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Trends in liver transplantation for autoimmune liver diseases: a Canadian study

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Background: To our knowledge, no analysis of data from liver transplantation registries exists in Canada. We aimed to describe temporal trends in the number of liver transplantation procedures, patient characteristics and posttransplantation outcomes for autoimmune liver diseases (AILDs) in Canada.

Methods: We used administrative data from the Canadian Organ Replacement Register, which contains liver transplantation information from 6 centres in Canada. This study included transplantation information from 5 of the centres, as liver transplantation procedures in children were not included. We included adult (age ≥ 18 yr) patients with a diagnosis of primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), autoimmune hepatitis (AIH) or overlap syndrome (PBC–AIH or PSC–AIH) who received a liver transplant from 2000 to 2018.

Results: Of 5722 primary liver transplantation procedures performed over the study period, 1070 (18.7%) were for an AILD: 489 (45.7%) for PSC, 341 (31.9%) for PBC, 220 (20.6%) for AIH and 20 (1.9%) for overlap syndrome. There was a significant increase in the absolute number of procedures for PSC, with a yearly increase of 0.6 (95% confidence interval 0.1 to 1.2), whereas the absolute number of procedures for PBC and AIH remained stable. The proportion of transplantation procedures decreased for PBC and AIH but remained stable for PSC. Recipient age at transplantation increased over time for males with PBC (median 53 yr in 2000–2005 to 57 yr in 2012–2018, $p = 0.03$); whereas the median age among patients with AIH decreased, from 53 years in 2000–2005 to 44 years in 2006–2011 ($p = 0.03$). The Model for End-stage Liver Disease score at the time of transplantation increased over time for all AILDs, particularly AIH (median 16 in 2000–2005 v. 24 in 2012–2018, $p < 0.001$). There was a trend toward improved survival in the PBC group, with a 5-year survival rate of 81% in 2000–2005 and 90% in 2012–2018 ($p = 0.06$).

Conclusion: Between 2000 and 2018, the absolute number of liver transplantation procedures in Canada increased for PSC but remained stable for PBC and AIH; proportionally, PBC and AIH decreased as indications for transplantation. Posttransplantation survival improved only for the PBC group. An improved understanding of trends and outcomes on a national scale among patients with AILD undergoing liver transplantation can identify disparities and areas for potential health care improvement.

Contexte : À notre connaissance, aucune analyse des données tirées des registres sur les transplantations hépatiques n'a été effectuée au Canada. Nous avons cherché à décrire l'évolution dans le temps du nombre de transplantations hépatiques, des caractéristiques des patients et des issues post-transplantation pour les patients atteints de maladie auto-immune du foie (MAIF) au Canada.

Méthodes : Nous nous sommes servis des données administratives du Registre canadien des insuffisances et des transplantations d'organes, qui contient les renseignements concernant les transplantations hépatiques de 6 centres au Canada. Dans le cadre de cette étude, seuls les renseignements sur les transplantations de 5 centres ont été utilisés, puisque nous avons exclu les transplantations réalisées chez des enfants. Nous y avons inclus les patients adultes (18 ans et plus) ayant reçu un diagnostic de cholangite biliaire primitive (CBP), de cholangite sclérosante primitive (CSP), d'hépatite auto-immune (HAI) ou de formes frontières (CBP-HAI ou CSP-HAI) ayant reçu une transplantation hépatique entre 2000 et 2018.

Résultats : Des 5722 transplantations réalisées durant la période de l'étude, 1070 (18,7 %) concernaient une MAIF : 489 (45,7 %) une CSP, 341 (31,9 %) une CBP, 220 (20,6 %) une HAI, et 20 (1,9 %) une forme frontière. En valeurs absolues, le nombre de transplantations effectuées en raison d'une CSP a augmenté significativement

(augmentation annuelle de 0,6, intervalle de confiance de 95 % 0,1–1,2), alors que pour les CBP et les HAI, il est resté stable. La proportion de transplantations effectuées en raison d'une CBP ou d'une HAI a connu une baisse, mais est demeurée stable pour la CSP. L'âge médian des receveurs lors de la transplantation a augmenté chez les hommes atteints de CBP (53 ans entre 2000 et 2005, comparativement à 57 ans entre 2012 et 2018, p = 0,03), alors qu'il a diminué chez les patients atteints d'une HAI (53 ans entre 2000 et 2005, comparativement à 44 ans entre 2006 et 2011, p = 0,03). Le score MELD (Model for End-stage Liver Disease) lors de la transplantation a augmenté avec le temps pour toutes les MAIF, particulièrement pour les HAI (score médian de 16 entre 2000 et 2005, comparativement à 24 entre 2012 et 2018, p < 0,001). Dans le groupe CBP, la survie a eu tendance à s'améliorer, le taux de survie à 5 ans étant passé de 81 % entre 2000 et 2005 à 90 % entre 2012 et 2018 (p = 0,06).

Conclusion : De 2000 à 2018, le nombre absolu de transplantations hépatiques a augmenté au Canada pour les patients atteints de CSP, mais il est resté stable pour les personnes atteintes de CBP et de HAI; la proportion de transplantations hépatiques effectuées en raison d'une CBP ou d'une HAI a toutefois connu une baisse. Le taux de survie post-transplantation s'est amélioré seulement pour les patients du groupe CBP. En comprenant mieux les tendances et les résultats pour les patients atteints de MAIH qui ont subi une transplantation hépatique, on pourra mettre en évidence des disparités et des domaines potentiels d'amélioration dans les soins de santé.

