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COVID-19 IMPACT ON LIVER TRANSPLANTATION RECIPIENTS

Impacto da Covid-19 em recetores de transplante hepático

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ABSTRACT

Introduction: Since the beginning of corona virus infectious disease (COVID-19) pandemic and the fact that liver transplantation (LT) recipients are immunosuppressed population, a discussion was started about the higher risk for contracting the disease: there was controversy of risk factors for the disease severity and mortality as to the baseline immunosuppression (IS) regimen and target therapy for COVID-19 management. **Purpose**: The present work intends to analyze publications (clinical cases and series) to conclude on demographic risk factors, baseline and management of the IS specific COVID-19 therapy and outcome in these patients. **Materials and Methods**: A research on MEDLINE and PubMed databases was conducted. A total of 127 articles were identified, and 55 included for the final quantitative analysis. Statistical analysis was conducted by using the chi-square test, spearman correlation, and logistic regression. Descriptive analysis were presented in number, percentage or mean and range. **Results**: A total of 111 single cases were analyzed (95 adults and 16 pediatric). Regarding the adult population, 66 (69.47%) were male and the mean age was 58,73 years. The most common comorbidities were obesity/overweight (35.79%), arterial hypertension (33.68%), and diabetes (27.37%). The most used immunosuppressant was tacrolimus (74.74%) and mycophenolate mofetil (45.26%). Forty-one patients (43.16%) presented complications during treatment and 12 (12.63%) required invasive ventilation. The mortality rate in the adult population was 20%. Regarding the pediatric population, seven (43.75%) were male and the mean age was 1.28 years. The most used immunosuppressant was tacrolimus (93.75%). Only four patients (25%) presented complications, and three (18.75%) required invasive ventilation. Mortality among the pediatric population was 18.75%. **Discussion**: Justifications were presented based on the literature for the main statistically significant associations. Whenever possible, comparisons were made with other works. Special emphasis was given to comorbidities and immunosuppression. **Conclusion**: Older age, diabetes, higher white blood cells and support ventilation were associated with worse outcome. Lymphopenia and higher C-reactive protein levels were associated with a severe course of the disease. Mycophenolate mofetil as a baseline immunosuppression regimen was associated with shock during hospital stay. Overall, the mortality rate was higher in LT recipients than in the general population.

Keywords: Liver transplantation; COVID-19; Postoperative Complications.

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INTRODUCTION

What was considered to be a “viral pneumonia” in Wuhan, China, evolved to a PHEIC, and on March 11, 2020, it was considered a pandemic by the WHO.[1] The etiological agent responsible was identified as severe acute respiratory syndrome coronavirus,[2] responsible for coronavirus infectious disease (COVID-19). Until October 7, 2020, there have been reported above 76 million COVID-19 cases, and above 1,7 million deaths in 235 countries, areas or territories.[2]

The first case of an infection by SARS-CoV-2 in Portugal was confirmed on March 2, 2020 [3] and, on March 18, 2020, the Emergency State was declared for the first time in modern democracy.[4] To date, there are 383 258 confirmed cases and 6 413 deaths by COVID-19 [5] in Portugal.

Many risk factors were associated with a severe SARS-CoV-2 infection in liver transplant (LT) recipients. Those are elderly patients (over 60 years old), male gender and one or more comorbidities (such as hypertension, diabetes, COPD, and malignant tumors).[6-11] Also, some laboratory results have been independently associated with poor prognosis, being lymphopenia,[12,13] elevated CRP,[11] a high SOFA score and high d-dimers at admission.[7]

Although there is some agreement on the risk factor for disease severity and poor prognosis, when talking about baseline and IS management there is still no consensus. On one hand, some authors defend that higher doses of immunosuppressants are at an elevated risk for the severe disease,[14] and, on the other hand, others present that long term LT recipients on low IS doses, results in prolonged shedding, and consequently, an increase of viral loads and severe clinical presentation, not directly related to the IS.[15,16] Moreover, some physicians showed that LT recipients are not at a higher risk of contracting COVID-19 [17] when compared to the general population, while others presented that LT recipients are at higher risk.[18]

Until this moment, there is no specific therapy for COVID-19. The first drugs used were HCQ and Lopinavir/Ritonavir. Recent studies showed that both therapies are ineffective, and should not be used in the treatment neither in the prevention of SARS-COV-2 infection.[19] Moreover, HCQ has important drug interactions with cyclosporine, TAC and SIR, and lopinavir/ritonavir with SIR, EVE, TAC and cyclosporine, requiring close surveillance of these drug levels.[20] Tocilizumab has shown promising results in reducing mortality of ventilated patients or in patients with severe disease, however, phase III studies have not demonstrated the efficacy of such IL-6 inhibitor.[19] Other potential pharmacological agents in study are remdesivir, and convalescent plasma.

Due to this urgent need for orientation, we conduct a study on all clinical cases in the literature until December 23, 2020 analyzing the age, post liver-transplantation time, comorbidities, baseline IS regimen, main laboratory findings, IS management during treatment, other pharmacological and COVID-19 treatments, complications during treatment, support ventilation, and outcome of all these patients.

MATERIALS AND METHODS

Study Identification

A search within MEDLINE and PubMed databases (https://pubmed.ncbi.nlm.nih.gov) was conducted using MeSH terms: “COVID-19” (related MeSH terms are: 2019 novel coronavirus, SARS-CoV-2 infection, 2019-nCoV infection) AND “liver transplantation” AND “recipient” from September 3rd to 23rd, December 2020. The database used for this systematic review was MEDLINE-PubMed. All terms used on the PubMed search were developed according to the PICO structure: population, intervention, comparison/control and outcome (PICO). Population: children and adults who were liver transplant recipients and diagnosed with COVID-19. Intervention: children and adults who were liver transplant recipients and diagnosed with COVID-19 that presented complications during treatment, died or were discharged home. Control/Comparison: all cases were compared as to comorbidities, laboratory findings, therapy received, and outcome. Outcome: medical management regarding immunosuppression, infectious therapy, established guidelines or consensus, and survival of COVID-19 liver recipients.

Study Selection

Case reports, original articles, reviews, correspondence, letters to editor, clinical randomized controlled trials, non-randomized controlled trials, consensus articles, and protocol studies were included. Papers published in languages other than English were translated using the Google Translate tool.

Studies on organs other than liver or with data impossible to differentiate from the liver transplantation, epidemiological studies, surveys, those on clinical presentation of COVID-19, and those unrelated to liver transplantation were excluded from this meta-analysis. Figure 1 presents a flow diagram of the research based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).[21]

