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SARS-CoV-2 infection in adult liver transplantation recipients: a systematic review of risk factors for mortality and immunosuppression role

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Abstract. – OBJECTIVE: Data on mortality, immunosuppression, and vaccination role regarding liver transplant (LT) recipients affected by COVID-19 are still under debate. This study aims to identify risk factors for mortality and the role of immunosuppression in COVID-19 LT recipients.

MATERIALS AND METHODS: A systematic review of SARS-CoV-2 infection in LT recipients was performed. The primary outcomes were risk factors for mortality, the role of immunosuppression and vaccination. A meta-analysis was not performed as there was a different metric of the same outcome (mortality) and a lack of a control group in most studies.

RESULTS: Overall, 1,343 LT recipients of 1,810 SOT were included, and data on mortality were available for 1,110 liver transplant recipients with SARS-CoV-2 infection. Mortality ranged between 0-37%. Risk factors of mortality were age >60 years, Mofetil (MMF) use, extra-hepatic solid tumour, Charlson Comorbidity Index, male sex, dyspnoea at diagnosis, higher baseline serum creatinine, congestive heart failure, chronic lung disease, chronic kidney disease, diabetes, BMI >30. Only 51% of 233 LT patients presented a positive response after vaccination, and older age (>65y) and MMF use were associated with lower antibodies. Tacrolimus (TAC) was identified as a protective factor for mortality.

CONCLUSIONS: Liver transplant patients present additional risk factors of mortality related to immunosuppression. Immunosuppression role in the progression to severe infection and mortality may correlate with different drugs. Moreover, fully vaccinated patients have a lower risk of developing severe COVID-19. The present research suggests safely using TAC and reducing MMF use during the COVID-19 pandemic.

Key Words:
Liver transplantation, COVID-19, Tacrolimus, Mycophenolate, mTOR, Everolimus.

Abbreviations

LT: Liver Transplant; SOT: Solid Organ Transplantation; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; COVID-19: Coronavirus disease 2019; ARDS: Acute Respiratory Distress Syndrome; MOF: Multiorgan Failure; ACE 2: Angiotensin-Converting Enzyme 2; MERS: Middle-East Respiratory Syndrome; IS: Immunosuppression; ICU: Intensive Care Unite; BMI: Body Mass Index; MMF: Mycophenolate; mTOR Inhibitors: Mammalian Targets of Rapamycin Inhibitors; CC; Index: Charlson Comorbidity Index; CNI: Calcineurin Inhibitor; RCT: Randomized Controlled Trial; MELD: Model for End-Stage Liver Disease; PBMCs: Peripheral blood mononuclear cells; SFUs: Spot-forming units.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a virus belonging to the Orthocoronavirinae subfamily, first identified in Wuhan, Hubei province, China, December 2019[1]. The SARS-CoV-2 infection, now termed Coronavirus Disease 2019 (COVID-19), is responsible for a clinical condition that ranges from mild-moderate respiratory symptoms to interstitial pneumonia with acute respiratory distress syndrome (ARDS), multiorgan failure (MOF) and high mortality. The virus targets airway epithelium using angiotensin-converting enzyme 2 (ACE 2) as a

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receptor, leading to the "novel coronavirus" related pneumonia[2]. The outbreak of SARS-CoV-2 infection has rapidly become a public health matter due to the high contagiousness and mortality rate. Since it was declared the outbreak of the SARS-CoV-2 pandemic on 11th March 2020 by the World Health Organization, the virus has caused several million deaths and more than forty million infection cases worldwide[3].

To date, robust knowledge about the disease outcomes is lacking, particularly in specific cohorts of patients. Data regarding populations with unique risks, such as solid organ transplant (SOT) recipients, are still under evaluation[4,5]. In the present setting, previous experience with similar coronaviruses, such as SARS-CoV in 2003 and MERS-CoV in 2015, suggests that SOT recipients would be prone to increased morbidity and mortality due to chronic immunosuppression (IS) and comorbidity[6].

