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ORIGINAL PAPER

Long-Term Survival after Orthotopic Liver Transplant: 20-year analysis at a Transplant Center in Campinas, Brazil

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ABSTRACT

Introduction: Orthotopic liver transplantation (OLT) is the primary therapy for end-stage liver disease. In Brazil, the number of liver transplants has significantly increased over the past decades, improving long-term outcomes. This study analyzes the long-term survival of patients who underwent OLT over 20 years at a reference transplant center. **Methods:** Medical records of 848 patients who underwent OLT between February 1995 and December 2017 were reviewed. Exclusion criteria included patients with survival below six months to minimize the impact of early postoperative complications on long-term outcomes. Thus, 174 patients were included. The analyzed variables involved the recipient, donor, graft, surgical procedure, and postoperative evolution. Survival was assessed using Kaplan–Meier analysis. **Results:** Among the 174 analyzed patients, 98 (56.3%) remained in outpatient follow-up, while 76 (43.7%) died. The mean age at transplantation was 47 years, and 75% of recipients were male. The main indications were viral hepatitis (59.8%) and hepatocellular carcinoma (11.6%). The mean MELD score was 18. The leading cause of death was cardiovascular events (36.4%), followed by liver disease recurrence (22.1%) and malignancies (15.6%). The mean survival time was 223 months for surviving patients and 112 months for deceased patients ($p < 0.0001$). Longer cold ischemia time, postoperative renal dysfunction, diabetes, and prolonged stay in the intensive care unit were associated with worse survival. Younger patients had significantly longer survival ($p = 0.00007$). **Conclusion:** The 20-year analysis demonstrated that OLT provides good long-term survival; however, factors such as diabetes, renal dysfunction, and prolonged cold ischemia time negatively impact the outcomes. Cardiovascular events and recurrence of liver disease were the leading causes of mortality.

Descriptors: Liver Transplantation; Survivorship; Hepatic Insufficiency; Chronic Liver Disease; Hospital Mortality; Prognostic Factors.

Sobrevivência a Longo Prazo após Transplante Ortotópico de Fígado: Análise de 20 anos em um Centro de Transplante em Campinas, Brasil

RESUMO

Introdução: O transplante ortotópico de fígado (TOF) é a principal terapia para doença hepática terminal. No Brasil, a realização de transplantes aumentou significativamente nas últimas décadas, com melhorias nos desfechos a longo prazo. Este estudo analisa a sobrevida de pacientes submetidos a TOF ao longo de 20 anos em um centro de referência. **Métodos:** Foram revisados os prontuários de 848 pacientes transplantados entre fevereiro de 1995 e dezembro de 2017. Aplicaram-se critérios de exclusão, incluindo pacientes com sobrevida inferior a 6 meses, visando minimizar o impacto de complicações precoces no desfecho de longo prazo. Dessa forma, 174 pacientes foram incluídos. As variáveis analisadas envolveram dados do receptor, doador, enxerto, procedimento cirúrgico e evolução pós-operatória. A sobrevida foi avaliada por Kaplan–Meier. **Resultados:** Dos 174 pacientes analisados, 98 (56,3%) mantiveram seguimento ambulatorial e 76 (43,7%) evoluíram a óbito. A média de idade no transplante foi de 47 anos, e 75% dos receptores eram do sexo masculino. As principais indicações foram hepatite viral (59,8%) e carcinoma hepatocelular (11,6%). A média do escore MELD foi 18. A principal causa de morte foi evento cardiovascular (36,4%), seguido de recidiva da doença hepática (22,1%) e neoplasias (15,6%). O tempo médio de sobrevida foi de 223 meses

entre os pacientes vivos e 112 meses entre os óbitos ($p < 0,0001$). Maior tempo de isquemia fria, insuficiência renal pós-operatória, diabetes e maior tempo de internação em UTI foram fatores associados a pior sobrevida. Pacientes mais jovens apresentaram sobrevida significativamente superior ($p = 0,00007$). **Conclusão:** A análise de 20 anos mostrou que o TOF apresenta boa sobrevida a longo prazo, mas fatores como diabetes, disfunção renal e tempo prolongado de isquemia fria impactam negativamente os desfechos. Eventos cardiovasculares e recidiva da doença hepática foram as principais causas de mortalidade.