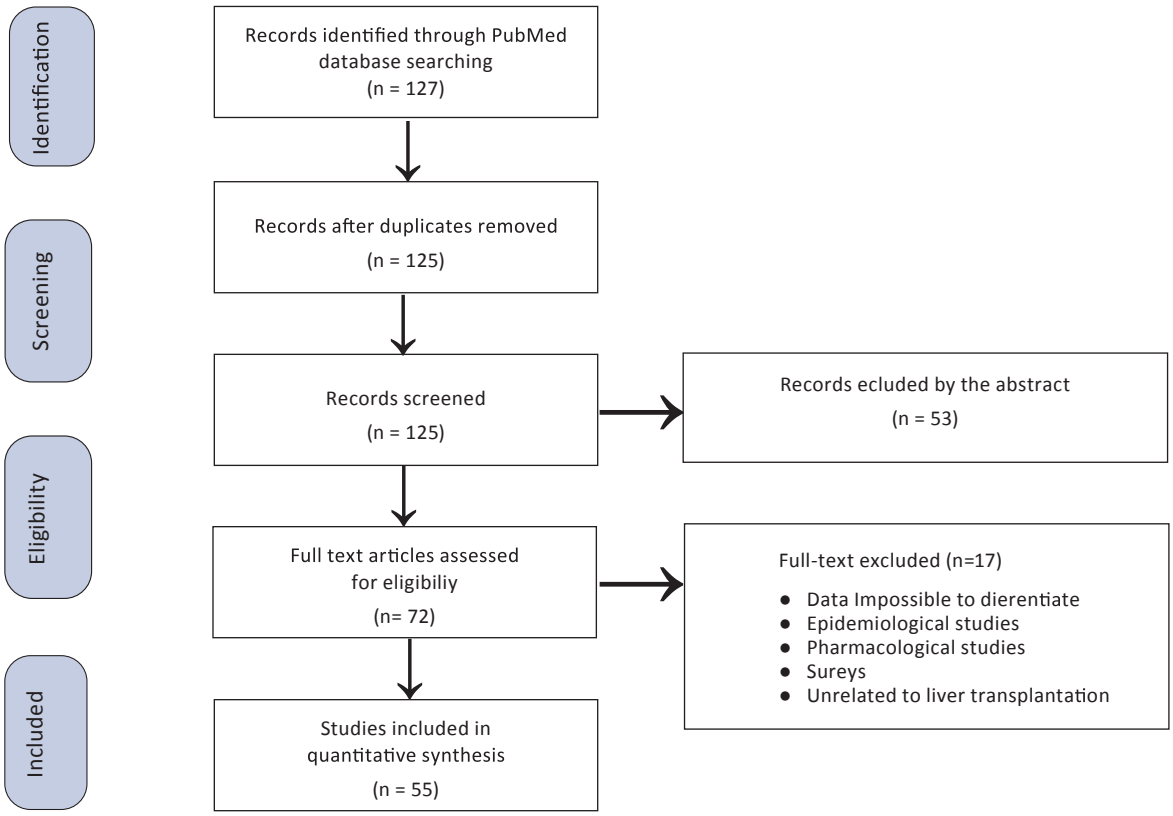
Statistical analysis

Statistical analysis was performed by using IBM SPSS 25 software.

Descriptive analysis was presented in number and percentage or mean, standard deviation and range.

Chi-square tests were used to test the independence between categorical variables (association between initial symptoms, baseline and IS management, other pharmacological therapy and support ventilation, with complications and outcome). Spearman rank order correlations (rho) were used to calculate the strength

Figure 1. *PRISMA flow diagram for the research.*



of the relationship between age and complications, age and outcome, time after LT and complications, and time after LT and outcome. Logistic regressions were used to test if comorbidities and main laboratory findings have an effect on the presence of complications (yes/no) and outcome (alive/dead) variables. A 95% confidence interval was established.

For all the analyses, a value of $p < .05$ was considered significant.

RESULTS

A total of 55 articles were analyzed. Regarding those articles, 111 single cases were reviewed, in which 95 (85.59%) were adult patients and the remaining 16 (14,41%) were pediatric.

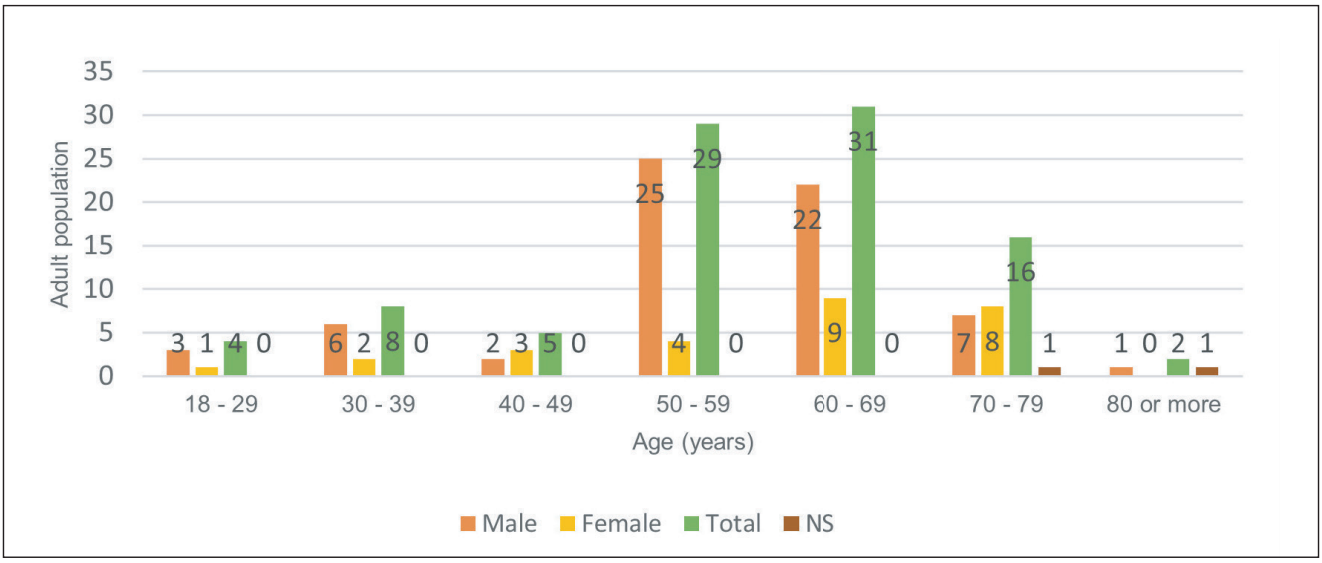
Adult population

Regarding the adult population, 66 (69,47%) were male, 27 (28.42%) female, and 2 (2.11%) cases have not been specified. The mean age was 58.73 years (σ = 13,57 years), ranging between 18 and 85 years. The distribution of the population by age and gender is represented in **Figure 2**. Four (4.21%) patients were white, 1 (1.05%) black, 1 (1.05%) Asian, 1 (1.05%) Indian, 1 (1.05%) Hispanic, 2 African American (2.11%), and 85 (89.47%) have not been specified. The mean time from liver transplantation to COVID-19 diagnosis was 6.98 years (σ = 7.129 years), ranging from 0 to 28.2 years. In one case, the time between transplantation to COVID-19 diagnosis have not been specified.

The most common cause for liver transplantation was hepatocellular carcinoma (n = 20; 21.05%) and HCV infection (n = 20; 21.05%), followed by hepatitis B virus infection (n = 14; 14.74%), alcoholic cirrhosis (n = 10; 10.53%), and PSC (n = 4; 4.21%). The most common comorbidities were overweight/obesity (n = 34; 35.79%), arterial hypertension (n = 32; 33.68%), diabetes mellitus (n = 26; 27.37%), cardiovascular disease (n = 15; 15.79%), and chronic kidney disease (n = 14; 14.74%). In 19 (20%) cases there were no comorbidities. The most frequent maintained immunosuppression regimen in monotherapy or in combination was TAC (n = 71; 74.74%), MMF (n = 43; 45.26%), prednisone (n = 21; 22.11 %), EVE (n = 7; 7.37%), and methylprednisolone (n = 7; 7.37%). All demographic data are presented in **Table 1**.

