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Trends in indications and outcomes of liver transplantation in Canada: A multicenter retrospective study

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SUMMARY

The liver transplantation (LT) landscape is continuously evolving. We sought to evaluate trends in indications for LT in Canada and the impact of primary liver disease on post-LT outcomes using a national transplant registry. Adult patients who underwent a primary LT between 2000 and 2018 were retrospectively identified in the Canadian Organ Replacement Registry. Outcomes included post-LT patient and graft survival. A total of 5,722 LTs were identified. The number of LT per year increased from 251 in 2000 to 349 in 2018. The proportion of patients transplanted for HCV decreased from 31.5% in 2000 to 3.4% in 2018. In contrast, the percentage of transplants for HCC increased from 2.3% in 2000 to 32.4% in 2018, and those performed for NASH increased from 0.4% in 2005 to 12.6% in 2018. Year of transplant (per 1 year) was protective for both patient (HR:0.96,95%CI:0.94-0.97; $P < 0.001$) and graft survival (HR:0.97, 95%CI: 0.96–0.99; $P = 0.001$). Post-LT outcomes have improved over time in this nationwide analysis spanning 18 years. Moreover, trends in the indications for LT have changed, with HCC becoming the leading etiology. The decrease in the proportion of HCV patients and increase in those with NASH has implications on the evolving management of LT patients.

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Introduction

Liver transplantation (LT) is the definitive treatment for end-stage liver disease (ESLD) [1]. In recent decades, the outcomes of LT have improved, and in many countries, 5-year survival rates exceed 70% [2,3]. Approximately 400 patients annually will receive a LT in Canada while the waitlist mortality ranges from 15 to 20% and has remained relatively stable [4–6]. To address the waitlist mortality, there have been changes to the allocation and use of marginal grafts [2,3].

Listing criteria for LT in Canada has evolved over the last two decades, not only because of the changing prevalence of liver disease but also as novel medical therapies evolve [6]. The type of donor used and the underlying liver disease heavily influences post-transplant outcomes, and therefore, the monitoring of changes in the indication for LT is vital for patients, clinicians, and policymakers [3,7]. The introduction of direct-acting antiviral (DAA) medications has almost eradicated hepatitis C (HCV) as an indication for LT in some countries [7,8]. In contrast, the rising prevalence of obesity and diabetes, particularly in the Western world, has exponentially increased transplantation for nonalcoholic steatohepatitis (NASH), while the successful transplantation of hepatocellular carcinoma (HCC) has led it to become the most common indication for LT in the UK and elsewhere [2,9–11]. Though there are previous reports on transplant trends from the United States [3] and Europe [2], a contemporary temporal analysis of trends and outcomes after liver transplantation in Canada has yet to be performed. In contrast to the United States, Canada represents a country with a universal healthcare system, a smaller number of centers (with resultant regionalization), and one of the highest living donor liver transplant proportions in the west [6]. Because LT represents a highly standardized surgical practice, large-scale national evaluations offer an opportunity to glean insight into differential practice patterns, trends, and outcomes across countries. This carries the potential for identifying areas for future quality improvement which may be of benefit to transplant patients globally.

Given the implications of primary liver disease on both the prioritization of patients on the waiting list and on post-transplant outcomes, we performed an exploratory analysis of the Canadian Organ Replacement Registry (CORR) from 2000 to 2018 to determine changes over time in the indication and post-transplantation outcomes for LT.

Patients and methods

Canadian organ replacement registry

The CORR dataset contains detailed information about all liver transplants carried out since 2000 in six liver transplant centers in Canada, representing all the Canadian provinces except Quebec [6]. The dataset is currently managed by the Canadian Institute for Health Information (CIHI) and is subject to internal checks [6,12].

Study population

Adult patients (age≥18 years) undergoing a first LT between 2000 and 2018 were included. To limit the study cohort's heterogeneity, patients receiving re-transplantation and multiorgan transplants were excluded (Figure 1). This study received REB approval (REB#19-5835) by the University Health Network. This study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for reporting observational research [13].

The study population was stratified into ten groups using the CORR organ diagnosis codes and was based on a classification used by Roberts et al. in a previous analysis of the United Network of Organ Sharing (UNOS) dataset [14,15], which categorized based on disease etiology at the time of listing: acute liver failure (ALF), hepatitis C virus (HCV), primary sclerosing cholangitis (PSC), hepatitis B virus, primary biliary cholangitis (PBC), alcohol-related liver disease (ALD), HCC, autoimmune and cryptogenic (AID), and metabolic liver diseases (MET; including NASH). Disease classification was performed in a hierarchical order: cancer, HCV, PSC, PBC, ALD, AID, MET, and others [14,15]. For example, a patient diagnosed with both HCV and HCC would be assigned to the HCC category [14,15]. A full grouping description of the liver disease classification is shown in Table S1.

Covariates

Donor and recipient characteristics were recorded. Continuous variables included donor age, donor body mass index (BMI), distance from donor procurement to the facility of LT, warm ischemia time (WIT), cold ischemia time (CIT), rewarm time (defined as the time in minutes between the removal of the organ from cold storage and reperfusion in the recipient), recipient age at transplant, recipient BMI, time on the waitlist, serum