Mortality rates following liver transplantation (LT) are well described. The overall 1-, 2-, 3- and 5-year survival rates after adult liver transplant are 89%, 85%, 82% and 76%, respectively[7]. Risk factors for mortality in adult LTs include most of the factors associated with high mortality in the general population during the COVID-19 pandemic[8]. Therefore, adult LT recipients are a population with multiple potential risk factors for more unsatisfactory outcomes during the pandemic[9] with additional concerns about the severe impact of COVID-19 concerning chronic immunosuppressive treatment[10,11]. Therefore, generalizable data from international cohorts of LT recipients are required to clarify the effects of such factors, assess the mortality rate, and guide the community in disseminating guidelines and protocols for managing this vulnerable group of patients[12,13]. The present study aimed to identify risk factors for mortality and the role of IS in LT recipients affected by COVID-19.

Materials and Methods

According to the PRISMA guidelines, a literature search was conducted (Preferred Reporting Items for Systematic reviews and Meta-Analyses). No ethical approval or informed consent was required. Statistical analysis was not performed as the manuscript is a systematic review.

Search Strategy

A computerised search of PubMed, Web of Science, Scopus and Cochrane Library was carried out, and articles published from the time of inception to 15th February 2022 were included. Reference lists of all obtained and relevant articles were screened manually and cross-referenced to identify any additional studies. The following terms were applied: (COVID-19) AND (liver transplantation).

Study Selection

Titles and abstracts of the records were independently screened by two reviewers (AV and FG). Studies were selected for the systematic review according to predefined criteria. Inclusion criteria were: (1) only original articles; (2) samples including LT recipients with a confirmed diagnosis of COVID-19; (3) only articles in the English language; (4) available data about mortality in LT recipients or data for LT extrapolation from the SOT cohort; (5) available data about risk factors for mortality; (6) available data about immunosuppressant use; (7) available data about vaccination status. Exclusion criteria were: (1) reviews, editorials, comments, study protocols, letter to the editor, consensus, communications, and guidelines; (2) case series (less than 10 patients included) and case reports; (3) articles outside the field of interest of this review (e.g., about donors, pathologies LT-related, liver surgery, atypical symptoms COVID-19 related, about COVID-19 related liver injury, surveys and questionnaires administered to transplant centres); (4) articles not available in English. Duplicates were removed (Figure 1).

The potential for overlap of patients between studies from the same hospital was evaluated. In this case, data was registered from one study only, and priority was given according to criteria in the following order: largest sample, statistically significant data, and most recent publication. Potential difficulties in selecting these studies were sorted through a consensus meeting between the reviewers.

Data Extraction

Two independent reviewers (AV, FG) initially retrieved the information about study characteristics (authors, year of publication, journal, country, study design, the time interval of the study), basic patient characteristics (age, gender, time since transplantation, comorbidities, underlying liver disease, IS at admission, non-liver cancer history, smoker and BMI), and clinical outcomes (mortality rate in LT cohort and the general population, number of deaths, risk factors for mortality and severe COVID-19, IS at baseline and follow-up, change of IS, antiviral therapy, ICU admission,