Descritores: Transplante de Fígado; Sobrevida; Insuficiência Hepática; Doença Hepática Crônica; Mortalidade Hospitalar; Fatores Prognósticos.

INTRODUCTION

Orthotopic liver transplantation (OLT) is a well-established therapy for end-stage liver failure, providing improved survival and quality of life for recipients. Advances in surgical techniques, perioperative management, and immunosuppression have significantly increased the longevity of liver transplant recipients. However, long-term complications, such as graft dysfunction, liver disease recurrence, cardiovascular events, and malignancies, remain major challenges.

Brazil has one of the largest public organ transplant programs in the world, with most liver transplants performed under the Unified Health System. Despite significant progress, long-term survival in Brazilian populations remains underexplored, and identifying predictive mortality factors is crucial for optimizing post-transplant outcomes. International studies indicate that recipient age, cold ischemia time, diabetes, renal dysfunction, and prolonged stay in the intensive care unit (ICU) may negatively impact survival[1-3]. However, there is a lack of national data evaluating these variables over an extended follow-up period.

This study analyzes the long-term survival of patients who underwent OLT over 20 years at a reference transplant center, aiming to identify risk factors associated with mortality and assess patient quality of life during late follow-up. Understanding these factors may assist in clinical decision-making and improve post-transplant management strategies.

METHODS

The scientific protocol for the conducted study has been approved by the Research Ethics Committee of the State University of Campinas. The committee understands that the free and informed consent term was not necessary, as the study involves a survey of clinical records.

Medical records of 848 patients who underwent OLT from February 1995 to December 2017 were reviewed and analyzed. All surgeries were performed by the same surgical team. The organ harvesting from deceased donors followed the protocol of our standard surgical technique, organs were preserved using HTK and IGL-1 solutions.

The techniques used in liver implant surgery were total hepatectomy with inferior vena cava preservation (the piggyback technique) or standard conventional technique, both without venovenous bypass. The chosen technique was based on the surgeon's discretion within the intraoperative evaluation.

A descriptive retrospective analysis was conducted based on medical data from those who underwent OLT, from the electronic medical record database of the Hospital de Clínicas of the University of Campinas (HC-Unicamp), located in the city of Campinas, São Paulo state, Brazil. The information was gathered during postoperative follow-up.

Patients younger than 18 years old or with a survival rate (SR) lower than 6 months were excluded. The exclusion of these cases was based on the fact that early mortality is usually associated with surgical and immediate postoperative complications, which were not the focus of the present study.

The analysis covered the following aspects:

- Organ recipient: On the day before OLT, age, sex, body mass index (BMI), Model for End-Stage Liver Disease (MELD), blood glucose, serum sodium, cause of the underlying disease, and creatinine were evaluated.
- Deceased donor: Before organ harvesting, serum sodium, age, and sex were evaluated.
- Donated organ (graft): The cold ischemia total time and organ dysfunction were measured. Expanded criteria donors were considered those meeting at least one of the following conditions: age > 60 years, presence of comorbidities such as diabetes or hypertension, moderate or severe hepatic steatosis (> 30%), or prolonged ICU stay before organ retrieval.
- Surgical procedure: The technique performed within the surgery was considered.
- Postoperative outcomes: ICU stay length, survival length, renal function, and patient global state 6 months and 10 years after OLT were considered.

In addition, the evaluation of clinical criteria such as obesity, renal insufficiency, and glucose levels was performed both preoperatively and during long-term follow-up, allowing us to determine their impact on post-transplant prognosis.

The study also aimed to assess graft survival; however, due to limitations in data collection, this analysis was not included in the initial version of the manuscript. We then incorporated an evaluation of graft survival, which will be detailed in the Results section.

The SR was assessed using the Kaplan–Meier plot and nonparametric test as chi-square and Cox Hazard model. The Liver Disease Quality of Life (LDQOL) questionnaire and Short Form Health Survey (SF-36) were used to assess patients' life quality post-transplant within 6 months and 10 years after the procedure. Values of $p < 0.05$ were considered significant (Statistical 11.0, NY, USA).

