Journal Pre-proof

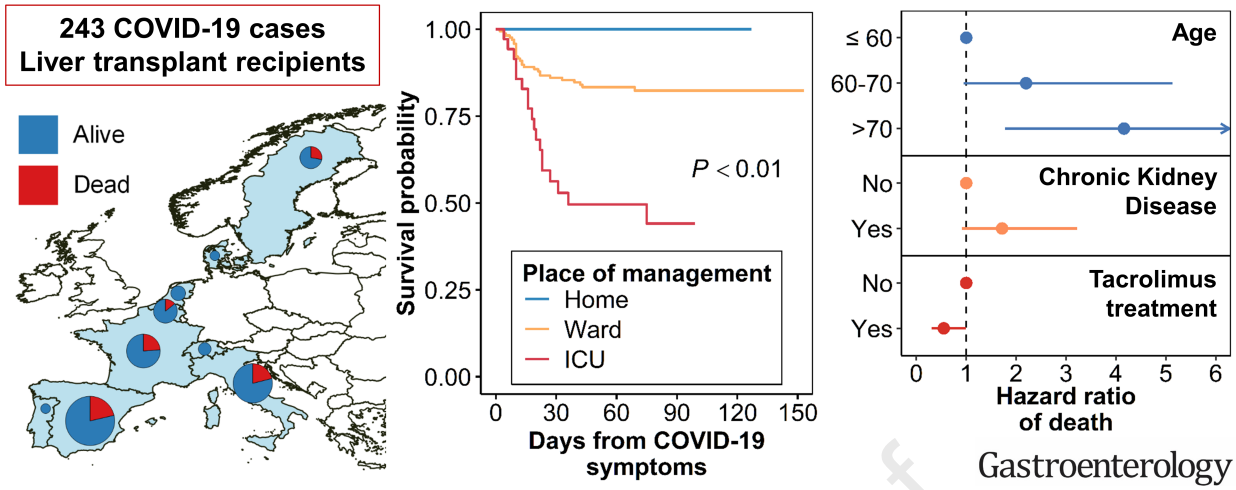
Protective role of tacrolimus, deleterious role of age and comorbidities in liver transplant recipients with Covid-19: results from the ELITA/ELTR multi-center European study.

Luca S. Belli, Constantino Fondevila, Paolo A. Cortesi, Sara Conti, Vincent Karam, Rene Adam, Audrey Coilly, Bo Goran Ericzon, Carmelo Loinaz, Valentin Cuervas-Mons, Marco Zambelli, Laura Llado, Fernando Diaz, Federica Invernizzi, Damiano Patrono, Francois Faitot, Sherrie Bhooori, Jacques Pirenne, Giovanni Perricone, Giulia Magini, LLuis Castells, Oliver Detry, Pablo Mart Cruchaga, Jordi Colmenero, Frederick Berrevoet, Gonzalo Rodriguez, Dirk Ysebaert, Sylvie Radenne, Herold Metselaar, Cristina Morelli, Luciano De Carlis, Wojciech G. Polak, Christophe Duvoux, for all the centres contributing to the ELITA-ELTR COVID-19 Registry

PII: S0016-5085(20)35514-1
DOI: https://doi.org/10.1053/j.gastro.2020.11.045
Reference: YGAST 63919

To appear in: *Gastroenterology*
Accepted Date: 20 November 2020

Please cite this article as: Belli LS, Fondevila C, Cortesi PA, Conti S, Karam V, Adam R, Coilly A, Ericzon BG, Loinaz C, Cuervas-Mons V, Zambelli M, Llado L, Diaz F, Invernizzi F, Patrono D, Faitot F, Bhooori S, Pirenne J, Perricone G, Magini G, Castells L, Detry O, Cruchaga PM, Colmenero J, Berrevoet F, Rodriguez G, Ysebaert D, Radenne S, Metselaar H, Morelli C, De Carlis L, Polak WG, Duvoux C, for all the centres contributing to the ELITA-ELTR COVID-19 Registry, Protective role of tacrolimus, deleterious role of age and comorbidities in liver transplant recipients with Covid-19: results from the ELITA/ELTR multi-center European study., *Gastroenterology* (2021), doi: https://doi.org/10.1053/j.gastro.2020.11.045.



Title.

Protective role of tacrolimus, deleterious role of age and comorbidities in liver transplant recipients with Covid-19: results from the ELITA/ELTR multi-center European study.

Short title

COVID-19 in liver transplant recipients (39 characters)

Luca S Belli[1], Constantino Fondevila[2], Paolo A Cortesi[3], Sara Conti[3], Vincent Karam[4], Rene Adam[4], Audrey Coilly[5], Bo Goran Ericzon[6] Carmelo Loinaz[7] Valentin Cuervas-Mons[8], Marco Zambelli[9], Laura Llado[10], Fernando Diaz[11], Federica Invernizzi[12], Damiano Patrono[13], Francois Faitot[14], Sherrie Bhooori[15], Jacques Pirenne[16], Giovanni Perricone[1], Giulia Magini[17], LLuis Castells[18], Oliver Detry[19], Pablo Mart Cruchaga[20], Jordi Colmenero[2], Frederick Berrevoet[21], Gonzalo Rodriguez[22], Dirk Ysebaert[23], Sylvie Radenne[24], Herold Metselaar[25], Cristina Morelli[26], Luciano De Carlis[27], Wojciech G Polak[28] and Christophe Duvoux[29] for all the centres contributing to the ELITA-ELTR COVID-19 Registry.

Affiliations

1. Department of Hepatology and Gastroenterology, Niguarda Hospital, Milan, Italy
2. Department of General and Digestive Surgery, Hospital Clínic, IDIBAPS CIBERehd, University of Barcelona, Spain
3. Research Centre on Public Health (CESP), University of Milan-Bicocca, Monza, Italy
4. European Liver Transplant Registry, Centre Hépatobiliaire, AP-HP, Hôpital Universitaire, Paul Brousse, Paris-Saclay University, Villejuif, France
5. Centre Hepato-Biliaire, AP-HP Hôpital Paul Brousse Hospital, Paris-Sud Saclay University, Villejuif, France
6. Division of Transplantation Surgery, Karolinska University Hospital Huddinge, Stockholm, Sweden
7. Chirugía General, Doce de Octubre Universidad Complutense de Madrid, Madrid, Spain
8. Departimento de Medicina, Hospital Universitario Puerta de Hierro, Universidad autonoma de Madrid, Madrid, Spain.
9. Dep of Surgery, Papa Giovanni XXIII" Hospital, Bergamo, Department of Surgery, Bergamo, Lombardia, IT
10. Liver Transplant Unit, Hospital Uniersitari de Bellvitge, Universitat de Barcelona, Spain.
11. Unidad de Trasplante Hepático. H.G.U.Gregorio Marañón, Madrid, Spain
12. Division of Gastroenterology and Hepatology, University of Milan, Milan, Italy.

13. Liver Transplantation Center, Molinette Hospital, Turin, Italy

14. Service de Chirurgie Hépatobiliaire et Transplantation, Hôpital de Hautepierre, Strasbourg, France.

15. Department of Surgery and Oncology, Istituto Nazionale Tumori, Milan, Italy

16. Department of Surgery, University Hospitals Leuven, Leuven, Belgium

17. Service de Transplantation,Hôpitaux Universitaires de Genève

18. Liver Unit, Department of Internal Medicine, Hospital Universitari Vall d'Hebron. Barcelona CIBERehd

19. Department of Abdominal Surgery and Transplantation, CHU Liege, University of Liege, Belgium

20. Cirugía General y Digestiva, Clínica Universidad de Navarra, España

21. Department of General and Hepatobiliary Surgery, Ghent University, Ghent, Belgium

22. Department of General & Digestive Surgery, ISABIAL, Hospital General Universitario de Alicante, Spain

23. Department of Surgery, Antwerp University Hospital, Antwerp University, Edegem, Belgium

24. Service d'Hépato-Gastroentérologie, HCL Hôpital de la Croix-Rousse, Lyon, France

25. Department of Gastroenterology and Hepatology, Erasmus Medical Center, Rotterdam, the Netherlands

26. Liver and Multi-organ Transplantation, Sant'Orsola-Malpighi Hospital, University of Bologna, Italy

27. General Surgery and Abdominal Transplantation Unit, Niguarda-Cà Granda Hospital, and School of Medi cine and Surgery, University of Milano-Bicocca, Milan, Italy

28. Department of Surgery, Erasmus MC, University Medical Center Rotterdam, The Netherlands.

29. Department of Hepatology and Medical Liver Transplant Unit, Henri Mondor Hospital APHP, Paris-Est University, Creteil, France.

Grant support No grant support

Conflict of interests statements No conflicts of interest for the content of study.

Abbreviations. ACE: Angiotensin converting enzyme; ALT: Alanine Aminotrafserase; Bil: bilirubin; BMI: Body Mass Index; CNI: calcineurin inhibitor; creat: creatinine; CsA: Cyclosporine A; CT: Computed Tomography; ELITA: European Liver Transplantation Association; ELTR: European Liver Transplant Registry; GDPR: General Data Protection Regulation; HBV: Hepatitis B Virus; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; HR: Hazard Ratio; ICU: Intensive Care Unit; IQR: Interquartile range; LT: Liver Transplant; NASH: non-alcoholic steato-hepatitis; KM: Kaplan-Meier; MMF: Mycofenolate mofetil; mTOR: mammalian target of rapamycin; RNA: Ribonucliec Acid; SARS-CoV2: Severe Acute Respiratory Syndrome Coronavirus 2; TAC: Tacrolimus; WBC: White blood cells.

Correspondence. Luca S Belli. Dep of Hepatology and Gastroenterology. ASST Niguarda Hospital, Piazza Ospedale Maggiore 3. 20162. Milan. Italy.

Luca.belli@ospedaleniguarda.it. –39-02-64444436 (office); 328 3627044 (cell phone)

Disclosures. Nothing to disclose in relation to this manuscript

Writing assistance: Maruska Nizzi. No funding.

Authors contribution

LSB: conceptualization, data curation and drafting., critical revision of the manuscript

PC, SC: formal analysis, critical revision of the manuscript

CF, WP, CD, RA, VK conceptualization, review and editing, critical revision of the manuscript

AC, BGE, CL, VCM, MZ, LL, FD,FI, DP, FF, SB, JP, GP, GM, LCF, PMC, JC, FB, GR; DY, SR, HM, CM : data curation, critical revision of the manuscript

LDC: critical revision of the manuscript

Acknowledgments. ELITA Board members: Ulrich Baumann, Giacomo Germani, Silvio Nadalin, Pavel Taimr, Christian Toso, Roberto Trosi, Krzysztof Zieniewicz for supporting and actively promoting the study

Maruska Nizzi for linguistic support

All centers participating to the ELITA/ELTR Covid-19 project in liver transplantation including all collaborators at each site (Table 4)

Abstract

Background and aims. Despite concerns that liver transplant (LT) recipients may be at increased risk of unfavorable outcomes from COVID-19 due the high prevalence of co-morbidities, immunosuppression and ageing, a detailed analysis of their effects in large studies is lacking

Methods. Data from adult LT recipients with laboratory confirmed SARS-CoV2 infection were collected across Europe. All consecutive patients with symptoms were included in the analysis,

Results. Between March 1st and June 27th2020, data from 243 adult symptomatic cases from 36 centers and 9 countries were collected. Thirty-nine (16%) were managed as outpatients while 204 (84%) required hospitalization including admission to the ICU (39/204, 19.1%). Forty-nine (20.2%) patients died after a median of 13.5 (10-23) days, respiratory failure was the major cause.