The most prevalent initial symptoms between the adult population were fever (n = 63; 66.32%), cough (n = 38; 40%), shortness of breath (n = 33; 34.74%) and diarrhea (n = 20; 21.05%). The mean time from the initial symptoms to hospital admission was 4.35 (σ = 6.31) days, ranging from 0 to 40 days. In 38 (40%) cases the time between initial symptoms to hospital admission have not been specified.

Figure 2. *Distribution of the adult population by age and sex*



All laboratory findings correspond to the peak of the disease. SpO2 varied between 50 and 100% (mean of 87.36%; σ = 10.30%), hemoglobin from 6.6 to 12.4 g/dL (mean of 9.81 g/dL; σ = 2.12 g/dL), WBC between 0.66 and 45.9 x109cells/L (mean of 7.50 x10^{9}cells/L; σ = 8.22 x10^{9}cells/L), lymphocytes from 0.04 to 2.5 x10^{9}cells/L (mean of 0.68 x10^{9}cells/L; σ = 0.46 x10^{9}cells/L), platelets from 20 000 to 310 000 cells/μL (mean of 101 346 cells/μL; σ = 84 805,64 cells/μL), ALT between 8 and 634 U/L (mean of 87.04 U/L; σ = 120.27 U/L), AST from 16 to 770 U/L (mean of 78.63 U/L; σ = 117.09 U/L), GGT between 24 and 3211 U/L (mean of 580.62 U/L; σ = 846.17 U/L), tBRB from 0.07 to 5.38 mg/dL (mean of 1.71 mg/dL; σ = 1.76 mg/dL), CRP between 0.56 and 106.04 mg/dL (mean of 11.57 mg/dL; σ = 16.61 mg/dL), IL-6 from 5 to 3385,06 pg/mL (mean of 665.91 pg/dL; σ = 1130.69 pg/dL), and ferritin form 18 to 2909 ng/mL (mean of 1153.95 ng/mL; σ = 896.28 ng/mL). Sixteen (16.84%) patients were admitted to the ICU. IS was lowered in 13 (13.68%) cases, withdrawn or stopped in 24 (25.26%) cases, added in five (5.26%) patients, not changed in 40 (42.11%) patients, and in 19 (20%) cases the IS management have not been specified. Also, MMF dose was lowered in four (4.21%) cases and withdrawn in 14 (14.74%) cases.

HCQ was administered in 32 (33.68%) patients, antiviral therapy in 16 (16.84%) cases, antibiotics in 30 (31.58%) cases, immunoglobulin in five (5.26%) patients, and corticosteroids in four (4.21%) cases. Invasive mechanical ventilation was used in 11 (11.58%) patients, facial mask in five (5.26%) patients, nasal cannula in 17 (17.89%) cases, CPAP in three (3.16%) cases, BiPAP in one (1.05%) case, ECMO in one (1.05%) patient, no support ventilation in 31 (32.63%) cases, and ventilation was not specified in 22 (23.16%) patients. Furthermore, 10 out of 11 patients (90.91%) on mechanical ventilation died, two out of five patients (40%) on facial mask also died and the same was observed in one case with CPAP and with ECMO.

During hospital stay, six (6.32%) patients developed ARDS, seven (7.37%) presented pneumonia, two (2.11%) patients refractory shock, three (3.16%) cases of graft dysfunction, four (4.21%) patients developed acute kidney injury (AKI), 21 (22.11%) patients did not develop any complication, and in 33 (34.74%) cases complications have not been specified.

Regarding the outcome, 75 (78.95%) patients were alive, 19 (20%) patients died, and in one (1.05%) case the outcome have not been specified. The distribution of death among the adult population by age and gender is represented in **Figure 3**. The mean time of hospital stay/follow-up was 21.7 days (σ = 16.18 days), ranging from 1 to 75 days. In 38 (40%) cases, the time of hospital stay/follow-up have not been specified. **Table 1** presents a summary of each clinical case.

Table 1. *Summary fo the clinical cases used forthe adult population*

Reference	Country	Population	Baseline IS (cases)	Main laboratory analyses (mean)	IS management (cases)	Outcome
Fernández-Ruiz et al [22]	Spain	3 males 3 females	EVE (3) TAC (2) MMF (2) Prednisone (1) AZA (1)	Lymphocytes 1.05 x10^9/L ALT 85.17 U/L CRP 9.78 mg/dL	Stopped EVE (2) Lower TAC dose (2) Stopped MMF (2) Added MMF (1) Added TAC (2) No change (1)	4 alive 2 dead
Zhong Z et al.[23] Qin J et al.[24]	China	1 male	TAC Methylprednisolone	Lymphocytes 0.48 x10^9/L Platelets 74 000 /µL ALT 424 U/L CRP 10.18 mg/dL	Stopped TAC Lower methylprednisolone dose	Alive
Huang JF et al.[25]	China	1 male	TAC MMF	Lymphocytes <0.1 x10^9/L ALT 60 U/L CRP 3.51 mg/dL	Lower TAC dose Lower MMF dose	Dead
Liu B et al.[26]	China	1 male	TAC	Lymphocytes 0.42 x10^9/L WBC 5.9 x10^9/L CRP 3.21 mg/dL	Stopped TAC Added methylprednisolone dose	Alive
Hammami MB et al.[27]	USA	1 male	TAC	Lymphocytes 0.65 x10^9/L Platelets 49 000 /µL ALT 27 U/L CRP 1.49 mg/dL	No change	Alive
Lee BT et al.[28]	USA	26 males 12 females	NS	Only related to the deaths: Lymphocytes 0.64 x10^9/L ALT 59.57 U/L CRP 13.87 mg/dL	NS	31 alive 7 dead
Hoek RAS et al.[29]	Netherlands	1 male	TAC	NS	No change	Alive
Kates OS et al.[30]	USA	1 male	Cyclosporine	Lymphocytes 0.9 x10^9/L WBC 1.93 x10^9/L ALT 12 U/L	No change	Alive
Gao F et al.[31]	China	3 males	TAC (3) MMF (1) Corticosteroids (1)	Lymphocytes 0.59 x10^9/L	Lower TAC dose (1) Lower corticosteroids dose (1) No change (1) IS withdrawal (1)	2 alive 1 dead
Verma A et al.[32]	UK	5 males	TAC (4) Prednisone (4) MMF (1) AZA (1)	Lymphocytes 0.61 x10^9/L WBC 4.19 x10^9/L	No change (4) Lower MMF dose (1) Higher prednisone dose (1)	5 alive
Fung M et al.[33]	USA	1 female	TAC MMF	Lymphocytes 0.54 x10^9/L WBC 4.9 x10^9/L Platelets 103 000 /µL ALT 14 U/L	No change	Alive
Muller H et al.[34]	Austria	1 male	TAC MMF	Normal WBC CRP 6.1 mg/dL	No change	Alive
Patrono D et al.[35]	Italy	8 males 2 females	TAC (10) MMF (5) Prednisone (3) EVE (2) MPA (1)	Lymphocytes 0.71 x10^9/L WBC 6.68 x10^9/L ALT 104 U/L CRP 6.19 mg/dL	Stopped TAC (3) No change (3) Stopped MMF (1) Lower MMF dose (1) Lower TAC dose (1) Higher prednisone dose (1) IS withdrawal (1)	8 alive 2 dead