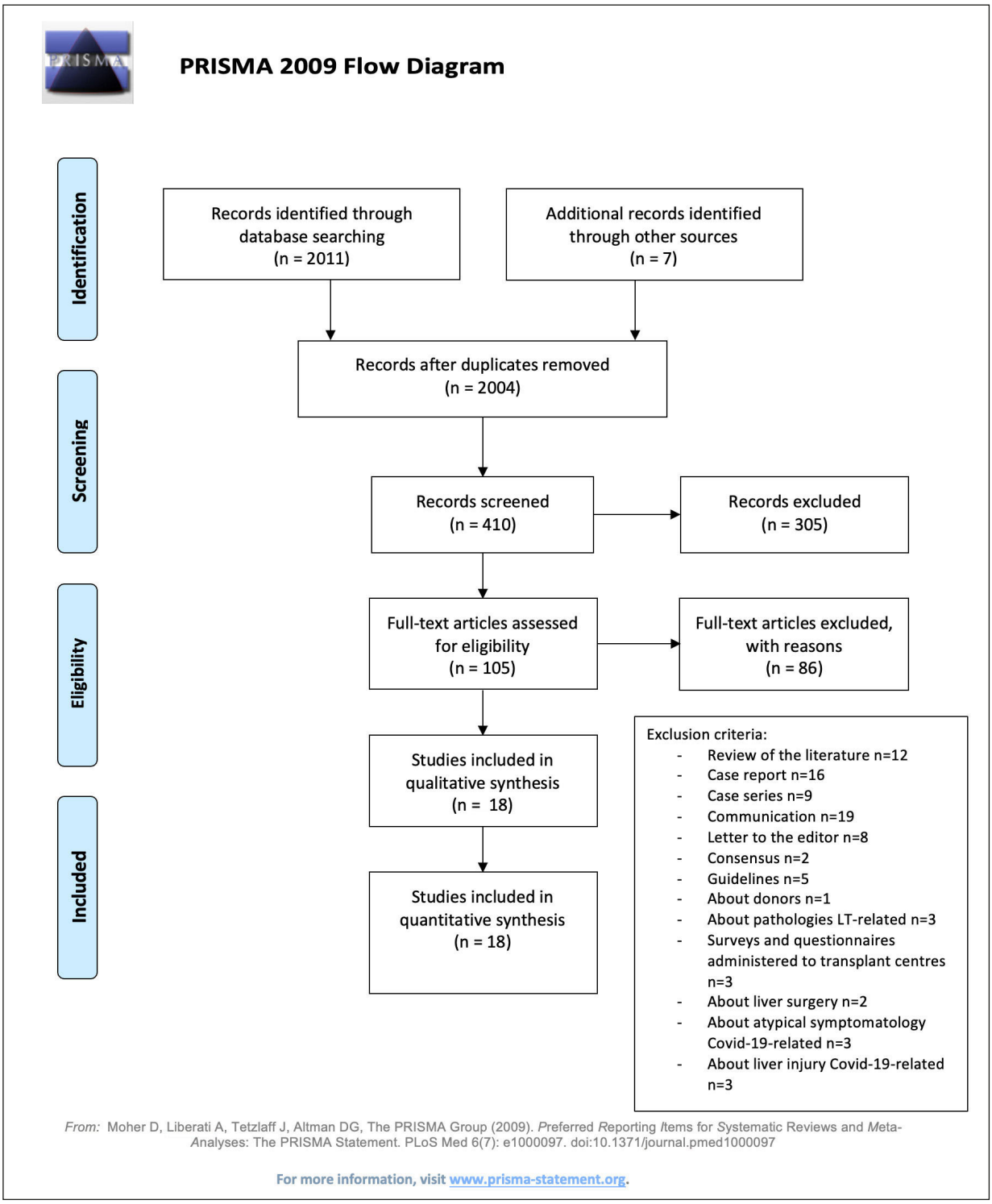

Figure 1. Prisma flow chart of the article included.

need for respiratory support, hospitalisation, moderate/severe COVID-19, protective factors, the effect of MMF, the effect of tacrolimus (TAC), vaccination efficacy).

Firstly, to limit selection bias, the reviewers independently recorded the data, and secondly, controversial manuscripts were discussed with the senior author (FG).

Outcomes

The primary outcome was to assess risk factors of mortality and the roles of IS and vaccination for SARS-CoV-2 infection after LT. A meta-analysis was not performed as there was a different metric of the same outcome (mortality) and a lack of a control group in most studies. PICO assessment is reported in **Supplementary Table I**. A *p*-value less than 0.05 was considered statistically significant for the interpretation of the included study.

Results

The number of studies screened, assessed, and excluded are shown in the PRISMA flow diagram (Figure 1). Eighty-eight full-text articles were assessed for eligibility, and 18 studies were included in the qualitative analysis[6,16-32]. An overall of 3,299 LT recipients was included in the studies[6,16-32], and data on mortality were available for 408 liver transplant recipients with COVID-19 infection (Table I).

Mortality After COVID-19

LT did not significantly increase the risk of death in patients with SARS-CoV-2 infection in a study[25] comparing mortality rate in LT and the general population (absolute risk difference 1.4% [95% CI –7.7 to 10.4])[25]. The mortality rate in the LT cohort ranged between 0 and 37%[14-27].

The COVID-19 infection rate in LT recipients by nosocomial transmission was reported by three studies[19,21,23] and ranged between 3% and 15.1%. The readmission rate to the hospital for COVID-19 infections in the same studies[19,21,23] was between 17% and 82.8%[19,21,23].

Moderate/Severe COVID-19

Three studies[16,23,24] reported data about LT recipients developing moderate/severe disease COVID-19 related[16,23,24]. An overall of 86 patients (9.91%) developed severe COVID-19.

Needs for ICU admission and respiratory support

Fourteen studies[6,16,19-32] reported the results of ICU admission with an admission rate between 5 and 50%[6,16, 19-32], and the need for invasive respiratory support was reported in eight studies (range: 0 to 35%)[6,16,17,21,23, 25].

