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ORIGINAL PAPER

Gender Differences in COVID-19 Among Liver Transplant Recipients - Results from a Multicenter Brazilian Cohort

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ABSTRACT

Introduction: Existing literature presents varying perspectives on the impact of COVID-19 on liver transplant recipients. However, no research has specifically investigated the role of gender differences in the manifestation of COVID-19 among liver transplant recipients. This study aims to examine the effects of COVID-19 on liver transplant recipients, with a focus on gender differences in disease presentation and progression. **Methods:** Conducted as a multicenter historical cohort study, this research collected patient records through an online questionnaire. Assessing COVID-related mortality was the main objective. Additionally, demographic, clinical, and laboratory data pertaining to disease presentation and progression were collected. **Results:** The study included a total of 283 patients, of whom 76 were female and 206 were male. The median follow-up period for males was 99 days (IQR 38-283), while for females, it was 126 days (IQR 44-291). A higher prevalence of cardiovascular disease was observed in males (p=0.002). Females frequently experienced a loss of smell (p=0.021), whereas males commonly exhibited fever (p=0.031). Levels of ALT and gamma-glutamyl transferase were significantly elevated in males (p=0.008 and 0.004, respectively). Although there was a trend towards increased mortality in males, it did not reach statistical significance.**Conclusion:** This study is the first attempt to investigate gender differences in COVID-19 among liver transplant recipients. Our findings highlight the need for a comprehensive and personalised approach to treating this patient population and underscore the importance of further elucidating the disease presentation in these individuals.

Descriptors: Liver Transplantation; COVID-19; Gender-Specific Needs.

Diferenças de Gênero na COVID-19 entre Receptores de Transplante de Fígado: Resultados de uma Coorte Multicêntrica Brasileira

RESUMO

Introdução: A literatura existente apresenta perspectivas variadas sobre o impacto da COVID-19 em receptores de transplante de fígado. No entanto, nenhuma pesquisa investigou especificamente o papel das diferenças de gênero na manifestação da COVID-19 entre os receptores de transplante de fígado. Este estudo pretende examinar os efeitos da COVID-19 em receptores de transplante de fígado, com foco nas diferenças de gênero na apresentação e progressão da doença. **Métodos:** Conduzida como um estudo de coorte histórico multicêntrico, esta pesquisa coletou registros de pacientes por meio de um questionário on-line. O principal objetivo foi avaliar a mortalidade relacionada à COVID. Além disso, foram coletados dados demográficos, clínicos e laboratoriais relativos à apresentação e progressão da doença. **Resultados**: O estudo incluiu um total de 283 pacientes, sendo 76 do sexo feminino e 206 do sexo masculino. O período médio de acompanhamento para os homens foi de 99 dias (IQR 38-283), enquanto para as mulheres foi de 126 dias (IQR 44-291). Foi observada uma maior prevalência de doença cardiovascular nos homens (p=0,002). As mulheres frequentemente apresentavam perda de olfato (p=0,021), enquanto os homens geralmente apresentavam febre (p=0,031). Os níveis de ALT e gama-glutamil transferase foram significativamente elevados nos homens (p=0,008 e 0,004, respectivamente). Embora tenha havido uma tendência de aumento da mortalidade nos homens, ela não alcançou significância estatística. **Conclusão:** Este estudo é a primeira tentativa de investigar as diferenças de gênero na COVID-19 entre os receptores de transplante de fígado. Nossos achados destacam a necessidade de uma abordagem abrangente e personalizada para tratar essa população de pacientes e ressaltam a importância de elucidar melhor a apresentação da doença nesses indivíduos.

Descritores: Transplante de Fígado; COVID-19; Necessidades Específicas de Gênero.

