Original Article

Biliary stenosis after liver transplant is not associated with cytomegalovirus infection

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Background: Liver transplantation (LT) is the best treatment for end-stage liver disease; however, biliary complications (BCs) still pose a significant challenge. Among the post-transplant BC, strictures and biliary fistulas are the most common. Biliary strictures are classified as anastomotic and non-anastomotic. Some previous studies suggest an association between post-transplant biliary strictures and cytomegalovirus (CMV) infection. In this study, we aimed to identify whether there is an association between CMV infection and biliary strictures in patients undergoing LT.

Methods: A retrospective study of 175 patients aged ≥18 years undergoing LT at Felicio Rocho Hospital between 2011 and 2017 was conducted. All included patients received grafts perfused with Institut Georges Lopez-1 (IGL-1) solution from brain-dead donors, survived post-transplantation for more than 120 days, and had a minimum follow-up of 12 months after LT. The diagnosis of CMV was made by antigenemia and biliary strictures by magnetic resonance cholangiopancreatography (MRCP).

Results: The average age of the recipients was 54 years. Postoperative BCs occurred in 12% of transplants. The most common BC was stricture (9.1%), with a predominance of anastomotic strictures (AS) over non-AS (NAS) (87.5% *vs.* 12.5%, respectively). CMV infection was confirmed in 22.9% of patients. In the univariate analysis, post-transplant CMV infection correlated with the development of BCs (P=0.01), as well as biliary strictures (P=0.008). In the multivariate analysis, however, only model for end-stage liver disease (MELD) >21 was a risk factor for the development of BCs in general (P=0.02) and biliary strictures (P=0.01).

Conclusions: CMV infection was not an independent risk factor for the development of non-anastomotic post-transplant biliary strictures in this study.

Keywords: Cytomegalovirus (CMV); liver transplant; biliary stenosis

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Introduction

Background

Liver transplantation (LT) stands as the gold standard for treating conditions such as end-stage liver disease, hepatocellular carcinoma, and fulminant hepatitis, among other critical liver diseases. Thomaz Starzl was the pioneer in the successful human liver transplants domain (1).

Over the years, LT's efficacy has soared, attributed to advancements in immunosuppressive treatments, surgical techniques, organ preservation methodologies, and enhanced postoperative care (2-4). Contemporary statistics highlight a post-liver transplant survival rate of 92% for the first year, extending to 75% over a 5-year span (5).

Post-transplantation, some recipients encounter complications like primary graft dysfunction, acute rejection, infections, and biliary anomalies. Current analyses estimate a 15% occurrence rate of these complications, notwithstanding the encouraging survival metrics of transplant recipients (6,7).

Although there's a notable decline in post-transplant complication rates (7,8), they can still adversely affect patients' quality of life and graft survival. Often, these complications are associated with repeated hospitalizations, surgical procedures, and in severe scenarios, retransplant.

Biliary complications (BCs) significantly influence LT's long-term outcomes. Notably, biliary strictures and fistulas emerge as predominant issues, contributing to roughly 30% of all post-transplant complications (3,9,10). Typically, biliary strictures manifest within the first post-transplant year, predominantly between the fifth and eighth months (11). Yet, recent research indicates a rising trend in their incidence, even after first year post-transplant (12).

Some factors correlate with post-LT biliary strictures occurrences, including donor age, extended organ ischemia, donor type, anatomical discrepancies, surgical methodologies, autoimmune conditions, rejection episodes, and cytomegalovirus (CMV) infections (12,13). Discerning the causative links between these elements is pivotal to devise strategies that minimize complication risks.

In categorizing biliary strictures, they're divided into anastomotic and non-anastomotic. Anastomotic strictures (AS) signify a narrowing at the anastomosis point, usually resulting from fibrotic reactions. The onset of AS often stems from diameter mismatches between the donor and recipient's biliary tracts or procedural techniques. Conversely, non-AS (NAS) can impact any biliary segment, like intra or extrahepatic. Such lesions may arise from ischemic or non-ischemic factors, often linked to immunological or infectious agents, termed ischemic cholangiopathy (CI).