Immunosuppression

Twelve studies[16-19,20-23,25,32] described the IS protocol[16-19,20-23,25,32]. CNIs were administered to 744 patients (67.1%), MMF to 536 (48%), mTOR inhibitor (not specified the drug) 129 (11.6%), Azathioprine 17 (1.5%), Cyclosporine 53 (4.7%), and steroids 317 (28.5%). A study[16] reported in a multivariate analysis MMF as a risk factor for severe COVID-19 and death in liver recipients (RR 3.94 [CI: 1.59-9.74], p=0.003) (Table II)[16], while two studies[15,32] reported CNIs as a protective factor for severe COVID-19 and death in LT recipients (RR 0.52 [CI: 0.29-0.95], p=0.0325)[15] (RR 0.55 [CI: 0.31-0.99], p=0.0472)[32].

Risk Factors for Severe COVID-19 and Death (Figure 2)

Nine studies[6,16,18-20,22,24,25] reported data about risk factors for severe COVID-19 and death analysed by multivariate analysis[6,16,18-20,22,24,25]. The significant variables were Charlson Comorbidity Index (CCI) and age-adjusted CCI, male gender, dyspnoea at diagnosis, MMF therapeutic regimen, older age, extra-hepatic cancer, higher baseline serum creatinine, congestive heart failure, chronic kidney disease, chronic lung disease, obesity (BMI>30), diabetes and increasing number of comorbidities. Two studies[6,32] identified TAC use as a protective factor for mortality[6,32].

Vaccination (Table III)

Four studies[27-30] assessed the percentage of positive response (>25SFUs/106 PBMCs for the S protein, >14SFUs/106 PBMCs for the N protein, and >21SFUs/106 PBMCs for the SARS-CoV-2 M protein) after vaccination among LT patients. 51% of 233 LT patients included presented a positive response after vaccination. Two studies[27,30] reported older age (>65y) as a risk factor for a negative or neutral response to the vaccination. In contrast, four studies[27-30] reported the IS regimen as a risk factor, suggesting that CNIs as monotherapy could be a protective factor for a positive response[30] and MMF could be a risk factor for developing antibodies after vaccination[27,29,30].

A study[31] compares SARS-CoV-2 infection outcomes (hospitalisation, ICU, death) among non-vaccinated, vaccinated with 1/2 doses and fully vaccinated LT recipients. The non-vaccinated group (n = 77) showed 33 (43%) cases of hospitalisation, 7 (9%) of ICU admission and 6 (8%) deaths. The vaccinated with ≥ 1 dose group (n:19) showed 6 (32%) cases of hospitalisation, 3 (16%) of ICU admission and 2 (11%) deaths. Finally, the fully vaccinated group (n:5) showed 2 (40%) hospitalisation cases, 0 ICU admission and 0 deaths[31].

Table I. General features of included studies. *data are expressed as years. °data are extracted from a national transplant registry.

Author	Year	Journal	N. of patients COVID-19 LT	Control group	Male (n) LT	Control group	Age (SD/IQR)	Control Group	Mortality (n)	Control Group	ICU	Control Group
Colmenero et al[16°]	2020	Journal of Hepatology	111	–	79	–	65.34 (±10.96)	–	20		20	–
Pereira et al[23]	2020	Am J Transplant	14	–	9	–	57 (46-68)	–	3	–	5	–
Webb et al[25]	2020	The Lancet	151	627	102	329	60 (47-66)	73 (55–84)	28	167	43	52
Loinaz et al[21]	2020	Transpl Infect Dis	19	–	14	–	58 (55-72)	–	4	–	1	–
Becchetti et al[6]	2020	Gut	57	–	40	–	65 (57-70)	–	7	–	4	–
Kates et al[19]	2020	Clin Infect Dis	73	–	45	–	57.5 (46-67)	–	15	–	24	–
Miarons[$] et al[22]	2020	Transplantation	3	166	33	122	62.7 (±12.6)	66.0 (±12.7)	2	38	1	25
Trapani et al[24]	2020	Am J Transplant	89	239	68	109	61 (53-67)	61 (47–80)	14	34	15	8
Donato et al[17]	2020	Clin Gastrohenterol Hepatol	8	–	6	–	63 (±9.44)	–	0	–	2	–
Yi et al[26]	2020	Transplantation	4	–	2	–	54.8 ± 10.9	–	0	–	1	–
Dumortier et al[18]	2020	Clin Res Hepatol Gastroenterol	91	–	64	–	64 (54.9-71.3)	–	18	–	17	–
Linares et al[20]	2020	PLoS One	4	–	3	–	58 (33-86)	–	1	–	1	–
Belli et al[32]	2021	Gastroenterology	243	–	171	–	63 (55.0-69.0)	–	49	–	37	–
Rahav et al[27]	2021	EClinicalMedicine	36	966	19	635	68	63	–	–	–	–
Fernández-Ruiz et al[28]	2021	Transplant Direct	14	28	8,6	–	52,4(+-11)	–	–	–	–	–
Moon et al[31]	2021	Hepatol Commun	19	77	11	42.35	60	53	2	6	3	7
Rashidi-Alavijeh et al[29]	2021	Vaccines (Basel)	43	20	26	9	47(36–54)	43.5	–	–	–	–
Ruether et al[30]	2022	Clin Gastroenterol Hepatol	141	56	82	23	55	50,9	–	–	–	–

