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End stage liver disease etiology & transplantation referral outcomes of major ethnic groups in British Columbia, Canada

A cohort study

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Abstract

Liver disease etiology and transplantation outcomes may vary by ethnicity. We aimed to determine if disparities exist in our province.

We reviewed the provincial database for liver transplant referrals. We stratified cohorts by ethnicity and analyzed disease etiology and outcomes.

Four thousand nine hundred sixteen referrals included 220 South Asians, 413 Asians, 235 First Nations (Indigenous), and 2725 Caucasians. Predominant etiologies by ethnicity included alcohol (27.4%) and primary sclerosing cholangitis (PSC) (8.8%) in South Asians, hepatitis B (45.5%) and malignancy (13.9%) in Asians, primary biliary cholangitis (PBC) (33.2%) and autoimmune hepatitis (AIH) (10.8%) in First Nations, and hepatitis C (35.9%) in Caucasians. First Nations had lowest rate of transplantation (30.6%, $P = .01$) and highest rate of waitlist death (10.6%, $P = .03$). Median time from referral to transplantation (268 days) did not differ between ethnicities ($P = .47$). Likelihood of transplantation increased with lower body mass index (BMI) (hazard ratio [HR] 0.99, $P = .03$), higher model for end stage liver disease (MELD) (HR 1.02, $P < .01$), or fulminant liver failure (HR 9.47, $P < .01$). Median time from referral to ineligibility status was 170 days, and shorter time was associated with increased MELD (HR 1.01, $P < .01$), increased age (HR 1.01, $P < .01$), fulminant liver failure (HR 2.56, $P < .01$) or South Asian ethnicity (HR 2.54, $P < .01$). Competing risks analysis revealed no differences in time to transplant ($P = .66$) or time to ineligibility ($P = .91$) but confirmed increased waitlist death for First Nations ($P = .04$).

We have noted emerging trends such as alcohol related liver disease and PSC in South Asians. First Nations have increased autoimmune liver disease, lower transplantation rates and higher waitlist deaths. These data have significance for designing ethnicity specific interventions.

Abbreviations: AIH = autoimmune hepatitis, BC = British Columbia, BMI = body mass index, ESLD = end stage liver disease, HCC = hepatocellular carcinoma, HR = hazard ratio, IBD = inflammatory bowel disease, MELD = model for end stage liver disease, NASH = Nonalcoholic steatohepatitis, PBC = primary biliary cholangitis, PSC = primary sclerosing cholangitis.

Keywords: alcohol, cirrhosis, disparity, epidemiology, ethnicity, etiology, liver disease, liver transplant, primary biliary cholangitis, primary sclerosing cholangitis, waitlist

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The data that support the findings of this study are available from a third party, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are available from the authors upon reasonable request and with permission of the third party.

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1. Introduction

Leading etiologies of end stage liver disease (ESLD) in North America include alcohol related liver disease, nonalcoholic steato-hepatitis (NASH) and chronic hepatitis C.[1] The epidemiology of liver disease suggests that etiology varies by ethnicity, and that certain etiologies may be more prevalent in specific ethnic communities.[2] As such, the study of major liver disease etiologies by ethnicity is important for public health measures.

It is also necessary to review transplant referral databases from an equity and quality assurance perspective. Persons of minority descent may be disadvantaged in transplantation access and outcomes. Studies have suggested a lower rate of transplantation of ethnic minorities independent of MELD score.[3] The incidence of delisting, waitlist mortality, graft loss and even post-transplant mortality may be higher in minority candidates.[3,4] Most of these studies utilize large American databases, and a similar study in a Canadian specific setting has, to date, not been carried out. From a clinical epidemiologic perspective, an analysis of a provincial liver transplant referral database can provide insight into the demographic distribution of ESLD within that province in the absence of a true population registry.

British Columbia (BC) is home to a large multi-ethnic population, including persons of Asian (e.g., China, Korea, Japan, etc.), South Asian (e.g. India, Pakistan, Fiji, etc.) and First Nation (i.e., Indigenous) descent. Patients of Asian descent are known to have higher rates of Hepatitis B and hepatocellular carcinoma (HCC).[5] Those of First Nations descent in BC appear to have higher rates of autoimmune disease such as Primary Biliary Cholangitis (PBC).[6] Lastly, the majority of South Asians in BC have roots in North India (Punjab), an area with a large burden of hepatitis C infection and alcohol use.[7] Again, the ethnic makeup of BC is distinct not only from the United States, but also distinct and much more diverse than other areas of Canada, thus warranting a province specific analysis.