Autoimmune liver diseases (AILDs) consist of 3 major diseases: primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC) and autoimmune hepatitis (AIH). The available pharmacologic treatment options differ for each AILD, which affects the rate of disease progression and subsequently the need for liver transplantation. For PBC, ursodeoxycholic acid (UDCA) has been an available treatment option since the early 1990s, with novel second-line therapies, including obeticholic acid[1] and fibrates,[2] becoming increasingly available in recent years. The standard treatment for AIH is corticosteroids, alone or in combination with azathioprine. In contrast, for PSC, no effective pharmacologic treatment option exists. Within this context, liver transplantation represents the optimal treatment for end-stage liver disease arising from either of these liver diseases.

The evolving pharmacologic treatments for AILDs and changes in the prevalence of other primary liver diseases that compete for liver transplants may have led to temporal changes in both the frequency of transplantation for AILD and the characteristics of recipients.[3] Investigating liver transplantation trends and outcomes across AILDs is important, as it can highlight differences in health care delivery and offer epidemiologic insight into these diseases. Furthermore, it can help identify the demand on the liver transplantation waiting list.

In the United States, an analysis using data from the United Network for Organ Sharing (UNOS) showed that, between 1995 and 2006, the absolute number of patients who received a liver transplant for PBC decreased, whereas the number who received a liver transplant for PSC remained stable.[4] These findings were within the context of an overall increase in the absolute number of liver transplantation procedures performed in that country. Data from the European Liver Transplant Registry (ELTR) showed that, between 1986 and 1996, there was a reduction in the absolute number of patients who received a liver transplant for PBC; these numbers then stabilized between 1996 and 2015. In addition, a proportional decrease in liver transplantation procedures for PBC from 1986 to 2015 was also noted.[5] To our knowledge, no such analysis exists in Canada, a country with a well-developed transplantation network and universal health care system.[6]

We aimed to describe trends in liver transplantation for AILDs and in recipient and donor characteristics, and the incidence of graft failure and overall patient survival over time (from 2000 to 2018) and across AILD types in Canada using a nationwide administrative database, the Canadian Organ Replacement Register (CORR), managed by the Canadian Institute for Health Information.

Methods

Organization of liver transplantation in Canada

There are 10 provinces in Canada: British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Quebec, New Brunswick, Nova Scotia, Prince Edward Island, and Newfoundland and Labrador. Each province has at least 1 organ procurement organization, except for Prince Edward Island, which is managed by Nova Scotia's organ procurement organization. Liver transplantation is performed in 5 provinces, by 7 different transplantation programs.[7] The CORR data set contains liver transplantation information from 6 centres in Canada: BC Children's Hospital, Vancouver; Vancouver General Hospital; the University of Alberta/Alberta Kidney Care North, Calgary; the London Health Sciences Centre, London, Ont.; The Hospital for Sick Children, Toronto; Toronto General Hospital; and the Queen Elizabeth II

Health Sciences Centre, Halifax.[8] This study included transplantation information from 5 of the transplantation centres, as liver transplantation procedures in children were not included.

Study design, patient population and data source

We performed a retrospective analysis of CORR data. This database contains information for all patients who underwent liver transplantation in Canada from 2000 through 2018, with the exception of patient and donor records from Quebec, which does not participate in CORR. Furthermore, there are no register data readily available on recipient posttransplantation outcomes from the Transplant Québec registry.

Adult (age ≥ 18 yr) patients who underwent a first liver transplantation procedure were included. To limit the heterogeneity of the study population, patients who underwent simultaneous transplantation of liver and other organs, including kidney, heart, lungs, intestine and pancreas, were excluded. We included patients who received liver transplants for PBC, PSC, AIH or overlap syndrome (PBC–AIH or PSC–AIH). We acquired established pretransplantation liver disease diagnoses from primary, secondary, tertiary and quaternary diagnoses. All patients were followed to Dec. 31, 2018, as collected in CORR. The study received approval from the University Health Network Research Ethics Board (REB#19–5835).

Donor and recipient characteristics were recorded in the CORR database. Donor characteristics included age, body mass index, smoking status, history of hypertension, history of diabetes, ethnicity, blood type and cause of death. Recipient characteristics included age at transplantation, sex, ethnicity, body mass index, blood type, time on the waitlist, medical status, serum bilirubin level, International Normalized Ratio (INR), Child–Pugh score, creatinine level and Model for End-stage Liver Disease (MELD) score at the time of transplantation.[9] Other variables were distance from donor harvest to facility of liver transplantation, warm ischemia time, cold ischemia time, rewarm time (defined as the time in minutes between removal of the organ from cold storage and release of the clamps in the recipient, allowing blood flow [also known as reperfusion time or anastomosis time]), use of donation after cardiac death liver allograft and type of graft used (whole liver, left lobe, right lobe, left lateral segment).

Statistical analysis

We expressed descriptive data for continuous variables as mean and standard deviation if the distribution was normal, and median and interquartile range (IQR) for nonnormal distributions. We compared these data using analysis of variance and Kruskal–Wallis tests, respectively. We expressed categoric variables as number and percentage, and compared them using the χ^2 or Fisher exact test. We compared patient characteristics, and long-term graft and patient survival across AILD types.