After multivariable Cox regression analysis, age > 70 (HR 4.16; 95%CI 1.78-9.73) had a negative effect and tacrolimus (TAC) use (HR 0.55; 95%CI 0.31-0.99) had a positive independent effect on survival. The role of co-morbidities was strongly influenced by the dominant effect of age where comorbidities increased with the increasing age of the recipients. In a second model excluding age, both diabetes (HR 1.95; 95%CI 1.06 - 3.58) and chronic kidney disease (HR 1.97; 95%CI 1.05 - 3.67) emerged as associated with death

Conclusions. Twenty-five per cent of patients requiring hospitalization for Covid-19 died, the risk being higher in patients older than 70 and with medical co-morbidities, such as impaired renal function and diabetes. Conversely, the use of TAC was associated with a better survival thus encouraging clinicians to keep TAC at the usual dose.

Keywords: COVID-19; Liver transplantation; Outcome; Tacrolimus

Introduction

The current COVID-19 pandemic has presented unforeseen challenges to health care systems worldwide with several issues remaining unmet. To date, firm knowledge on disease evolution, risk factors and optimal management in specific categories of patients is lacking. All transplant recipients are potentially vulnerable to SARS-CoV-2 infection with immune suppression, aging and metabolic or cardiovascular co-morbidities likely being risk factors for symptomatic disease and its severe complications (2). Liver Transplant (LT) patients in particular, represent one of the largest immunosuppressed cohorts in Europe with 102.116 alive recipients being reported in the European Liver Transplant Registry (ELTR), 42.432 (41.6%) of whom are in their sixties and 12.669 in

their seventies or older (3). At present, available data related to COVID-19 in LT patients is limited to a small number of case series (4-6), to preliminary reports from 2 international registries (7-9) and to a single international prospective cohort on 57 cases (10). All authors agreed that greater case numbers were urgently required to accurately improve our understanding of individual risk in LT recipients. Thus, a large-scale collaborative study promoted by the European Liver Transplant Association (ELITA) and European Liver Transplant Registry (ELTR) was performed, the main aim being the search for risk factors associated with mortality during the COVID-19 pandemic and with a specific focus on comorbidities and immunosuppression

METHODS

Study population

ELITA called for a COVID-19 study which was circulated on March 30, 2020 among 149 LT centres affiliated to ELTR) and located in 30 European countries. All centres that reported at least one case were provided with a database and instructions on how to record structured data. Data collection was managed by ELTR. One hundred and fourteen centres (76.5%) responded, with 56 centres (38%) having observed COVID-19 cases in adult LT recipients between March 1st and May 19th, 2020. All patients with symptoms and having SARS-CoV-2 infection confirmed by a positive result on a reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay of a specimen collected on a nasopharyngeal swab or on broncho alveolar lavage, were included in the study.

Data collection and definitions

Demographic and clinical data, including clinical symptoms or signs at presentation, laboratory and radiologic results during COVID-19 management as well as administered antiviral therapies and anti-thrombotic prophylaxis were retrospectively collected. All laboratory tests and radiologic assessments were performed on the discretion of the treating physician discretion. Serum creatinine was converted to mg/dl for analysis. Information on baseline immunosuppression and on changes during Covid-19, namely reduction or discontinuation, were also obtained. Obesity was defined as a given BMI of >30 kg/m2. Liver injury during Covid-19 was defined as alanine amino-transferase (ALT) level > 30 IU/L for male and 19 IU/L for female in those patients with normal ALT levels at last outpatient visit.[14] Hepatic flare was defined as ALT level ≥5 x upper limit of normality. The time on study started at occurrence of COVID symptoms. All submitted files from each centre were manually reviewed to assess for data quality, completeness and inconsistencies. In addition, submitting clinicians were contacted and asked to provide corrections or data integration whenever needed.

Ethical and regulatory approval

Data was collected in accordance with General Data Protection Regulation (GDPR), the European Union legislation and the ELTR privacy policy.

Statistical Analysis

Analysis was led by the Research Centre on Public Health (CESP), University of Milan-Bicocca, Monza, Italy. A descriptive analysis of the cohort was carried out on the overall population and after stratifying the population by site of management: at home, in general wards or in intensive care units (ICU). Categorical variables were summarized through percentages, while continuous variables through median, first quartile (Q1) and third quartile (Q3). Categorical variables were compared using the $\chi 2$ or the Fisher's exact tests; continuous variables were compared using the Mann-Whitney U-test or the Kruskall-Wallis test, when appropriate. All tests were two-sided and used a significance level of 0.05.

The rates of missing data for each variable were reported. For each patient, the time between the date of COVID symptoms and death or end of follow-up was computed, and the association between mortality and baseline patients' characteristics was evaluated through univariate Cox proportional hazard models. All characteristic analyzed in univariate model were included in a stepwise selection process that identified the best multivariate model. The same process was repeated after excluding age from potential predictors. Given the exploratory nature of the study and the limited sample size, a 0.1 significance level was established to retain predictors in the final multivariate models possibly favoring the tracing of borderline significant associations that could be the basis for further studies on wider samples. All statistical analyses were conducted using SAS version 9.4 (The SAS institute, Cary, NC) and R version 4.0.0 (R Core Team, Vienna, Austria). The map was drawn using QGIS software version 3.10 (QGIS Development Team).

RESULTS

Demographic and general characteristics of patients

The COVID-19 pandemic was experienced not uniformly in Europe, with large areas being spared. This explains why of the 111 centers responding to the ELITA/ELTR call, only 36 centers from nine European countries observed at least one patient with PCR confirmed SARS-CoV-2 infection (Fig 1 and Fig 2). Of the 29.981 alive patients in regular follow up at the participating centers, 258 (0.9%) have been consecutively reported in the Registry. Eleven of them (4.3%) were asymptomatic at the time of diagnosis, the PCR test being performed according to surveillance protocols in case of contact with a SARS-CoV-2 positive subject; these patients were excluded from the study. Four additional patients were excluded because aged < 18 years. The remaining 243 symptomatic cases were considered for statistical analysis with 39 patients (16%) receiving homecare, the remaining 204

requiring hospitalization (Fig 2). Of these, 167 (68.7%) patients were treated in a general ward and 37 in intensive care units. Baseline patient characteristics are reported in Table 1. Thirty-two LT recipients with Covid-10 analyzed in this study were also included in the report from Becchetti et al (10).

Co-morbidities.

One hundred-eleven (45.7%) patients had arterial hypertension, 94 (38.7%) diabetes mellitus, 49 (20.2%) chronic kidney disease with a creatinine > 2mg/dL and 25 (10.3%) chronic lung diseases. Concurrent co-morbidities were frequent with 107 (44%) patients having two or more (Table 1). The prevalence of at least 2 co-morbidities increased with age being observed in 25.3%, 53.4% and 64.2% in recipient aged < 60, from 60 to 70 or > 70 years, respectively.

Immunosuppressive drugs and other drugs

Tacrolimus (TAC) and cyclosporinne (CsA) were considered as the main immunosuppressive drugs. Since, some of the patients were off CNI, the proportion of patients receiving each immunosuppressive drug or combination of drugs were also obtained. At the time of analysis, 162 (66.7%) patients were on tacrolimus (TAC), alone or in combination, 29 (11.9%) on Cyclosporine A (CsA) alone or in combination, 119 (49.0%) on mycofenolate-mofetil (MMF) alone or in combination and 37 (15.2%) on mTOR inhibitors alone or in combination. (Table 1).

Clinical presentation and course of liver transplant recipients with covid-19

At the time of diagnosis, the most commonly self-reported symptoms included fever (190 patients, 78.2%), cough (143 patients, 58.8%), dyspnea (82 patients, 33.7%), muscle pain or asthenia (90 patients, 37.0%), anosmia or dysgeusia (21 patients, 8.6%) and diarrhea (55 patients, 22.6%). Radiological findings, either on CT scan or on chest radiography, showed typical ground glass opacities in 145 cases (59.7%) (Table 2). Overall 137 (56.4%) patients required respiratory support during hospitalization with 26 requiring non-invasive ventilation and 25 mechanical ventilation (Table 2). One hundred forty-nine patients received specific anti-SARS-CoV-2 treatment: 116 (47.7%) patients were treated with hydroxy-chloroquine either alone or in combination, 41 (16.9%) with lopinavir–ritonavir; 34 (14.0%) with high doses of corticosteroids and 15 (6.2%) with tocilizumab. Thrombo-prophylaxis, mainly with low molecular weight heparin, was started on COVID-19 diagnosis in 117 patients (48.2%). Seven hospitalized patients (7/204=3.4%) experienced thrombotic events, 3 pulmonary embolism, 2 deep vein thrombosis and 2 strokes. An acute liver injury was observed in 56 patients with previous persistently normal ALT, being in the flare range in 10 cases Three patients were reported as having acute rejection. Notably, CNI had been withdrawn in 2 cases and the dose of TOR dose had been halved in the third case.

Forty-nine (20.2%) patients died after a median of 13.5 (10-23) days from diagnosis of COVID-19. Causes of death were the following: respiratory failure in 39 (77.6%) patients, end-stage-liver disease with respiratory failure in 2, end stage liver disease without respiratory failure in 1, hemorrhagic shock in 2, pulmonary embolism in 1, metastatic cancer in 1 septic shock in 1 and septic complication from tracheal fistula in 1. Overall KM survival from date of COVID symptoms is given in Fig 3. Estimated a probability of survival was 88.2% (95% CI: 82.5 – 92.1) at 30 days, and of 84.4% (95%CI: 77.7 – 89.2) at 90 days.

Clinical features and outcomes of liver transplant recipients with Covid-19 treated at home, in general wards and in ICU.

Baseline patients-characteristics of patients with less severe symptoms who could be treated at home and those with more severe symptoms requiring hospitalization in general wards and ICU are reported in Table 2**.** Patients treated at home were younger, had less co-morbidities and were more frequently receiving TAC as primary immunosuppressant. KM survival after stratification by place of management, at home, general ward or ICU is provided in Figure 3: patients managed at home survived, while the probability of survival at 30 days was 93.1% (95% CI: 86.7 – 96.5) and 57.0% (95% CI: 37.6 – 72.4) respectively for patients in ward and in ICU, and it declined at 89.8% (95% CI: 82.1 – 94.3) and 46.6% (95% CI: 26.2 – 64.6) at 90 days. Notably, 12 patients with advanced Covid-19 disease were not admitted to ICU, 8 because deemed too sick for ICU due to a combination of advanced age and severe co-morbidities and four because ICU were overwhelmed.

Factors associated with death.