INTRODUCTION

During the ongoing COVID-19 pandemic, transplant centers have faced significant reductions in the number of procedures performed and have encountered new challenges in the follow-up and management of solid organ transplant (SOT) recipients. Within this context, the impact of SARS-CoV-2 infection on these patients is a matter of great concern, especially due to their perceived higher vulnerability resulting from immunosuppression and comorbidities.[1-5]

The existing literature presents conflicting findings regarding the effects of COVID-19 on SOT recipients, particularly in the case of liver transplant (LT) recipients. Some authors have noted an increased risk of mortality associated with older age and greater comorbidity burden among these patients,[6-13] while other reports, including meta-analyses, have not reached similar conclusions.[14-16] Notably, no studies have yet investigated gender differences in the presentation of COVID-19 among LT recipients.

Moreover, the studies containing some sub-analysis on this topic rely on relatively small, predominantly male samples with limited ethnic variability and utilise varying methodologies. As such, this study seeks to report the impact of COVID-19, disease characteristics, and progression in LT recipients, focusing on the gender differences encountered in disease presentation and progression in this population.

MATERIALS AND METHODS

We designed this study as a multi-centric historical cohort study, analysing patient records submitted by an online standardized questionnaire in all enrolled institutions. The study included LT recipient patients with confirmed COVID-19 already in follow-up at the study centres and who sought medical attention between December 2019 and October 2021. Patients received follow-up until either death or the end of the study period.

We gathered demographic, clinical, and laboratory information pertaining to the presentation and progression of the disease. To ensure ethical compliance, all participants provided their consent by agreeing to a standardized term approved by the ethics committee of each respective institution, adhering to the principles outlined in the Declaration of Helsinki.

While we collected data on specific treatments for COVID-19, it is important to note that the study was conducted during a period when many of the current COVID-19-specific treatments were either unknown or not yet in use. Consequently, the focus of the study on this topic was collection of data related to the utilisation of anticoagulation and corticosteroid therapy.

As the study commenced before the availability of any COVID-19 vaccines in the country, we did not collect information regarding vaccination status. It was presumed that patients were unvaccinated since, until the final months of the study, less than 10% of the country's population had received complete vaccination coverage.[17]

The statistical analysis was conducted utilising the SPSS program, version 23 (IBM, Armonk, NY, USA). Descriptive analysis was performed, and parametric or nonparametric comparative tests were employed based on the normality of the variables. Non-normal continuous variables were assessed using the Mann-Whitney Q test, while t-Student and ANOVA tests were utilised for normal variables. The chi-squared test was applied to normal and non-normal discrete binary variables, and multinomial logistic regression was employed for non-binary categorical variables.

RESULTS

We included 282 patients in the study, of which 76 were female, and 206 were male. The overall median age was 60 years old (IQR: 53-67). The median time from transplantation was 2.6 (IQR 1.0-6.3). Both characteristics were homogenous between genders. Patients were mostly white (59%) and overweight, with a median BMI of 27 (IQR 24-32). Demographic data on the sample population, comorbidities, and symptoms at admission is displayed in Table 1. The median follow-up time was 99 days (IQR 38-283) for males and 126 for females (IQR 94-291).

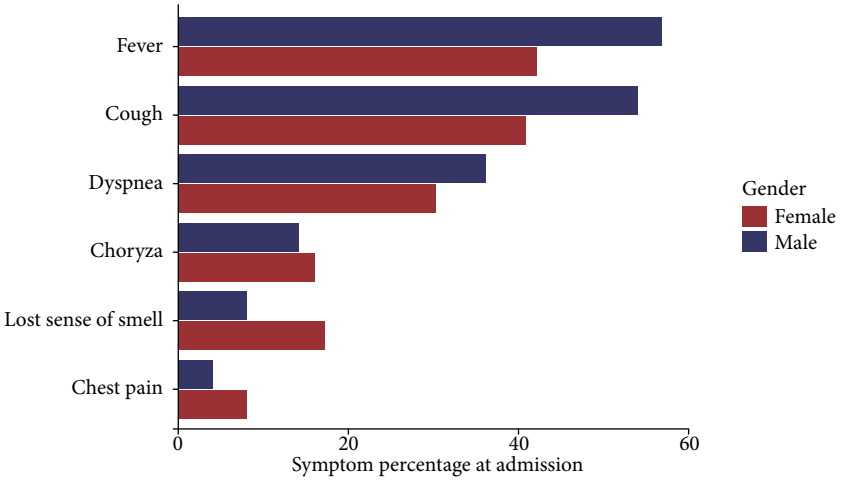
Table 1. General characteristics of the studied population, by gender.