$> 1y in 88% of patients.

Table II. Immunosuppression treatments in Liver Transplanted Patients affecetd by COVID-19.

Author	Year	CNI (%)	MMF (%)	Azathiopirine (%)	Steroids (%)	mTOR (%)	Cyclosphorine (%)
Colmenero et al°	2020	66 (86)	57 (51.3)	-	24 (21.6)	-	6 (5.4)
Pereira et al[23]	2020	77 (85.5)	65 (72)	-	53 (59)	6 (7)	-
Webb et al[25]	2020	135 (89.4)	77 (50.9)	13 (8.6)	67 (44.3)	-	8 (5.3)
Loinaz et al[21]	2020	8 (42.1)	10 (52.6)	1 (5.3)	3 (15.8)	-	-
Becchetti et al[6]	2020	13 (22.8)	2 (3.5)	-	1 (1.7)	2 (3.5)	3 (5.2)
Kates et al[19]	2020	-	-	-	-	32 (6.6)	-
Miarons et al[22]	2020	41 (89.1)	28 (60.9)	-	39 (84.8)	-	1 (2.2)
Belli et al[32]	2020	162 (66.6)	119 (49)	-	56 (23)	37 (15.2)	29 (11.9)
Donato et al[17]	2020	7 (87.5)	6 (75)	-	2 (25)	-	-
Dumortier et al[8]	2020	70 (77.8)	53 (58.2)	3 (3.3)	16 (17.6)	14 (15.4)	6 (6.7)
Linares et al[20]	2020	3 (63)	-	-	-	1 (37)	-

°MMF as a risk factor for severe COVID-19 and death in liver recipients (RR 3.94 [CI: 1.59-9.74], p=0.003). °88% of the patients had a decreased dose of MMF.