Rationale and knowledge gap

CMV infection ranks among the prevalent infectious setbacks for transplant recipients, bringing significant morbidity and mortality. Its incidence fluctuates between 22% and 62% in LT recipients (14,15). Experimental studies ascertain that CMV presence in bile exacerbates the graft's biliary epithelium damage. Consequently, it might correlate with post-transplant biliary strictures (16). However, clinical studies present conflicting conclusions regarding this correlation in the literature (17-19).

Objective

In this study we set out to identify whether there is an association between CMV infection and biliary stricture in patients undergoing LT. We present this article in accordance with the STROBE reporting checklist (available at https://tgh.amegroups.com/article/view/10.21037/tgh-23-110/rc).

Highlight box

Key findings

- No direct link found between cytomegalovirus (CMV) infection and non-anastomotic biliary stenosis in liver transplant recipients. Previous CMV infection and a high model for end-stage liver disease (MELD) score (>21) emerged as potential risk factors for biliary complications.

What is known and what is new?

- Liver transplantation involves the risk of post-transplant complications, including biliary strictures. Earlier studies have explored the CMV-biliary complications link, with mixed findings. Various risk factors for biliary complications are documented.
- This study provides nuanced understanding of multifactorial causes of biliary complications in liver transplant recipients, highlights the importance of monitoring patients with prior CMV infection and high MELD scores, and emphasizes the need for comprehensive risk assessment and early intervention.

What is the implication, and what should change now?

- Clinicians should closely monitor at-risk patients to detect and address biliary complications. Further research is required to explore the complex mechanisms behind biliary complications and optimize patient care. This study contributes to the ongoing efforts to improve liver transplantation outcomes and guides future research in this field.

Methods

Patients

This cross-sectional study evaluated 175 patients from a total of 201 patients who underwent LT at Felicio Rocho

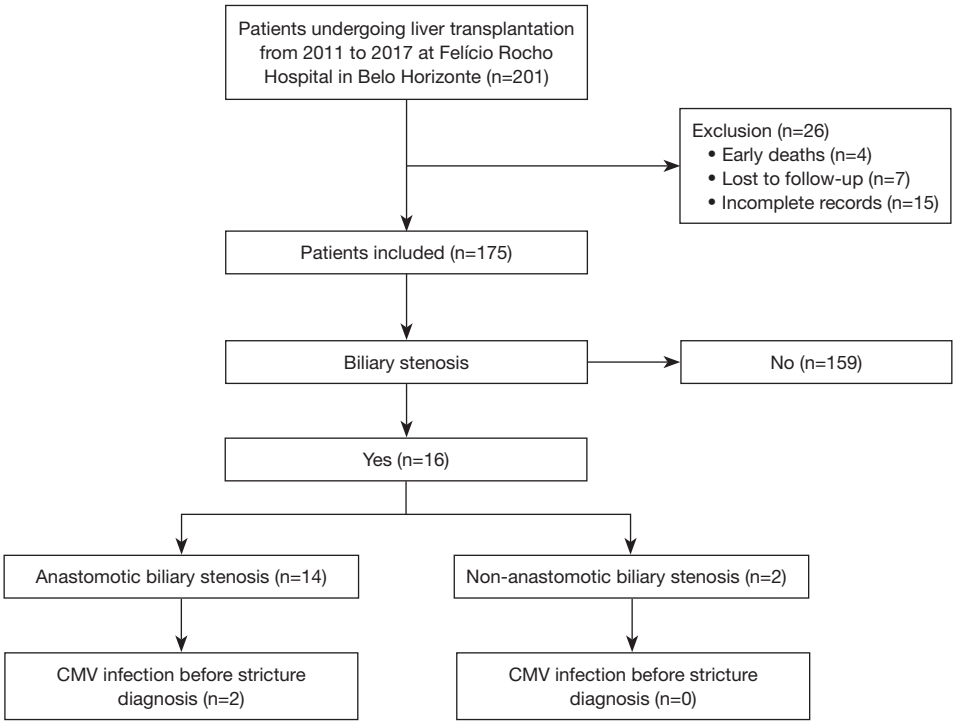

Figure 1 Flow diagram of participants included. CMV, cytomegalovirus.