We described the yearly absolute number of liver transplantation procedures and the proportion for each AILD, and assessed trends with a linear regression least-square model. To assess changes over time in patient characteristics and 5-year posttransplantation outcomes, we stratified patients into 3 eras based on the year of transplantation (2000–2005, 2006–2011 and 2012–2018); these 3 periods allowed for relatively equal year distribution across the observed study period. We compared the 5-year incidence of posttransplantation graft failure and patient survival across eras. We analyzed the incidence of graft failure as a competing risk with death and compared it across eras using the Gray test. We used the Fine–Gray competing risk model to estimate the subdistribution hazard ratio (HR) for the incidence of graft failure and to adjust for additional covariates. We estimated patient survival using the Kaplan–Meier method and compared it across eras using the log-rank test. We used Cox proportional hazard regression models to obtain HRs with 95% confidence intervals (CIs) for patient survival.

A p value < 0.05 was considered statistically significant. All statistical analyses were 2-sided and performed with SPSS Statistics for Windows, version 25.0 (IBM Corp.) and R (R Project for Statistical Computing).

Results

A total of 5722 primary liver transplantation procedures were performed in Canada from 2000 to 2018. Of the 5722 procedures, 1070 (18.7%) were performed for an indication of AILD: 489 (45.7%) for PSC, 341 (31.9%) for PBC, 220 (20.6%) for AIH and 20 (1.9%) for overlap syndrome.

The patient characteristics for each AILD are shown in Table 1. Patients who underwent tranlantation for PBC were older than those with PSC and AIH (p < 0.001); this difference held irrespective of sex. The sex proportion differed across AILDs: most patients with PBC and AIH were female (277 [81.2%] and 153 [69.5%], respectively), whereas most of those with PSC were male (352 [72.0%]) (p < 0.001). The INR at the time of transplantation was significantly higher in the AIH group than in the PBC and PSC groups (p < 0.001). Graft type, donor age, bilirubin level, creatinine level and MELD score at the time of transplantation were similar across the 3 groups. Eight patients with PBC, 7 patients with PSC and 7 patients with AIH had hepatocellular carcinoma, and 1 patient in the PSC group had cholangiocarcinoma.

The characteristics of patients with overlap disease are shown in Appendix 1 (available at www.canjsurg.ca/lookup/doi/10.1503/cjs.012121/tab-related-content). One patient in this group had hepatocellular carcinoma.

Table 1. Baseline characteristics of patients who underwent liver transplantation for an autoimmune disease in Canada, 2000–2018

Characteristic	Group; no. (%) of patients*			*p* value
	Primary biliary cholangitis *n* = 341	Primary sclerosing cholangitis *n* = 489	Autoimmune hepatitis *n* = 220	
Age of recipient, median (Q1–Q4), yr				
Overall	56 (48–61)	45 (35–53)	48 (33–58)	< 0.001
Female	55 (47–61)	45 (34–54)	48 (35–59)	< 0.001
Male	58 (51–64)	44 (35–53)	49 (32–57)	
Sex of recipient				< 0.001
Female	277 (81.2)	137 (28.0)	153 (69.5)	
Male	64 (18.8)	352 (72.0)	67 (30.4)	
Age of donor, median (Q1–Q4), yr	42 (28–54) *n* = 338	39 (28–53) *n* = 477	43 (30–52) *n* = 208	0.8
Sex of donor				0.003
Female	180 (53.4)	200 (41.8)	105 (50.5)	
Male	157 (46.6)	278 (58.2)	103 (49.5)	
Missing	4 (1.2)	11 (2.2)	12 (5.4)	
Donor type				0.07
DCD	13 (3.8)	19 (3.9)	10 (4.5)	
NDD	243 (71.3)	331 (67.7)	170 (77.3)	
LDLT	85 (24.9)	139 (28.4)	40 (18.2)	
MELD score, median (Q1–Q4)	18 (13–24) *n* = 216	18 (13–24) *n* = 295	18 (14–28) *n* = 143	0.2
Creatinine level, median (Q1–Q4), μmol/L	77 (59–105) *n* = 227	73 (61–102) *n* = 307	78 (62–98) *n* = 147	0.5
Bilirubin level, median (Q1–Q4), μmol/L	92 (41–280) *n* = 216	115 (48–281) *n* = 297	74 (43–317) *n* = 143	0.3
INR, median (Q1–Q4)	1.4 (1.2–1.8) *n* = 217	1.4 (1.2–1.8) *n* = 297	1.7 (1.4–2.3) *n* = 145	< 0.001

DCD = donation after cardiac death; INR = International Normalized Ratio; LDLT = living donor liver transplantation; MELD = Model for End-stage Liver Disease; NDD = neurologic determination of death; Q = quartile.
*Except where noted otherwise.

Temporal trends in absolute number and proportion of liver transplantation procedures

Irrespective of AILD type, the overall number of primary liver transplantation procedures increased over time, from 251 in 2000 to 349 in 2018. There was a significant increase in the absolute number of procedures for PSC over the study period, with a yearly increase of 0.6 (95% CI 0.1 to 1.2) (Figure 1A and B). There was no significant difference in the absolute number of procedures for PBC or AIH, with an average of 18 for PBC and 12 for AIH across all years. In contrast, the proportion of patients who received a liver transplant for PSC remained stable over the study period (average 9%) (Figure 1C and D), whereas the proportion of those who received a liver transplant for PBC or AIH decreased over time, with a yearly change of –0.3 (95% CI –0.4 to –0.1) and –0.1 (95% CI –0.2 to 0.0), respectively.