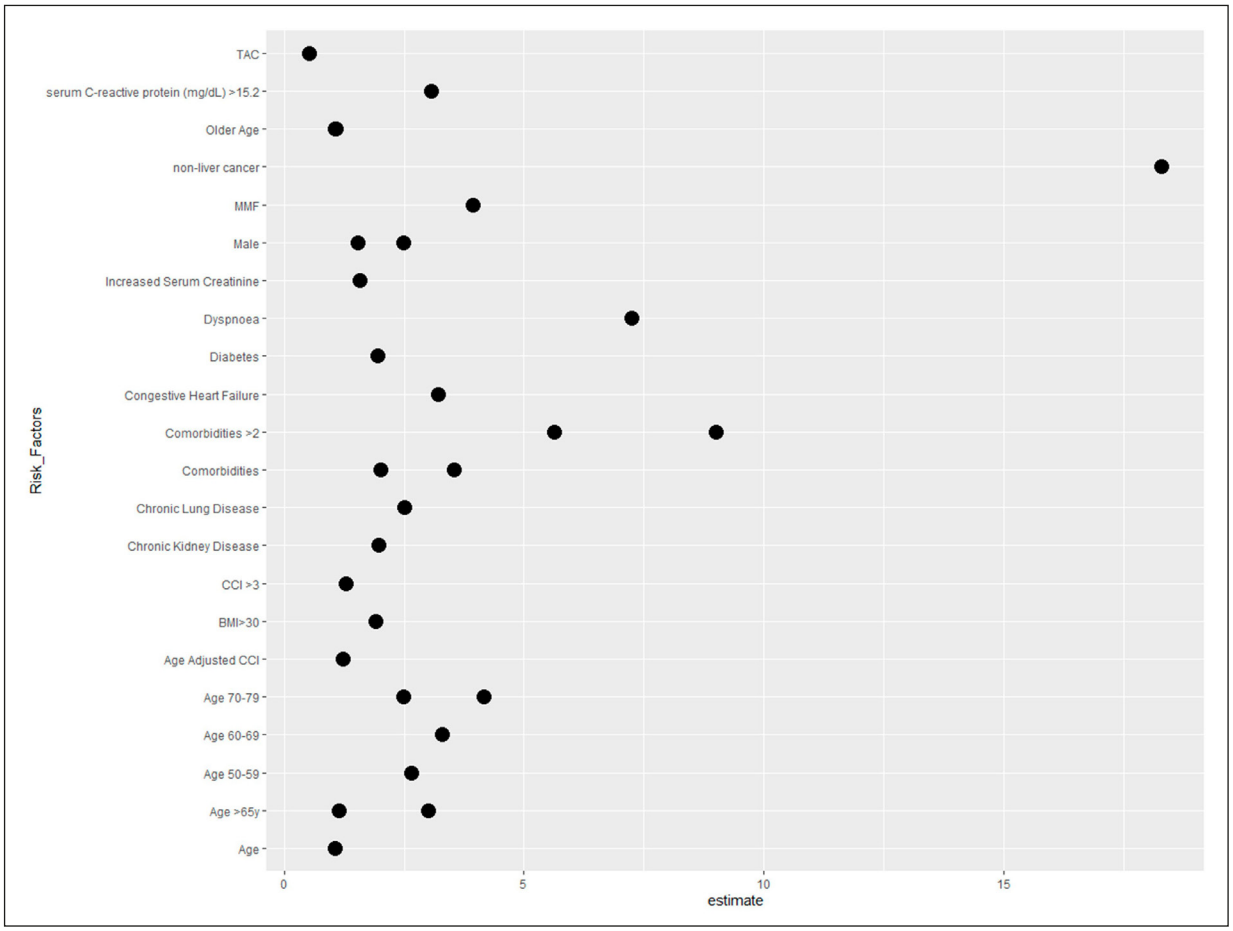

Figure 2. Effect sizes for risk of mortality.

Table III. Study reporting results of vaccination in LT patients.

Author	Year	Journal	LT recipients vaccinated	Positive response after 2nd Vaccination (%)	Mortality after COVID-19 (%)	Control Group (unvacci -nated)	Control group Mortality after COVID-19 (%)
Rahav et al[27]	2021	EClinicalMedicine	36	25 (69.4)	–		–
Fernández-Ruiz et al[28]	2021	Transplant Direct	14	7 (53)	–	–	–
Moon et al[31]	2021	Hepatol Commun	19	–	2 (11)	77	6 (8)
Rashidi-Alavijeh et al[29]	2021	Vaccines (Basel)	43	34 (79)	–	–	–
Ruether et al[30]	2022	Clin Gastroenterol Hepatol	138	88	–	–	–

Discussion

The present study has shown a variable mortality rate for the LT populations with COVID-19 infection[14-32]. However, the mortality rate seems related to age, gender, comorbidities and antimetabolite IS, suggesting that LT patients would be prone to increased mortality because of those risk factors[32,34-37]. Therefore, high mortality percentages in the LT recipient cohort may be explained by the over-representation of those risk factors in the LT population, notoriously presenting increased comorbidities and advanced age. The present study analyses a sample of LT patients of the prevalent male gender (up to 60% in all articles included), advanced age and with a high number of comorbidities, factors considered associated with mortality were also found associated in the general population[6,16-32].

Several studies[16,19,22,32] identify "increased comorbidities" as a risk factor for mortality, showing a cumulative effect of baseline comorbidities on mortality[16,19,22,32]. In particular, two studies[19,32] assessed the association of comorbidities numbers with mortality with increased mortality risk in the multivariable analysis for the number of comorbidities[19,32]. Male gender was an independent risk factor in LT recipients and the general population[16,24,38,39]. Notably, there was a disproportion across some studies[14,19,22,25,32] that showed a higher number of men in the LT cohort (59-75.6%) with an association of mortality and male sex of 100% in the study[22]. As, epidemiologically, the male sex is more represented in the LT population, the high mortality rate found in the present study may eventually be explained by that unbalanced sex distribution[35].