Hospital, in Brazil, between 2011 and 2017 (*Figure 1*). All the patients in the study received grafts perfused with Institut Georges Lopez-1 (IGL-1) solution from brain-dead adult donors, with a minimum follow-up of 12 months post-LT. Patients diagnosed with primary sclerosing cholangitis or incomplete data were excluded from the study. The standard surgical approach was employed, utilizing a whole graft implanted via the piggyback technique. Biliary anastomosis was done by end-to-end duct to duct without T-tube. All patients received tacrolimus and steroid immunotherapy. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional Ethics Committee of Felicio Rocho Hospital (CAAE: 77877417.9.1001.5125). All subjects gave their informed consent for inclusion before they participated in the study.

Biliary stenosis diagnosis

Donor and recipient data were meticulously compiled from medical records. Patients with clinical and/or laboratory indications suggestive of cholestasis underwent an upper abdomen magnetic resonance cholangiopancreatography (MRCP). The service's seasoned radiologists identified the presence of strictures and classified them into anastomotic and non-anastomotic categories, and one reference radiologist from the team, with experience in hepatobiliary cases, subsequently reviewed all the included cases.

CMV infection diagnosis

Antigenemia was performed throughout the first three post-transplant months: weekly during the first month and then bi-weekly for the second and third months. Patients requiring preemptive treatment underwent repeated antigenemia for up to 6 months post-treatment. Viral detection for CMV was carried out using standard indirect immunofluorescence techniques against CMV pp65 antigen. The quantitative assessment employed in this study involved titrating the number of positive cells per 200,000 evaluated. A threshold of 7 positive cells per 200,000 evaluated cells was set.

Statistical analysis

Descriptive statistics consisted of the mean and standard deviation. Categorical variable comparisons with the variable group were conducted using the Chi-square test,

Table 1 Demographic and clinical characteristics of patients undergoing liver transplantation from 2011 to 2017 at Felicio Rocho Hospital in Belo Horizonte, Brazil

Variable	Value, N (%)
Sex	
Male	129 (73.7)
Female	46 (26.3)
Child†	
A	23 (18.4)
B	60 (48.0)
C	42 (33.6)
Causes of cirrhosis	
Alcoholic	61 (34.9)
Viral	37 (21.1)
Autoimmune	9 (5.1)
Primary biliary cirrhosis	4 (2.3)
NASH	5 (2.9)
Others‡	59 (33.7)
Hepatocellular carcinoma	
No	128 (73.1)
Yes	47 (26.9)
CMV	
No	135 (77.1)
Yes	40 (22.9)
Cold ischemia time	
<10 h	160 (91.4)
≥10 h	15 (8.6)
Vasoactive drugs	
No	59 (33.7)
Yes	116 (66.3)

†, the absolute number of patients with Child-Pugh score: 125. ‡, cryptogenic cirrhosis, polycystic disease, epithelioid hemangioendothelioma, metabolic disorders, fulminant hepatitis. NASH, nonalcoholic steatohepatitis; CMV, cytomegalovirus.

Fisher's exact test, and Monte-Carlo simulations. P values <0.05 were considered statistically significant. The IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA), facilitated the analysis.

Table 2 Primary indications for liver transplant at Felício Rocho Hospital from January 2011 to September 2017

Transplant indication	Value, N (%)
Alcoholic	61 (31.1)
Cryptogenic	25 (12.8)
HCV	32 (16.3)
HBV	8 (4.1)
Autoimmune hepatitis	9 (4.6)
NASH	5 (2.5)
Hepatocellular carcinoma	47 (24.0)
Polycystic disease	2 (1.0)
Metabolic deficiencies†	7 (3.6)

†, alpha-1-antitrypsin deficiency, primary hyperoxaluria, hemochromatosis, glycogen storage disease type 1A, etc. HCV, hepatitis C virus; HBV, hepatitis B virus; NASH, nonalcoholic steatohepatitis.