RESULTS

After applying the exclusion criteria, 174 patients who underwent liver transplantation at HC-Unicamp between 1995 and 2017 were included in the final analysis. Among them, 98 patients (56.3%) survived and have been followed up on an outpatient basis, while 76 patients (43.7%) died during the analyzed period.

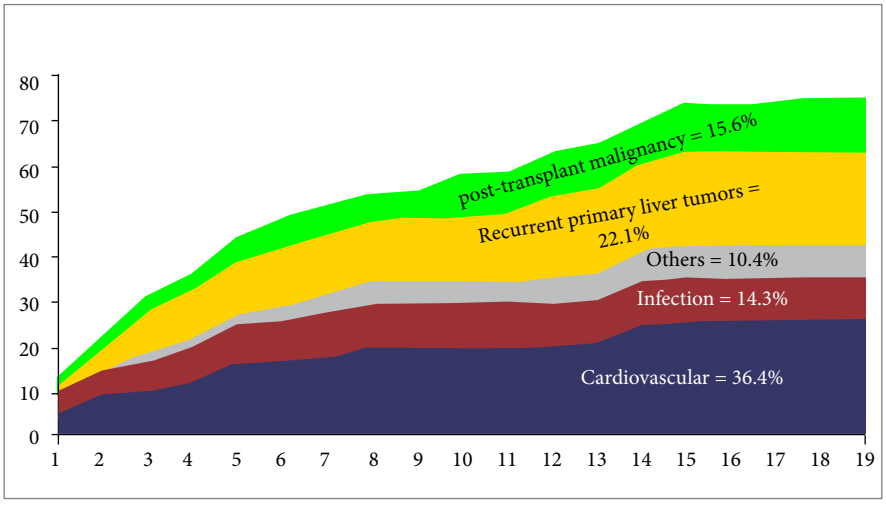
Regarding the recipient's medical records, the mean age at the time of transplantation was 47 years. Male patients accounted for 75% of cases. Obesity was present in 14% of patients, with an average BMI of 25. The primary indications for transplantation were viral hepatitis (59.8%) and alcohol-related cirrhosis (11.6%), followed by hepatocellular carcinoma (HCC) (11.6%).

The average MELD, CTP, and serum sodium values were 18 (range: 8–31), 10 (range: 6–15), and 136 mEq/L (range: 113–147 mEq/L), respectively.

The leading causes of donor brain death were traumatic brain injury (43%) and stroke (35%), with a predominance of male donors (65%). The average cold ischemia time was 690 min (range: 360–1,200 min), corresponding to 6 to 20 h. Mild or moderate steatosis was observed in 27% of donor livers, while 48% of donors met expanded criteria, as defined by the United Network for Organ Sharing classification. The average donor glucose level was 95 mg/dL (range: 62–291 mg/dL).

The mean ICU stay was 6 days (range: 2–240 days). Patients required an average of 4 red blood cell transfusions (range: 0–27 units) per transplant. Renal function was assessed through pre- and post-transplant creatinine clearance, with mean values of 103 mL/min (range: 39–165 mL/min) pretransplant and 69 mL/min (range: 30–165 mL/min) post-transplant.

The long-term analysis revealed that cardiovascular events (36.4%) were the primary cause of death, followed by liver disease recurrence (22.1%), neoplasms (15.6%), and infections (14.3%) (Fig. 1).