Table 1. *Summary fo the clinical cases used forthe adult population (cont.)*

Reference	Country	Population	Baseline IS (cases)	Main laboratory analyses (mean)	IS management (cases)	Outcome
Hann A et al.[36]	UK	2 males 1 female	TAC (3) AZA (3) Prednisone (2)	NS	NS	2 alive 1 dead
Donato MF et al.[37]	Italy	6 males 2 females	TAC (7) MMF (6) Prednisone (2)	NS	NS	8 alive
Mehta SA et al.[38]	USA	2 males 1 female	TAC (3) MMF (2) Prednisone (2)	Lymphocytes 0.60 x10^9/L WBC 3.13 x10^9/L CRP 20.83 mg/dL	No change (2) Stopped TAC (1) Stopped MMF (1)	3 alive
Prieto M et al.[39]	Italy	1 male	MMF Prednisone	Lymphocytes 0.2 x10^9/L WBC 4.9 x10^9/L Platelets 48 000 /µL ALT 634 U/L Ferritin 783 ng/mL	Added TAC	Alive
Jamir I et al.[40]	India	1 male	TAC MMF Methylprednisolone	Lymphocytes 0.11 x10^9/L WBC 6.67 x10^9/L Platelets 31 114 /µL ALT 405 U/L CRP 106.04 mg/dL	Stopped MMF	Alive
Eslami P et al.[41]	Iran	1 male	TAC Methylprednisolone	Lymphocytopenia WBC 15.7 x10^9/L Platelets 20 000 /µL ALT 110 U/L	NS	Dead
García-Juaréz I et al.[42]	Mexico	1 female	TAC	Lymphocytes 0.87 x10^9/L WBC 2.8 x10^9/L Platelets 115 000 /µL ALT 13 U/L CRP 3.9 mg/dL	Lower TAC dose	Alive
Hatami B et al.[43]	Iran	1 female	TAC MMF Prednisone	WBC 10.1 x10^9/L Platelets 310 000 /µL ALT 15 U/L CRP 1.8 mg/dL	Stopped MMF	NS
Bosch F et al.[44]	Germany	1 male 1 female	MMF (2) EVE (1)	NS	Stopped MMF (1) No change (1)	2 alive
Antony SJ et al.[45]	USA	1 male	TAC Prednisone MPA	Lymphocytes 0.2 x10^9/L WBC 12.13 x10^9/L ALT 64 U/L CRP 3.7 mg/dL	IS withdrawal Added methylprednisolone	Alive
Loinaz C et al.[46]	Spain	11 males 2 females	MMF (7) TAC (6) Prednisone (2) EVE (1) MPA (1)	Lymphocytes 0.72 x10^9/L WBC 4.54 x10^9/L ALT 36.38 U/L CRP 9.67 mg/dL	No change (13)	13 alives
Modi AR et al.[47]	USA	1 male	TAC MMF Prednisone	Lymphocytes 1.22 x10^9/L WBC 7.41 x10^9/L ALT 87 U/L CRP 2 mg/dL	Lower TAC dose Stopped MMF	Alive
Felldin M et al.[48]	Sweden	1 male 7 females	TAC (8) MMF (4) Prednisone (3) AZA (1) Methotrexate (1)	NS	No change (4) Stopped MMF (2) Lower MMF dose (1) Stopped methotrexate (1)	

Table 1. *Summary fo the cliical cases used forthe adult population (cont.)*

Reference	Country	Population	Baseline IS (cases)	Main laboratory analyses (mean)	IS management (cases)	Outcome
Kolonko A et al.[49]	Poland	1 male	TAC MMF Prednisone	ALT 55 U/L AST 18 U/L GGT 101 U/L Low CRP	Stopped MMF Lower prednisone dose	Alive
Sessa A et al.[50]	Italy	1 male	TAC	Lymphocytes 0.39 x10^9/L Platelets 122 000 /µL ALT 28 U/L CRP 11.23 mg/dL	No change	Alive
Waisberg DR et al.[51]	Brazil	4 males 1 female	TAC (5) MMF (4)	Lymphocytes 0.87 x10^9/L WBC 16.99 x10^9/L ALT 133.4 U/L CRP 12.02 mg/dL	No change (2) Stopped MMF (2) Lower TAC dose (1) IS withdrawal (1)	3 alive 2 dead
Mathiasen VD et al.[52]	Denmark	1 female	TAC MMF	Lymphocytes 1.11 x10^9/L WBC 5.1 x10^9/L Normal ALT CRP 3.72 mg/dL	No change	Alive
Kutzler HL et al.[53]	USA	2 cases	TC (2)	NS	No change	2 alive
Mocchegiani F et al.[54]	Italy	1 male	TAC	ALT 30 U/L AST 84 U/L	No change	Dead
Goss MB et al.[55]	USA	4 males 6 females	TAC (10) Prednisone (4) SIR (2) MMF (2)	Normal lymphocytes levels Low WBC in 2 cases	No change (9) Lower sirolimus dose (1) Lower TAC dose (1)	10 alive
Imam A et al.[56]	Turkey	3 males	TAC (3) Corticosteroids (3)	NS	NS	3 dead
Heinz N et al.[57]	USA	1 female	TAC MMF Methylprednisolone	Lymphocytes 4.5 x10^9/L WBC 18 x10^9/L ALT 980 U/L CRP 4.63 mg/dL	Stopped MMF Lower methylprednisolone dose Added prednisone	Alive
Lagana et al[59]	USA	1 female	MMF	ALT 1253 U/L AST 908 U/L GGT 473 U/L	IS withdrawal	Alive

**The bold line separates the adult data (above the line) from the pediatric data (below the line).*

ALT: alanine aminotransferase; AST: aspartate aminotransferase; AZA: azathioprine; CRP: C-reactive protein; EVE: Everolimus; GGT: gamma-glutamyltransferase; IS: immunosuppression; MMF: mycophenolate mofetil; MPA: mycophenolic acid; NS: not specified; SIR: sirolimus; TAC: tacrolimus; UK: United Kingdom; USA: United States of America; WBC: white blood cells.