Factors significantly associated with death by univariable analysis were the following: increased age of the recipient, time from LT, diabetes, chronic kidney disease, number of comorbidities and use of TAC (Table. 3). After multivariable analysis, advanced age (>70 yrs vs < 60yrs) remained independently associated with an increased mortality risk (HR 4.16; 95CI 1.78-9.73) while use of TAC was confirmed independently associated with a reduced mortality risk (HR 0.55; 95CI 0.31-0.99). The Kaplan-Meier survival curves stratified by age >70 or <70, and type of immunosuppressant, TAC vs non TAC, may be helpful for the clinician to better understand the individual risk. (supplementary Fig.1). Since the number of co-morbidities increased with the increasing age of the recipient, a second model excluding age was constructed. This allowed diabetes and chronic renal failure to emerge as predictors of mortality, their effect having been shadowed in the first model by the dominant effect of age (supplementary Table 1). The interplay among age of the recipient, primary immunosuppressant and chronic renal failure is shown in supplementary Table 2 and supplementary Fig 2 where the negative impact of- chronic kidney disease is dramatically evident in recipients not maintained on TAC. Finally, in supplementary Table 3

patients receiving TAC based vs non-TAC based regimens are compared with respect to some relevant clinical variables such as age, time from transplant, chronic renal failure, concurrent exposure to ACE, or ARB and presence of HCC. In fact, patients receiving TAC were younger and had less co-morbidities, these variables being potentially associated with a better outcome. Conversely patients on TAC were much less frequently treated with ACE or ARB inhibitors, this therapy being associated with a better outcome. All these variables were included in the multivariable analysis which confirmed the independent protective role of TAC.

DISCUSSION

As more than 200 countries world-wide are still struggling with the COVID-19 pandemic, all solid organ transplant recipients are at risk of infection and poor outcome due to chronic immunosuppression, high rates of comorbidities, advanced age and frequent hospitalization. We have analyzed the characteristics, management and outcome of a large multinational European cohort of liver transplant recipients with symptomatic SARS-CoV-2 infection.

Rates of hospitalization and death in the current study were 85% and 20.2%, confirming what has already shown in our preliminary report on the first 103 cases (8) where some patients were still experiencing their disease course. These findings concur with the 23% mortality risk reported by Webb et al (7), however compare unfavorably with the 12% mortality risk observed by Becchetti et al (10), possibly due to the lower percentage of patients requiring hospitalization in this latter study. Our study confirmed that abdominal symptoms and more specifically diarrhea is at least twice more frequent than in the general population (10) and it is possibly associated to MMF. This hypothesis is supported by the fact that almost 50% of the 26 patients maintained on MMF as primary immunosuppressant had diarrhea as presenting symptom. Clinicians should therefore be vigilant and consider SARS-CoV2-testing in transplanted patients presenting with diarrhea particularly if using MMF.

However, the main finding of the present study is the significant variation in mortality risk with both age of the recipients and use of TAC as immunosuppressant. The role of advanced age confirms what has been extensively observed in the general population, with patients older than 70 having an increased four-fold mortality risk (1,11-13). The lower risk of death for patients maintained on TAC was unexpected and had not been previously reported. In particular Becchetti et al. (10) could not explore this association in their prospective cohort of 57 LT recipients with Covid-19, as the great majority of their patients were receiving tacrolimus. Notably, in our analysis, the beneficial impact of TAC was robust and persisted after controlling for various confounders. The biologi-

cal explanation of the potential favorable role of TAC is unknown but may be dual, inhibition of the viral replication and interaction with the immune response. Some studies have shown that Coronavirus replication (CoV), depends on active immunophyllin pathways and TAC is capable to strongly inhibit the growth of some human coronavirus, notably SARS COV1, probably by binding the immunophyllin FKBP although not specifically SARS - CoV-2 (14-16). Another potential driver of the TAC protective effect could be related to the immunosuppressive property of this CNI (17). By inhibiting calcineurin and suppressing the early phase of T-cell activation, TAC reduces the production of many cytokines, notably pro inflammatory cytokines, as TNFα and IFNγ, and possibly mitigate the cytokine storm which characterizes Stage III COVID 19. Interestingly, this background recently prompted a group of Spanish investigators to test the effect of TAC in combination with steroids in the management of COVID 19 occurring in immunocompetent subjects (clinicaltrials.gov/ct2/show/NCT04341038). While waiting for studies on larger cohorts of transplants that would allow a more precise estimate of the protective effect of TAC, reducing or withdrawing the doses of TAC during Covid-19 should be discouraged, if not indicated for other clinical reasons.

The role of co-morbidities as relevant risk factors for mortality has been clearly demonstrated in the general population with Covid-19 (18). Despite being highly prevalent among liver transplant recipients (19), neither a specific comorbidity nor their combination, emerged as independently associated with outcome. This is at least in part explained by the dominant effect of age as comorbidities increased with the increasing age of the recipients. Nevertheless, in our exploratory analysis, chronic renal failure defined by a serum creatinine greater than 2 mg/dL, maintained a trend of significance ($p < 0.1$) even if shadowed by the dominant effect of increasing age. Notably, the negative impact of renal failure on survival was particularly relevant in patients who are not receiving Tacrolimus, once again pointing to its possible protective role against Covid-19, at least in liver transplant recipients.

Finally, therapy for Covid-19 differed across centers and countries and varied overtime with the increasing knowledge in treating this new disease. As large prospective randomized trials have recently demonstrated that corticosteroids and remdesivir are effective in severe cases while hydroxychloroquine and lopinavir-ritonavir are not, new patients should be treated accordingly (20,21)

This study has some strengths. It is at the time of writing the largest cohort of consecutive transplant recipients affected by COVID-19 with a relatively long median follow up of around 2 months. It focuses only on symptomat-

ic cases and analyses the role of clinical features at admission and diagnosis on mortality risk. The quality of the data was guaranteed by maintaining constant communications with the contributing centres. Finally, the international multicentric pattern of the study copes with any individual center effect.

Some limitations are also to be acknowledged. Firstly, although we attempted to collect data on major covariables there remains the possibility of missing confounders. Secondly, we focused on symptomatic cases with confirmed positive SARS-CoV-2 PCR test despite test sensitivity below 80%. Thus, some cases were excluded.

In conclusion, this study including more than 240 liver transplant recipients confirmed that 25% of patients requiring hospitalization for Covid-19 died, the mortality risk being greater in patients older than 70 and with medical co-morbidities, such as impaired renal function and diabetes. Conversely, the use of TAC was associated with an increased survival probability. Although the biological explanation of this latter finding is currently unknown, our preliminary evidence should encourage clinicians to keep TAC at the usual dose as it may be beneficial when treating COVID-19. A more precise estimate of the protective effect of TAC requires studies on larger cohorts of transplants.

REFERENCES

1. World Health Organization. Coronavirus Disease (COVID-19) Pandemic. World Health 284 Organization. 2020; Accessed July 2020. 285 https://www.who.int/emergencies/diseases/novel-coronavirus-2019
2. **ZhouF, YuT, Du R,** et al.: Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study [pub- lished correction appears in Lancet 395: 1038, 2020]. Lancet 395: 1054–1062, 2020
3. European Liver Transplant Registry (ELTR).www..eltr.eu
4. Bhoori S, Rossi RE, Citterio D, et al. COVID-19 in long-term liver transplant patients: preliminary experience from an Italian transplant centre in Lombardy. Lancet Gastroenterol Hepatol 2020;5:532–3.
5. Fernández-Ruiz M, Andrés A, Loinaz C, et al. COVID-19 in solid organ transplant recipients: a single-center case series from Spain. Am J Transplant 2020. doi:10.1111/ jt.15929. [Epub ahead of print: 16 Apr 2020].
6. Pereira MR, Mohan S, Cohen DJ, et al. COVID-19 in solid organ transplant recipients: initial report from the US EpiCenter. Am J Transplant 2020. doi:10.1111/ajt.15941. [Epub ahead of print: 24 Apr 2020].
7. Webb GJ, Moon AM, Barnes E, et al. Determining risk factors for mortality in liver transplant patients with COVID-19. Lancet Gastroenterol Hepatol 2020. doi:10.1016/ S2468-1253(20)30125-4. [Epub ahead of print: 24 Apr 2020].

8. Belli LS**,** Duvoux C, Karam V, et al. COVID-19 in liver transplant recipients:317 preliminary data from the ELITA/ELTR registry [published online ahead of print, 2020 318 Jun 4]. Lancet Gastroenterol Hepatol. 2020;S2468-1253(20)30183-7. doi:10.1016/S2468-319 1253(20)30183-7.
9. Polak WG, Fondevila C, Karam V, Adam R, Baumann U, Germani G, et al. Impact of COVID-19 on liver transplantation in Europe: alert from an early survey of European Liver and Intestine Transplantation Association and European Liver Transplant Registry. Transpl Int. 2020 Jul 1:10.1111/tri.13680. doi: 10.1111/tri.13680. Online ahead of print
10. Becchetti C, Zambelli MF, Pasulo L, et al. COVID-19 in an international European liver transplant recipient cohort. Gut. 2020 Jun 22: gutjnl-2020-321923. doi: 10.1136/gutjnl-2020-321923. Online ahead of print. PMID: 32571972
11. **Huang C, Wang Y, Li X,** et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020, 395, 497–506.
12. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA 2020. doi:10.1001/jama.2020.6775. [Epub ahead of print: 22 Apr 2020].
13. **Wu C, Chen X, Cai Y,** et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med 2020. doi:10.1001/jamainternmed.2020.0994. [Epub ahead of print: 13 Mar 2020].
14. Carbajo-Lozoya J, Müller MA, Kallies S, Thiel V, Drosten C, von Brunn A: Replication of human coronaviruses SARS-CoV, HCoVNL63 and HCoV-229E is inhibited by the drug FK506. Virus Res 165:112–117, 2012
15. Russell B, Moss C, George G, Santaolalla A, Cope A, Papa S, Van Hemelrijck M. Associations between immune-suppressive and stimulating drugs and novel COVID-19-a systematic review of current evidence. Ecancer medical science. 2020 Mar 27;14:1022. doi: 10.3332/ecancer.2020.1022. eCollection 2020. PMID: 32256705
16. Tanaka Y, Sato Y, Sasaki T. Suppression of coronavirus replication by cyclophilin inhibitors. Viruses 2013;5:1250-60.
17. Willicombe M, Thomas D, and McAdoo S. COVID-19 and Calcineurin Inhibitors: Should They Get Left Out in the Storm? JASN 31: 1145–1146, 2020. doi: https://doi.org/10.1681/ASN.2020030348
18. **Guan WJ, Liang WH, Zhao Y**, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Eur Respir J. 2020;55(5):2000547. Published 2020 May 14. doi:10.1183/13993003.00547-2020.
19. Tovikkai C, Charman SC, Praseedom et al. Time varying mpact of comorbidities on mortality after liver transplantation: a national cohort study using linked clinical and administrative data. BMJ Open 2015;5:e006971.
20. Horby P, Lim WS, Emberson JR, et al. Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report. NEJM. 2020 doi: 10.1056/NEJMoa2021436
21. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, Hohmann E, Chu HC, Luetkemeyer A, Kline S, et al. Remdesivir for the Treatment of Covid-19 — Preliminary Report. NEJM. 2020. https ://doi.org/10.1056/NEJMo a2007 764.