Specific liver transplant indications and outcomes for these Canadian specific ethnic groups have not been well studied. Although it may be argued that this information can be extrapolated by reviewing liver disease studies arising from the originating countries of non-Indigenous ethnic groups, given that many liver diseases are not congenital or inborn and given that many members of the ethnic communities have lived in a Canadian environment for years, and possibly generations, this may not be a valid assumption. We aimed to profile the specific etiologies of ESLD in these ethnic communities and compare them to the larger Caucasian population using a Canadian specific provincial database. We also examined how ethnicity impacted decisions regarding eligibility and transplantation, and how ethnicity influenced graft survival and death whilst on the waitlist.

2. Methods

2.1. Ethics and data

This study was reviewed and approved by the Clinical Research Ethics Board of the University of British Columbia. The BC Transplant Database was reviewed for all unique referrals to the provincial liver transplantation program for the years 1984 (first documented referral, although the liver transplant program was not established until 1989) to 2019. BC Transplant is an agency of the Ministry of Health that provides funding and informational technology support for the province's solid organ transplant programs. In BC, organ allocation policy is based on clinical status and MELD score. All transplants are carried out Vancouver General Hospital (VGH), the province's only transplant center. In recent years, between 50 and 80 liver transplants have occurred annually at VGH.

We included both pediatric and adult referrals. Data extracted included patient age, gender, ethnicity, whether they were deemed ineligible, whether they received a transplant, whether they died on the waitlist, whether their graft failed, whether they were re-transplanted, as well as their current status. Reasons for death on waitlist and graft failure were also extracted. MELD and Child-Pugh scores at time of listing were collected. Data regarding dropout from the waiting list, or MELD or Child-Pugh score at time of transplant, were not available. Re-transplantation was defined as the first instance of receiving a second liver transplant for any indication. Date of referral, date of graft failure, date of being declared ineligible (if applicable), and date of transplant (if applicable) were extracted. Graft failure was defined as a composite endpoint that encompassed isolated organ failure requiring re-transplantation or patient death. Graft survival time was defined as time of transplant to time of graft failure. Time to ineligibility was defined as time of referral to the time the patient was deemed ineligible for transplant. Time to transplant was defined as time of referral to time of transplant. The initial aim of our analysis was to determine if etiology of disease varied between ethnicities. Additionally, we sought to determine if transplantation rate, death on waitlist, graft failure, graft survival time, time to ineligibility status, and time to transplant were impacted by ethnicity. We also examined how age and gender within ethnicity influenced these parameters.

2.2. Statistical analysis

Continuous variables were summarized by means, medians, and standard deviations, and categorical variables as counts and percentages. Chi-Squared test and Analysis of Variance were used to compare categorical and continuous variables between ethnicities, respectively. Kaplan–Meier curves were created for time to being deemed ineligible, time to transplant, and graft survival. Date of referral to the liver transplant program was used as the starting time. Patients who died while on the waiting list were excluded from the time to ineligibility analysis. Patients were censored if there were no data regarding outcomes or if they were lost to follow-up. Curves between different cohorts were compared using Log-rank (Mantel-Cox) test. Multivariate linear regression, logistic regression and Cox regression were utilized to identify predictive factors of interest for continuous outcomes, categorical outcomes and survival curves, respectively. In addition to standard Kaplan–Meier curves, we calculated cumulative incidence functions and carried out Gray test.[8] For this analysis, we used time to transplant as the primary outcome with competing risks of ineligibility or death. Tests were considered significant with P values $<.05$. GraphPad Prism version 8.3.0 (GraphPad Software LLC) and R version 3.1.1 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria, 2014) were employed for these analyses.

3. Results

3.1. Demographics

There was a total of 4916 unique referrals (Table 1). There were 1234 without any documented ethnicity, and as such, were excluded from analysis. The remaining patients consisted of 220

Table 1

Demographics of patients stratified by ethnicity.

	All patients	South Asian	Asian	First nation	Caucasian	P
Number (n)	4916	220	413	235	2725	
Male (n, %)	2933 (59.7)	139 (63.2)	276 (66.8)	71 (30.2)	1644 (60.3)	.02
Age (SD)	52.5 (12.9)	50.9 (12.7)	52.5 (11.4)	47.8 (11.4)	52.2 (11.6)	<.01
BMI (SD)	27.4 (12.4)	25.3 (5.6)	24.7 (4.3)	28.6 (6.1)	27.3 (7.4)	<.01
MELD (SD)	16.3 (9.4)	19.2 (10.2)	15.9 (9.9)	17.5 (9.4)	16.5 (9.3)	<.01
CP (SD)	8.5 (2.4)	9.2 (2.7)	7.8 (2.4)	9.1 (2.1)	8.7 (2.3)	<.01