Results

Recipient and donor demographics and clinical characteristics are presented in *Tables 1-3*. All donors had prior exposure to CMV (IgG positive test) and among the recipients, 172 (98.3%) had CMV IgG positive test before transplantation. Positive pp65 antigenemia was identified in 40 (22.9%) patients during follow-up. Notably, only two of these cases had a CMV infection before stricture diagnosis, and did receive pre-emptive treatment (*Table 4*). Among those with positive antigenemia, 28 (70%) underwent preemptive treatment, while 12 (30%) exhibited signs of active CMV disease. Six patients received primary prophylaxis with ganciclovir for three to 6 months post-transplant, due to tests confirming no prior exposure to the virus (CMV IgG neg test).

Twenty-one patients (12%) encountered BCs, with nine of them (42.8%) experiencing multiple issues. The predominant BC was stricture, observed in 16 patients, resulting in an overall incidence rate of 9.1% for biliary strictures. On average, the diagnosis of biliary stricture was made 7.42 months post-transplantation, with a range between 1 and 23 months. Of the 16 patients diagnosed with a biliary stricture, 14 (87.5%) exhibited AS, while 2 (12.5%) had NAS (*Table 5*).

When examining the entire study population, the incidence of NAS stood at 1.1%. Analyzing only the subgroup with BCs, biliary strictures represented 76.2%

Table 3 Characteristics of liver transplant patients and their donors at Felício Rocho Hospital from January 2011 to September 2017 (n=175)

Variable	Mean	Median [min–max]	Standard derivation
Recipient age (years)	54.3	57 [15–72]	11.05
Donor age (years)	35.3	34 [8–65]	13.4
Cold ischemia time (hours)	6.7	6.3 [3–13]	2.2
TB receptor (mg/dL)	5.4	3.7 [0.3–22.9]	4.9
AST receptor (U/L)	1,936	750 [1–19,310]	3,342
Na donor (mEq/L)	150.2	150 [123–178]	9.6
MELD	17.5	17 [6–43]	6.04

TB, total bilirubin; AST, aspartate aminotransferase; Na, sodium; MELD, model for end-stage liver disease.

Table 4 Antigenemia in patients with pre-existing CMV before stenosis

Recipient	CMV antigenemia
1	12 cells/200,000
2	92 cells/200,000

CMV, cytomegalovirus.

of all such complications. This was followed by cholangitis and fistulas, each with an incidence of 23.9%, and bile-duct stones at 23.9%. The overall incidence rates for these complications were 2.9% and 2.9%, respectively (*Table 6*).

Among the CMV positive patients, 2 out of 40 (5%) had BCs following their CMV diagnosis. In the univariate analysis, prior presence of CMV showed a correlation with the onset of BCs (P=0.01) as well as with strictures (P=0.008). However, the multivariate assessment did not yield significant results. Pertaining to the cold ischemic time (CIT), all patients, 21 out of 21 (100%), who developed BCs had a CIT of less than 10 hours (P=0.22).

Twelve patients (6% of the total) encountered thrombosis or hepatic artery stenosis, and among them, three (25%) developed BCs. There was no established link between hepatic artery thrombosis or stenosis and the onset of BCs (P=0.16). Similarly, the use of vasoactive amines did not correlate with complications. Patients classified as Child C had a higher incidence of BCs, with 7 out of 11 (63.6%) being affected, although this was not statistically significant (P=0.055). A model for end-stage liver disease (MELD) score greater than 21 was associated with a higher frequency of BCs, with 9 out of 15 (60.0%) being affected, which was statistically significant (P=0.006) (*Table 7*).

In the multivariate analysis, only MELD >21 showed association with the development of BCs odds ratio (OR) 4.17 [95% confidence interval (CI): 1.34–12.95; P=0.01] (*Table 8*).