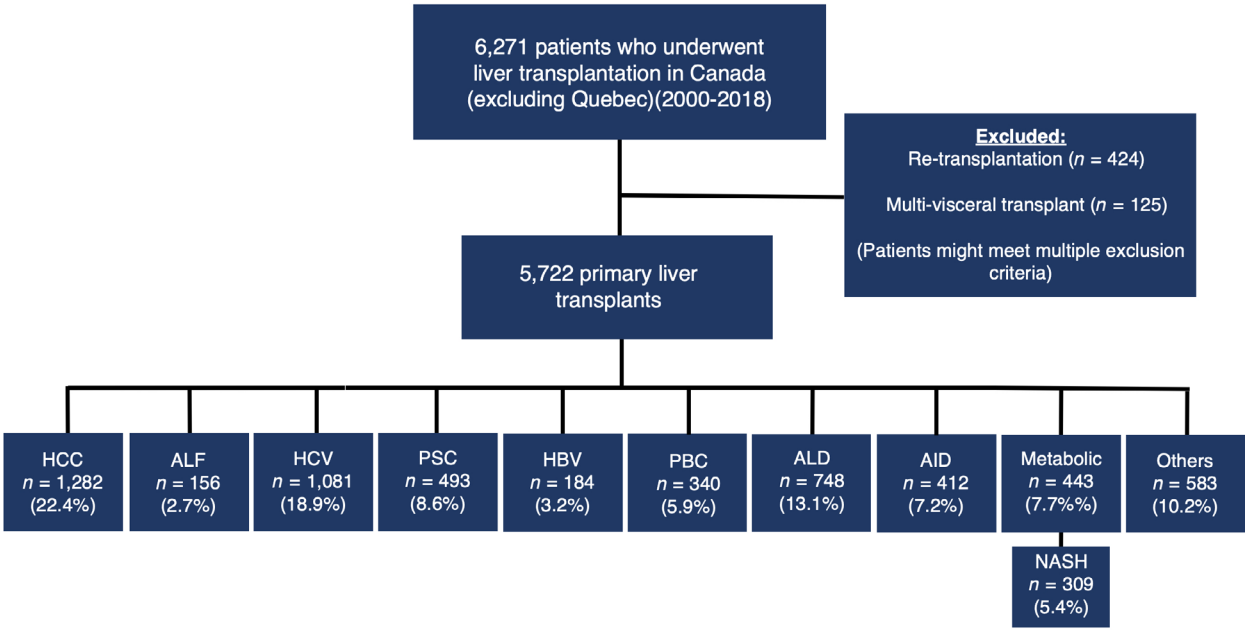

Figure 1 Patient flowchart.

bilirubin (mg/dL), international normalized ratio (INR), Child–Pugh score, creatinine (mg/dL), and Model for End-stage Liver Disease (MELD) score. Categorical variables include donor smoking status, history of hypertension, history of diabetes, ethnicity, use of deceased after circulatory death liver allograft, donor blood type, donor cause of death, recipient sex, recipient ethnicity, recipient blood type, type of graft used (whole liver, left lobe, right lobe, and left lateral segment), and recipient medical status at the time of transplant. The recipient medical status in Canada refers to a patient's status at the time of listing and provides a measure of illness severity. Prior to adoption of the MELD-score-based system, it was also used for organ allocation before the MELD-score-based system (i.e., the CanWAIT algorithm) [16]. As such, the categorization is as follows: Status 1 and Status 1T refers to patients who are at home, or are tumor patients (typically HCC), respectively; Status 2 are hospitalized patients; Status 3 are hospitalized in the intensive care unit (ICU); Status 3F have fulminant hepatic failure in the ICU; Status 4 patients are in the ICU incubated and ventilated; and Status 4F are Status 4 patients with fulminant liver failure.

Outcome measure

Patient and graft survival from the time of transplant were compared among disease etiologies. Both unadjusted and adjusted survival analyses were performed. Patients were censored at death or last known follow-up. All patients were followed up to 31 December 2018 or last known follow-up. The median follow-up time for the entire patient cohort was 71.0 months (IQR 25.4–129.6).

Statistical analyses

Descriptive data for continuous variables were expressed as means with standard deviation if the distribution was normal and median with interquartile range (IQR) for non-normal distributions. These were compared using the Student's *t*-test and Mann–Whitney U-test, respectively. Categorical variables were expressed as numbers and percentages and compared using the chi-square test. Trend analysis for LT performed over time was implemented using the nonparametric Cox-Stuart trend test, based on the binomial distribution. Patient survival was analyzed from the time of LT to death or last known follow-up using the Kaplan–Meier method and groups compared with log-rank tests. Multiple pairwise comparisons between groups with corrections for multiple testing were performed using the Benjamini–Hochberg method. Analyzed time points included 1-, 3-, 5-, and 10-year post-LT.

Cox proportional hazard regression models were built to identify predictors for post-LT patient survival, adjusting for donor and recipient characteristics. Graft

loss was assessed using a cumulative incidence approach with death considered a competing event for graft loss [17]. Cumulative incidence was calculated using subdistribution estimates for each cause (graft and death). A Gray's modified log-rank test was used to compare subdistribution estimates for each cause (unadjusted incidence estimates) and to evaluate the quality of the cumulative incidence curves [18]. Multiple pairwise comparisons between groups with corrections for multiple testing were performed using the Bonferroni's method. To assess the relative change in the hazard of graft failure, a proportional subdistribution hazards' regression model using Fine and Gray competing risk was used to account for death as a competing event [19]. This model allowed the assessment of covariate effects on the subdistribution for graft failure. Variables selected for inclusion in the multivariable models were based on previously identified factors associated with post-LT patient and graft survival [1,20–26]. A *P*-value <0.05 was considered statistically significant.

Missing donor and recipient characteristics were imputed using multivariate imputation by chained equations, creating twenty complete datasets with multivariable analysis results pooled using Rubin's rules [27,28]. Continuous variables were imputed using predictive mean matching, factors with one level using logistic regression, and multilevel factors using polynomial regression. Both complete case analysis and imputed pooled regression results are presented for completion.

All statistical analyses were performed using R (R version 4.0.2 [2020-06-22], R foundation for Statistical Computing, Vienna, Austria URL http://www.R-project.org/). Competing risk analyses were performed using the package "cmprsk" version 2.2-10. The Cox-Stuart test was performed using the package "trend" version 1.1.4. Multiple imputations were performed using the package "mice" version 3.12.

Results

Indications for liver transplantation

A total of 5,722 adult LTs were performed in Canada between 2000 and 2018. The number of transplants per year increased from 251 in 2000 to 349 in 2018 (*P*-value for trend = 0.008) (Figure 2). The proportion of patients transplanted for HCV-related liver disease has decreased from 31.9% in 2000 to 3.4% in 2018. In contrast, the percentage of patients transplanted for HCC has increased from 2.3% in 2000 to 32.4% in 2018.