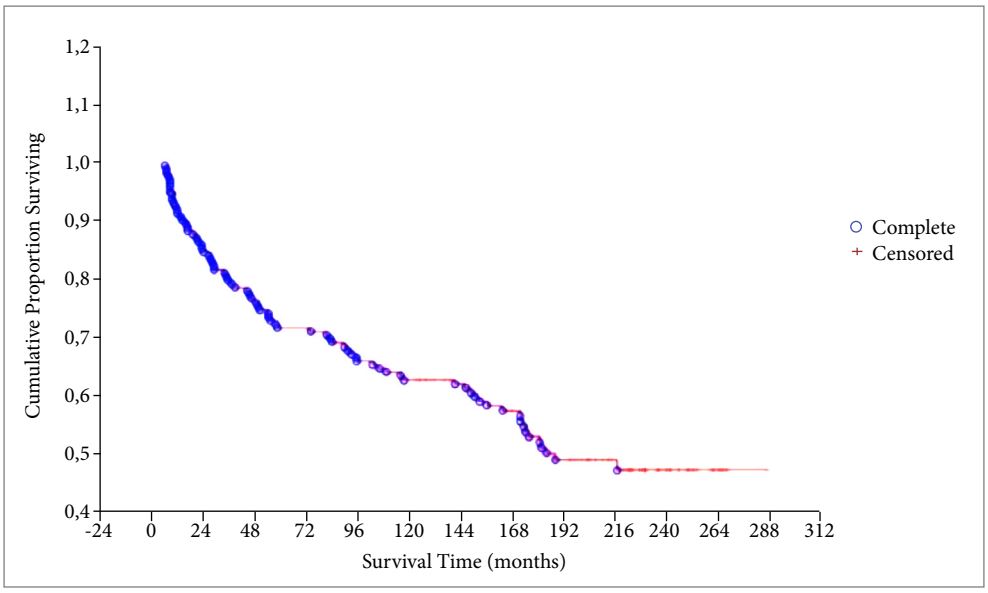


Source: Elaborated by the authors.

Figure 1. Cumulative value of causes of death per year of 76 patients followed up between 1995 and 2007.

The average SR was 223 months for patients still under follow-up and 112 months for deceased patients ($p = 0.0001$).

Figure 2 illustrates the overall SR.

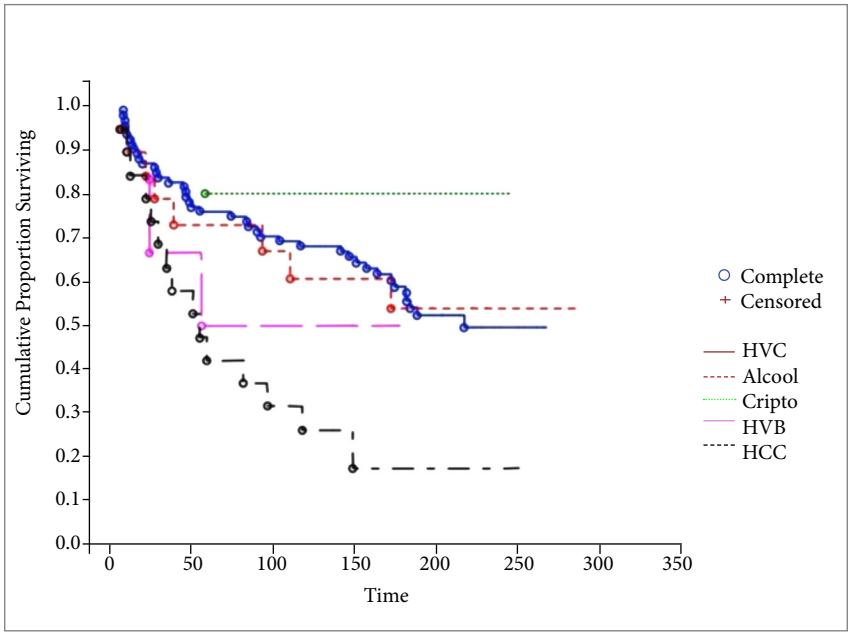


Source: Elaborated by the authors.

Figure 2. Overall survival rate after liver transplant in 174 patients followed up between 1995 and 2007.

The younger age of the recipient significantly impacted survival outcomes ($p = 0.00007$). Additionally, increased cold ischemia time, worsening creatinine clearance after transplantation, diabetes, and prolonged ICU stay were identified as significant risk factors for mortality.