Discussion

Key findings

The primary findings of our study suggest that CMV infection was not an independent risk factor for the development of non-anastomotic biliary stenosis after LT. However, the presence of CMV infection before stricture diagnosis and a MELD score greater than 21 emerged as risk factors for the development of BCs in general, with only MELD >21 being a risk factor for the occurrence of biliary stenosis in multivariate analysis.

Strengths and limitations

The strength of this study lies in its relevance to clinical practice, the clear research objective, and the use of a multi-faceted approach to data collection. The study's longitudinal design allows for the detection of biliary strictures over time, enhancing the quality of the results. Additionally, the study includes a substantial number of patients, further enhancing the robustness of the findings.

However, our study also grapples with certain limitations. Our study is retrospective, which inherently imposes limitations on data acquisition. The diagnosis of NAS was exclusively conducted through MRCP, precluding the ability to characterize lesions in small biliary ducts or microscopic lesions. For the latter, graft biopsies would have been required, a procedure rendered unfeasible due to the retrospective nature of the study. The absence of

Table 5 Analysis of the association between CMV infection and the presence of anastomotic and non-anastomotic biliary strictures in liver transplant patients at Felício Rocho Hospital from 2011 to 2017

Variable	Stenosis type, n (%)		OR	95% CI	P value
	Anastomotic (n=14)	Non-anastomotic (n=2)			
Previous CMV			1.16	0.94–1.44	0.57[†]
Yes	2 (14.2)	0			
No	12 (85.8)	2 (100.0)			
MELD >21[§]			0.75	0.50–1.11	0.49[‡]
Yes	6 (54.5)	2 (100.0)			
No	5 (45.5)	0			

[†], Chi-square test; [‡], Fisher's exact test; [§], the number of patients with anastomotic strictures with MELD assessment: 11. CMV, cytomegalovirus; OR, odds ratio; CI, confidence interval; MELD, model for end-stage liver disease.

Table 6 Incidence of biliary complications in patients undergoing liver transplantation at Felício Rocho Hospital from January 2011 to September 2017

Biliary complications	N (%)
Stenosis	
No	159 (90.9)
Yes	16 (9.1)
Stenosis type (n=16)	
Anastomotic	14 (87.5)
Non-anastomotic	2 (12.5)
Fistula	
No	170 (97.1)
Yes	5 (2.9)
Gallstone	
No	171 (97.7)
Yes	4 (2.3)
Cholangitis	
No	170 (97.1)
Yes	5 (2.9)

endoscopic retrograde cholangiopancreatography (ERCP) as a diagnostic modality, a technique employed in various earlier studies, could also be considered a limitation, potentially resulting in underreporting the number of patients with non-anastomotic biliary lesions. The choice of MRCP as the diagnostic method for BCs in our study was influenced by its non-invasiveness and high diagnostic accuracy, aligning with previous research indicating that MRCP exhibits a sensitivity of 95%, a positive predictive value of 98%, and an overall accuracy of 95% when diagnosing BCs in liver transplant recipients (20). We acknowledge that pp65 antigen detection may be less sensitive than quantitative PCR for CMV monitoring. Nevertheless, it's important to highlight that, at the time of transplantation for our study participants, antigenemia was the standard test in our hospital.

Comparison with similar researches

Notably, earlier research, like the study by Gotthardt *et al.*, made strides in this field by isolating CMV DNA in the biliary tract of patients with suspected biliary stenosis. They examined bile samples from 124 patients who underwent ERCP over a 4-year period. Their findings indicated that a significant proportion of patients with non-anastomotic biliary stenosis had CMV detected in their bile samples (16.9%), whereas only a small fraction had CMV detected in their blood samples (3.8%). This suggests a potential link between occult CMV infections in the biliary tract and non-anastomotic biliary stenosis (16).