Temporal trends in patient characteristics

Changes over time in donor and recipient characteristics are described in separate tables for each of the AILDs (Table 2, Table 3 and Table 4). The median length of follow-up was 6.9 (IQR 2.2–12.0) years for the PBC group, 6.5 (IQR 2.4–11.2) years for the PSC group and 7.2 (IQR 2.2–12.3) years for the AIH group. There was a significant increase in the proportion of procedures using living donor liver for all AILDs over time. Notably, donation after cardiac death donors were observed only after 2005, and the proportion of these donors increased over time for all AILDs. Recipient age increased only for males who received transplants for PBC (median 53 yr in 2000–2005 and 57 yr in 2012–2018) (p = 0.03). For patients who received a transplant for AIH, there was a significant decrease in median age between 2000–2005 (53 yr) and 2006–2011 (44 yr) (p = 0.03). Age at transplantation was similar across time for the PSC group. For all AILDs, recipient and donor sex, and donor age were consistent over time. The MELD score at the time of transplantation increased over time for all AILDs, particularly AIH (median 16 in 2000–2005 v. 24 in 2012–2018, $p < 0.001$).

Posttransplantation outcomes

No significant differences in the overall incidence of graft failure were observed between the AILD types over the

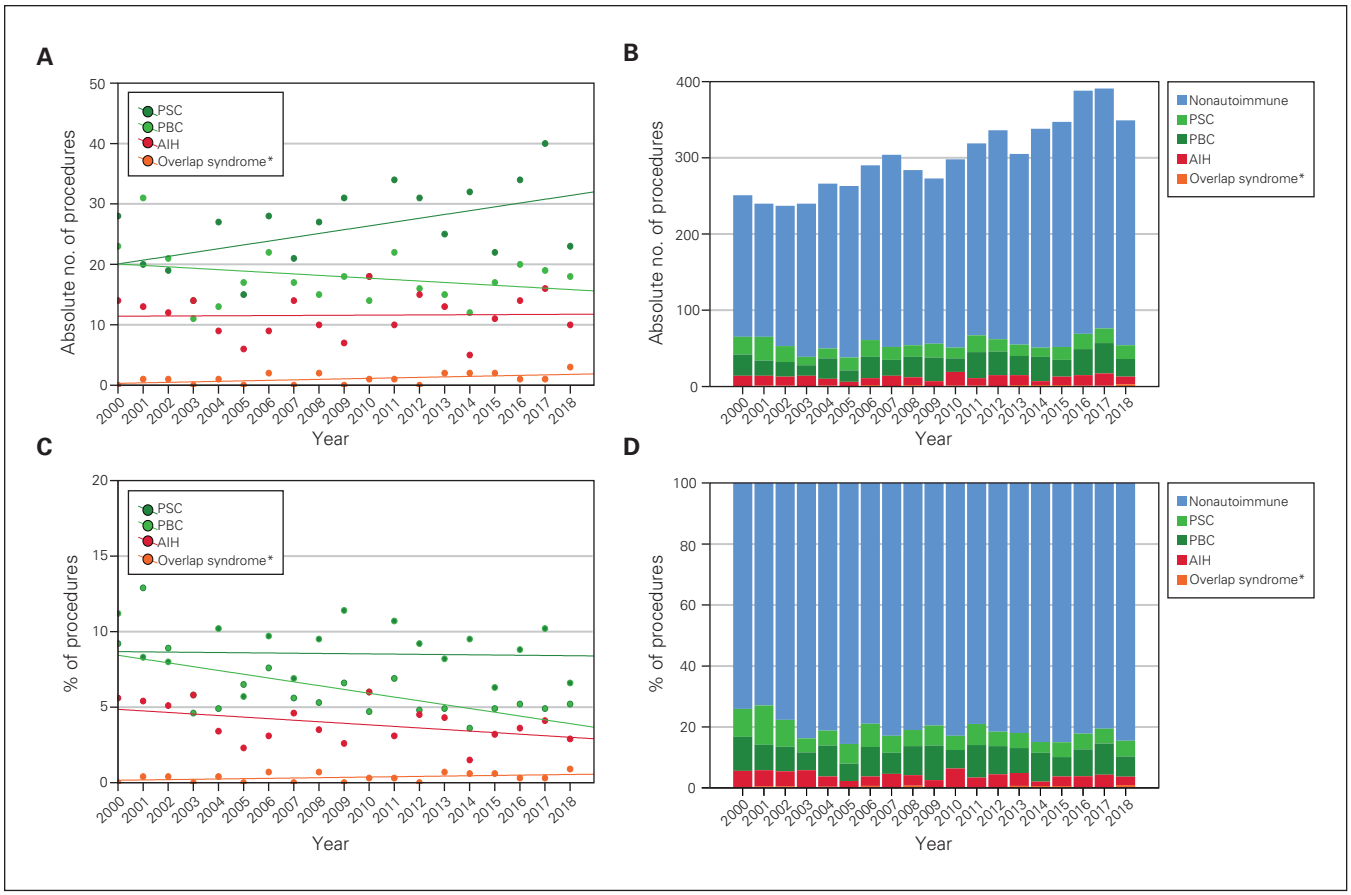

Fig. 1. Absolute number (A, B) and proportion (C, D) of liver transplantation procedures for autoimmune and nonautoimmune liver diseases in Canada, 2000–2018. AIH = autoimmune hepatitis; PBC = primary biliary cholangitis; PSC = primary sclerosing cholangitis. *PBC–AIH or PSC–AIH.

study period (p = 0.1) (Figure 2A). The 5-, 10- and 15-year incidence rates of graft failure were 11.4%, 11.9% and 16.6%, respectively, among patients with PBC; 12.1%, 17.8% and 21.1%, respectively, among those with PSC; and 6.5%, 9.6% and 15.2%, respectively, among those with AIH.