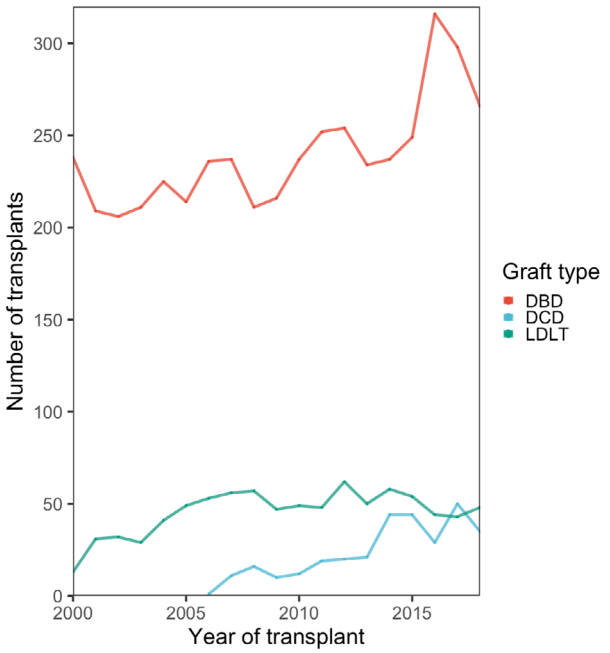

Figure 2 Absolute number of liver graft types used for LT in Canada over time.

Most of this change occurred between 2013 and 2016. For patients with HCC (n = 1,282), additional liver disease etiologies included the following: HCV (n = 310 [24.2%]), ALD (n = 125 [9.8%]), HBV (n = 76 [5.9%]), NASH (n = 32 [2.5%]), PSC (n = 8 [0.6%]), PBC (n = 8 [0.6%]), acute liver failure (n = 1 [0.1%]), and missing/not reported (n = 722 [56.3%]). Furthermore, the proportion of transplants for NASH has progressively increased from 2005 when it represented 0.4% of all transplants, to 12.6% in 2018 (Figure 3).

Comparison of donor and recipient characteristics

Between 2000 and 2018, there were 4,546 (79.4%) LT performed with deceased after brain death donors (DBD), 864 (15.1%) with living donors (LDLT), and 312 (5.4%) with donors after circulatory death (DCD). While the proportion of LDLTs has remained relatively stable between 15 and 20%, the proportion of DCDs has increased from 0.3% in 2006 to 10.0% in 2018 (Figure S1). Recipient, donor, and transplant characteristics can be seen in Table S2 and Table S3.

Post-transplant outcomes

Patient survival

For all indications combined, the 1-, 3-, 5-, and 10-year post-LT survival was 91.1%, 85.5%, 83.9%, and 72.4%

Figure 3 Proportion of patients transplanted annually during 2000–2018 for various indications in Canada.

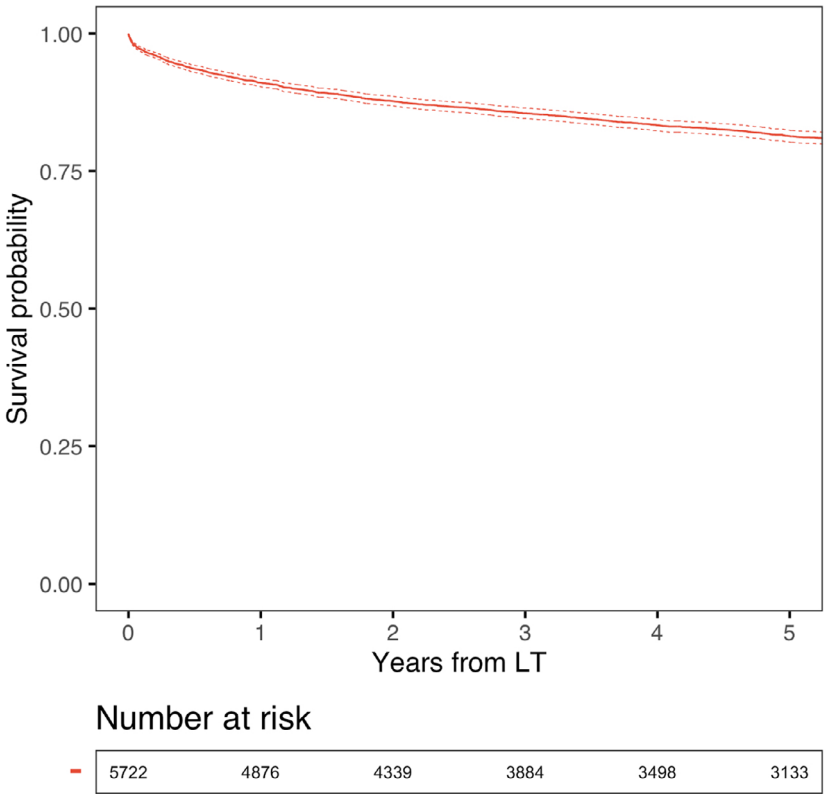

Figure 4 Overall 5-year patient survival with 95% confidence interval.