Figure 3. *Distribution of death in the adult population by age and sex.*

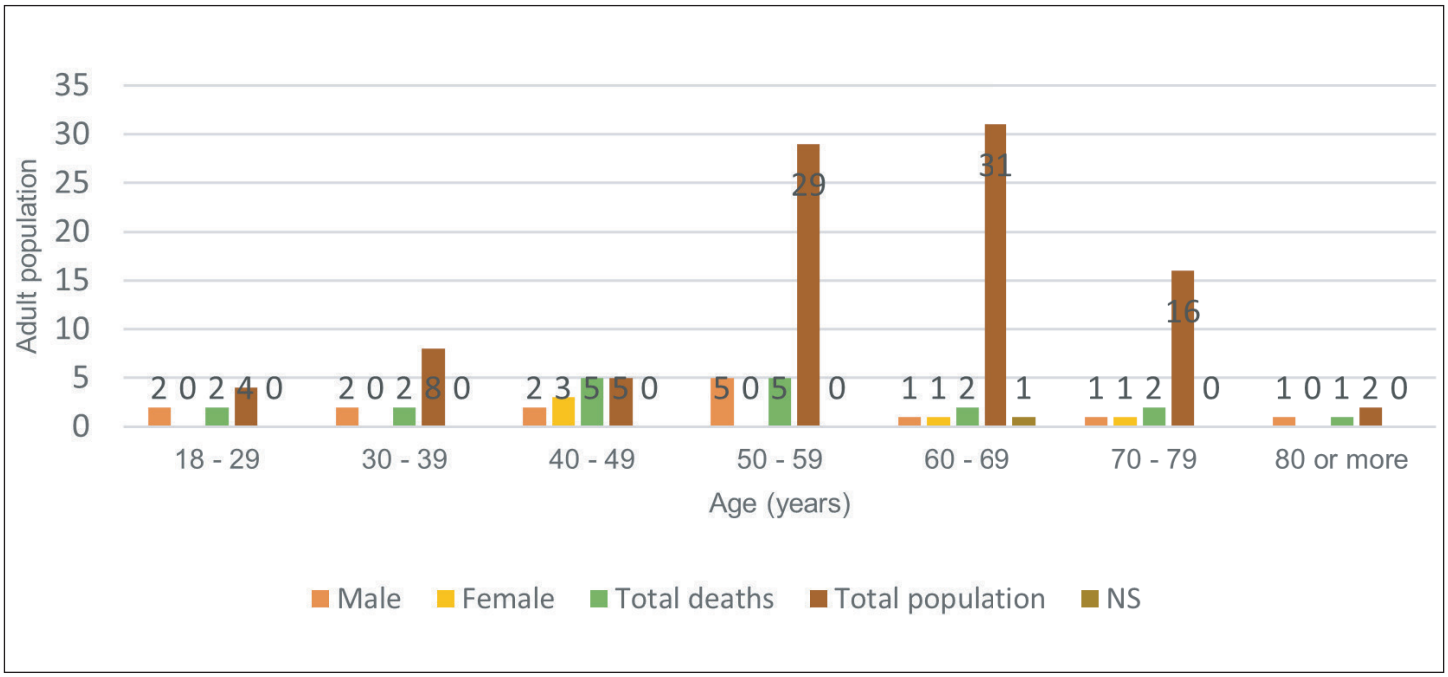


Table 2. *Demographics for the study population*

		Adult Cases (n=95) n (%)	Pediatric Cases (n=16) n (%)
Gender			
	Male	66 (69.47)	7 (43.75)
	Female	27 (28.42)	9 (56.25)
	NS	2 (2.11)	0 (0)
Age			
	Mean (SD)	58.73 (13.57)	1.28 (1.49)
	NS	0 (0)	10 (62.5)
Ethnicity/Race			
	White	4 (4.21)	4 (25)
	Black	1 (1.05)	0 (0)
	Asian	1 (1.05)	0 (0)
	Hispanic	1 (1.05)	7 (43.75)
	African American	2 (2.11)	0 (0)
	Indian	1 (1.05)	0 (0)
	NS	85 (89.47)	5 (31.25)
Time after LT			
	Mean (years)	6.98	3.50
	NS	1 (1.05)	0 (0)

Table 2. *Demographics for the study population (cont.)*

		Adult Cases (n=95) n(%)	Pediatric Cases (n=16) n (%)
Etiology for LT			
	HCC	20 (21.05)	0 (0)
	HCV infection	20 (21.05)	0 (0)
	HBV infection	14 (14.74)	0 (0)
	Alcoholic cirrhosis	10 (10.53)	0 (0)
	PSC	4 (4.21)	0 (0)
	Cryptogenic cirrhosis	3 (3.16)	1 (6.25)
	NASH	3 (3.16)	0 (0)
	ALF	3 (3.16)	0 (0)
	AI hepatitis	2 (2.11)	0 (0)
	Chronic rejection	2 (2.11)	0 (0)
	Budd-Chiari Syndrome	2 (2.11)	0 (0)
	Familial Amyloid Polyneuropathy	1 (1.05)	0 (0)
	Vasculitis	1 (1.05)	0 (0)
	Antiretroviral-induced hepatotoxicity	1 (1.05)	0 (0)
	Biliary atresia	0 (0)	5 (31.25)
	Hepatic adenomatosis	0 (0)	1 (6.25)
	Cholestatic liver disease	0 (0)	1 (6.25)
	NS	32 (33.68)	8 (50)
Comorbities			
	Overweigh/Obesity	34 (35.79)	3 (18.75)
	AHT	32 (33.68)	2 (12.5)
	DM	26 (27.37)	2 (12.5)
	CVD	15 (15.79)	0 (0)
	CKD	14 (14.74)	1 (6.25)
	Lung disease	9 (9.47)	1 (6.25)
	HIV	5 (5.26)	0 (0)
	Others	27 (28.42)	12 (75)
	None	19 (20)	5 (31.25)
	NS	18 (18.95)	1 (6.25)
Baseline IS regimen			
	TAC	71 (74.74)	15 (93.75)
	MMF	43 (45.26)	4 (25)
	Prednisone	21 (22.11)	4 (25)
	EVE	7 (7.37)	0 (0)
	Methylprednisolone	9 (9.47)	1 (6.25)
	AZA	6 (6.32)	0 (0)
	MPA	3 (3.16)	0 (0)
	Cyclosporine	1 (1.05)	0 (0)
	Corticosteroid NS	1 (1.05)	3 (18.75)
	Methotrexate	1 (1.05)	0 (0)
	SIR	0 (0)	2 (12.5)
	NS	7 (7.37)	0 (0)

**The bold line separates the adult data (above the line) from the pediatric data (below the line). ALT: alanine aminotransferase; AST: aspartate aminotransferase; AZA: azathioprine; CRP: C-reactive protein; EVE: Everolimus; GGT: gamma-glutamyltransferase; IS: immunosuppression; MMF: mycophenolate mofetil; MPA: mycophenolic acid; NS: not specified; SIR: sirolimus; TAC: tacrolimus; UK: United Kingdom; USA: United States of America; WBC: white blood cells.*

A significant correlation between age and outcome was identified (r_s=-0.235, p=0.022), meaning that older age is associated with a worse outcome (death). Moreover, age was also associated with graft rejection (r_s=-0.409, p<0.001) and with neurological complications (r_s=0.315, p=0.035), meaning that older age is associated with no graft rejection and with neurological complications.

No statistical association was found between time after LT and the outcome (r_s=0.037, p=0.726). However, time after LT had significant correlations with graft rejection (r_s=-0.362, p=0.016) and presence of other complications during treatment (r_s=-0.360, p=0.016) (except for ARDS, AKI, pneumonia, shock and neurological complications).

Regarding comorbidities, diabetes was associated with a worse outcome (B=-2.033, p=0.043, 95% CI = -54.065; -0.065) and obesity/overweight was associated with a better outcome (B=2.528, p<0.001, 95% CI = 0.000; 89,467). No significant statistical associations were found between all other comorbidities (AHT, CKD, CVD, respiratory disease, gastrointestinal disease and HIV), and between complications during treatment.

MMF as a baseline IS regimen was associated with complications during treatment (60% of the cases with complications were on MMF, and 100% of the cases with no complications were not on MMF) and with shock ($X^2_{[1]}$ = 5.200, p=0.023). An association between AZA and ARDS was found (X2[1] = 5.645, p=0.018). Furthermore, statistical significance was found between cyclosporine and AKI ($X^2_{[1]}$ = 6.979, p<0.001), methylprednisolone and graft rejection ($X^2_{[1]}$ = 10.900, p<0.001), and between an unspecified corticoid and graft rejection ($X^2_{[1]}$ = 8.980, p<0.001). No statistical significance was found between any baseline IS regimen and the outcome. The presence of initial symptoms was associated with complications during treatment when compared to asymptomatic patients ($X^2_{[1]}$ = 9.124, p<0.001). In fact, some symptoms were associated with specific complications, mainly fever with neurological complications ($X^2_{[1]}$ = 9.124, p<0.001) and fatigue to AKI ($X^2_{[1]}$ = 6.723, p=0.01). SOB, cough and headache were also associated with complications in general ($X^2_{[1]}$ = 8.862, p<0.001; $X^2_{[1]}$ = 10.820, p<0.001; and $X^2_{[1]}$ = 4.864, p=0.027; respectively). Regarding the outcome, patients with cough and diarrhea were associated with worse outcome ($X^2_{[1]}$ = 5.309, p=0.021; and $X^2_{[1]}$ = 8.594, p=0.003).