Characteristic	N (%)	Female, N = 76[1]	Male, N = 207[1]	p-value[2]
Age	283	61 (47, 68)	60 (54, 66)	0.8
Ethnicity	276			0.2
Asian		2 (2.6%)	1 (0.5%)	
Black		4 (5.3%)	15 (7.2%)	
Mixed-race		27 (36%)	61 (29%)	
White		43 (57%)	123 (59%)	
BMI	254	27 (23, 33)	28 (25, 32)	0.3
Years since LTX	259	2.0 (1.0, 5.0)	3.0 (1.0, 6.0)	0.2
Comorbidities				
Charlson Comorbidity Scale	283	1.0 (1.0, 1.0)	2.0 (2.0-2.0)	0.4
Diabetes	259	29 (41%)	91 (48%)	0.3
Dyslipidemia	259	3 (4.3%)	5 (2.6%)	0.4
Chronic Kidney Disease	259	9 (13%)	25 (13%)	>0.9
Hypertension	259	30 (43%)	92 (49%)	0.4
Cardiovascular Disease	259	0 (0%)	23 (12%)	0.002
Symptoms at admission				
Fever	283	32 (42%)	117 (57%)	0.031
Nausea	283	3 (3.9%)	13 (6.3%)	0.6
Odynophagia	283	4 (5.3%)	5 (2.4%)	0.3
Cough	283	31 (41%)	111 (54%)	0.056
Coryza	283	12 (16%)	29 (14%)	0.7
Dyspnea	283	23 (30%)	75 (36%)	0.3
Abdominal pain	283	1 (1.3%)	4 (1.9%)	>0.9
Diarrhea	283	20 (26%)	40 (19%)	0.2
Hypoxemia	283	0 (0%)	3 (1.4%)	0.6
Lost sense of smell	283	13 (17%)	16 (7.7%)	0.021
Asymptomatic	283	4 (5.3%)	11 (5.3%)	>0.9
Disease wave	277			0.2
First wave		30 (41%)	101 (50%)	
Second wave		44 (59%)	102 (50%)	
Inpatient or Outpatient treatment	283			0.9
Inpatient		46 (61%)	127 (61%)	
Outpatient		30 (39%)	80 (39%)	
ICU admission	172	16 (35%)	52 (41%)	0.4
Patient Deaths	259	9 (13%)	42 (22%)	0.092
Follow-up time	268	99 (38, 283)	126 (44, 291)	0.4

[1]Median (IQR); n (%). [2]Wilcoxon rank-sum test; Fisher's exact test; Pearson's Chi-squared test. Source: Authors.

Most patients presented with at least one comorbidity, with only 18% displaying none (14 females and 37 males). The median of the Charlson comorbidity index was 2 for males (IQR:2) and 1 for females (IQR:1). The prevalence of specific comorbidities was similar between genders, with a greater incidence of cardiovascular disease in males when compared to females (p=0.002).

Most patients displayed at least one COVID symptom at admission. Only 15 patients (5.3%) were asymptomatic, of which 4 were female, and 11 were male. Most symptoms were evenly distributed between genders, except for females more frequently presenting with a lost sense of smell (p=0.021) when compared to males, and males more frequently presenting fever (p=0.031) compared to females. Symptom distribution between genders is displayed in Fig. 1.



Source: Authors.

Figure 1. COVID symptom percentual incidence at presentation by gender

Transaminase levels and liver function tests at admission also displayed differences between genders. Median ALT levels were significantly higher in males than females (p =0.008). Median gamma-glutamyl transferase levels were also more than two times higher in males (p=0.040). Alkaline phosphatase and AST also tended to be higher in males in our sample; however, this trend did not reach statistical significance. Detailed information on laboratory profiles is displayed in Table 2.