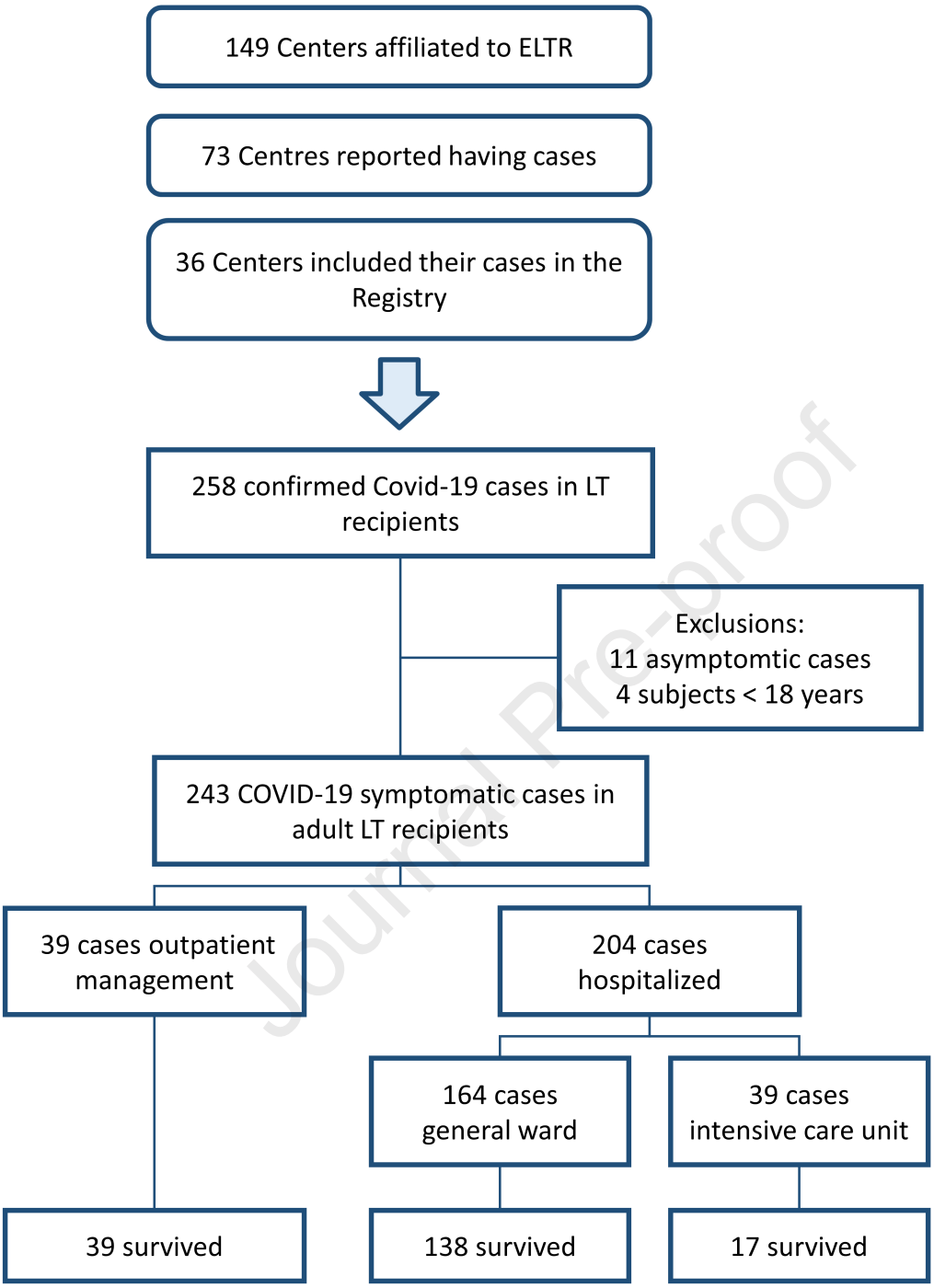
"Author names in bold designate shared co-first authorship"

Figures legends

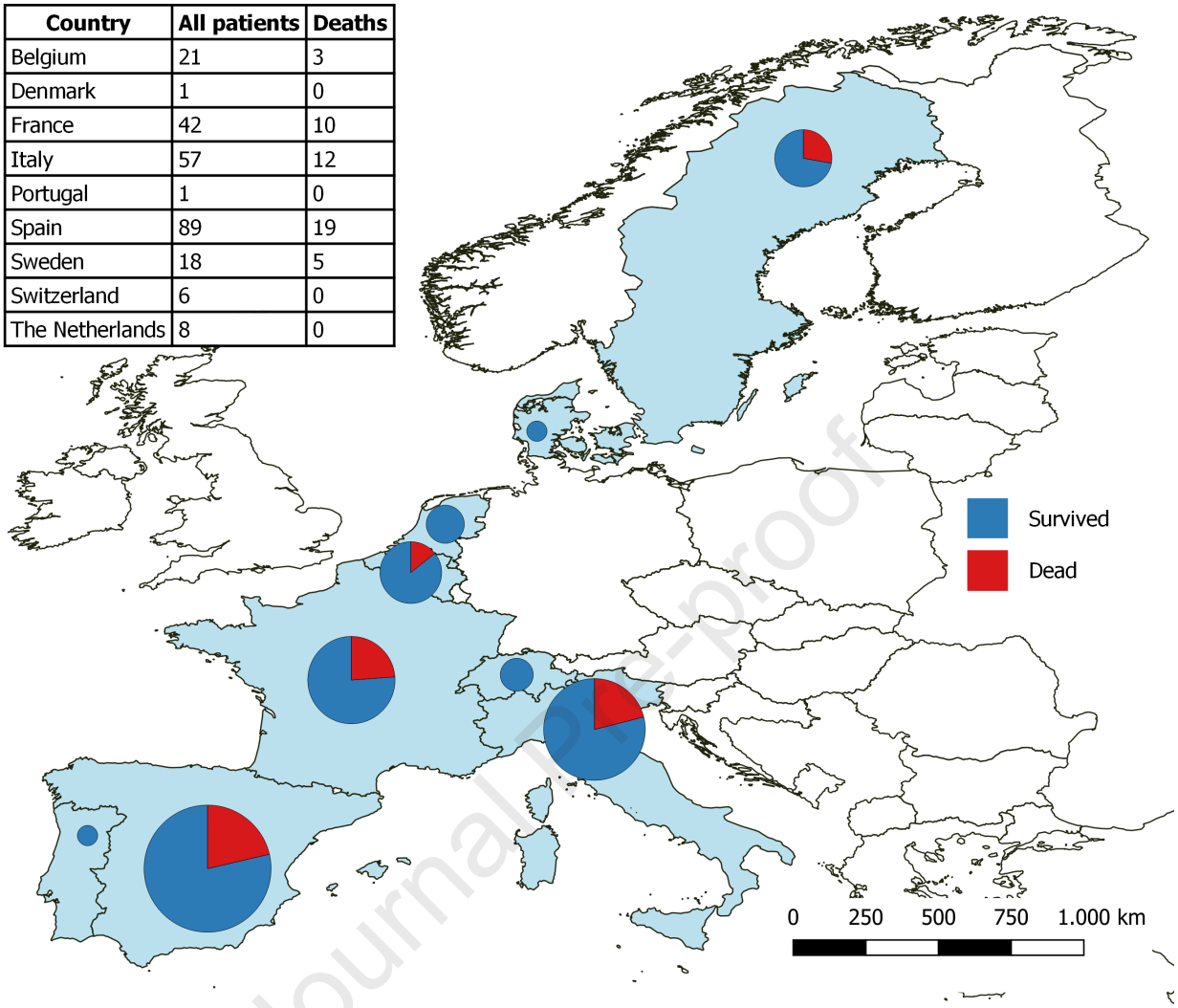
Figure 1. Flowchart showing the selection of the study population

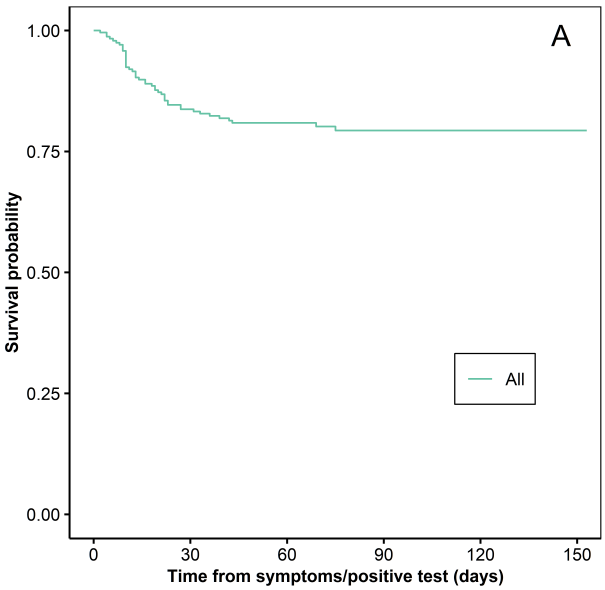
Figure 2. Patients with COVID-19 included in the study by country

Figure 3. Kaplan-Meier survival curve from the date of COVID-19 symptoms, overall (panel A) and stratified by place of management (panel B).



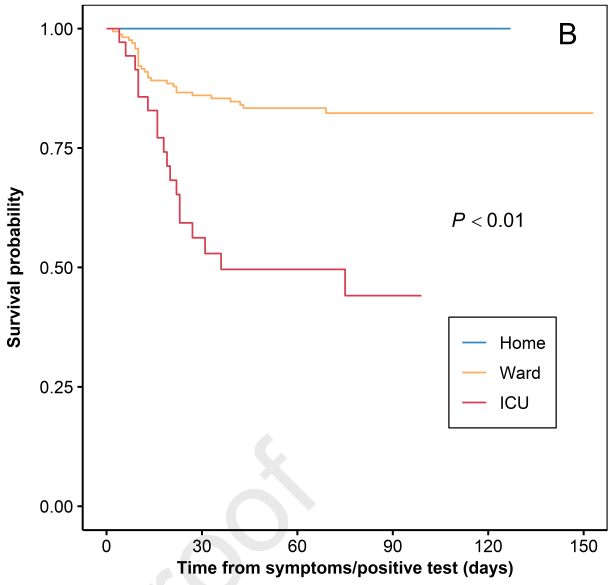
Country	All patients	Deaths
Belgium	21	3
Denmark	1	0
France	42	10
Italy	57	12
Portugal	1	0
Spain	89	19
Sweden	18	5
Switzerland	6	0
The Netherlands	8	0





Number at risk

237	185	133	49	2	1



Number at risk

Home	36	31	21	8	1	0
Ward	166	137	100	36	1	1
ICU	35	17	12	5	0	0

Suppl Figure 1. Kaplan-Meier survival curves from the date of COVID-19 diagnosis, stratified by age (2 categories), and main immunosuppressant.

Suppl Figure 2 Kaplan-Meyer survival from the date of Covid-19 diagnosis: interplay between age of the recipient, primary immunosuppressant and chronic renal failure

Supplementary material

Supplementary table 1. Results from multivariate analysis of predictors of mortality, from Cox proportional hazard regression models, excluding age from the predictors. All predictors with a p-value <= 0.1 were retained in the model.