Interestingly, time from the LT and immunosuppressant use showed no association with mortality in most included articles[14-16,19,21,23-25]. A study[16] identified MMF as an independent predictor of poorer outcomes at a multivariable level in a dose-dependent manner[16]. Other studies[15,16,23] showed that MMF was the most discontinued therapy even though the results did not confirm its association with mortality[15,16,23]. MMF cytostatic effect on activated lymphocytes may explain the association with a worse outcome. SARS-CoV-2 also has a direct cytotoxic effect on lymphocytes. Therefore, the association of both may exert a synergic effect causing a significant peripheral lymphocyte depletion[41,42].

Moreover, a study[15] showed the association between MMF use and atypical abdominal symptomatology (diarrhoea); almost 50% of patients maintained on MMF as a primary immunosuppressant had diarrhoea as presenting symptom[15,34,35,37]. The present findings suggest that, in LT recipients with a COVID-19 confirmed diagnosis, MMF should be suspended or reduced. Clinicians should carefully consider gastrointestinal symptoms in LT patients with suspected SARS-CoV-2 infection[43].

According to results on similar viruses (MERS-CoV and SARS-CoV), COVID-19 may trigger the deregulation of CD4+ T cells, the activation of CD8+ T cells, and a cytokine storm causes the most severe forms of COVID-19. Many studies[34,35,37] speculated that immunomodulatory agents could decrease this immune response[34,35,37]. Calcineurin inhibitors (CNIs) have previously shown the ability to inhibit the replication of coronaviruses, such as mTOR inhibitors, increase memory T cells' func-

tionality, and reduce the replication of many viruses. Therefore, baseline immunomodulation could protect LT recipients against severe COVID-19 and ARDS development[36,44].

Indeed, two studies[15,32] identified TAC use as a protective factor for mortality in LT recipients at a multivariable level[15,32]. TAC reduces the replication of many human coronaviruses such as SARS-CoV-1 and suppresses T cell activation, reducing the production of pro-inflammatory cytokines leading to the cytokine storm characterising the most severe forms of COVID-19. Interestingly, a study[32] shows how TAC exerts its immunosuppressive effect by inhibiting the transcriptional activation of multiple cytokine genes, including IL-2. TAC inhibits coronavirus replication *in vitro*, so the benefit seems to be correlated to a direct antiviral effect rather than an immunomodulatory one; however, an antiviral effect has not yet been confirmed *in vivo*[32]. These findings suggest that reducing TAC use should be discouraged in LT recipients with SARS-CoV-2 confirmed diagnosis, although two studies[45, 46] show an increased TAC concentration[45,46]. However, further data should be collected to consider TAC alone as monotherapy during SARS-CoV-2 infection[47,48].

Interestingly, two studies[14,16] proposed a positive role of TAC in the antiviral treatment of SARS-CoV-2. In both studies[14,16], TAC-based IS was more frequent in the non-severe COVID-19 group. However, without statistical significance in the first study[14,16] and the second, since 88% of the patients were treated with CNIs, the author couldn't assess its effect[14,16].

However, conclusions about the benefits of TAC remain a controversial topic. Although the use of TAC may potentially be less harmful during COVID-19 infection than other IS agents, a possible antiviral effect of TAC or a role in the attenuation of a cytokine both remain somewhat speculative in comparison with other immunosuppressant agents[49]. TAC, in place of other immunosuppressive agents, may be an indirect marker of better kidney function. As higher creatinine levels have been identified as an independent risk factor, this has yet to be considered to explain some of its presumed protective effects. Therefore, more evidence is needed to support the recommendation for reducing TAC levels during COVID-19 infection[45,46].

Severe COVID-19 disease is associated with a high level of ICU admission. The present study showed a high admission rate in the LT population, with respiratory distress as the leading cause. In the present study, severe COVID-19 was defined as the need for invasive respiratory support and ICU admission[50]. Several studies[51] reported the misinterpretation of the initial diagnosis caused by atypical symptoms as the reason for severe disease progression and high ICU admission. A typical presentation of those patients was diarrhoea, initially interpreted as a side effect of chronic IS. Therefore, LT patients with gastrointestinal symptoms should be screened for COVID-19.