Table 2. Laboratory values at admission, by gender

Characteristic	N	Overall N = 283[1]	Female N = 76[1]	Male N = 207[1]	p-value[2]
AST	175	39 (25, 66)	32 (22, 63)	39 (26, 67)	0.4
ALT	176	34 (22, 72)	26 (18, 38)	38 (24, 79)	0.008
Alkaline phosphatase	138	125 (85, 252)	102 (81, 278)	131 (88, 248)	0.5
Gamma Glutamyl Transferase	130	172 (72, 428)	105 (71, 280)	226 (74, 469)	0.040
Total bilirubin	29	0.5 (0.3, 1.0)	0.8 (0.5, 0.9)	0.4 (0.3, 0.9)	0.3

[1]Median (IQR); n (%). [2]Wilcoxon rank-sum test; Fisher's exact test. Source: Authors.

Immunosuppressive drug use in our sample did not significantly differ, with both females and males mainly enrolled in regimens containing Tacrolimus (84% of females and 87% of males) and Mycophenolate (54% of females and 60% of males). Both males and females had similar proportions of immunosuppression modifications along with COVID infection (53% and 52%, respectively). Detailed information on immunosuppressive regimens is displayed in Table 3.

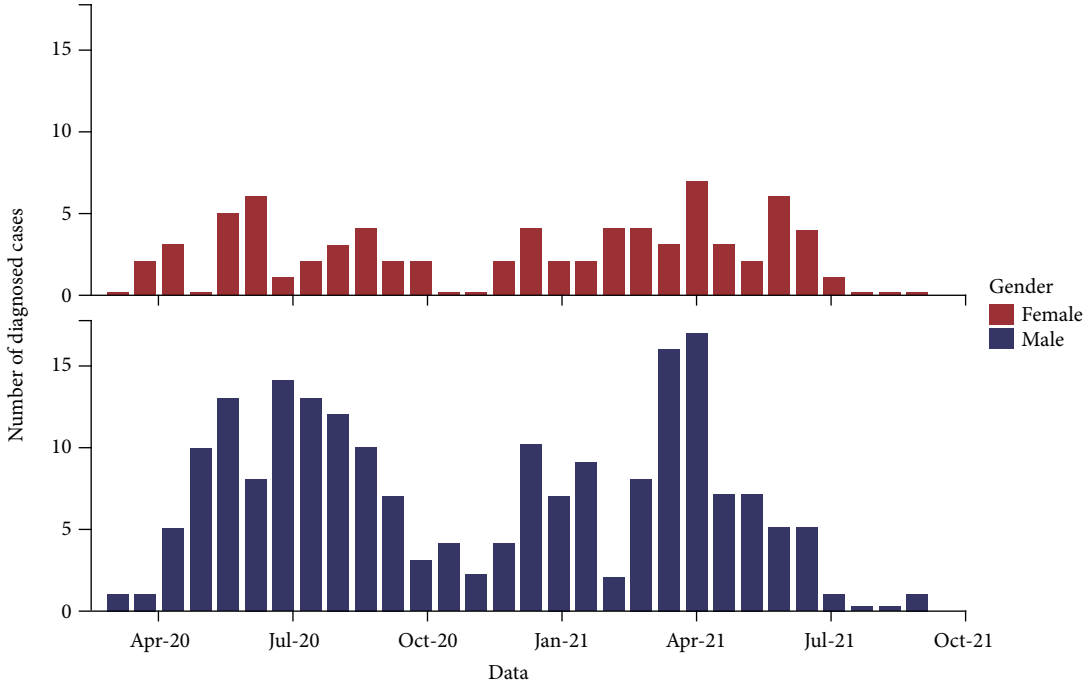
Table 3. Imunossupressor use and management after admission, by gender.