(Figure 4). Overall patient survival stratified for various disease etiologies is displayed in Figure 5 and described in Figure S2. Though patient survival consistently improved over time for both non-HCV and HCV patients, HCV patients had a more marked improvement after 2009 compared with before (Figures S3 and S4). Multivariable Cox proportional hazards regression analyses, adjusted for recipient and donor variables, demonstrated an etiology of PSC and MET as proportionally most protective for patient survival relative to an indication of HCC. Moreover, the year of transplant also represented an independent protective factor for

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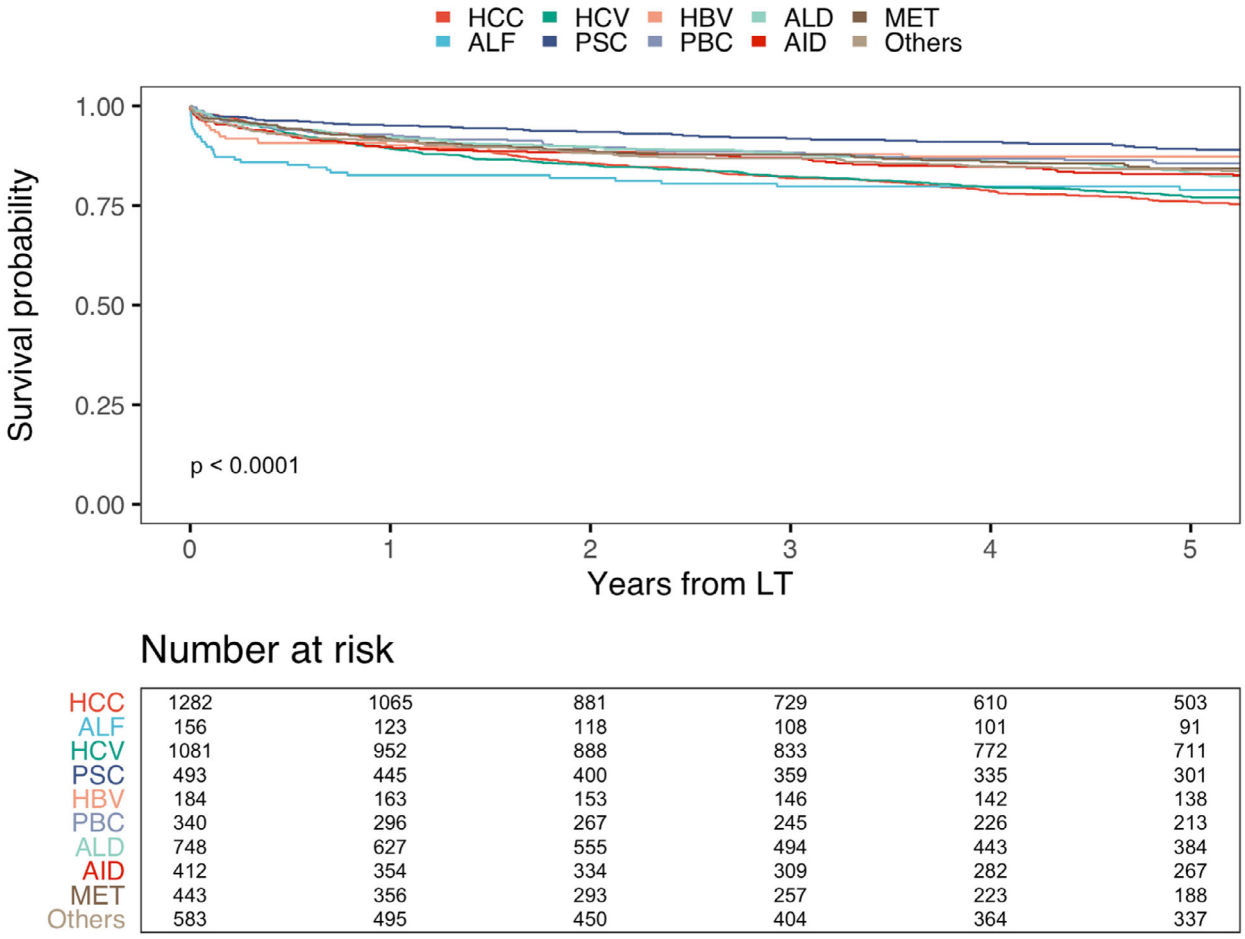

Figure 5 Patient survival comparing patients transplanted for various indications in Canada.

post-LT survival (per year increase HR:0.96, 95%CI: 0.94–0.97; $P < 0.001$) (Table S4). Type of graft was not associated with an increased hazard of death post-LT.

Graft survival

The overall 1-, 3-, 5-, and 10-year post-LT graft survival was 93.5%, 90.7%, 88.8%, and 85.2% (Figure 6, Figure 7 and Figure S5). The cumulative 1-, 5-, and 10-year incidence of graft failure of all first LT was 6.4% (95%CI: 5.7–7.0), 10.7% (95%CI: 9.8–11.5), and 13.7% (95%CI: 12.7–14.7) (Figure S6). The cumulative incidence of graft failure for various etiologies is shown in Figure 7. The cumulative incidence of graft failure in both non-HCV and HCV patients remained overall stable over time (Figures S8 and S9). The cumulative incidence of graft failure by graft type is shown in Figure S10. On Fine-Gray proportional hazard analysis of graft failure, after adjustment for donor and recipient variables, factors associated with graft failure included donor age, CIT, and LDLT. Protective factors for graft failure included a diagnosis of ALD, AID, and MET (ref: HCC). Year of transplant (per 1-year increase) again represented an independent protective factor for graft survival (HR:0.97, 95%CI: 0.96–0.99; $P = 0.001$) (Table S5).

Discussion

To the best of our knowledge, this is the first study to describe the different etiologies and trends in LT in Canada using a multi-institutional national database. Currently, the two most common etiologies for LT are HCC and ALD. Temporally, there has been a substantial increase in the proportion of LT performed for NASH and HCC over time. Conversely, there has been a significant decrease in the proportion of LTs performed for HCV. Notably, through the 18-year study period, both patient and graft survival have increased significantly.