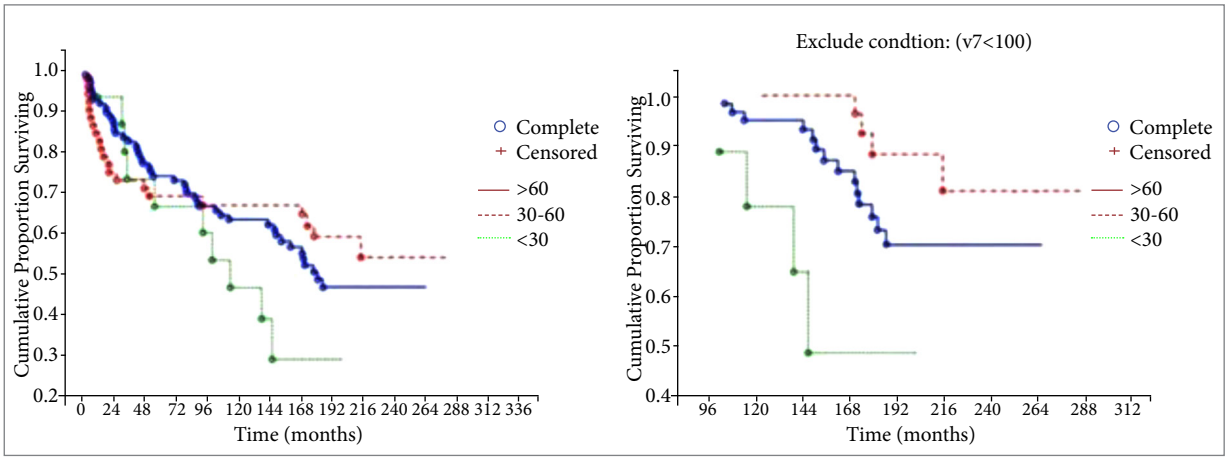
Regarding the etiology of liver disease leading to transplantation (Fig. 3), patients with HCC had higher mortality compared to those with viral hepatitis. However, viral hepatitis-related cases demonstrated post-transplant SRs similar to alcohol-related cirrhosis cases. The highest SRs were observed in patients with cryptogenic cirrhosis.



Source: Elaborated by the authors.
Note: (HVC) hepatitis C; (Alcool) alcohol; (Cripto) Cryptogenic cirrhosis; (HVB) hepatitis B; (HCC) hepatocarcinoma.

Figure 3. Cumulative survival proportion regarding the cause that led to liver transplantation.

Graft survival analysis has now been included to address previous gaps in the study (Fig. 4). Patients with post-transplant creatinine clearance below 30 mL/min had significantly lower SRs compared to those with creatinine clearance above 30 mL/min.

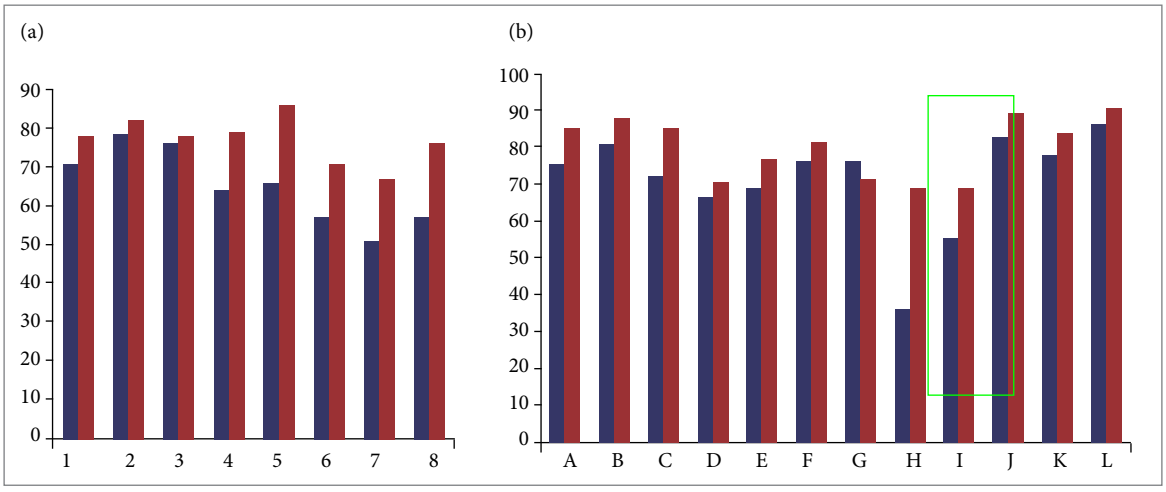


Source: Elaborated by the authors.
Note: Lines are related to three groups: (1) creatinine clearance < 30 mL/min; (2) creatinine clearance 30–60 mL/min; (3) creatinine clearance > 60 mL/min.