The percentage of LT recipients achieving an adequate antibody response after vaccination is variable among the included studies; multivariate analysis revealed that older age (>65 years) and IS (MMF as monotherapy specifically) were significantly associated with lower antibodies[27-30]. These findings should encourage clinicians to reduce MMF[52,53] and increase CNI use, positively affecting the humoral response and improving vaccination efficacy[54]. Indeed, even if more data should be analysed to assess vaccine efficacy[55], non-vaccinated LT recipients register 8% of deaths and 9% of ICU admission. In comparison, fully vaccinated LT recipients register none of death or ICU admission[31]. These findings should encourage the booster dose administration while MMF is suspended[27-30,52,53]; results also show that LT recipients' vaccination response is lower than general population[27-30], so even fully vaccinated patients must be stimulated to adopt a safe behaviour, even if vaccination is associated with lower risk of developing severe COVID-19[31].

Limitations

The present study presents several limitations. Firstly, the present data are biased by including studies analysing all the SOTs COVID-19 mortality rate and extrapolating data from the LT subgroups[15,19-24,26]. The mortality rate was higher in a study[22] due to the excess mortality in the lung recipient group (54%)[22]. Therefore, the mortality in the LT cohort may be under or overestimated related to the differences in SOT outcomes independently of the COVID-19 disease. Secondly, data about MMF should be carefully interpreted. Even if many studies[15,19-24,26] report a decrease or a suspension of MMF, only a study[16] showed a statistically significant association between MMF and mortality. Finally, in several studies[15,19-24,26], the IS rate referred to the overall SOT recipients and not only to the LT group.

Two systematic reviews have been published about the impact of SARS-CoV-2 infection on SOT patients, and none of them investigated the risk factors associated with COVID-19-related mortality[54,55].

Furthermore, there were no limitations in the inclusion criteria regarding the study design (case reports, letters to the editor, correspondences and consensus). These reviews also investigated the clinical outcomes and treatment strategies for COVID-19 in all SOT patients. At the same time, the present study aimed to investigate the impact of COVID-19 on LT patients, specifically.

Recent systematic reviews and meta-analyses have shown that increasing age was a risk factor for mortality. However, in that meta-analysis, the authors pooled different metrics for the effect size[4,57]. Moreover, the meta-analysis focused on hospitalised patients. On the contrary, the current study was limited to a systematic review to avoid significant methodological biases and included LT recipients not requiring hospitalisation. In addition, it analysed the role of IS therapy in LT patients with SARS-CoV-2.

Current evidence about the impact of SARS-CoV-2 infection in LT recipients is based on uncontrolled case series or case reports with small samples and contradictory conclusions[19,57-60]. Whereas some researchers report higher percentages of fatal outcomes in SOT recipients, others suggest that chronic immunosuppressive status could be a protective factor. Our study suggests key evidence about risk factors for mortality of COVID-19 related in LT recipients, given that older age, comorbidities, male gender and MMF use were significantly associated with mortality. Therefore, in the case of SARS-CoV-2 high infection rates, those results suggest prioritising during COVID-19 future wave patients with low MELD score and absence of identified risk factors (advanced age, significant comorbidities, and male sex) to minimise the mortality risk[62]. However, further data is still needed to support this recommendation. As chronic IS association is controversial except for MMF and TAC use, greater emphasis should be placed on coexisting comorbidities rather than immunosuppressed status per se[36,62-65].

Conclusions

LT recipients may present with atypical symptomology (gastrointestinal symptoms) and should be carefully screened for SARS-CoV-2 infection, mainly if the IS therapy contains MMF. These could lead to early diagnoses and reduced time to recover. In LT recipients with associated risk factors for mortality and severe COVID-19, clinicians should consider reducing MMF and increasing TAC use.

Authors' Contributions

FG and AV contributed equally to this article. Conceptualisation, FG, AV and SA; methodology, FG and MMP; formal analysis, FG, AV, MMP, FC, FF, FG, GS; investigation, FG, FF and GS; data curation, AV, FC, FG, MMP; writing—original draft preparation, FG, AV, MMP, FC, FF, FG, GS; writing—review and editing, FG, AV, SA; supervision, FG and SA. All authors have read and agreed to the published version of the manuscript.

Ethics Approval and Informed consent

Not applicable.

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Conflicts of Interest

The authors declare no conflict of interest.

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The text has been reviewed by George Clark MD, British native speaker.

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