Moreover, Lattanzi *et al.* conducted a study encompassing 51 patients transplanted at a single center between 2000 and 2011. They identified a 35.3% incidence of BCs, with biliary stenosis affecting 29.4% of the transplant population. In their multivariate analysis, the presence of biliary stenosis, hepatic artery stenosis or thrombosis, CMV infection, and graft hepatic artery abnormalities emerged as risk factors for the development of non-anastomotic biliary stenosis following LT (21).

Table 7 Univariate analysis: risk factors in patients undergoing liver transplantation at Felício Rocho Hospital from 2011 to 2017

Variable	Biliary complications, n (%)		Total, n (%)	P value
	No (n=154)	Yes (n=21)		
CMV				0.58†
Yes	34 (22.1)	6 (28.6)	40 (22.9)	
No	120 (77.9)	15 (71.4)	135 (77.1)	
Previous CMV				0.01‡
Yes	0 (0)	2 (9.5)	2 (1.1)	
No	154 (100.0)	19 (90.5)	173 (98.9)	
Sex				0.78‡
Male	113 (73.4)	16 (76.2)	129 (73.7)	
Female	41 (26.6)	5 (23.8)	46 (26.3)	
Child-Pugh§				0.055‡
A	25 (21.2)	0	25 (19.4)	
B	58 (49.2)	4 (36.4)	62 (48.1)	
C	35 (29.7)	7 (63.6)	42 (32.6)	
Arterial thrombosis/stenosis				0.16†
Yes	9 (5.8)	3 (14.3)	12 (6.9)	
No	145 (94.2)	18 (85.7)	163 (93.1)	
Cold ischemia time				0.22¶
<10 h	139 (90.3)	21 (100.0)	160 (91.4)	
≥10 h	15 (9.7)	0	15 (8.6)	
Vasoactive drugs§				0.40‡
Yes	101 (71.1)	15 (83.3)	116 (72.5)	
No	41 (28.9)	3 (16.7)	44 (27.5)	
MELD >21§				0.006†
Yes	31 (24.2)	9 (60.0)	40 (28.0)	
No	97 (75.8)	6 (40.0)	103 (72.0)	

†, Fisher's exact test; ‡, Chi-square test; §, the absolute number of patients with CHILD classification: 129, vasoactive drugs assessment: 160, and MELD assessment: 143; ¶, Chi-square test with Monte Carlo simulation. CMV, cytomegalovirus; MELD, model for end-stage liver disease.

Table 8 Univariate and multivariate analysis. Risk estimation of variables for the development of biliary complications in patients undergoing liver transplantation at Felício Rocho Hospital from 2011 to 2017

Variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	P value	OR	95% CI	P value
Previous CMV	9.1	5.95–13.91	0.01	ns	ns	ns
MELD >21	3.86	1.47–10.15	0.006	4.17	1.34–12.95	0.01

OR, odds ratio; CI, confidence interval; CMV, cytomegalovirus; ns, not studied; MELD, model for end-stage liver disease.

A comprehensive systematic review by Nemes *et al.* evaluated data from 14,411 liver transplant patients. This review reported an overall BC incidence of 23%. The authors identified risk factors for the development of BCs, which included preoperative sodium levels, MELD scores exceeding 25, primary sclerosing cholangitis, extended anhepatic phase, prolonged cold ischemia time, CMV infection, and hepatic artery thrombosis (22).

In our study, we reported a 12% incidence of BCs, with a particular focus on non-anastomotic biliary stenosis, which accounted for 9.8% of the cases. However, it's important to note that the majority of our observed stenoses were of the anastomotic type (87.5%), typically associated with various technical factors, including discrepancies in biliary tract caliber between the donor and recipient, reconstruction techniques, materials used, the presence of drains, excessive dissection, prolonged organ ischemia time, donor age, and ischemic events (12,13).

Our analysis of non-anastomotic biliary stenosis occurrence suggested that technical factors may play a significant role, as variables such as cold ischemia time, donor age, and arterial thrombosis were not statistically significant. While CMV infection was more prevalent among patients who developed biliary stenosis, most cases were still anastomotic.