Figure 4. Cumulative survival proportion regarding post-transplant renal function.

A statistically significant association was observed between prolonged cold ischemia and reduced survival (hazard ratio [HR] 1.004; 95% confidence interval [CI] 1.002–1.006; $p < 0.0001$), obesity (HR 5.825; 95% CI 2.000–16.969; $p = 0.0012$), prolonged ICU stay (HR 1.014; 95% CI 1.003–1.024; $p = 0.0112$), grade III graft failure (HR 3.027; 95% CI = 1.278–7.166; $p = 0.0118$), and impaired renal function post-transplant (HR 1.035; 95% CI = 1.016–1.054; $p = 0.0001$).

Regarding quality of life, we applied two clinical assessment tools: the SF-36 and the LDQOL questionnaire. The results, now expanded, indicate that sleep disturbances and sexual dysfunction were the most reported issues among both male and female patients, potentially influenced by emotional and physical factors.



Source: Elaborated by the authors.
Note: (1) General health; (2) Functional capacity; (3) Physical limitations; (4) Emotional limitations; (5) Social aspects; (6) Pain; (7) Sexual activity; (8) Mental health. (A) Symptoms of liver disease; (B) Effects of liver disease; (C) Concentration; (D) Memory; (E) Social aspects; (F) Worry about the disease; (G) Sexual activity; (H) Sexual problems; (I) Sleep quality; (J) Loneliness; (K) Hopefulness; (L) Clinical aspects of liver disease.

Figure 5. SF-36 and LDQOL scores. Blue columns are men and red columns are women.

DISCUSSION

The retrospective study performed by Wong et al. used the United Network for Organ Sharing database from 2014 to 2019, with 51,329 adults, for a cohort study to evaluate trends in liver disease etiology among adults registered for liver transplantation (LT) waiting lists in the United States. The study found that nonalcoholic steatohepatitis (NASH) and alcoholic liver disease (ALD) have become the most common etiologies of liver disease among LT waiting list registrants without HCC,

and NASH is becoming a leading indication in patients with HCC[4]. In the present study, most LT was performed due to viral hepatitis (59.8%), alcohol (11.6%), and HCC (11.6%).

Early complications can be mentioned, such as vascular complications (e.g., hepatic artery and/or portal vein thrombosis; usually in the early postoperative period); biliary complications (e.g., stricture, biliary leak, cholangitis, sphincter of Oddi dysfunction and stone disease; usually in 6–12 months after transplant); post-transplant malignancy (e.g., recurrent primary liver tumors, such as hepatocellular or cholangiocarcinoma; tumors associated with immunosuppression, such as Kaposi sarcoma and nonmelanotic skin cancers; metastases and post-transplant lymphoproliferative disorder). Specifically, Lima et al. showed that low recipient International Normalized Ratio before the operation, bile duct diameter < 3 mm, and positive antigenemia for Cytomegalovirus or disease manifestation is correlated with biliary complications[5]. The present study excluded the first six months of mortality; therefore, the authors missed a relatively large number of patients with early postoperative data regarding early complications.

The present data showed that prolonged cold ischemia time, length of ICU stay, and patient mean age are related to increased mortality, in agreement with other studies. However, the results have shown a considerable survival gain in active years in the last decade when compared to the first 10 analyzed years. Probably, the improving SR over the years is secondary to several factors, including better patient selection, advances in surgical and anesthesia techniques, enhanced perioperative care, antibiotics, and immunosuppression.