HCC and ALD are the most common etiologies for LT, accounting for 45% of all LTs in Canada. The percentage of patients transplanted for HCC has increased

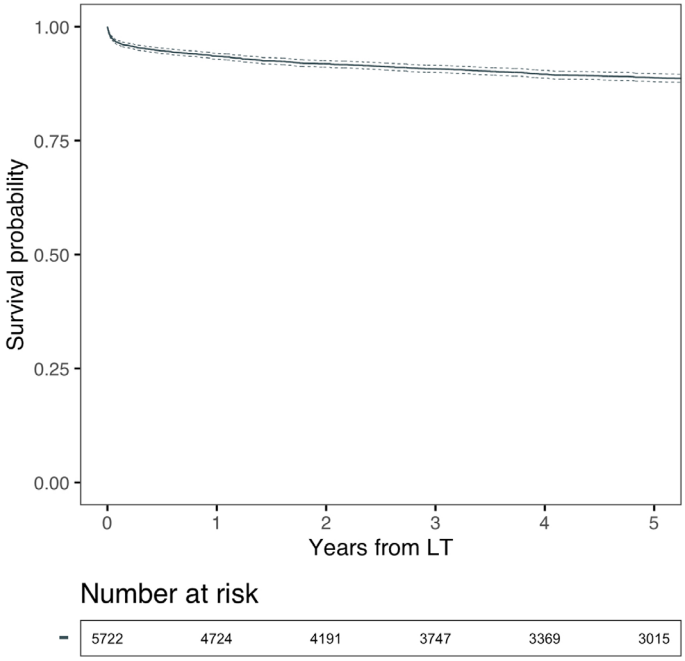

Figure 6 Overall 5-year graft survival with 95% confidence interval.

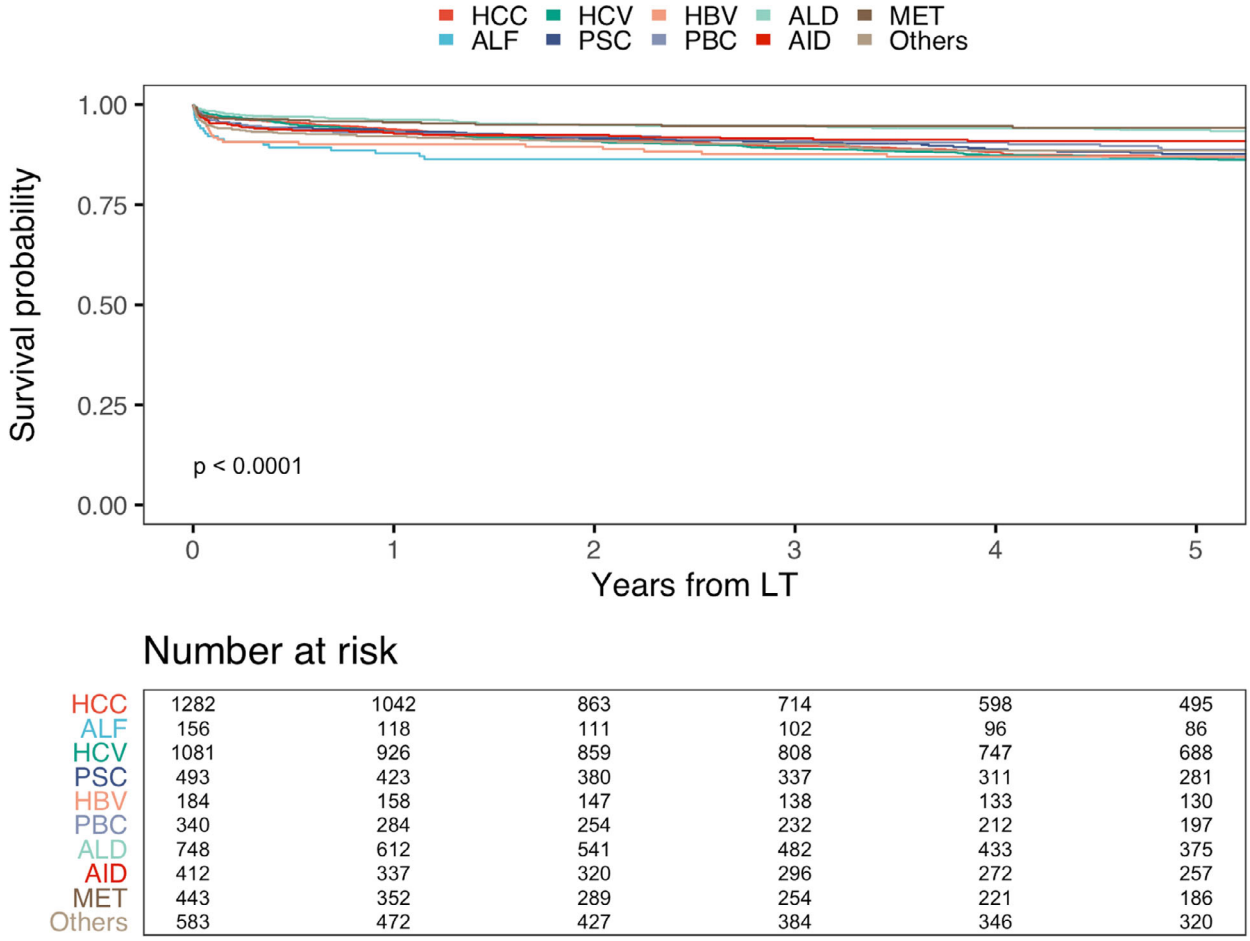

Figure 7 Liver graft survival comparing patients transplanted for various indications in Canada.

significantly from 2.3% in 2000 to 32.4% in 2018. The introduction of selection criteria that better identify suitable HCC patients for LT and improved post-transplant outcomes thereafter, and the introduction of MELD exception points system helps to explain the rise in LT for HCC patients [29,30]. Though the indication for LT in HCC patients has largely stabilized in the last couple of years, it still represents a significant indication for LT. According to different indicators in the United States, this is expected to increase in the years to come [31]. In addition, as a result of the obesity epidemic, HCC associated with nonalcoholic fatty liver disease and NASH will likely contribute to this increase [32–34]. The proportion of patients transplanted for ALD in Canada remained relatively stable at approximately 15%. This is similar to the percentage of LTs for ALD in the United States (15%) and in Europe (20%) [35–38]. There are data to suggest a bias among gastroenterologists and hepatologists regarding the referral of patients with ALD for LT [39,40], and controversy persists as 17-30% of these patients relapse to alcohol use after LT. However, with comparable outcomes following LT for other etiologies as well as a low rate of graft failure following recidivism, referrals for ALD patients requiring transplant are anticipated to increase [41–44]. There are a number of potential reasons for an expected increase in the proportion of LTs performed for ALD including a proportional decrease in HCV transplants (with a resultant increase in the proportion of ALD and other non-HCV etiologies), an improved understanding of the role of LT and patient selection for acute alcoholic hepatitis including the need to obviate the historical six-month abstinence rule, an evolving understanding of factors influencing recidivism, an increase in HCC in the setting of ALD, and favorable post-transplant survival relative to other etiologies [45–47].