South Asians, 413 Asians, 235 First Nations, and 2725 Caucasians. Other ethnicities included 16 African Canadians, 24 Middle-Easterners, 12 Latin-Canadians, and 37 of other or mixed ethnicity (Fig. 1). Mean age was 52.5 +/- 12.9 years; patients aged 19 years or younger made up only 75 patients. Mean age varied between ethnicities, with Asian being the oldest (52.5 +/- 11.4) and First Nations being the youngest (47.8 +/- 11.4) ($P < .01$). There were 1983 females and 2933 males. First Nations patients were more likely to be female compared to other ethnicities (69.8%, $P = .02$). Mean BMI was 27.4 +/- 12.4 and differed between ethnicities, with Asian patients having the lowest BMI (25.3 +/- 5.6) and First Nations patients having the highest (28.6 +/- 6.1) ($P < .01$). Mean MELD score was 16.3 +/- 9.4 and differed between ethnicities with South Asians having the highest (19.2 +/- 10.2) and Asians having the lowest (15.9 +/- 9.9) ($P < .01$). Mean Child Pugh score was 8.5 +/- 2.4 and again differed between ethnicities in a similar vein to MELD score ($P < .01$).

3.2. Disease etiology

In terms of specific disease etiologies of the referred patients, chronic hepatitis C accounted for most disease (30.1%), followed by alcohol related cirrhosis (20.4%) (Table 2). Chronic hepatitis B (6.1%), cryptogenic cirrhosis (5.8%), malignancy (6.5%), autoimmune hepatitis (AIH) (5.0%), NASH (5.2%), PBC (6.3%), and primary sclerosing cholangitis (PSC) (5.6%) also accounted for large proportions. The remainder was made up of a variety of other causes. Etiologies that varied significantly between ethnicities included Alpha-1 Anti-trypsin ($P < .01$), autoimmune hepatitis ($P < .01$), cryptogenic cirrhosis ($P = .02$), hepatitis B ($P < .01$), hepatitis C ($P < .01$), alcohol related cirrhosis ($P < .01$), hemochromatosis ($P = .05$), NASH ($P < .01$), PBC ($P < .01$), and PSC ($P < .01$).

South Asian patients had the highest burden of alcohol related cirrhosis (27.4%), cryptogenic cirrhosis (10.2%), and PSC (8.8%). They also had relatively high burden of hepatitis C (22.3%) AIH (7.4%). Stratifying by gender revealed that South Asian males had much higher frequency of alcohol related cirrhosis (40.0%) compared to South Asian females (5.2%). In fact, of 59 South Asian patients with alcohol related cirrhosis, 55 were male and only 4 were female.

Asian patients had highest burden of hepatitis B (45.5%) and malignant disease (13.9%). They also had the lowest burden of NASH (1.0%) and alcohol related disease (2.2%). First Nations patients had the highest burden of PBC (33.2%) and AIH (10.8%), with a moderately high burden of hepatitis C (21.6%). Caucasian patients had the highest burden of hepatitis C (35.9%). Caucasian patients also had high burdens of alcohol related disease (20.0%) and PSC (7.2%). Caucasian patients were the only ones diagnosed with Alpha-1 Antitrypsin (0.9%) and hemochromatosis (0.6%).

3.3. Transplantation rates & time to transplant

Overall, 25.8% of referrals resulted in transplant. South Asians and Caucasians had the highest cumulative rate of transplanta-

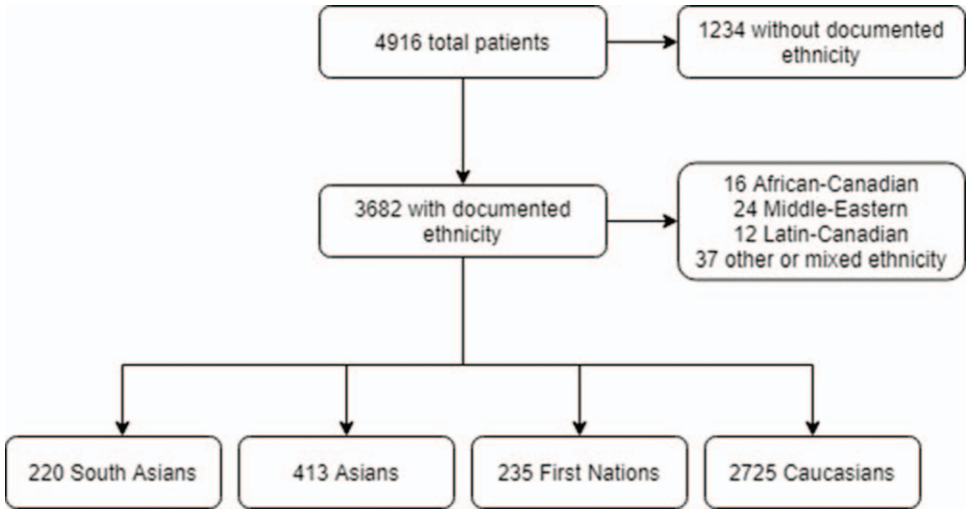

Figure 1. Flow chart detailing patients excluded and included in the final analysis. From the total cohort of patients, we identified 4 ethnicities with sufficient patient numbers for analysis. Patients without a documented ethnicity, or those ethnicities who were not represented in sufficient quantity, were excluded from analysis.