The 5-, 10- and 15-year survival rates for the PBC group were 86%, 78% and 67%, respectively, compared to 89%, 83% and 76%, respectively, for the PSC group (p = 0.01) (Figure 2B). The corresponding rates for the AIH group were 86%, 82% and 66%, respectively, which were not significantly different from the rates for PBC/PSC. The unadjusted HR for death for the PSC group compared to the PBC group was 0.67 (95% CI 0.49 to 0.92). Adjustment for recipient age at transplantation and sex resulted in no significant differences in overall survival across AILDs (p = 0.4), and the adjusted HR for the PSC group compared to the PBC group was 0.81 (95% CI 0.56 to 1.17).

Temporal trends in posttransplantation outcomes

There were no statistically significant differences in the incidence of graft failure over time for any of the AILDs (Figure 3A, B and C). The 5-year incidence rates of graft failure in 2000–2005, 2006–2011 and 2012–2018 were 13.8%, 11.1% and 9.2%, respectively, for the PBC group; 13.0%, 10.7% and 13.3%, respectively, for the PSC group; and 4.4%, 7.4% and 8.7%, respectively, for the AIH group.

There was a trend toward improvement in 5-year survival over time among patients with PBC, from 81% in 2000–2005 to 90% in 2012–2018 (p = 0.06) (Figure 3D). Compared to 2000–2005, the HR for death in 2012–2018 was 0.48 (95% CI 0.22 to 1.06). After adjustment for recipient age and sex, there was a significantly lower risk of death in 2012–2018 compared to 2000–2005 (HR 0.44, 95% CI 0.20 to 0.97). There were no differences in patient survival over time for the PSC group or the AIH group (Figure 3E and F).

Discussion

The absolute number of liver transplantation procedures in Canada increased between 2000 and 2018 among patients with PSC but remained stable among those with PBC and AIH. Proportionally, the transplantation procedures for PBC and AIH decreased. The long-term incidence rates of

Table 2. Characteristics of patients with primary biliary cholangitis at the time of liver transplantation, by era

Characteristic	Era; no. (%) of patients* 2000–2005 *n* = 116	2006–2011 *n* = 108	2012–2018 *n* = 117	*p* value
Length of follow-up, median (Q1–Q4), yr	13.6 (5.0–16.7)	9.1 (7.3–11.2)	2.9 (1.3–4.6)	—
Age of recipient, median (Q1–Q4), yr				
Overall	53 (46–60)	58 (49–63)	56 (48–61)	0.01
Female	53 (46–60)	56 (48–62)	56 (47–61)	0.09
Male	53 (44–62)	61 (54–66)	57 (54–64)	0.03
Sex of recipient				0.6
Female	91 (78.4)	88 (81.5)	98 (83.8)	
Male	25 (21.6)	20 (18.5)	19 (16.2)	
Age of donor, median (Q1–Q4),	42 (25–53)	47 (29–57)	38 (28–56)	0.2
Sex of donor				0.2
Female	55 (48.7)	56 (51.8)	69 (59.5)	
Male	58 (51.3)	52 (48.1)	47 (40.5)	
Missing	3 (2.6)	0 (0)	1 (0.8)	
Donor type				< 0.001
DCD	0 (0)	0 (0)	13 (11.1)	
NDD	94 (81.0)	78 (72.2)	71 (60.7)	
LDLT	22 (19.0)	30 (27.8)	33 (28.2)	
MELD score, median (Q1–Q4)	17 (11–22)	18 (15–25)	20 (16–26)	0.004
Creatinine level, median (Q1–Q4), μmol/L	77 (60–99)	73 (56–107)	84 (56–120)	0.7
Bilirubin level, median (Q1–Q4), μmol/L	75 (34–217)	97 (42–272)	105 (67–327)	0.06
INR, median (Q1–Q4)	1.3 (1.2–1.7)	1.4 (1.2–1.9)	1.5 (1.3–2.0)	0.002
Retransplantation	11 (9.5)	8 (7.4)	5 (4.3)	—
Retransplantation in first year	6 (5.2)	4 (3.7)	3 (2.6)	—

DCD = donation after cardiac death; INR = international normalized ratio; LDLT = living donor liver transplantation; MELD = Model for End-stage Liver Disease; NDD = neurologic determination of death; Q = quartile.
*Except where noted otherwise.

graft failure and patient survival after transplantation were similar across the AILDs. However, survival improved significantly over time only for the PBC group. In addition, although recipient age fluctuated over time among patients who received a transplant for PBC or PSC, it remained stable for those with AIH. The MELD score increased over time for all AILD types, particularly AIH. This increase seems to have been driven primarily by differences in bilirubin level and INR, as these were also statistically significantly different over time.