While HCV-related liver disease represented the most common indication for LT in the early 2000s, the proportion of LTs performed for this indication has decreased from 31.9% in 2000 to 3.4% in 2018. Historically, HCV-related liver disease has been the most prevalent LT indication in North America and Europe [2,48]. However, in the past few years, the incidence of LT for HCV-related liver disease has decreased significantly in Western countries [48]. Using the European Liver Transplant Registry (ELTR), Belli et al. showed that the listings for HCV declined from 22% in 2007 to 17% in 2017 [7]. Further, the authors showed a dramatic decrease in LT for HCV-associated HCC. Similarly, using the UNOS registry, Chirag et al. demonstrated a steep reduction in the number of patients with a diagnosis of HCV who were on the LT waiting list in the United States from 37% in 2012 to 24% in 2016 [49]. These changes are likely as a result of a reduction in the number of HCV progressing to end-stage liver disease and requiring a LT secondary to the introduction of DAA-therapy and near-universal cure [7,50]. The more dramatic decrease in HCV in this Canadian LT cohort compared with earlier US and European studies is likely multifactorial and cannot be fully elucidated using the CORR dataset. However, it is conceivable that universal health care access may have contributed with these trends. Though patient and graft survival increased over time for both non-HCV and HCV patients in this cohort, HCV patients had a more dramatic improvement in the last two eras (2010–2014 and 2014–2018) compared to earlier eras, suggesting the positive effect of antiviral treatment following LT.

The introduction of NASH as a cause of end-stage liver disease has brought to light its importance as an etiology for LT [51]. The proportion of transplants for NASH has progressively increased in Canada from 2005 when it was 0.4% of all transplants, to 12.6% in 2018. In the United States, LTs performed for NASH are markedly increasing secondary to the obesity epidemic, and it has become the second leading etiology of liver disease on the waitlist, and, as in Europe, represents the most rapidly growing indication for LT [37,52,53]. These trajectories suggest that NASH will become the most common indication for LT in the United States before 2025 [53]. NASH patients are often obese and have multiple comorbidities such as hypertension, hyperlipidemia, obesity, and type 2 diabetes mellitus. Also, recipients with NASH are usually older than recipients who have other chronic liver diseases [54,55].

This study is limited by its retrospective nature, with the potential for misclassification and selection bias. Though the CORR dataset represents the most comprehensive transplant dataset in Canada, several missing variables are not routinely collected at the individual transplant center level. The CORR dataset does not contain information of patients who were listed for LT but dropped out either from disease progression, death, or clinical status improvement, and the findings of this study cannot be extrapolated to that cohort of patients. Data reporting to CORR is voluntary, and compliance is not monitored or required [56]. In patients with HCC, roughly half of patients only have a diagnosis of HCC reported. This may be because of missing information or an unknown underlying etiology. For the remainder, a secondary, tertiary, or quaternary liver disease etiology was reported and is presented. Further, CORR dataset does not contain information on which

center performed the transplant, whether a patient received hepatitis treatment, immunosuppression regimen, or other medical therapies for their liver disease. Despite covariate adjustments in multivariable group comparisons, there is thus potential for residual confounding. Notwithstanding these limitations, the CORR dataset represents the most comprehensive and most extensive dataset of transplantation in Canada and offers significant insight into the trends and outcomes of liver transplantation on a national scale.

In conclusion, HCC is currently the most common indication for LT in Canada. Effective treatment options have resulted in a decrease in the number of LTs for HCV. As the number of LTs performed for NASH patients is increasing significantly, it can be expected to become the most common etiology for liver transplant in the upcoming years. Ongoing improvement in post-LT outcomes remains encouraging for further increased use of marginal allografts such as DCD and further expansion of indications for transplantation.

Author contributions

TI: contributed to conception of project, literature review, data analysis, interpretation of results and write up of the manuscript. **CS, MP, DW, and GS:** contributed to conception of project, literature review, interpretation of results, and write up of the manuscript. **MC, PY, NR, HM, FM, BH, and NS:** contributed to interpretation of results and write up of the manuscript. All authors: provided final approval for this manuscript to be submitted to Transplant International.

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Conflicts of interest

None of the authors have any conflicts of interest. CIHI/CORR and the centers participating in the CORR are the source of the data used herein; they have not verified and are not responsible for the statistical validity of the data analysis of the conclusions derived by the authors.

Acknowledgments

The data reported here have been supplied by CORR and CIHI. The interpretation and reporting of these data are the authors' responsibility and in no way should be seen as the official policy of or interpretation by CORR or CIHI.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Proportion of DCD use over time in Canada.

Figure S2. Patients survival comparing patients transplanted for various indications in Canada (with Benjamini–Hochberg multiple pairwise comparisons and estimated patient survival at various time points post-LT).

Figure S3. Patient survival for non-HCV patients.

Figure S4. Patient survival for HCV patients.

Figure S5. Liver graft survival comparing patients transplanted for various indications in Canada (with Benjamini–Hochberg multiple pairwise comparisons and estimated patient survival at various time points post-LT).

Figure S6. Cumulative incidence of graft failure (first liver transplant).

Figure S7. Cumulative incidence of graft failure by liver disease etiology (with Bonferroni's adjustment [Pairwise adjustment with Gray test] and estimated cumulative incidence of graft failure with 95% confidence intervals at various time points post-LT).

Figure S8. Cumulative incidence of graft failure for non-HCV patients (with Bonferroni's adjustment [Pairwise adjustment with Gray test] and estimated cumulative incidence of graft failure with 95% confidence intervals at various time points post-LT).