Variable	HR (95% CI)	p-value
Comorbidities		
Diabetes	**1.95 (1.06 - 3.58)**	**0.0313**
Chronic kidney disease*	**1.97 (1.05 - 3.67)**	**0.0336**
Other	1.92 (0.97 - 3.82)	0.0608
Main immunosuppressant (Tacrolimus vs CsA/mTOR/MMF)	**0.52 (0.29 - 0.95)**	**0.0325**

** p-creatinine > 2 mg/dL*
CsA = Cyclosporine A, MMF = Mycophenolate mofetil, mTOR=mTOR inhibitors

Supplementary table 2. Estimated probability of survival 50 days after the symptoms, stratified by age (2 categories), main immunosuppressant and chronic kidney disease. Estimates are based on Kaplan-Meier curves.

Age	Main immunosuppressant	Chronic kidney Disease*	N patients	Probability of survival at 50 days (95% CI)
≤ 70	TAC	No	113	0.89 (0.82 - 0.94)
		Yes	16	0.86 (0.55 - 0.96)
	CsA/mTOR/MMF/Other	No	39	0.90 (0.75 - 0.96)
		Yes	13	0.54 (0.25 - 0.76)
>70	TAC	No	16	0.75 (0.46 - 0.90)
		Yes	10	0.77 (0.34 - 0.94)
	CsA/mTOR/MMF/Other	No	20	0.50 (0.27 - 0.69)
		Yes	7	0.29 (0.01 - 0.69)

** p-creatinine > 2 mg/dL*

TAC = Tacrolimus, CsA = Cyclosporine A, MMF = Mycophenolate mofetil

Supplementary Table 3. Baseline characteristics of the study population, stratified by type of CNI

	Immunosuppressant			
	Cyclosporin A/ Other (N=81)	Tacrolimus (N=162)	Total (N=243)	p-value
Males - N(%)	66 (81.48)	105 (64.81)	171 (70.37)	0.0073
Age at symptoms				<.0001
Median (IQR)	68 (60.5 - 73.5)	61 (53.0 - 68.0)	63 (55.0 - 69.0)	
Location of patient at occurrence of symptoms - N(%)				0.4631
Home	74 (91.36)	143 (88.27)	217 (89.30)	
Hospital	7 (8.64)	19 (11.73)	26 (10.70)	
Place of management - N(%)				0.0831
Home	7 (8.64)	32 (19.75)	39 (16.05)	
Ward	61 (75.31)	106 (65.43)	167 (68.72)	
ICU	13 (16.05)	24 (14.81)	37 (15.23)	
Time between last LT and COVID symptoms (years)				<.0001
Median (IQR)	12 (6.2 - 18.9)	7 (2.0 - 13.3)	8 (3.1 - 15.0)	
Missing	1 (1.23)	5 (3.09)	6 (2.47)	
Indication for LT - N(%)				
Decompensated cirrhosis	51 (62.96)	90 (55.56)	141 (58.02)	0.27
HCC	21 (25.93)	42 (25.93)	63 (25.93)	1
Other	9 (11.11)	31 (19.14)	40 (16.46)	0.1118
BMI				
Median (IQR)	26.3 (23.5 - 29.7)	25.7 (23.4 - 29.4)	25.9 (23.4 - 29.4)	0.6612
Chronic kidney disease*	22 (27.16)	27 (16.67)	49 (20.16)	0.0546
Coronary artery disease	3 (3.70)	14 (8.64)	17 (7.00)	0.1548
Number of comorbidities - N(%)				0.0003
0	11 (13.58)	46 (28.40)	57 (23.46)	
1	20 (24.69)	59 (36.42)	79 (32.51)	
≥ 2	50 (61.73)	57 (35.19)	107 (44.03)	
Drugs - N(%)				
Beta blockers	20 (24.69)	30 (18.52)	50 (20.58)	0.2618
ACE inhibitors or angiotensin-II-receptor antagonists	33 (40.74)	26 (16.05)	59 (24.28)	<.0001
Type of immunosuppressant - N(%)				
CsA	29 (35.80)	0 (0.00)	29 (11.93)	<.0001
TAC	0 (0.00)	162 (100.00)	162 (66.67)	<.0001
MMF	50 (61.73)	69 (42.59)	119 (48.97)	0.0049
mTOR	23 (28.40)	14 (8.64)	37 (15.23)	<.0001
Steroids	14 (17.28)	42 (25.93)	56 (23.05)	0.1316
Other	0 (0.00)	1 (0.62)	1 (0.41)	1
Outcome - N(%)				0.0033
Alive	56 (69.14)	138 (85.19)	194 (79.84)	
Dead	25 (30.86)	24 (14.81)	49 (20.16)	
Time between symptoms and last follow-up (days)				
Median (IQR)	60 (23 - 83)	66 (39 - 87)	65 (35 - 87)	0.127
Missing - N(%)	1 (1.23)	5 (3.09)	6 (2.47)	

Cause of death - N(%)				
Refractory pneumonia	21 (84.00)	17 (70.83)	38 (77.55)	0.2695
Liver related death w/o lung failure	0 (0.00)	1 (4.17)	1 (2.04)	0.4898
Liver related death with lung failure	2 (8.00)	1 (4.17)	3 (6.12)	1
Other	2 (8.00)	5 (20.83)	7 (14.29)	0.2467

** p-creatinine > 2 mg/dL*

ICU = Intensive care unit, IQR=interquartile range (1^{st}-3^{rd} quartile), LT = Liver transplant, HCC= Hepatocellular carcinoma, NASH = Non-alcoholic steatohepatitis, HBV = hepatitis B virus, HCV = hepatitis C virus. CsA = Cyclosporine A, TAC = tacrolimus, MMF = Mycophenolate mofetil*, mTOR=mTOR inhibitors.*

Supplementary material

Supplementary table 1. Results from multivariate analysis of predictors of mortality, from Cox proportional hazard regression models, excluding age from the predictors. All predictors with a p-value <= 0.1 were retained in the model.

Variable	HR (95% CI)	p-value
Comorbidities		
Diabetes	**1.95 (1.06 - 3.58)**	**0.0313**
Chronic kidney disease*	**1.97 (1.05 - 3.67)**	**0.0336**
Other	1.92 (0.97 - 3.82)	0.0608
Main immunosuppressant (Tacrolimus vs CsA/mTOR/MMF)	**0.52 (0.29 - 0.95)**	**0.0325**

** p-creatinine > 2 mg/dL*
CsA = Cyclosporine A, MMF = Mycophenolate mofetil, mTOR=mTOR inhibitors

Supplementary table 2. Estimated probability of survival 50 days after the symptoms, stratified by age (2 categories), main immunosuppressant and chronic kidney disease. Estimates are based on Kaplan-Meier curves.

Age	Main immunosuppressant	Chronic kidney Disease*	N patients	Probability of survival at 50 days (95% CI)
≤ 70	TAC	No	113	0.89 (0.82 - 0.94)
		Yes	16	0.86 (0.55 - 0.96)
	CsA/mTOR/MMF/Other	No	39	0.90 (0.75 - 0.96)
		Yes	13	0.54 (0.25 - 0.76)
>70	TAC	No	16	0.75 (0.46 - 0.90)
		Yes	10	0.77 (0.34 - 0.94)
	CsA/mTOR/MMF/Other	No	20	0.50 (0.27 - 0.69)
		Yes	7	0.29 (0.01 - 0.69)

** p-creatinine > 2 mg/dL*

TAC = Tacrolimus, CsA = Cyclosporine A, MMF = Mycophenolate mofetil

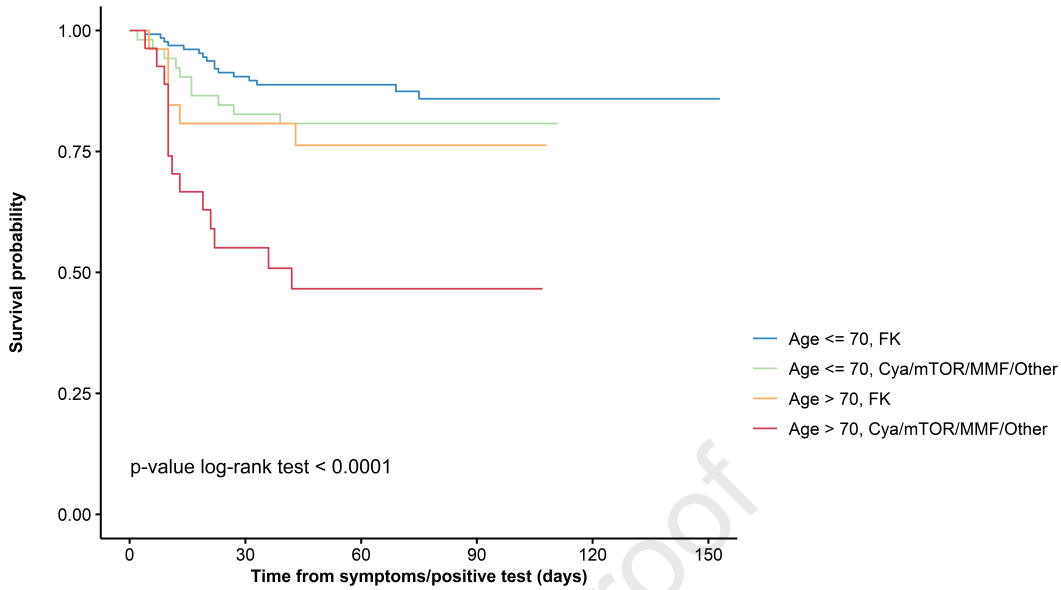
Supplementary Table 3. Baseline characteristics of the study population, stratified by type of CNI