Characteristic	N	Female, N = 76[1]	Male, N = 207[1]	p-value[2]
AZA	283	2 (2.6%)	4 (1.9%)	0.7
CsA	283	2 (2.6%)	9 (4.3%)	0.7
PRED	283	8 (11%)	15 (7.2%)	0.4
SIROLIMUS	283	1 (1.3%)	3 (1.4%)	>0.9
TAC	283	64 (84%)	180 (87%)	0.6
MFS	283	41 (54%)	124 (60%)	0.4
EVR	283	12 (16%)	41 (20%)	0.4
Imunossupressor alteration or suspension	268	37 (53%)	103 (52%)	>0.9

[1]n (%). [2]Fisher's exact test; Pearson's Chi-squared test. Source: Authors.

Both males and females were equally affected in the first and second disease waves and displayed the same proportions of inpatient and outpatient management and similar frequency of ICU admissions, ICU length of stay, need for mechanical

ventilation and pronation. While there was a tendency of increased mortality in males (42 patients or 22%) compared to females (9 patients or 13%), this trend did not reach statistical significance. Case incidence for females and males followed a bimodal pattern and is displayed in Fig. 2.



Source: Authors.

Figure 2. Histogram of diagnosed cases within the study period, by gender.

DISCUSSION

The results gathered in this study display a novel approach to understanding COVID-19 infections in liver transplantation recipients and suggest slight but fundamental differences between disease presentation and the effect of COVID-19 on the liver graft.

To our knowledge, this is the first study to approach gender differences between COVID-19 infection in LT recipients. Therefore, the results of this study are paramount to the comprehensive and individualised treatment of this multifaceted patient population and stand as a stepping stone for further understanding of the disease presentation in these patients.

Regarding the vaccination status within our population, the initiation of the study preceded the widespread availability of immunizations in Brazil. Consequently, all patients enrolled in the study were categorised as non-vaccinated, as national data indicates that until the final months of the study, less than 10% of the country's population had received vaccination.[17]

While these characteristics distinguish the sample from the current majority of liver transplant recipients who have been vaccinated, such differences may be mitigated by evidence suggesting lower vaccine effectiveness in this specific population.[18,19]

Furthermore, the findings of the study may still be representative of the subset of patients who have not received complete or any vaccination, as these individuals are typically associated with higher rates of mortality and severe cases. These cases are particularly concerning as they raise questions about potential adjustments to immunosuppression.[20-22]

Our data has shown crucial differences in COVID symptoms at admission depending on gender. To our knowledge, no other studies have performed this analysis in the transplant setting. However, in non-transplant individuals, no gender-based differences in the presentation of symptoms were observed,[23] although others found cough and loss of smell or taste in females more often.[24] Similarly, our study has shown differences in liver function tests between genders, which is not found in any other studies including solid organ transplant population. On the other hand, laboratory parameters of liver function were abnormally higher in non-transplant male individuals, indicating a gender-based burden of COVID-19.[24,25]

Be that as it may, some previous studies have analysed gender as a risk factor for increased mortality in LT recipients with COVID-19. Most studies have not found an association between these factors.[6,8,10,11] A single study by Colmenero et al. has reported an association between the male gender and increased mortality.[26]

Studies in the general population have already suggested the association between severe COVID and gender.[27] This finding is explained by several mechanisms, including the fact that SARS-CoV-2 binds to ACE2 (angiotensin-converting enzyme-2) more frequently in men, as the ACE2 gene is regulated by the X chromosome, as well as by gender-based differences in innate and adaptive immunity.[28,29] Our study did not find differences in hospitalisation or ICU admission between genders, concurring with current literature that seems to deny this association in LT recipients with COVID-19.[12,30] Noteworthy is the median age (60 years) of female LT recipients, indicating that most of them were in the postmenopausal period, which jeopardises the estrogen advantage. Therefore, similar rates of COVID-19 progression and mortality were found between male and postmenopausal women in non-transplanted individuals.[31]