Statistical significance was also found between some of the laboratory results and the outcome. A higher level of WBC was associated with a worse outcome (B=-0.188, p=0.015, 95% CI = 0.713; 0,964) and higher levels of AST were also associated with worse final results (B=-0.016, p=0.01, 95% CI = 0.971; 0,996). Regarding the significance between main laboratory analyzes and complications, lymphopenia was associated with a severe evolution (B=-1.953, p=0.036, 95% CI = 0.023; 0,884) as well as higher levels of CRP (B=0.173, p=0.048, 95% CI = 1.001; 1.412).

None of the drugs used in other pharmacological therapy (HCQ, tocilizumab, lopinavir/ritonavir, remdesivir, umifenovir, oseltamivir, IFN-a, IFN-b, azithromycin, other antibiotics and fresh convalescence plasma) were associated with the outcome. Nonetheless, the use of other pharmacological therapy was associated with complications in general ($X^2_{[1]}$ = 4.648, p=0.031). Azithromycin demonstrated a dependency relationship with pneumonia ($X^2_{[1]}$ = 5.692, p=0.017).

Support ventilation had also shown a statistical dependence on complications during treatment ($X^2_{[1]}$ = 21.860, p<0.01). In fact, 93.5% of patients with support ventilation developed at least one complication during hospital stay, while only 6.5% of the cases with complications were not on support ventilation. Moreover, ventilation and outcome had presented statistical dependence ($X^2_{[1]}$ = 13.935, p<0.001), with 100% of patients with no ventilation alive. Mechanical ventilation was associated with poor outcome ($X^2_{[1]}$ = 16.593, p<0.001) and ECMO with ARDS ($X^2_{[1]}$ = 4.971, p=0.026) and AKI ($X^2_{[1]}$ = 4.971, p=0.026).

Pediatric population

Regarding the pediatric population, seven (43.75%) were male, and nine (56.25%) were female. The mean age of patients was 1.28 years (σ = 1.49 years), ranging from 0.5 to 4.58 years. In 10 (62.5%) cases the age of the patient have not been specified. Regarding the race/ethnicity of the patient, seven (43.75%) were Hispanic, four (25%) white, and five (31.25%) have not been specified. The mean time from liver transplantation to SARS-CoV-2 infection diagnosis was 3.50 years (σ = 4.80), ranging from 0.01 to 18.01 years.

The most frequent cause for liver transplantation was biliary atresia (n = 5; 31.25%), followed by cryptogenic cirrhosis (n = 1; 6.25%), cholestatic liver disease (n = 1; 6.25%), and hepatic adenomatosis (n = 1; 6.25%). In 8 (50%) cases, the cause of liver transplantation has not been specified. Obesity/overweight was the most common comorbidity present in three (18.75%) cases, followed by AHT, diabetes mellitus, asthma and hepatoblastoma in two (12.5%) cases, and CKD, hypothyroidism and Ellis-van Creveld syndrome in one (6.25%) case. In five (31.25%) cases there were no comorbidities, and in one (6.25%) case it was not specified. The most used baseline immunosuppressive regimen in monotherapy or associated with another immunosuppressant was TAC (15 [93.75%] cases) followed by MMF (four [25%] cases), prednisone (four [25%] cases), corticosteroids (three [18.75%] cases), SIR (two [12.5%] cases), and methylprednisolone (one [6.25%] case). **Table 2** presents all pediatric demographic data.

Fever was identified as a primary symptom in eight (50%) cases, cough in six (37.5%) cases, SOB in four (25%) cases, diarrhea in three (18.75%) cases, chest pain in two (12.5%) patients, and sore throat, rhinorrhea, headache, respiratory deterioration and nasal congestion in one (6.25%) patient. The time between the unset of COVID-19 symptoms to hospital admission ranged between 0 and 3 days (mean of 0.5 days; σ = 1.12). In 10 (62.5%) cases, it was not specified.

The only data regarding SpO2 was found in only two (12.5%) cases presenting 96% and 99% of peripheral oxygen saturation (mean of 97.5%; σ = 2.12%). The values of hemoglobin were within the normal range in nine (56.25%) cases, lower in one (6.25%) case, and not specified in six (37.5%) cases. WBC count was normal in seven (43.75%) cases, higher in one (6.25%) patient (value of 18 x10^9cells/L), lower in three (18.75%) cases, and not specified in five (31.25%) cases. Absolute lymphocyte count was normal in 11 (68.75%) cases, and not specified in five (31.25%) cases. The platelet count was normal in 10 (62.5%) patients, although not specified in the other six (37.5%) cases. ALT and AST were specified in only three patients, presenting values of 980, 3 and 1253 U/L (mean of 743.33 U/L; σ = 657,21 U/L), and 908, 4 and 908 U/L (mean of 606.67 U/L; σ = 521,93 U/L), respectively. In the remaining patients, ALT and AST values were not specified. GGT was also specified in the same three patients, with values of 656, 5 and 473 U/L (mean of 378 U/L; σ = 335,74 U/L). In 15 (93.75%) patients, tBRB have not been specified. The only tBRB value presented was 3.6 md/dL. CRP was high in three (18.75%) patients, normal in four (25%) cases and not specified in nine (56.25%) other cases (mean of 2.48 mg/dL; σ = 2.16 mg/dL). IL-6 have not been specified in any of the patients. Finally, ferritin was normal in five (31.25%) cases, while not specified in the remaining 11 (68.75%) cases.

A total of five (31.75%) patients were admitted to the ICU. Regarding the IS management, it was withdrawn in one (6.25%) case, the dose was lowered in three (18.75%) cases, a new immunosuppressant was added in one (6.25%) case, not changed in nine (56.25%) cases and not specified in three (18.75%) cases. Azithromycin was added in four (25%) cases, followed by HCQ (n = 3; 18.75%), other antibiotics (n = 2; 12.5%), and immunoglobulin (n = 1; 6.25%). In six (37.5%) cases no additional pharmacological therapy was prescribed, and in three (18.75%) cases it have not been specified.

ECMO was necessary in three (18.75%) patients, CPAP in two (12.5%) patients, and in 11 (68.75%) cases support ventilation was not necessary. The most frequent complication during admission was ARDS (n = 3; 18.75%), followed by acute liver rejection (n = 2; 12.5%), and hepatitis (n = 1; 6.25%). No complications were found in 11 (68.75%) cases. In one (6.25%) patient the complications during hospital stay have not been specified.

By the end, 13 (81.25%) patients were alive and three (18.75%) had passed away. The mean time for follow-up/hospital stay was 14.83 days (σ = 11.07 days), ranging from 4 to 36 days. In 10 (62.5%) patients, this information have not been specified. **Table 1** presents a summary of each clinical case.

