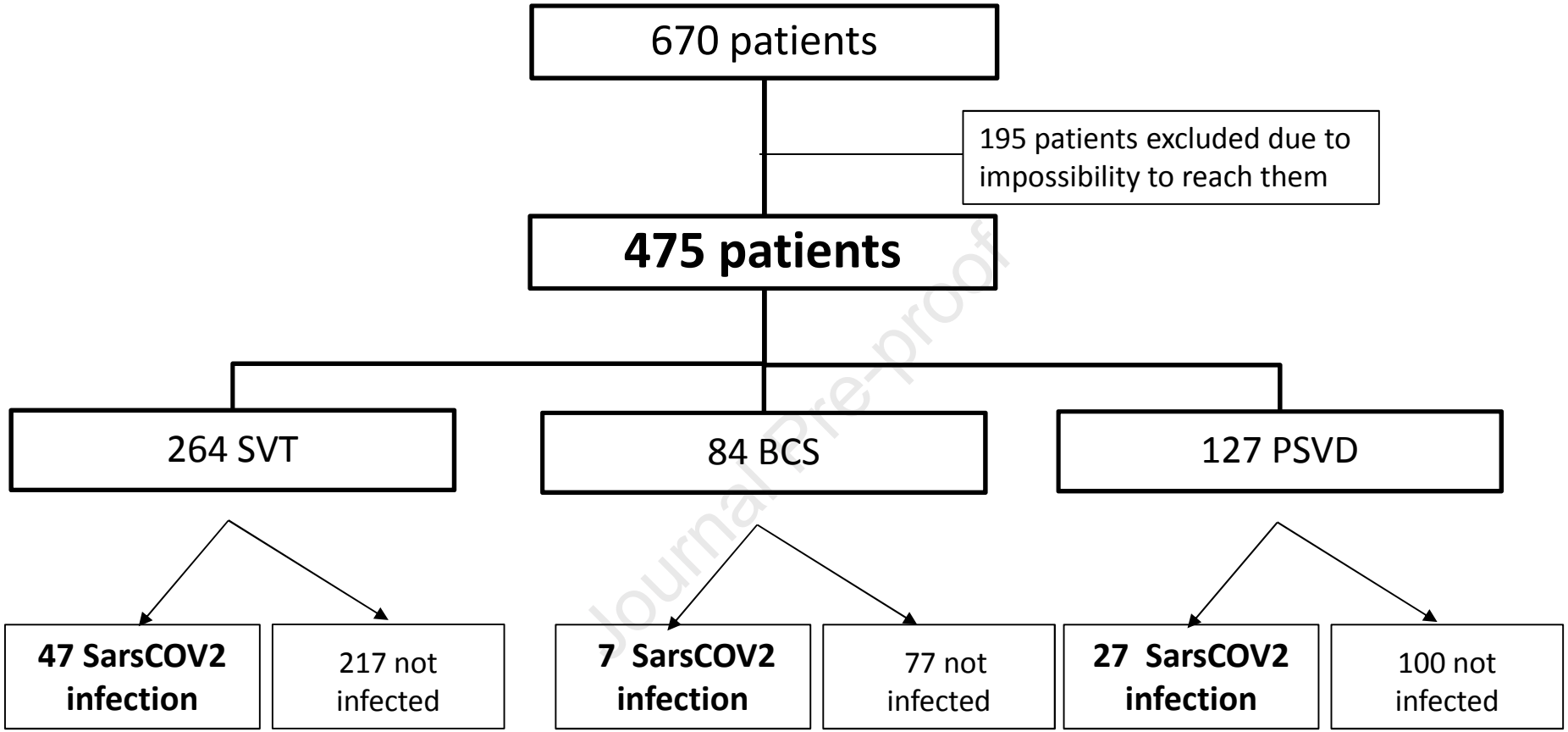
*****HR Hazard ratio; CI confidence interval

Supplementary Table 7. Severity of SARS-CoV-2 infection and need of hospital admission, ICU admission and COVID-19-relatedmortality, stratified by age groups

		Admission; n (%)	P	ICU; n (%)	p	Death; n (%)	p
Age group <40	**GP (n=**1,410,888**)**	17,069 (**1.2%**)		1, 217(**0.1%**)		191 (**0%**)	
	PSVD (n=9)	1 (11%)	**0.00**	1 (11%)	**0.00**	1 (11%)	**0.00**
	SVT (n=19)	3 (16%)	**0.00**	1 (5%)	**0.00**	0	**1**
Age group 40-59	**GP (n=**966,713**)**	54,529 (**5.60%)**		6,026 (**0.6%)**		2,059 (**0.20%)**	
	PSVD (n=30)	3 (10%)	0.23	0	0.66	0	0.8
	SVT (n=38)	6 (16%)	**<0.01**	1 (2.6%)	0.12	2 (5%)	**<0.01**
Age group 60-69	**GP (n=** 285,591**)**	38, 881 (**13.6%)**		6,346 (**2.2%)**		4,247 (**1.5%)**	
	PSVD (n=10)	0	0.24	0	0.78	0	0.69
	SVT (n=12)	3 (25%)	0.32	0	0.75	0	0.65
Age group >70	**GP (n=**369,143)	10,5840 (**28%)**		6,724 (**1.8%)**		39,132 (**10.6%)**	
	PSVD (n=4)	1 (25%)	0.87	1 (25%)	**0.00**	0	0.49
	SVT (n=8)	2 (25%)	0.81	0%	0.7	2 (25%)	0.33

*****GP General population; PSVD Portosinusoidal vascular disorder; SVT Splanchnic vein thrombosis; ICU intensive care unit





What you need to know

Background: It is unknown whether patients with vascular liver diseases constitute a high-risk population for complications and greater mortality from SARS-CoV-2 infection.

Findings: Patients with portosinusoidal vascular disorder and patients with splanchnic vein thrombosis could be at higher risk of infection by SARS-CoV-2 and at higher risk of severe COVID-19 disease.

Implications for patient care: Given the higher risk of severe COVID-19 disease in this population, it would seem reasonable to recommend checking the anti-SARS-CoV-2 antibody levels after full vaccination in patients with vascular liver diseases and administer a third dose to all patients not showing good antibody response.