The increase in the absolute number of transplantation procedures for PSC occurred in the context of a stable proportional trend over time. This may have been due to the increase in the overall number of transplantation procedures for other indications. This suggests that the burden of PSC-related end-stage liver disease may be increasing over time in Canada: to date, there is no effective treatment for PSC. Similar findings were observed in an ELTR study, in which the number of PSC-related liver transplantation procedures increased progressively over time from 1980 to 2017.[10] However, our findings contrast with those from UNOS, which found no significant changes in the absolute number of liver transplantation procedures for PSC from 1995 to 2006.[4]

In contrast to our findings, decreases in the absolute number and proportion of liver transplantation procedures for PBC have been noted in Europe and the US since the 1990s.[4,11,12] A likely explanation is the introduction of UDCA, particularly in light of data showing that UDCA improves transplant-free survival,[11,12] with reduced risk of disease recurrence, graft loss and death.[13] Since then, there have been further advances in the treatment of PBC, mainly the approval of obeticholic acid by Health Canada in 2017;[14] whether this has affected recent liver transplantation trends remains to be determined. Obeticholic acid is used as second-line therapy for patients who do not respond to or cannot tolerate UDCA monotherapy, as it has been shown to decrease levels of alkaline phosphatase, an important biochemical marker that is considered a surrogate end point for transplant-free survival.[1,15] However, our findings regarding trends in the absolute number of liver transplantation procedures for PBC are in line with those from an ELTR-based study, which showed stability in the number of liver transplantation procedures from 1997 to 2015.[5]

We found that the median age at transplantation for male patients with PBC varied according to the era of transplantation, from 53 in 2000–2005 to 57 in 2012–2018.

Table 3. Characteristics of patients with primary sclerosing cholangitis at the time of liver transplantation, by era

Characteristic	Era; no. (%) of patients* 2000–2005 *n* = 123	2006–2011 *n* = 159	2012–2018 *n* = 207	*p* value
Length of follow-up, median (Q1–Q4), yr	14.5 (10.4–17.0)	8.5 (7.2–10.7)	2.6 (1.3–4.9)	—
Age of recipient, median (Q1–Q4), yr				
Overall	46 (36–53)	43 (32–53)	44 (35–54)	0.3
Female	46 (34–52)	41 (29–57)	48 (37–56)	0.2
Male	47 (36–54)	43 (33–52)	44 (35–53)	0.5
Sex of recipient				0.2
Female	29 (23.6)	42 (26.4)	66 (31.9)	
Male	94 (76.4)	117 (73.6)	141 (68.1)	
Age of donor, median (Q1–Q4), yr	39 (25–52)	43 (31–53)	38 (28–53)	0.4
Sex of donor				0.3
Female	45 (37.8)	72 (46.8)	83 (40.5)	
Male	74 (62.2)	82 (53.2)	122 (59.5)	
Missing	4 (3.2)	5 (3.1)	2 (1.0)	
Donor type				
DCD	0 (0)	6 (3.8)	13 (6.3)	0.001
NDD	100 (81.3)	105 (66.0)	126 (60.9)	
LDLT	23 (18.7)	48 (30.2)	68 (32.8)	
MELD score, median (Q1–Q4)	17 (11–22)	20 (14–27)	18 (14–23)	0.01
Creatinine level, median (Q1–Q4), μmol/L	76 (65–102)	73 (63–108)	71 (54–85)	0.04
Bilirubin level, median (Q1–Q4), μmol/L	86 (32–196)	170 (52–377)	103 (61–268)	0.004
INR, median (Q1–Q4)	1.3 (1.1–1.7)	1.4 (1.2–1.9)	1.4 (1.2–1.7)	0.02
Retransplantation	13 (10.6)	18 (11.3)	19 (9.2)	—
Retransplantation in first year	4 (3.2)	8 (5.0)	12 (5.8)	—

DCD = donation after cardiac death; INR = international normalized ratio; LDLT = living donor liver transplantation; MELD = Model for End-stage Liver Disease; NDD = neurologic determination of death; Q = quartile.
*Except where noted otherwise.

In the ELTR study, an increase in median age from 54 years to 56 years was noted among females during 1986–2016.[5] That study showed an increase in the proportion of male patients over time, from 11% in 1986–1996 to 15% in 2006–2016. However, we found a decrease in the proportion of male patients over time, from 22% in 2000–2005 to 16% in 2012–2018, although the difference was not statistically significant.

The 5-, 10- and 15-year survival rates among patients who received transplants for AIH in the present study were 86%, 82% and 66%, respectively, compared to 79%, 71% and 60%, respectively, in an ELTR study.[16] In the UNOS population, patients with AIH were at increased risk for death compared to patients with PBC and those with PSC.[17] Although both of these studies showed worse survival after transplantation for AIH than for other types of AILD, this was not seen in our cohort. This may be due to the overall improved survival rates compared to the ELTR and UNOS cohorts.

The only trend in posttransplantation outcomes observed in our cohort was improved survival over time among patients with PBC. This difference may have been related to more routine use of preventive UDCA after transplantation.

The discrepancies noted in liver transplantation trends and posttransplantation outcomes across geographic regions may also be due to differences in health care systems and allocation policies across regions. Although Canada has a universal health care system, the US has varying health care coverage. Furthermore, Canada uses combined MELD and centre-specific allocation policies, whereas the US tends to focus mainly on an allocation policy based on MELD score.[18] Although relying solely on a sickest-first allocation policy is presumed to be linked to increased posttransplantation mortality, studies have failed to show an association of increased mortality with higher MELD scores.[19] Differences in posttransplantation immunosuppression regimens may also be a contributing factor, given that a lack of calcineurin inhibitor, cyclosporine, or combined cyclosporine and tacrolimus within 1 month of transplantation is associated with worse survival in patients with AIH.[16]

Limitations

One of the strengths of this study is the long-term follow-up of patients from a nation-wide registry, including

Table 4. Characteristics of patients with autoimmune hepatitis at the time of liver transplantation, by era