Figure S9. Cumulative incidence of graft failure for HCV patients (with Bonferroni's adjustment [Pairwise adjustment with Gray test] and estimated cumulative incidence of graft failure with 95% confidence intervals at various time points post-LT).

Figure S10. Cumulative incidence of graft failure by graft type (with Bonferroni's adjustment [Pairwise adjustment with Gray test] and estimated cumulative incidence of graft failure with 95% confidence intervals at various time points post-LT).

Table S1. Liver disease classification scheme.

Table S2. Baseline recipient and donor characteristics.

Table S3. Baseline recipient and donor characteristics.

Table S4. Multivariable Cox Proportional Hazard model for patient survival.

Table S5. Multivariable Fine-Gray Proportional Hazard model for graft survival.

REFERENCES

1. Merion RM, Schaubel DE, Dykstra DM, Freeman RB, Port FK, Wolfe RA. The survival benefit of liver transplantation. *Am J Transplant* 2005; **5**: 307.
2. Adam R, Karam V, Cailliez V, *et al.* 2018 Annual Report of the European Liver Transplant Registry (ELTR) – 50-year evolution of liver transplantation. *Transpl Int* 2018; **31**: 1293.
3. Kwong A, Kim WR, Lake JR, *et al.* OPTN/SRTR 2018 Annual Data Report: Liver. *Am J Transplant* 2020; **20**(s1): 193.
4. Kim SJ, Fenton SS, Kappel J, *et al.* Organ donation and transplantation in Canada: insights from the Canadian Organ Replacement Register. *Can J kidney Heal Dis* 2014; **1**: 31.
5. Sela N, Croome KP, Chandok N, Marotta P, Wall W, Hernandez-Alejandro R. Changing donor characteristics in liver transplantation over the last 10 years in canada. *Liver Transplant* 2013; **19**: 1236.
6. CIHI. Canadian Institute for Health Information, Canadian Organ Replacement Register: Methodological notes and supplementary information, 2009 to 2018. 2019. Available from: https://www.cihi.ca/sites/default/files/document/corr-methodological-notes-2019-en.pdf
7. Belli LS, Perricone G, Adam R, *et al.* Impact of DAAs on liver transplantation: Major effects on the evolution of indications and results. An ELITA study based on the ELTR registry. *J Hepatol* 2018; **69**: 810.
8. Cholankeril G, Wong RJ, Hu M, *et al.* Liver transplantation for nonalcoholic steatohepatitis in the US: Temporal trends and outcomes. *Dig Dis Sci* 2017; **62**: 2915.
9. Yang JD, Larson JJ, Watt KD, *et al.* Hepatocellular Carcinoma Is the Most Common Indication for Liver Transplantation and Placement on the Waitlist in the United States. *Clin Gastroenterol Hepatol* 2017; **15**: 767.
10. Millson C, Considine A, Cramp ME, *et al.* Adult liver transplantation: A UK clinical guideline - part 1: preoperation. *Frontline Gastroenterol* 2020; **11**: 375.
11. Wallace D, Cowling TE, Walker K, *et al.* Short- and long-term mortality after liver transplantation in patients with and without hepatocellular carcinoma in the UK. *Br J Surg* 2020; **107**: 896.
12. Badovinac K, Greig PD, Ross H, Doig CJ, Shemie SD. Organ utilization among deceased donors in Canada, 1993–2002. *Can J Anesth* 2006; **53**: 838.
13. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol* 2008; **61**: 344.
14. Dawwas MF, Gimson AE, Lewsey JD, Copley LP, Van Der Meulen JHP. Survival after liver transplantation in the United Kingdom and Ireland compared with the United States. *Gut* 2007; **56**: 1606.
15. Roberts MS, Angus DC, Bryce CL, Valenta Z, Weissfeld L. Survival after liver transplantation in the United States: a disease-specific analysis of the UNOS database. *Liver Transplant* 2004; **10**: 886.
16. Burak KW, Meeberg GA, Myers RP, *et al.* Validation of the model of end-stage liver disease for liver transplant allocation in Alberta: Implications for future directions in Canada. *Canadian J Gastroenterol Hepatol* 2016; **2016**: 1–7.
17. Varadhan R, Weiss CO, Segal JB, Wu AW, Scharfstein D, Boyd C. Evaluating health outcomes in the presence of competing risks: a review of statistical methods and clinical applications. *Med Care* 2010; **48**: S96.
18. Zhang X, Zhang M-J, Fine J. A proportional hazards regression model for the subdistribution with right-censored and left-truncated competing risks data. *Stat Med* 2011; **30**: 1933.
19. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc [Internet]* 1999; **94**: 496.
20. Schoening WN, Buescher N, Rademacher S, *et al.* Twenty-year longitudinal follow-up after orthotopic liver transplantation: a single-center experience of 313 consecutive cases. *Am J Transplant* 2013; **13**: 2384.
21. Jay C, Ladner D, Wang E, *et al.* A comprehensive risk assessment of mortality following donation after cardiac death liver transplant - an analysis of the national registry. *J Hepatol* 2011; **55**: 808.
22. de Boer JD, Braat AE, Putter H, *et al.* Outcome of liver transplant patients with high urgent priority: are we doing the right thing? *Transplantation* 2019; **103**: 1181.
23. Germani G, Zeni N, Zanetto A, *et al.* Influence of donor and recipient gender on liver transplantation outcomes in Europe. *Liver Int Off J Int Assoc Study Liver* 2020; **40**: 1961.
24. Furukawa H, Todo S, Imventarza O, *et al.* Effect of cold ischemia time on the early outcome of human hepatic allografts preserved with UW solution. *Transplantation* 1991; **51**: 1000.
25. Cotter TG, Minhem M, Wang J, *et al.* Living-donor liver transplantation in the united states: evolution of frequency, outcomes, center volumes and factors associated with outcomes. *Liver Transplant* 2021. https://doi.org/10.1002/lt.26029
26. Blok JJ, Detry O, Putter H, *et al.* Long-term results of liver transplantation from donation after circulatory death. *Liver Transplant* 2016; **22**: 1107.
27. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med* 2011; **30**: 377.
28. Rubin DB. *Multiple Imputation for Nonresponse in Surveys*. vol. **81**. New York: John Wiley & Sons, 2004.
29. Santopaolo F, Lenci I, Milana M, Manzia TM, Baiocchi L. Liver transplantation for hepatocellular carcinoma: Where do we stand? *World J Gastroenterol* 2019; **25**: 2591.
30. Yang JD, Hainaut P, Gores GJ, Amadou A, Plymoth A, Roberts LR. A global view of hepatocellular carcinoma: trends, risk, prevention and management. *Nat Rev Gastroenterol Hepatol* 2019; **16**: 589
31. Rahib L, Wehner MR, Matrisian LM, Nead KT. Estimated projection of US cancer incidence and death to 2040. *JAMA Netw Open* 2021; **4**: e214708.
32. Younossi Z, Stepanova M, Ong JP, *et al.* Nonalcoholic steatohepatitis is the fastest growing cause of hepatocellular carcinoma in liver transplant candidates. *Clin Gastroenterol Hepatol* 2019; **17**: 748.
33. Myers S, Neyroud-Caspar I, Spahr L, *et al.* NAFLD and MAFLD as emerging causes of HCC: A populational study. *JHEP reports Innov Hepatol* 2021; **3**: 100231.