In a study with three clinical centers based on the National Institute of Diabetes and Digestive and Kidney Diseases Liver Transplantation Database between April 1990 to June 1994, with 798 patients and a median follow-up of 10 years, 327 died, mainly by hepatic-related causes (28%), and approximately 2/3 of all deaths occur after the first post-transplant year. Hepatitis C, retransplantation, post-LT diabetes, hypertension, and renal insufficiency were significant risk factors for liver-related death with graft failure. Other important causes were malignancy (22%), cardiovascular events (11%), infection (9%), and renal failure (6%). Risk factors for overall death > 1 year (univariate) were: male sex, age/decade, pre-LT diabetes, post-LT diabetes, post-LT hypertension, post-LT renal insufficiency, retransplantation > 1 year, pre-LT malignancy, ALD, and metabolic liver disease, with similar risks noted for death > 5 years. Differently from the literature presented, the highest mortality rate found in this study after OLT was related to cardiovascular events, accounting for 36% of all deaths, while the highest mortality in the US and UK remained malignancy, whether primary, metastatic or recurrent[6]. On the other hand, malignancy was allocated second place among the causes of death in the present study, which leads us to question whether the disagreeing results are associated with populational factors, aspects of primary health care, or even the biomolecular characteristics of the patients' liver neoplasms.

Nitski et al. showed predictive variables for graft-related mortality, such as Hepatitis C Virus as indication for LT, donor age, rejection after transplantation, post-LT diabetes, hypertension, and adrenal insufficiency.[7]

In Brazil, a prospective study tracked 252 liver transplant patients over one year and found a 30-day SR of 79.76%, with an average MELD score of 21.17. For patients with MELD scores up to 12 across all three indices (n = 172), the 30-day SR was 87.79%, while it was 36.36% for those with scores over 12. This 12-point threshold is clinically useful for predicting post-transplant outcomes[8]. In the present study, the mean MELD score was 18, which may account for improved results in early postoperative care.

Unfortunately, most liver transplants in Brazil, as in this study, are performed with deceased donor liver transplant (DDLT), mainly due to the barriers of Western culture. Living donor liver transplant (LDLT) has been culturally well-accepted in Brazil in the pediatric population. Asian and European countries have performed LDLT for more than two decades. As an example, since the first LDLT in June 1990 up to April 2020, nearly 2,000 LTs have been performed at Kyoto University; only 80 (4%) have been DDLT. Similar to other Japanese institutions, the vast majority of LT (96%) are thus LDLTs. A recent Japanese article showed an SR of over 95% within a one-year follow-up. The author showed the institution's protocol for such results: left graft first had a lower complication rate than right lobe graft donors (18.8% v. 44.2%; $p < 0.001$); portal vein pressure modulation with splenectomy, shunt ligation, and other procedures based on the portal pressure; laparoscopic-assisted living donor hepatectomy; expanded criteria for LDLT for HCC (Kyoto criteria); diagnosing and treating infection promptly and discriminating infection from rejection with procalcitonin (PCT), cutoff levels of 0.5 and 2.0 ng/mL could be useful to diagnose bacteremia or its absence, associated with hand hygiene with contact precautions, and nutritional support.[9]

The increasing potency of immunosuppression agents resulted in significantly decreased rates of steroid resistant rejection and rejection-related graft loss. After the introduction of calcineurin inhibitors (CNI), they soon became the first line of immunosuppression drugs in most LT centers both in Europe and the US. Currently, the present authors and most Brazilian transplant centers gradually taper off glucocorticoids after immunosuppression induction, and use CNI, particularly tacrolimus, in the long term, associated with MPA (inosine monophosphate dehydrogenase inhibitor) as CNI sparing agent, to avoid nephrotoxicity[2,10]. Special cases, such as autoimmune disease and graft rejection, may require medication optimization,

such as azathioprine and other immunosuppressive medications, respectively[11-13]. The present results have not demonstrated a significant impact on overall mortality during the analyzed period regarding immunosuppressant therapy. This data may be justified by the fact that the same standard immunosuppression protocol has been used at the institution over the last 20 years. This also raises the hypothesis that the high mortality from hepatitis C virus and malignancy may be associated with more intense immunosuppression rates that not only prevented graft rejection but also provided a favorable environment for hepatospecific neoplastic lines. In previous studies, sirolimus and tacrolimus trough levels in the University Health Network dataset were important variables for cancer-related mortality.[11-13]