Characteristic	Era; no. (%) of patients* 2000–2005 *n* = 68	2006–2011 *n* = 68	2012–2018 *n* = 84	*p* value
Length of follow-up, median (Q1–Q4), yr	14.6 (10.9–16.4)	8.7 (7.5–11.2)	2.5 (0.9–5.2)	—
Age of recipient, median (Q1–Q4), yr				
Overall	53 (40–59)	44 (27–57)	47 (33–59)	0.04
Female	53 (40–58)	45 (27–57)	47 (33–61)	0.1
Male	53 (40–60)	42 (28–58)	44 (31–56)	0.3
Sex of recipient				0.5
Female	50 (73.5)	44 (64.7)	59 (70.2)	
Male	18 (26.5)	24 (35.3)	25 (29.8)	
Age of donor, median (Q1–Q4), yr	45 (34–54)	43 (30–53)	41 (27–52)	0.5
Sex of donor				0.4
Female	33 (52.4)	36 (56.2)	36 (44.4)	
Male	30 (47.6)	28 (43.8)	45 (55.6)	
Missing	5 (7.4)	4 (5.9)	3 (3.6)	
Graft type				0.07
DCD	0 (0)	3 (4.4)	7 (8.3)	
NDD	59 (86.8)	52 (76.5)	59 (70.2)	
LDLT	9 (13.2)	13 (19.1)	18 (21.4)	
MELD score, median (Q1–Q4)	16 (13–20)	20 (15–27)	24 (18–33)	< 0.001
Creatinine level, median (Q1–Q4), µmol/L	77 (59–97)	82 (66–104)	78 (64–98)	0.5
Bilirubin level, median (Q1–Q4), µmol/L	64 (33–113)	76 (44–314)	92 (58–430)	0.04
INR, median (Q1–Q4)	1.5 (1.2–1.8)	1.7 (1.5–2.3)	2.1 (1.6–3.0)	< 0.001
Retransplantation	4 (5.9)	8 (11.8)	6 (7.1)	—
Retransplantation in first year	3 (4.4)	3 (4.4)	5 (6.0)	—

DCD = donation after cardiac death; INR = international normalized ratio; LDLT = living donor liver transplantation; MELD = Model for End-stage Liver Disease; NDD = neurologic determination of death; Q = quartile.
*Except where noted otherwise.

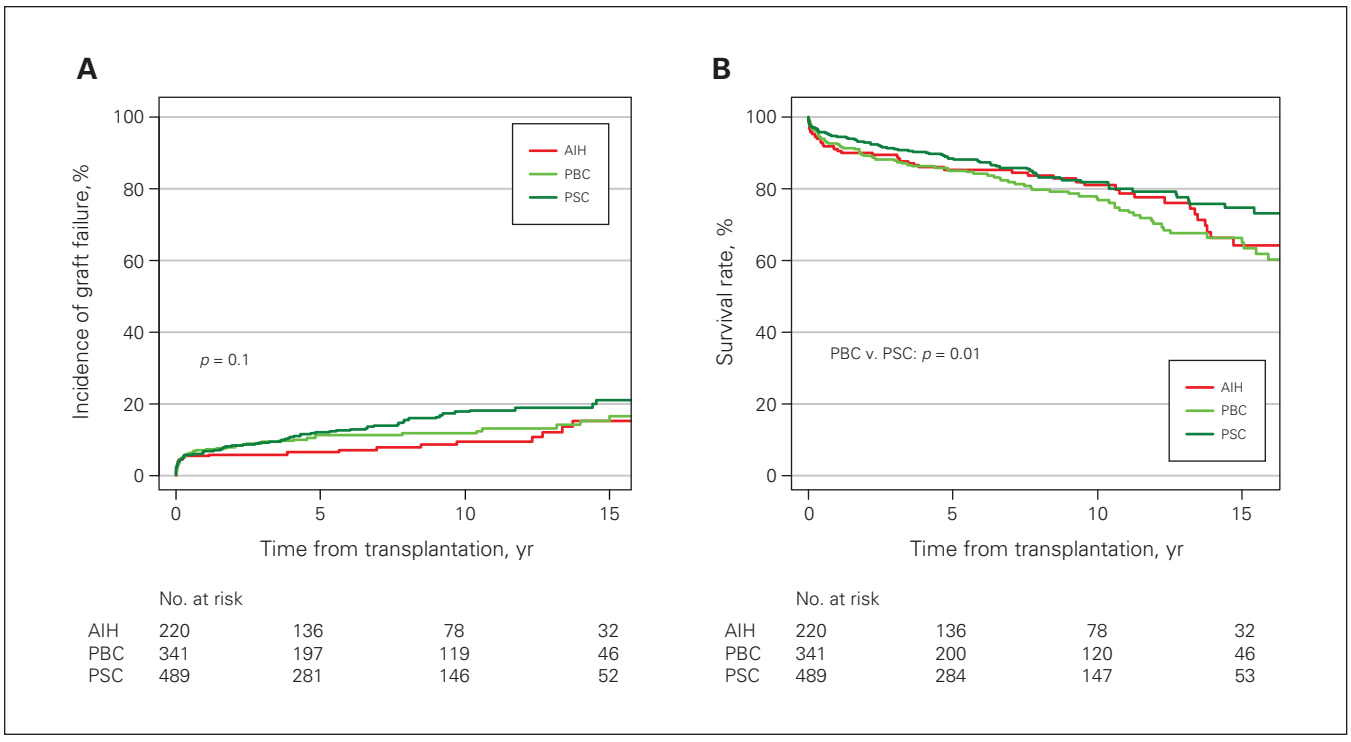

Fig. 2. Incidence of graft failure (A) and patient survival (B) after liver transplantation over time according to autoimmune liver disease. AIH = autoimmune hepatitis; PBC = primary biliary cholangitis; PSC = primary sclerosing cholangitis.