	Immunosuppressant			
	Cyclosporin A/ Other (N=81)	Tacrolimus (N=162)	Total (N=243)	p-value
Males - N(%)	66 (81.48)	105 (64.81)	171 (70.37)	0.0073
Age at symptoms				<.0001
Median (IQR)	68 (60.5 - 73.5)	61 (53.0 - 68.0)	63 (55.0 - 69.0)	
Location of patient at occurrence of symptoms - N(%)				0.4631
Home	74 (91.36)	143 (88.27)	217 (89.30)	
Hospital	7 (8.64)	19 (11.73)	26 (10.70)	
Place of management - N(%)				0.0831
Home	7 (8.64)	32 (19.75)	39 (16.05)	
Ward	61 (75.31)	106 (65.43)	167 (68.72)	
ICU	13 (16.05)	24 (14.81)	37 (15.23)	
Time between last LT and COVID symptoms (years)				<.0001
Median (IQR)	12 (6.2 - 18.9)	7 (2.0 - 13.3)	8 (3.1 - 15.0)	
Missing	1 (1.23)	5 (3.09)	6 (2.47)	
Indication for LT - N(%)				
Decompensated cirrhosis	51 (62.96)	90 (55.56)	141 (58.02)	0.27
HCC	21 (25.93)	42 (25.93)	63 (25.93)	1
Other	9 (11.11)	31 (19.14)	40 (16.46)	0.1118
BMI				
Median (IQR)	26.3 (23.5 - 29.7)	25.7 (23.4 - 29.4)	25.9 (23.4 - 29.4)	0.6612
Chronic kidney disease*	22 (27.16)	27 (16.67)	49 (20.16)	0.0546
Coronary artery disease	3 (3.70)	14 (8.64)	17 (7.00)	0.1548
Number of comorbidities - N(%)				0.0003
0	11 (13.58)	46 (28.40)	57 (23.46)	
1	20 (24.69)	59 (36.42)	79 (32.51)	
≥ 2	50 (61.73)	57 (35.19)	107 (44.03)	
Drugs - N(%)				
Beta blockers	20 (24.69)	30 (18.52)	50 (20.58)	0.2618
ACE inhibitors or angiotensin-II-receptor antagonists	33 (40.74)	26 (16.05)	59 (24.28)	<.0001
Type of immunosuppressant - N(%)				
CsA	29 (35.80)	0 (0.00)	29 (11.93)	<.0001
TAC	0 (0.00)	162 (100.00)	162 (66.67)	<.0001
MMF	50 (61.73)	69 (42.59)	119 (48.97)	0.0049
mTOR	23 (28.40)	14 (8.64)	37 (15.23)	<.0001
Steroids	14 (17.28)	42 (25.93)	56 (23.05)	0.1316
Other	0 (0.00)	1 (0.62)	1 (0.41)	1
Outcome - N(%)				0.0033
Alive	56 (69.14)	138 (85.19)	194 (79.84)	
Dead	25 (30.86)	24 (14.81)	49 (20.16)	
Time between symptoms and last follow-up (days)				
Median (IQR)	60 (23 - 83)	66 (39 - 87)	65 (35 - 87)	0.127
Missing - N(%)	1 (1.23)	5 (3.09)	6 (2.47)	

Cause of death - N(%)				
Refractory pneumonia	21 (84.00)	17 (70.83)	38 (77.55)	0.2695
Liver related death w/o lung failure	0 (0.00)	1 (4.17)	1 (2.04)	0.4898
Liver related death with lung failure	2 (8.00)	1 (4.17)	3 (6.12)	1
Other	2 (8.00)	5 (20.83)	7 (14.29)	0.2467

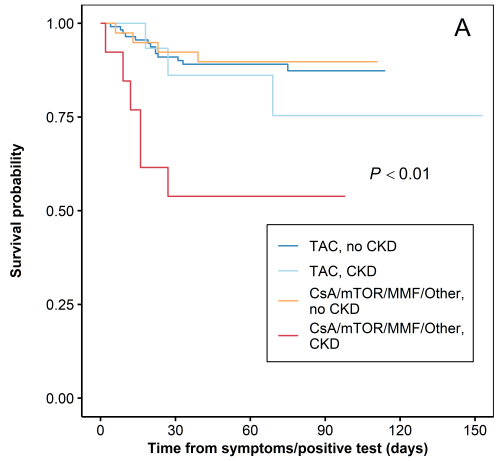
** p-creatinine > 2 mg/dL*

ICU = Intensive care unit, IQR=interquartile range (1^{st}-3^{rd} quartile), LT = Liver transplant, HCC= Hepatocellular carcinoma, NASH = Non-alcoholic steatohepatitis, HBV = hepatitis B virus, HCV = hepatitis C virus. CsA = Cyclosporine A, TAC = tacrolimus, MMF = Mycophenolate mofetil*, mTOR=mTOR inhibitors.*



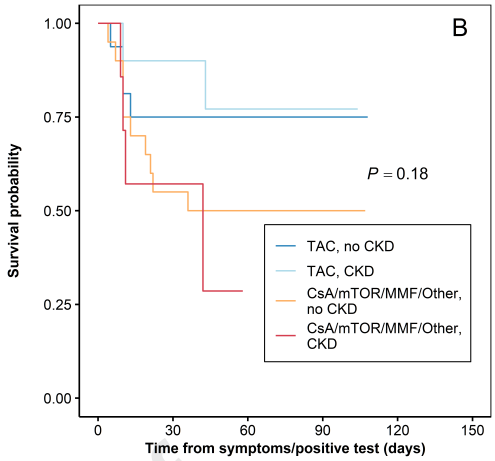
Number at risk

Age <= 70, FK	129	108	77	27	2	1
Age <= 70, Cya/mTOR/MMF/Other	52	43	31	12	0	0
Age > 70, FK	26	19	16	7	0	0
Age > 70, Cya/mTOR/MMF/Other	27	14	9	3	0	0



Number at risk

TAC, no CKD	113	96	68	25	0	0
TAC, CKD	16	12	9	2	2	1
CsA/mTOR/MMF/Other, no CKD	39	36	26	11	0	0
CsA/mTOR/MMF/Other, CKD	13	7	5	1	0	0



Number at risk

TAC, no CKD	16	11	11	5	0	0
TAC, CKD	10	8	5	2	0	0
CsA/mTOR/MMF/Other, no CKD	20	11	9	3	0	0
CsA/mTOR/MMF/Other, CKD	7	3	0	0	0	0

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT
Few studies have analyzed the impact of Cocid-19 in liver transplant recipients and the association of co-morbidities, immunosuppression and ageing on the mortality risk.

NEW FINDINGS
Age > 70 and tacrolimus use had respectively a negative and a positive independent effect on survival. The role of co-morbidities was strongly influenced by the dominant effect of age as the number of comorbidities increased with the increasing age of the recipients.

LIMITATIONS
Although we attempted to collect data on major co-variables there remains the possibility of missing confounders.

IMPACT
Thees findings should encourage clinicians to keep Tacrolimus at the usual dose as it may be beneficial when treating COVID-19.

LAY SUMMARY (25-30 words limit)
In liver transplant recipients with Covid-19, tacrolimus use had a positive independent effect on survival. This novel finding should encourage clinicians to keep Tacrolimus at the usual dose as it may be beneficial when treating COVID-19.

Tables

Table 1. Baseline characteristics of the study population

	Place of management			Total (N=243)	p-value
	Home (N=39)	Ward (N=167)	ICU (N=37)		
Males - N(%)	24 (61.54)	121 (72.46)	26 (70.27)	171 (70.37)	0.4051
Age at symptoms					
Median (IQR)[ab]	54 (37.0 - 61.0)	64 (57.0 - 72.0)	64 (58.0 - 68.0)	63 (55.0 - 69.0)	<.0001
Age class at symptoms - N(%)[ab]					<.0001
≤ 50	16 (41.03)	20 (11.98)	3 (8.11)	39 (16.05)	
50 - 60	11 (28.21)	39 (23.35)	10 (27.03)	60 (24.69)	
60 - 70	9 (23.08)	59 (35.33)	20 (54.05)	88 (36.21)	
> 70	1 (2.56)	48 (28.74)	4 (10.81)	53 (21.81)	
Location of patient at occurrence of symptoms - N(%)[b]					0.0119
Home	39 (100.00)	148 (88.62)	30 (81.08)	217 (89.30)	
Hospital	0 (0.00)	19 (11.38)	7 (18.92)	26 (10.70)	
Time between last LT and COVID symptoms (years)					
Median (IQR)	6 (2.2 - 10.9)	9 (3.8 - 15.4)	5 (1.5 - 13.3)	8 (3.1 - 15.0)	0.0295
Time between last LT and COVID symptoms - N(%)					0.1005
< 1 year	5 (12.82)	19 (11.38)	7 (18.92)	31 (12.76)	
1-5 years	12 (30.77)	32 (19.16)	11 (29.73)	55 (22.63)	
5-10 years	9 (23.08)	34 (20.36)	7 (18.92)	50 (20.58)	
≥ 10 years	10 (25.64)	81 (48.50)	10 (27.03)	101 (41.56)	
Missing	3 (7.69)	1 (0.60)	2 (5.41)	6 (2.47)	
Indication for LT - N(%)					
Decompensated cirrhosis	21 (53.85)	96 (57.49)	24 (64.86)	141 (58.02)	0.6034
HCC	8 (20.51)	43 (25.75)	12 (32.43)	63 (25.93)	0.4933
Other[b]	10 (25.64)	29 (17.37)	1 (2.70)	40 (16.46)	0.0226
Etiology - N(%)					
Alcohol[a]	3 (7.69)	49 (29.34)	8 (21.62)	60 (24.69)	0.0149
Post NASH	2 (5.13)	10 (5.99)	6 (16.22)	18 (7.41)	0.1262
HBV	5 (12.82)	34 (20.36)	4 (10.81)	43 (17.70)	0.2492
HCV active or inactive	10 (25.64)	41 (24.55)	11 (29.73)	62 (25.51)	0.8282
Other[a]	20 (51.28)	49 (29.34)	10 (27.03)	79 (32.51)	0.0256
Missing	0 (0.00)	2 (1.20)	0 (0.00)	2 (0.82)	
BMI					
Median (IQR)	25.5 (22.0 - 28.9)	25.8 (23.4 - 29.4)	27.9 (24.5 - 29.9)	25.9 (23.4 - 29.4)	0.1701
Missing - N(%)	3 (7.69)	18 (10.78)	1 (2.70)	22 (9.05)	
BMI >30	7 (17.95)	30 (17.96)	9 (24.32)	46 (18.93)	0.7924
Comorbidities - N(%)					
No[ab]	19 (48.72)	35 (20.96)	3 (8.11)	57 (23.46)	<.0001
Diabetes[b]	8 (20.51)	67 (40.12)	19 (51.35)	94 (38.68)	0.0176
Hypertension[bc]	11 (28.21)	71 (42.51)	29 (78.38)	111 (45.68)	<.0001
Chronic lung disease	3 (7.69)	20 (11.98)	2 (5.41)	25 (10.29)	0.5267