Liver transplant recipients experience notable improvements in SR and quality of life post-transplant compared to their preoperative condition. However, they still face higher morbidity and mortality rates than the general population, largely due to lifelong immunosuppressive therapy and its adverse effects[10,14]. Extended use of immunosuppressants is linked to increased risks of diabetes, hypertension, dyslipidemia, renal dysfunction, and cancers. A Nordic multicenter study comparing survival between LT recipients (n = 299) and a matched general population revealed that transplant recipients who lived past the first postoperative year had a 2.4-fold higher risk of death and a 5.8-fold higher risk of premature death (before age 75)[15]. Notably, four out of five deaths were related to immunosuppressive therapy, including malignancies, cardiovascular disease, and infections. In this study, long-term analysis indicated that immunosuppression-related causes accounted for three of the four primary mortality factors: cardiovascular events (36.4%), neoplasms (15.6%), and infections (14.3%).

Retrospective studies from single centers have examined predictors of long-term complications in LT patients at a population level. In liver transplants, factors such as male sex, advanced recipient age, post-transplant diabetes, hypertension, renal dysfunction, fibrosis biomarkers, Caucasian race, nonalcoholic fatty liver disease as the reason for transplantation, donor age, and graft type (deceased v. living) have been identified as outcome influencers. This article primarily aimed to validate machine learning algorithms that could provide LT recipients with 1-year and 5-year survival estimates for the four leading causes of mortality—cardiovascular issues, graft failure, malignancies, and infections—at any post-transplant point. Findings suggest that machine learning could improve post-transplant management, especially in areas with limited clinical guidelines due to a lack of definitive research.[16-19]

In this study, renal function was estimated pre- and post-transplant via creatinine clearance, showing average levels of 103 mL/min pretransplant and 69 mL/min post-transplant. This decline could heighten cardiovascular mortality risk, as previous studies have associated serum creatinine levels 12 months post-LT with long-term cardiovascular events and mortality risk.[16,20,21]

Lastly, younger LT recipients, averaging around 40 years, showed better overall survival, similar to findings from the UK and US. In a comparison by Gil et al. between middle-aged and elderly LT recipients (> 70 years), the mortality risk was found to be approximately four times higher in recipients over 70 (odds ratio [OR] 4.1; 95% CI 2.21–7.58) and nearly three times higher when adjusted for liver disease and perioperative complications (OR 2.92; 95% CI 1.37–6.24). Additionally, the costs associated with LT increased with recipient age, underscoring the need for caution when considering LT in elderly patients[22]. A systematic review and meta-analysis further supported these findings, showing increased mortality associated with older recipient age (HR 2.07, 95% CI 1.71–2.50, $p = 0.40$)[23]. In Brazil, patients over the age of 70 must receive approval from the State Technical Chamber before undergoing LT.

CONCLUSION

Orthotopic liver transplantation has proven to be an effective therapy for end-stage liver disease and HCC, providing an excellent cumulative SR. The rates should be better in the future as the medication efficiency is still improving regarding viral hepatitis treatment and HCC's early detection. The established risk factors for death in patients undergoing liver transplantation were prolonged graft cold ischemia, longer ICU stay, presence of diabetes in the recipient, and renal dysfunction. Cardiovascular events and the recurrence of the underlying liver disease have been cited as the main causes of death in the long-term analysis.

CONFLICT OF INTEREST

Nothing to declare.

AUTHOR'S CONTRIBUTION

Substantive scientific and intellectual contributions to the study: Ivano VK, Jucá RH; **Conception and design:** Ivano VK, Jucá RH; **Data analysis and interpretation:** Ivano VK, Jucá RH, Martins Neto AN; **Article writing:** Ivano VK, Jucá RH, Martins Neto AN; **Critical revision:** Boin IFSF, Kreve F, Diniz T, Foratto A, Munhoz DC, Ricetto E, Alves C, Perales SR, Ataide EC; **Final approval:** Boin IFSF.

DATA AVAILABILITY STATEMENT

All datasets were generated or analyzed in the current study.

FUNDING

Not applicable.

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