In addition, both male and female LT recipients were overweight/obese in our study, which may have contributed to similar rates of COVID-19 outcomes. Obesity is an independent risk factor for severe disease and mortality in patients with COVID-19,[32] as this pre-existing comorbidity led to immune-metabolic dysfunction characterised by an increase in ACE2 expression in bronchial cells and adipose tissue, impaired alveolar macrophage metabolism, and hyperactivation of the innate immune system.[33] Likewise, male and female LT recipients in our study were equally affected by underlying comorbidities, such as diabetes mellitus , chronic kidney disease , and hypertesion, which are associated with higher rates of COVID-19 related mortality.[34]

Importantly, our findings in this study fill important knowledge gaps within the pathogenesis and presentation of COVID-19 in LT recipients, offering novel analyses between genders and suggesting possible factors for improving individualised management of these patients.

Nonetheless, our data has its limitations - mostly because it is retrospective and based on patient records, which increases the risk of reporting bias. Yet, the volume of patients and the multicenter design of the study greatly attest to the quality of the collected data.

In light of the presented findings, it is clear that there is still the possibility of better understanding the pathogenesis of COVID-19 in LT recipients. Further research are needed to establish causality between these factors and compare different patient management based on the differences in presence of this study.

CONCLUSION

In conclusion, despite the volume of research toward understanding the disease course of COVID-19 in special populations, notably LT recipients, our novel findings display clear gender differences in these patients and suggest the need to strive towards more individualised care plans, as well as to conduct further studies to better understand these gender differences.

CONFLICT OF INTEREST

The authors declare that they have no affiliations with or involvement in any organization or entity with any financial interest in the subject matter or materials discussed in this manuscript.

AUTHOR'S CONTRIBUTION

Substantive scientific and intellectual contributions to the study: Elaine Cristina Ataide, Eduardo Riccetto, Tercio Genzini, Regina Gomes Santos, Lucio Figueira Pacheco Moreira, Laura Cristina Machado Pinto, Raquel SB Stucchi, Simone Reges Perales, Leticia Zanaga, Renato Fereira da Silva, Rita CM Fereira da Silva, Luciana Haddad, Luiz A C D´Albuquerque, Marcio Dias de Almeida, Andre Watanabe, Gustavo S Peixoto, Claudio Moura Lacerda de Melo, Renata Ferreira Bezerra, Nertan Luiz Tefilli, Marcia Halpern, Maira Silva Godoy, Marcelo Nogara, Jorge Marcelo Padilla Mancero, Huda Maria Noujaim, Jose Huygens Parente Garcia, Érika Bevilaqua Rangel, Ilka de Fátima Santana Ferreira Boin; **Conception and design:** Elaine Cristina Ataide, Eduardo Riccetto, Ilka de Fátima Santana Ferreira Boin; **Data analysis and interpretation:** Eduardo Riccetto, Ilka de Fátima Santana Ferreira Boin; **Article writing:** Elaine Cristina Ataide, Eduardo Riccetto, Ilka de Fátima Santana Ferreira Boin; **Critical revision: Elaine** Cristina Ataide, Eduardo Riccetto, Tercio Genzini, Regina Gomes Santos, Lucio Figueira Pacheco Moreira, Laura Cristina Machado Pinto, Raquel SB Stucchi, Simone Reges Perales, Leticia Zanaga, Renato Fereira da Silva, Rita CM Fereira da Silva, Luciana Haddad, Luiz A C D´Albuquerque, Marcio Dias de Almeida, Andre Watanabe, Gustavo S Peixoto, Claudio Moura Lacerda de Melo, Renata Ferreira Bezerra, Nertan Luiz Tefilli, Marcia Halpern, Maira Silva Godoy, Marcelo Nogara, Jorge Marcelo Padilla Mancero, Huda Maria Noujaim , Jose Huygens Parente Garcia , Érika Bevilaqua Rangel , Ilka de átima Santana Ferreira Boin; **Final approval:** Elaine Cristina Ataide, Ilka de Fátima Santana Ferreira Boin.

DATA AVAILABILITY STATEMENT

Data is available upon request.

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