DISCUSSION

In our study, we tried to identify prognosis factors for disease severity and worse outcome. As expected, older age was a poor outcome factor. This may be explained by physiological modifications, typical of elderly people that cause frailty and susceptibility to more diseases. Another finding was that the severity and outcome were not affected by the post-LT time. This hypothesis is due to, as in most cases, patients with a shorter post-LT time are on higher doses of immunosuppressant, this leads to a more severe immunosuppression, and consequently, an increased disease severity. In a study conducted by Malekhosseini et al. in Iran,[60] he reported a total of 85 cases of COVID-19, being 66 from LT (77.65%), 16 from kidney transplantation (18.82%), two from kidney-pancreas transplantation (2.35%) and one from liver-kidney transplantation (1.18%). The average age of their patients was 46.4 years and the main comorbidities were diabetes (25.9%) and AHT (18.8%). Overall, 17 patients died, and 21.9% were LT recipients. Although including some transplants other than liver, their results were very similar to ours (medium age of 58.73 years and overall death of 20%). However, the authors referred to an association between the post-LT time and the outcome: they reported that of five patients who had LT within one month, four died. Another point of view is presented by Belli et al.[61] and by Bhoori et al.[16] in their correspondence, and by Merli et al.[62] in their letter to the editor. All concluded that mortality could be worse in patients with longer LT time. Both these associations were not found in our report (p=0.726), as well as in other similar case series.[9]

It is unanimous that the presence of comorbidities is associated with a poor outcome and/or disease severity. The most frequent comorbidities in our report were AHT and diabetes. This fact is similar in many other case series.[63] In our study, the only comorbidity associated with a worse prognosis was diabetes. In fact, in our report, the probability of a diabetic patient to die after

being infected with SARS-CoV-2 is 7.[63] higher than a non-diabetic patient. Diabetes is a multifactorial disease with long-term metabolic and vascular abnormalities and a higher susceptibility to infectious diseases. Insulin resistance and hyperglycemia result in a promotion of pro-inflammatory cytokines, oxidative stress and stimulating the production of mediators of tissue inflammation.[64] This pro-inflammatory status may be the underlying cause for this relation between diabetes and COVID-19.

An interesting finding was that obesity/overweight was a protective factor for worse outcome. Obese/ Overweight patients with COVID-19 have 12.54 more chance of being alive than patients with normal/ low weight. This may be evidence for the "obesity survival paradox" (a higher severity of disease, but a lower mortality rate in obese patients), which is present in other diseases, such as pneumonia.[65] Although this relation is still very controversial, some pathophysiological mechanisms can partially explain this phenomenon: a higher level of serum cholesterol may bind endotoxin and the excess of energy stored in adipose tissues, and probably others that are still unidentified.[65] A larger study focused on overweight and obese patients with COVID-19 should provide some help in understanding this relationship. CVD was not associated with a poor outcome. This finding was similar to an international European liver transplant recipient cohort by Becchetti et al.[12] who included 57 LT recipients infected with SARS-CoV-2.

Another interesting finding was that MMF was associated with more complications and with shock. MMF is an antimetabolite drug that disrupts the making of RNA and DNA, thus preventing the replication of B and T lymphocytes.[18] When infected by SARS-CoV-2, the levels of these lymphocytes in the patient, plus NK cells, face a significant decrease in the total number, and consequently, a dysregulation of immune response, thus being more prone to other infections and septic shock. In fact, this evidence is considered by some liver societies. British Transplant Society advocates that any LT recipient with a positive COVID-19 test should stop MMF.[66] The same position is taken by the Spanish Society of Liver Transplantation, adding that if MMF regimen is in monotherapy, a conversion to CNIs, mTOR inhibitors or steroids should be considered,[67] and by the American Association for the Study of Liver Diseases, which advises that all LT recipients should suspend or reduce the dose of MMF.[68]

It is evidenced in the literature that CNIs, especially cyclosporine, can cause AKI by strongly constricting the afferent renal arteriole, concomitantly, activating the renin-angiotensin-aldosterone system leading to an impaired renal function.[69] This may be the reason that in our work we found a positive association between cyclosporine and AKI. In this case, it is recommended to decrease the cyclosporine dose or to replace it by steroids, to avoid graft rejection. A study led by Lee et al. from Recanati/Miller Transplantation Institute [28] with 38 LT recipients infected with SARS-CoV-2 reached the same association between CNIs and AKI.

Another conclusion that can be drawn is regarding the laboratory data. In our report, we found out that higher levels of WBCs and AST can be associated independently to a worse outcome. In a multicenter observational cohort study of 112 LT recipients with COVID-19, Rabiee and Sadowski et al.[63] revealed that liver injury is an independent factor for increased mortality. They showed that patients with a peak of liver enzymes during SARS-CoV-2 infection had a worse outcome. Although their focus was on ALT, as it is more specific to the liver than AST, they conclude that all liver enzymes should be closely monitored during hospital stay as they can predict a poor ending.

A pro-inflammatory state can also be associated with increased mortality and with a more severe course of the disease. This is supported by a positive association by increasing WBCs levels and mortality, and by higher levels of CRP and a higher complication rate. Moreover, lymphopenia was also associated to an increased disease severity. The infection by SARS-CoV-2 is known to create lymphopenia, and in a severe form of the disease, it is characterized by an excessive pro-inflammatory production mainly by IL-2, IL-7, IL-6 and TNF-a.18 This phenomenon associated with an incompetent immune system, is responsible by the severity and mortality of this disease. Similar to our study, lymphopenia was present in many other series.[28,60]

None of the specific pharmacological therapies were associated with the outcome in our study. Most of patients in our series had done HCQ or lopinavir/ritonavir during hospital stay, as a targeted therapy for COVID-19. Although guidelines now prove the ineffectiveness of these drugs, most of our cases were from the initial days of the pandemic, and these two drugs were the first approved for SARS-CoV-2 infection. In fact, because of the interactions with the most used immunosuppressant, there is an increased risk for graft failure if the IS is not strictly regulated. Regarding the association between azithromycin and pneumonia, we interpret it as being used as a therapeutic, as this antibiotic is used in most cases, as a first-line therapy.

In our study, 16.84% of the adult population was admitted to the ICU. In the study referred before, Malekhosseini et al.[60] reported a slightly higher ICU admission with 33.9%

of cases. The authors also described 20% mortality, being the same in our study. In another series, Belli et al.[61] presented an ICU admission rate of 15% in his 103 LT recipients. He also reported that 66% of patients required support ventilation (vs 44.21% in our work) and, of those, 15% needed invasive ventilation (vs 12.63%). His overall mortally rate for LT recipients was 16% (vs 20%). Finally, in a series by Coll et al.,[70] he reported a death rate of 22% between his 76 LT recipients. According to the WHO, the mortality rate of COVID-19 in the general population is 2.22%.[2] When comparing the overall mortality with the one from our study (2.22% vs 20%, respectively) we can conclude that LT recipients have a death rate almost 10 times higher. This may be evidence that LT recipients with COVID-19 are at higher risk of dying.

We also included some pediatric patients in our study. However, because of the low number of cases and the missing data, no statistical conclusions were made. D'Antiga et al.[17] presented a study with 700 children on which only three were infected with SARS-CoV-2, and none died, concluded that the pediatric population was not at higher risk for the disease severity and mortality. Another series from Italy led by Doná [71] presented an European survey on transplantation centers that reported three LT recipients with COVID-19. All patients had mild symptoms and none died. In our study, the mortality rate was 18.75%. This overall mortality in the pediatric population must be taken carefully, as only 16 single cases were analyzed, and mortally was only present in one article. In this work, Imam et al.[56] presented three liver pediatric recipients with COVID-19. The first case was a 10-month-old male that, on the eighth post-operatory day developed fever and SOB that causes the need for ECMO, and the patient eventually died. The second case was also a 10-month male that also developed fever and needed ECMO. In this case, a high level of liver enzymes and neutropenia was found. The final case was a 5-month male that needed ECMO for worsen respiratory function on day three, and died on that same day.