34. Shingina A, DeWitt PE, Dodge JL, *et al*. Future trends in demand for liver transplant: birth cohort effects among patients with NASH and HCC. *Transplantation* 2019; **103**: 140.
35. Singal AK, Bataller R, Ahn J, Kamath PS, Shah VH. ACG clinical guideline: Alcoholic liver disease. *Am J Gastroenterol* 2018; **113**: 175.
36. Goldberg D, Ditah IC, Saeian K, *et al*. Changes in the prevalence of hepatitis C virus infection, nonalcoholic steatohepatitis, and alcoholic liver disease among patients with cirrhosis or liver failure on the waitlist for liver transplantation. *Gastroenterology* 2017; **152**: 1090.
37. Haldar D, Kern B, Hodson J, *et al*. Outcomes of liver transplantation for non-alcoholic steatohepatitis: A European Liver Transplant Registry study. *J Hepatol* 2019; **71**: 313
38. Kwong AJ, Kim WR, Lake JR, *et al*. OPTN/SRTR 2019 annual data report: liver. *Am J Transplant* 2021; **21**(Suppl 2): 208.
39. Julapalli VR, Kramer JR, El-Serag HB. Evaluation for liver transplantation: Adherence to AASLD referral guidelines in a large Veterans Affairs center. *Liver Transplant* 2005; **11**: 1370.
40. Vidal-Trecan G, Kone V, Pilette C, *et al*. Subjective parameters markedly limit the referral of transplantation candidates to liver transplant centres. *Liver Int* 2016; **36**: 555–562.
41. Burra P, Senzolo M, Adam R, *et al*. Liver transplantation for alcoholic liver disease in Europe: a study from the ELTR (European Liver Transplant Registry). *Am J Transplant* 2010; **10**: 138.
42. Singal AK, Bashar H, Anand BS, Jampana SC, Singal V, Kuo Y-F. Outcomes after liver transplantation for alcoholic hepatitis are similar to alcoholic cirrhosis: exploratory analysis from the UNOS database. *Hepatology* 2012; **55**: 1398.
43. Dimartini A, Dew MA, Day N, *et al*. Trajectories of alcohol consumption following liver transplantation. *Am J Transplant* 2010; **10**: 2305.
44. Mathurin P, Lucey MR. Liver transplantation in patients with alcohol-related liver disease: current status and future directions. lancet. *Gastroenterol Hepatol* 2020; **5**: 507.
45. Burra P, Mioni D, Cecchetto A, *et al*. Histological features after liver transplantation in alcoholic cirrhotics. *J Hepatol* 2001; **34**: 716.
46. Rice JP. The ongoing evolution of liver transplantation in alcohol-associated liver disease. *Liver Trans* 2021; **27**: 12.
47. Rogal S, Shenai N, Kruckenberg K, Rosenberger E, Dew MA, DiMartini A. Post-transplant outcomes of persons receiving a liver graft for alcoholic liver disease. *Alcohol Alcohol* 2018; **53**: 157.
48. Kwong A, Kim WR, Lake JR, *et al*. OPTN/SRTR 2018 annual data report: liver. *Am J Trans* 2020; **20**: 193.
49. Chirag ML, Arjun KM, Jian Y, Peter MV, Chirag JP. Department BTT. 乳鼠心肌提取 HHS public access. *Physiol Behav*. 2019; **176**: 139.
50. Terrault NA, Pageaux GP. A changing landscape of liver transplantation: King HCV is dethroned, ALD and NAFLD take over!. *J Hepatol* 2018; **69**: 767.
51. Singal AK, Guturu P, Hmoud B, Kuo Y-F, Salameh H, Wiesner RH. Evolving frequency and outcomes of liver transplantation based on etiology of liver disease. *Transplantation* 2013; **95**: 755.
52. Wong RJ, Aguilar M, Cheung R, *et al*. Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. *Gastroenterology* 2015; **148**: 547.
53. Charlton MR, Burns JM, Pedersen RA, Watt KD, Heimbach JK, Dierkhising RA. Frequency and outcomes of liver transplantation for nonalcoholic steatohepatitis in the United States. *Gastroenterology* 2011; **141**: 1249.
54. Patel YA, Berg CL, Moylan CA. Nonalcoholic fatty liver disease: key considerations before and after liver transplantation. *Dig Dis Sci* 2016; **61**: 1406.
55. Mikolasevic I, Filipec-Kanizaj T, Mijic M, *et al*. Nonalcoholic fatty liver disease and liver transplantation - Where do we stand? *World J Gastroenterol* 2018; **24**: 1491.
56. Gill JS, Klarenbach S, Cole E, Shemie SD. Deceased organ donation in Canada: An opportunity to heal a fractured system. *Am J Transplant* 2008; **8**: 1580.