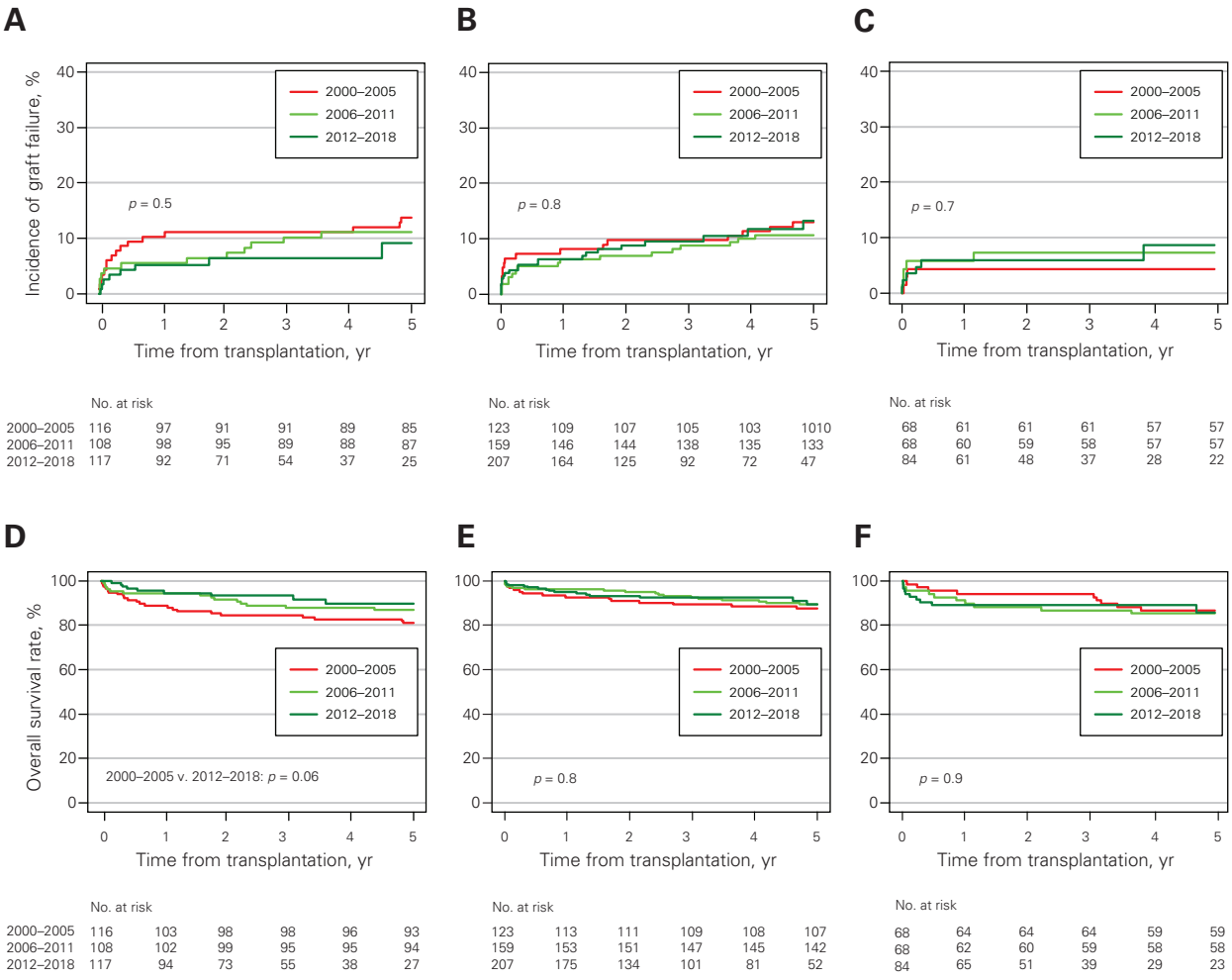

Fig. 3. Changes over time in the incidence of graft failure and patient survival among patients with primary biliary cholangitis (A, D), primary sclerosing cholangitis (B, E) and autoimmune hepatitis (C, F).

transplantation procedures in recent years. Limitations include the absence of waitlist status in the Canadian database, which prevented analysis of waitlist survival and potential changes over time, and the performance of intention-to-treat analyses. Liver transplantation procedures conducted in Quebec are not included in CORR, and this may have affected the findings from a Canadian experience perspective. However, since posttransplantation outcomes are not available in the Transplant Québec registry, we would not have been able to assess differences over time. There were some aspects we could not consider, such as posttransplantation immunosuppression regimens and their impact on outcomes, because the data were not available. Centre-specific data also could not be evaluated, as CORR differentiates between patients from the University Health Network, Toronto, and those from all other centres. There were missing data, particularly for biochemical variables. Finally, owing to the relatively small sample, we did not carry out extensive multivariable analyses when assessing trends over time in posttransplantation outcomes.

Conclusion

There was an increase in the absolute number of liver transplantation procedures in Canada from 2000 to 2018 for PSC but not for PBC and AIH; numbers for the latter AILDs remained stable. Transplantation procedures for PBC and AIH decreased proportionally. Posttransplantation survival improved significantly over time only among patients with PBC. Although recipient age differed over time for the PBC and PSC groups, it was stable for the AIH group. The MELD score at the time of transplantation increased over time. An improved understanding of trends and outcomes on a national scale among patients with AILD undergoing liver transplantation can identify disparities and areas for potential health care improvement.

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