Chronic kidney disease*	4 (10.26)	37 (22.16)	8 (21.62)	49 (20.16)	0.2419
Coronary artery disease	3 (7.69)	9 (5.39)	5 (13.51)	17 (7.00)	0.2071
Other	4 (10.26)	34 (20.36)	5 (13.51)	43 (17.70)	0.2541
Number of comorbidities class - N(%)[ab]					0.0002
0	19 (48.72)	35 (20.96)	3 (8.11)	57 (23.46)	
1	11 (28.21)	57 (34.13)	11 (29.73)	79 (32.51)	
≥ 2	9 (23.08)	75 (44.91)	23 (62.16)	107 (44.03)	
Drugs - N(%)					
Beta blockers	6 (15.38)	34 (20.36)	10 (27.03)	50 (20.58)	0.4515
ACE inhibitors or angiotensin-II-receptor antagonists [ab]	1 (2.56)	47 (28.14)	11 (29.73)	59 (24.28)	0.0025
Smoke - N(%)					0.3508
Missing	0 (0.00)	1 (0.60)	1 (2.70)	2 (0.82)	
No	35 (89.74)	151 (90.42)	30 (81.08)	216 (88.89)	
Yes	4 (10.26)	15 (8.98)	6 (16.22)	25 (10.29)	
Type of Immunosuppressant - N(%)°					
TAC	32 (82.05)	106 (63.47)	24 (64.86)	162 (66.67)	0.0831
MMF	15 (38.46)	80 (47.90)	24 (64.86)	119 (48.97)	0.0627
Steroids	7 (17.95)	35 (20.96)	14 (37.84)	56 (23.05)	0.0625
mTOR	5 (12.82)	27 (16.17)	5 (13.51)	37 (15.23)	0.8296
CsA	1 (2.56)	23 (13.77)	5 (13.51)	29 (11.93)	0.1188
Other	0 (0.00)	1 (0.60)	0 (0.00)	1 (0.41)	1
Combinations of immunosuppressants - N(%)					
CsA only	1 (2.56)	10 (5.99)	2 (5.41)	13 (5.35)	0.8264
CsA,MMF	0 (0.00)	7 (4.19)	2 (5.41)	9 (3.70)	0.3842
CsA,Steroids	0 (0.00)	3 (1.80)	0 (0.00)	3 (1.23)	1
CsA,MMF,Steroids	0 (0.00)	3 (1.80)	1 (2.70)	4 (1.65)	0.5697
TAC only	12 (30.77)	36 (21.56)	6 (16.22)	54 (22.22)	0.2918
TAC,MMF	12 (30.77)	35 (20.96)	5 (13.51)	52 (21.40)	0.1806
TAC,mTOR	2 (5.13)	10 (5.99)	0 (0.00)	12 (4.94)	0.4209
TAC,Steroids or Other	6 (15.38)	16 (9.58)	5 (13.51)	27 (11.11)	0.4473
TAC,MMF,mTOR	0 (0.00)	0 (0.00)	1 (2.70)	1 (0.41)	0.1523
TAC,MMF,Steroids[b]	0 (0.00)	9 (5.39)	6 (16.22)	15 (6.17)	0.011
TAC,MMF,mTOR,Steroids	0 (0.00)	0 (0.00)	1 (2.70)	1 (0.41)	0.1523
MMF only	3 (7.69)	17 (10.18)	4 (10.81)	24 (9.88)	0.8966
MMF,mTOR	0 (0.00)	7 (4.19)	3 (8.11)	10 (4.12)	0.1712
MMF,Steroids	0 (0.00)	2 (1.20)	1 (2.70)	3 (1.23)	0.4484
mTOR only	2 (5.13)	9 (5.39)	0 (0.00)	11 (4.53)	0.4577
mTOR,Steroids	1 (2.56)	1 (0.60)	0 (0.00)	2 (0.82)	0.5286
Steroids only	0 (0.00)	2 (1.20)	0 (0.00)	2 (0.82)	1
WBC (10^9/L): most recent value before symptoms					
Median (IQR)	5.1 (4.4 - 6.5)	5.2 (3.9 - 6.7)	6.0 (4.3 - 6.7)	5.2 (4.0 - 6.7)	0.9274
Bil (mg/dL): most recent value before symptoms					
Median (IQR)	0.8 (0.5 - 1.0)	0.6 (0.4 - 1.0)	0.6 (0.5 - 1.0)	0.7 (0.5 - 1.0)	0.7569
Creat (mg/dL) : most recent value before symptoms					
Median (IQR)[ab]	1.0 (0.9 - 1.1)	1.1 (0.9 - 1.5)	1.2 (1.0 - 1.6)	1.1 (0.9 - 1.4)	0.019

ALT (U/L): more recent value before symptoms					
Median (IQR)	23.0 (17.0 - 32.0)	20.0 (15.0 - 31.0)	23.0 (17.0 - 34.0)	20.0 (16.0 - 32.0)	0.3607

[a] *p-value Ward vs Home ≤0.05*

[b] *p-value ICU vs Home ≤0.05*

[c] *p-value ICU vs Ward ≤0.05*

** p-creatinine > 2 mg/dL*

° patients can be treated with more than one therapy, therefore percentages do not sum to 100

ICU = Intensive care unit, IQR=interquartile range (1st-3rd quartile), LT = Liver transplant, HCC= Hepatocellular carcinoma, NASH = Non-alcoholic steatohepatitis, HBV = hepatitis B virus, HCV = hepatitis C virus, CsA = Cyclosporine A, TAC = tacrolimus, MMF = Mycophenolate mofetil*, mTOR=mTOR inhibitors.*

Table 2. Clinical presentation and course after COVID symptoms

	Place of management				
	Home (N=39)	**Ward (N=167)**	**ICU (N=37)**	**Total (N=243)**	**p-value**
Symptoms: at clinical diagnosis - N(%)					
Fever >37.2[a]	25 (64.10)	137 (82.04)	28 (75.68)	190 (78.19)	0.0468
Cough	21 (53.85)	106 (63.47)	16 (43.24)	143 (58.85)	0.0609
Polypnea or dyspnea[abc]	4 (10.26)	57 (34.13)	21 (56.76)	82 (33.74)	0.0001
Diarrhea[a]	3 (7.69)	46 (27.54)	6 (16.22)	55 (22.63)	0.0171
Anosmia and disgeusia[a]	9 (23.08)	10 (5.99)	2 (5.41)	21 (8.64)	0.0061
Muscle pain[a]	13 (33.33)	24 (14.37)	4 (10.81)	41 (16.87)	0.0098
Confusion	0 (0.00)	4 (2.40)	3 (8.11)	7 (2.88)	0.0969
Thoracic pain	3 (7.69)	11 (6.59)	1 (2.70)	15 (6.17)	0.717
Asthenia	11 (28.21)	34 (20.36)	4 (10.81)	49 (20.16)	0.1669
Other	4 (10.26)	11 (6.59)	0 (0.00)	15 (6.17)	0.1591
Time between symptoms and positive test (days)					
Median (IQR)[b]	9 (3 - 19)	5 (2 - 9)	3 (0 - 7)	4 (2 - 10)	0.0226
Chest xray or Thorax CT scan - N(%)					
No[ab]	16 (41.03)	8 (4.79)	4 (10.81)	28 (11.52)	<.0001
Yes, normal[bc]	15 (38.46)	51 (30.54)	0 (0.00)	66 (27.16)	0.0002
Yes, Ground Glass Opacities[abc]	7 (17.95)	106 (63.47)	32 (86.49)	145 (59.67)	<.0001
Yes, lobar opacities[c]	1 (2.56)	6 (3.59)	7 (18.92)	14 (5.76)	0.0044
Ground glass opacities or lobar opacities - N(%)[abc]	8 (20.51)	108 (64.67)	33 (89.19)	149 (61.32)	<.0001
Respiratory support - N(%)[c]					<.0001
O_2 support	1 (50.00)	78 (79.59)	7 (18.92)	86 (62.77)	
Non-invasive ventilation	1 (50.00)	17 (17.35)	8 (21.62)	26 (18.98)	
Mechanical ventilation	0 (0.00)	3 (3.06)	22 (59.46)	25 (18.25)	
Added Lung infection - N(%)					
None[bc]	39 (100.00)	154 (92.22)	25 (67.57)	218 (89.71)	<.0001
Bacterial[b]	0 (0.00)	11 (6.59)	7 (18.92)	18 (7.41)	0.0064
Fungal[c]	0 (0.00)	1 (0.60)	5 (13.51)	6 (2.47)	0.0011
Other	0 (0.00)	2 (1.20)	0 (0.00)	2 (0.82)	1
Renal replacement therapy - N(%)[bc]	0 (0.00)	10 (5.99)	11 (29.73)	21 (8.64)	<.0001
Vaso active drugs (NA) - N(%)[bc]	1 (2.56)	1 (0.60)	19 (51.35)	21 (8.64)	<.0001
Myocarditis - N(%)	0 (0.00)	0 (0.00)	1 (2.70)	1 (0.41)	0.1523
BIL (mg/dL):peak value					
Median (IQR)[c]	0.8 (0.5 - 1.1)	0.7 (0.4 - 1.0)	1.2 (0.8 - 2.7)	0.8 (0.5 - 1.2)	0.0034
INR: peak value					
Median (IQR)[bc]	1.1 (1.0 - 1.2)	1.1 (1.1 - 1.3)	1.3 (1.1 - 1.7)	1.1 (1.1 - 1.3)	0.0039
Creatinine (mg/dL): peak value					
Median (IQR)[bc]	1.0 (0.9 - 1.6)	1.2 (0.9 - 1.8)	2.2 (1.2 - 4.0)	1.3 (0.9 - 2.0)	0.0009
ALT (U/L): peak value					
Median (IQR)[bc]	28.0 (19.0 - 39.0)	32.0 (19.0 - 51.5)	59.5 (32.5 - 134.5)	34.0 (20.0 - 55.0)	0.0014
COVID Therapy - N(%)					

None[ab]	33 (84.62)	46 (27.54)	15 (40.54)	94 (38.68)	<.0001
Lopinavir/ritonavir[ab]	0 (0.00)	35 (20.96)	6 (16.22)	41 (16.87)	0.007
OH-clorochina[abc]	4 (10.26)	99 (59.28)	13 (35.14)	116 (47.74)	<.0001
High dose steroids[ab]	0 (0.00)	26 (15.57)	8 (21.62)	34 (13.99)	0.0144
Remdesevir	0 (0.00)	0 (0.00)	1 (2.70)	1 (0.41)	0.1523
Tocilizumab	0 (0.00)	11 (6.59)	4 (10.81)	15 (6.17)	0.0962
Azythromicin[a]	2 (5.13)	57 (34.13)	8 (21.62)	67 (27.57)	0.0009
Other[b]	1 (2.56)	15 (8.98)	8 (21.62)	24 (9.88)	0.0215
Immunosuppression changes - N(%)					
Yes[ab]	4 (10.26)	71 (42.51)	22 (59.46)	97 (39.92)	<.0001
Stop CNI	0 (0.00)	11 (6.59)	5 (13.51)	16 (6.58)	0.0441
25-50% reduction CNI	2 (5.13)	28 (16.77)	8 (21.62)	38 (15.64)	0.1091
Stop antimetabolites[b]	1 (2.56)	26 (15.57)	8 (21.62)	35 (14.40)	0.0455
Stop mTOR	0 (0.00)	9 (5.39)	1 (2.70)	10 (4.12)	0.3305
Other	1 (2.56)	5 (2.99)	0 (0.00)	6 (2.47)	0.1479
Outcome - N(%)[abc]					<.0001
Alive	39 (100.00)	138 (82.63)	17 (45.95)	194 (79.84)	
Dead	0 (0.00)	29 (17.37)	20 (54.05)	49 (20.16)	
Time between symptoms and last follow-up (days)					
Median (IQR)[bc]	70 (48 - 88)	66 (42 - 88)	29 (17 - 75)	65 (35 - 87)	0.007
Missing - N(%)	3 (7.69)	1 (0.60)	2 (5.41)	6 (2.47)	
Cause of death - N(%)					
Refractory pneumonia		23 (79.31)	15 (75.00)	38 (77.55)	0.7405
Liver related death w/o lung failure		1 (3.45)	0 (0.00)	1 (2.04)	1
Liver related death with lung failure		2 (6.90)	1 (5.00)	3 (6.12)	1
Other		3 (10.34)	4 (20.00)	7 (14.29)	0.4221
Heparin - N(%)[ab]					<.0001
Missing	13 (33.33)	20 (11.98)	6 (16.22)	39 (16.05)	
No	24 (61.54)	53 (31.74)	10 (27.03)	87 (35.80)	
Yes	2 (5.13)	94 (56.29)	21 (56.76)	117 (48.15)	
Average CNI level pre COVID - N(%)					0.0235
No CNI	4 (10.26)	5 (2.99)	1 (2.70)	10 (4.12)	
Cyclosporine ≤50	1 (2.56)	6 (3.59)	4 (10.81)	11 (4.53)	
Cyclosporine 50-100	1 (2.56)	2 (1.20)	0 (0.00)	3 (1.23)	
Cyclosporine >100	0 (0.00)	35 (20.96)	6 (16.22)	41 (16.87)	
Tacrolimus ≤4 ng/mL	3 (7.69)	22 (13.17)	6 (16.22)	31 (12.76)	
Tacrolimus 4-6 ng/mL	10 (25.64)	25 (14.97)	6 (16.22)	41 (16.87)	
Tacrolimus >6 ng/mL	6 (15.38)	25 (14.97)	6 (16.22)	37 (15.23)	

[a] *p-value Ward vs Home ≤0.05*

[b] *p-value ICU vs Home ≤0.05*

[c] *p-value ICU vs Ward ≤0.05*

IQR=interquartile range (1st-3rd quartile), CNI = Calcineurin inhibitors

Table 3. Results from univariate and multivariate analysis of predictors of mortality, from Cox proportional hazard regression models.