COVID-19 is also known to cause myocardial lesions like atrial fibrillation, systolic/diastolic abnormalities and ischemic or non-ischemic cardiomyopathy, resulting from direct viral invasion, thromboembolism, STEMI and/or pro-inflammatory state. In fact, measuring the levels of troponins and BNP/Pro-BNP could help to identify these patients.[72] Myocardial lesion was absent in all of the cases analyzed for this research.

Another known fact of SARS-CoV-2 infection is that it may lead to long-term sequelae. The main long-term symptoms can be respiratory (cough, SOB), cardiovascular (palpitations, chest pain, thrombotic events), neurological (cognitive impairment, headache, peripheral neuropathic symptoms, delirium), general (fatigue, fever, pain), and others.[73] During our research period, no study on long-term complications in LT recipients was found. In our study, the follow-up ranges between 1 day and 75 days (mean of 21.7 days). Therefore, when accessing the main long-term complications by a close follow-up of the surviving patients, it could be a very interesting and important investigation.

Our study had some limitations. The main limitation was regarding the missing data. This may have contributed to an absence of association between some of the variables, for example, only 9 of 95 adult cases have platelet count and 48 of 95 have CRP serum value. In order to reduce the missing data, it is important to publish the complete clinical information, IS management, laboratory finds, as well as specific COVID-19 therapy, if available. A possible bias is related to a sample with only symptomatic patients tested, or at risk contact with an infected patient during hospital stay. This fact may justify the overall increased mortality in LT recipients because, when comparing to the overall population, no mass screenings were conducted in this specific population, resulting in an under diagnosis of asymptomatic LT recipients.

CONCLUSION

Older age and diabetes were independently associated with the worse outcome, as well as a higher level of WBC and the need for support ventilation. On the another hand, higher levels of CRP and lower levels of lymphocytes were associated with a more severe course of the disease. Obesity or overweight, interestingly, was associated with a lower death rate, proving the evidence of an "obesity survival paradox". An important association between MMF as a baseline IS regimen and shock during hospital stay was found. No association between post-LT time to COVID-19, specific antiviral therapy and outcome were found. Overall, liver transplantation recipients may be at higher risk of dying with the infection of SARS-CoV-2.

RESUMO

Introdução: Devido à pandemia COVID-19 e ao facto dos recetores de transplante hepático serem uma população imunodeprimida, iniciou-se discussão sobre o risco acrescido nesta população: existe controvérsia na identificação de fatores de pior prognóstico, mas também no manuseamento da imunossupressão de manutenção e terapia específica para a COVID-19. **Objetivo:** O presente trabalho pretende analisar publicações (casos e séries) sobre fatores demográficos de risco, imunossupressão de base e manuseamento, terapia específica para COVID-19 e resultados em transplantados hepáticos. **Material e Métodos**: Foi realizada pesquisa nas bases de dados MEDLINE e PubMed. Foram identificados 127 artigos e 55 incluídos na análise quantitativa final. Utilizaram-se os testes chi-quadrado, correlação de spearman e regressão logística para análise estatística. As análises descritivas são apresentadas com número e percentagem, juntamente com média e intervalo de alcance. **Resultado**: Foram analisados 111 casos clínicos (95 adultos e 16 pediátricos). No que diz respeito a adultos, 69.47% eram homens, e a média da idade foi de 58.73 anos. As co-morbilidades mais comuns foram: obesidade/excesso de peso (35.79%), hipertensão arterial (33.68%) e diabetes (27.37%). Os imunossupressores mais utilizados foram o tacrolimus (TAC) (74.74%) e micofenolato mofetil (MMF) (45.26%). Quarenta e um doentes (43.16%) apresentaram complicações durante o tratamento e 12 (12.63%) necessitaram de ventilação invasiva. A taxa de mortalidade referente à população adulta foi de 20%. Quanto à população pediátrica, 43.75% eram rapazes e a idade média foi de 1.28 anos. O imunossupressor mais utilizado foi o TAC (93.75%). Apenas quatro doentes (25%) apresentaram complicações e três (18.75%) precisaram de ventilação invasiva. A mortalidade da população pediátrica foi de 18.75%. **Conclusão**. Idade avançada, diabetes, neutrofilia e o uso de ventilação foram associados a pior prognóstico. Elevados níveis de proteína C reativa e linfopenia foram associados a severidade da doença. O uso de MMF foi associado a choque sético durante o internamento. A mortalidade nos transplantados hepáticos infetados com COVID-19 foi superior à da população em geral.

Descritores: Transplantação Hepática; COVID-19; Complicações pós-operatórias.

LIST OF ABBREVIATIONS

AHT – arterial hypertension; **AI** – autoimmune; **AKI** – acute kidney injury; **ALF** – acute liver failure; **ALT** – alanine aminotransferase; **ARDS** – acute respiratory distress syndrome; **AST** – aspartate aminotransferase; **AZA** – azathioprine; **BiPAP** – bilevel positive airway pressure; **BNP** – brain natriuretic peptide; **CKD** – chronic kidney disease; **CNI** – calcineurin inhibitor; **COPD** – chronic obstructive pulmonary disease; **COVID-19** – coronavirus infectious disease 2019; **CPAP** – continuous positive airway pressure; **CRP** – C-reactive protein; **CVD** – cardiovascular disease; **DM** – diabetes mellitus; **EBV** – Epstein-Barr virus; **CMO** – extracorporeal membrane oxygenation; **EVE** – everolimus; **GGT** – gamma-glutamyltransferase; **HBV** – hepatitis B virus; **HCC** – hepatocellular carcinoma; **HCQ** – hydroxychloroquine; **HCV** – hepatitis C virus; **HIV** – human immunodeficiency virus; **ICU** – intensive care unit; **INF-a** – interferon alpha; **IFN-b** – interferon beta; **IL** – interleukin; **IS** – immunosuppression; **LMWH** – low molecular weight heparin; **LT** – liver transplantation; **MeSH** – medical subject headings; **MMF** – mycophenolate mofetil; **MPA** – mycophenolic acid; **mTOR** – mammalian target of rapamycin; **NASH** – nonalcoholic steatohepatitis; **NS** – not specified; **PCR** – polymerase chain reaction; **PICO** – population, intervention, control/comparison, outcome; **PHEIC** – public health emergency of international concern; **PRISMA** – preferred reporting items for systematic reviews and meta-analyses; **PSC** – primary sclerosing cholangiopathy; **ReTx** – re-transplantation; **rhG-CSF** – recombinant human granulocyte colony-stimulating factor; **SARS-CoV-2** – severe acute respiratory syndrome coronavirus 2; **SIR** – sirolimus; **SOB** – shortness of breath; **SOFA** – Sequential Organ Failure Assessment; **SpO2** – peripheral oxygen saturation; **STEMI** – ST elevated myocardial infarction; **TAC** – tacrolimus; **tBRB** – total bilirubin; **UK** – United Kingdom; **USA** – United States of America; **WBC** – white blood cells; **WHO** – World Health Organization;

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