The discrepancies observed between various studies in the incidence and significance of CMV infection in the development of post-liver transplant BCs can be attributed to differing definitions, diagnostic imaging techniques, and the variation in follow-up periods among studies. Therefore, the implications of CMV infection in non-anastomotic biliary stenosis development remain a subject of debate in the literature. Our study, however, emphasizes the significance of CMV presence prior to the diagnosis of BCs, particularly non-anastomotic biliary stenosis, and suggests that a MELD score exceeding 21 may be a key factor influencing these developments. Further research is warranted to clarify the intricacies of this relationship and to explore potential preventive strategies and interventions to optimize patient care in the context of LT.

Explanations of findings

The lack of a direct association between CMV infection and non-anastomotic biliary stenosis in our study prompts the need to delve deeper into the mechanisms behind the development of BCs post-LT. While earlier research, such as the study by Gotthardt *et al*., suggested a potential link between occult CMV infections in the biliary tract and non-anastomotic biliary stenosis (16), our findings underscore the complexity of this relationship. It is plausible that the occurrence of BCs involves multifactorial elements, including technical factors in the surgical procedure, graft quality, and immunological responses.

The pronounced impact of a MELD score exceeding 21 on the occurrence of BCs, particularly non-anastomotic biliary stenosis, raises questions about the interplay between liver function and the risk of complications. This might reflect the deteriorating hepatic function in patients with higher MELD scores, which could affect biliary duct integrity or regenerative capacity, potentially leading to biliary stenosis. It's crucial to recognize that LT patients are a diverse population, and individual patient characteristics may greatly influence their outcomes.

Further exploration into the role of CMV infection before stricture diagnosis and the MELD score in the context of BCs is warranted. Elucidating the intricate factors involved in biliary stricture development can potentially guide tailored interventions to reduce these complications, such as optimizing patient selection, graft management, and post-transplant monitoring.

Implications and actions needed

The findings of this study have implications for clinical practice and future research. While the direct link between CMV infection and non-anastomotic biliary stenosis remains inconclusive, clinicians must recognize the significance of CMV infection before stricture diagnosis and a high MELD score as potential risk factors for the development of BCs in liver transplant recipients. This knowledge can aid in risk assessment and patient management.

In clinical practice, it is imperative to monitor patients with these identified risk factors more closely during the post-transplantation period. Early detection and intervention may help mitigate the impact of BCs, particularly in patients with high MELD scores or a history of CMV infection.

Future research should focus on unraveling the multifaceted nature of BCs following LT. Investigations should explore the interplay of various factors, including immunological responses, graft quality, and surgical techniques. This will lead to a more comprehensive understanding of the causes and risk factors of these complications, ultimately guiding strategies to reduce their

incidence.

Furthermore, the potential benefits of prophylactic measures, such as antiviral therapy, should be explored to mitigate the risk of CMV infection and its consequences. Continued research efforts in this area will enhance patient care and improve the long-term outcomes of LT.

Conclusions

In conclusion, our study sheds light on the intricate landscape of BCs in liver transplant recipients. While the direct association between CMV infection and non-anastomotic biliary stenosis did not emerge as a singular risk factor in our findings, we identified the significance of CMV infection before stricture diagnosis and a MELD score exceeding 21 as contributors to the development of BCs. These findings underscore the multifactorial nature of BCs and emphasize the need for comprehensive risk assessment and close monitoring of patients with these identified risk factors.

This research contributes to the ongoing quest to optimize patient care in LT and provides a basis for future investigations to unravel the complex mechanisms behind BCs. By deepening our understanding of these processes, we can develop strategies to reduce the incidence of BCs and enhance the long-term outcomes of liver transplant recipients.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tgh.amegroups.com/article/view/10.21037/tgh-23-110/rc

Data Sharing Statement: Available at https://tgh.amegroups.com/article/view/10.21037/tgh-23-110/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tgh.amegroups.com/article/view/10.21037/tgh-23-110/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional Ethics Committee of Felicio Rocho Hospital (CAAE: 77877417.9.1001.5125). All subjects gave their informed consent for inclusion before they participated in the study.

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