	Univariate models		Multivariate models	
Variable	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Age				
Linear (1-year increase)	**1.06 (1.03 - 1.10)**	**<.0001**		
60-70 vs ≤60	**2.58 (1.12 - 5.94)**	**0.025 5**	2.20 (0.94 - 5.13)	0.068
>70 vs ≤60	**5.49 (2.42 - 12.48)**	**<.0001**	**4.16 (1.78 - 9.73)**	**0.001**
Gender - Males vs Females	1.39 (0.71 - 2.73)	0.3438		
Indication for LT				
Decompensated cirrhosis	1.11 (0.61 - 2.00)	0.736		
HCC	1.25 (0.67 - 2.34)	0.4846		
Other	0.63 (0.25 - 1.61)	0.3362		
Time between LT and COVID symptoms (1-year increase)	**1.05 (1.01 - 1.09)**	**0.005 4**		
BMI (1-unit increase)	1.00 (0.94 - 1.07)	0.9936		
Comorbidities				
Diabetes	**1.98 (1.11 - 3.54)**	**0.021 2**		
Hypertension	1.76 (0.98 - 3.17)	0.0584		
Chronic lung disease	0.55 (0.17 - 1.76)	0.3126		
Chronic kidney disease*	**2.20 (1.19 - 4.08)**	**0.012 3**	1.72 (0.92 - 3.22)	0.0912
Coronary artery disease	1.37 (0.49 - 3.81)	0.5518		
Other	1.71 (0.89 - 3.31)	0.1095		
N° Comorbidities				
1 vs 0	**3.54 (1.02 - 12.33)**	**0.046 8**		
2+ vs 0	**5.63 (1.72 - 18.50)**	**0.004 4**		
Smoke (Yes vs No)	1.62 (0.72 - 3.63)	0.241		
Type of immunosuppressant				
CsA vs all other	**2.29 (1.13 - 4.60)**	**0.020 9**		
TAC vs all other	**0.43 (0.24 - 0.77)**	**0.004 2**	**0.55 (0.31 - 0.99)**	**0.047 2**
MMF vs all other	1.30 (0.73 - 2.33)	0.3704		
mTOR vs all other	1.37 (0.66 - 2.84)	0.3969		
Treatment with ACE inhibitors or angiotensin-II-receptor antagonists (Yes vs No)	**1.92 (1.06 - 3.49)**	**0.032 8**		
Country				
Spain vs Other	1.52 (0.67 -	0.3178		

	3.48)		
Italy vs Other	1.34 (0.54 - 3.34)	0.5253	
France vs Other	1.48 (0.55 - 3.94)	0.4355	
Center recruiting more than 9 patients vs other centers	1.47 (0.82 - 2.65)	0.1993	

** p-creatinine > 2 mg/dL*

LT= Liver transplant, TAC = tacrolimus, CsA = Cyclosporine A, MMF = Mycophenolate mofetil, mTOR = mTOR inhibitors.

Table 4
ELITA/ELTR COVID-19 Registry for LT candidates and recipients: collaborators **with affiliations**
1. Division of Transplantation, Department of Surgery, Medical University of Vienna, Austria: Gabriela Berlakovich, Dagmar Kollmann, Georg Györi
2. Universitair Ziekenhuis Antwerpen, Edegem, Belgium. Dirk Ysebaert, Patrick Hollants
3. Universitair Ziekenhuis Dienst voor Algemene en Hepatopancreaticobiliaire Heelkunde en Levertransplantatie, Ghent, Belgium. Frederik Berrevoet, Aude Vanlander
4. Universitair Ziekenhuis, Dienst Voor Levertransplantatie En Digestieve Heelkunde, Ghent, Belgium. Frederck Berrevoet, Eric Hoste, Christel Walraevens, Roberto Ivan Troisi.
5. Liver Transplant Programme, University Leuven, Belgium : Jacques Pirenne, Frederick Nevens, Natalie Vandenende
6. CHU Liege,University of Liege, Belgium. Oliver Detry, Josee Monard , Nicolas Meurisse
7. Cliniques Universitaires Saint Luc, Catholic University of Louvain, Brussels, Belgium. Olga Ciccarelli
8. Hopital Erasme Universite Libre De Bruxelles, Department of Abdominal Surgery, Brussels, Belgium. Valerio Lucidi
9. Hopital Cantonal Universitaire De Geneve, Departement De Chirurgie, Geneve, Switzerland. Giulia Magini, Thierry Berney, Anne-Catherine Saouli
10. University Hospital Copenhagen, Department for Surgery and Transplantation Rigshospitalet, Copenhagen, Denmark. Allan Rasmussen
11. Hôpital De La Croix Rousse, Chirurgie Générale Et Digestive, Lyon, France. Sylvie Radenne, Mickael Lesurtel
12. Hôpital Henri Mondor, Service d'Hepatologie, Créteil, France. Christophe Duvoux, Norbert Ngongang
13. Hôpital Paul Brousse, Centre Hépato Biliaire, Villejuif, France. Audrey Colly
14. C.H.R.U. De Strasbourg, Hôpital Hautepierre, Strasbourg, France. Francoise Faitot
15. C.H.R.U. Trousseau, Tours, France. Laure Elkrief
16. Hôpital Bicêtre, Hépatologie et transplantation hépatique pédiatriques, AP-HP Université Paris-Saclay, Le Kremlin-Bicêtre, France. Emmanuel Gonzales
17. The Queen Elizabeth Hospital, Queen Elisabeth Medical Center, Birmingham, United Kingdom. Darius Mirza, Thamara Perera, Ann Angus
18. University of Edinburgh Royal Infirmary, Liver Transplantation Unit, Edinburgh, United Kingdom. Gabriel Oniscu, Chris Johnston

19. Papa Giovanni 23 Hospital, Chirurgia Iii E Centro Trapianti Di Fegato, Bergamo, Italy. Luisa Pasulo, Michela Guizzetti, Marco Zambelli
20. Azienda Ospedaliero-Universitaria di Bologna, Via Albertoni 15, Bologna- Cristina Morelli, Giovanni Vitale
21. Istituto Nazionale Tumori Milano, Department of Hepatology, Hepato-pancreatic-biliary Surgery and Liver Transplantation, Istituto Nazionale Tumori, Milan, Italy. Sherrie Bhoori, Vincenzo Mazzaferro, Roberta Elisa Rossi
22. Ospedale Maggiore Di Milano, U.O. Chirurgia Generale E Dei Trapianti, Milano, Italy. Federica Invernizzi, Francesca Donato, Giorgio Rossi
23. Ospedale Niguarda Ca Granda, Divisione Di Chirurgia Generale E Dei Trapianti, Milano, Italy. Luca S Belli, Giovanni Perricone, Raffaella Viganò, Chiara Mazzarelli, Luciano De Carlis
24. University of Modena E Reggio Emilia, Policlinico Di Modena, Modena, Italy. Fabrizio Di Benedetto, Paolo Magistri, Antonia Zuliani
25. Ospedale Cisanello, U.O Trapiantologia Epatica Universitaria Azienda Ospedaliera, Pisa, Italy. Paolo De Simone, Paola Carrai, Stefania Petruccelli
26. Liver Transplant Unit, AOU Città della Salute e della Scienza di Torino, Torino, Italy Damiano Patrono, Silvia Martini, Renato Romagnoli
27. University Medical Center Groningen, Department of Gastroenetrology and Hepatology, Groningen, Netherlands. Aad Van Der Berg, Frank Cuperus
28. Erasmus MC, University Medical Center Rotterdam, Rotterdam, Netherlands. Wojciech Polak, Herold Metselaar
29. Hospital Gal De Santo Antonio, Dep. Of Surgery and Organ Transplantation, Porto, Portugal. Jorge Daniel
30. Hospital General Universitario De Alicante, Unidad Transplantes Hepatico, Alicante, Spain. Gonzalo Rodriguez, Sonia Pascual
31. Hospital Clinic I Provincial De Barcelona, Gastrointestinal Surgery Department, Barcelona, Spain. Costantino Fondevila, Jorde Colmenero
32. Hospital Universitari De Bellvitge, Unidad De Trasplante Hepatico Unidad De Trasplante Hepatico, Barcelona, Spain. Laura LLado, Carme Baliellas
33. Hospital Universitari Vall D Hebron, Liver Unit (Lluís Castells, Isabel Campos-Varela) and Liver Transplant Unit (Ernest Hidalgo) , Barcelona, Spain
34. Hospital Universitario 12 de Octubre, HBP And Transplant Unit, General Surgery, Madrid, Spain Carmelo Loinaz Segurola, Alberto Marcacuzco and Felix Cambra
35. Hospital Gregorio Maranon, Liver Transplant Unit, Madrid, Spain. Magdalena Salcedo Plaza, Fernando Diaz
36. Hospital Universitario Puerta de Hierro, Unidad de Trasplante Hepatico, Madrid, Spain. Valentin Cuervas-Mons, Ana Arias Milla, Alejandro Muñoz
37. Liver Transplant Unit, Hospital Virgen del Rocio, Seville, Spain. Jose Maria Alamo
38. Cirurgia HPB y transplante hepatico, Hospital Universitario de Badajoz, Spain Gerardo Blanco
39. Hospital Universitario, Virgen De La Arrixaca, El Palmar (Murcia), Spain. Victor Lopez Lopez.
40. Clinica Universitaria, Universidad De Navarra, Facultad De Medicina, Pamplona, Spain. Pablo Marti-Cruchaga
41. Hospital Universitario Marques De Valdecilla, Unidad De Traspante Hepatico, Santander, Spain. Rodriguez San Juan
42. Hospital Universitario Virgen De La Nieves, Servicio De Cirugia General, Granada,

Spain. Esther Brea Gomes
43. Huddinge Hospital, Department of Transplantation Surgery, Huddinge, Sweden. Bo Goran Ericzon, Carl Jorns