Table 2

Disease etiology by ethnicity (n%).

	All patients	South Asian	Asian	First nation	Caucasian	*P*
Drug/Toxic	88 (1.8)	2 (0.9)	5 (1.2)	6 (2.6)	31 (1.2)	.07
Acute viral	46 (1.0)	0 (0.0)	8 (2.0)	3 (1.3)	18 (0.7)	.86
A1AT	28 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	25 (0.9)	<.01
AIH	243 (5.0)	16 (7.4)	10 (2.5)	25 (10.8)	129 (4.8)	<.01
Budd chiari	20 (0.4)	1 (0.5)	1 (0.2)	0 (0.0)	8 (0.3)	.25
Malignancy	314 (6.5)	13 (6.0)	56 (13.9)	8 (3.4)	146 (5.4)	.10
Cryptogenic	280 (5.8)	22 (10.2)	16 (4.0)	6 (2.6)	155 (5.8)	.02
Hep B	293 (6.1)	4 (1.9)	183 (45.5)	2 (0.9)	52 (1.9)	<.01
Hep C	1454 (30.1)	48 (22.3)	62 (15.4)	50 (21.6)	967 (35.9)	<.01
EtOH	984 (20.4)	59 (27.4)	9 (2.2)	35 (15.1)	540 (20.0)	<.01
Hemochrom.	25 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	15 (0.6)	.05
NASH	253 (5.2)	11 (5.1)	4 (1.0)	10 (4.3)	137 (5.1)	<.01
Fulminant	78 (1.6)	6 (2.8)	7 (1.7)	9 (3.9)	30 (1.1)	.32
PBC	303 (6.3)	5 (2.3)	13 (3.2)	77 (33.2)	163 (6.0)	<.01
PSC	268 (5.6)	19 (8.8)	4 (1.0)	0 (0.0)	193 (7.2)	<.01
Other Biliary	54 (1.1)	3 (1.4)	12 (3.0)	1 (0.4)	29 (1.3)	.27
Wilsons	23 (0.5)	2 (0.9)	4 (1.0)	0 (0.0)	14 (0.6)	.37
Genetic	69 (1.4)	4 (1.9)	8 (2.0)	0 (0.0)	43 (1.6)	.06

tion (34.5%) whilst First Nations patients had the lowest (30.6%) ($P=.01$) (Table 3). In those patients deemed suitable transplant candidates, the median time from referral to transplantation was 268 days. South Asians had the shortest time to transplant (197 days), and Asians the longest (285 days), but differences between ethnicities did not reach significance ($P=.47$). Cox-proportional hazards analysis utilizing all referred patients with the event of interest being transplantation, revealed an increased likelihood of being transplanted with lower BMI (hazard ratio [HR] 0.99, 95 CI 0.98–0.99, $P=.03$), higher MELD (HR 1.02, 95 CI 1.01–1.03, $P<.01$), higher Child-Pugh (HR 1.16, 95 CI 1.12–1.19, $P<.01$) and a diagnosis of fulminant liver failure (HR 9.47, 95 CI 4.34–20.63, $P<.01$) (Table S3, Supplemental Digital Content, http://links.lww.com/MD2/A549). South Asian ethnicity also trended towards increased likelihood of transplantation, but did not reach significance (HR 2.18, 0.89–5.30, $P=.08$). Decreased likelihood of transplantation arose with a diagnosis of cryptogenic cirrhosis (HR 0.46, 95 CI 0.22–0.97, $P=.04$), hepatitis C (HR 0.46, 95 CI 0.22–0.93, $P=.03$) and alcohol related cirrhosis (HR 0.48, 95 CI 0.24–1.00, $P=.05$). Cumulative incidence with Gray test did not reveal any significant differences between ethnicities when competing risks of ineligibility and waitlist death were added to the analysis ($P=.66$) (Fig. 2, Table 4).

3.4. Time to ineligibility

In those patients who were determined to be not suitable, the median time from referral to decision regarding ineligibility was 170 days (Table 3). There was a statistically significant difference between ethnicities, which was driven by South Asians who had the shortest times with a of 97 days ($P<.0001$). When time to ineligibility of South Asian patients was stratified by gender, South Asian males had faster time to ineligibility than South Asian females (71 days vs 190 days, $P=.06$). Cox-proportional hazards analysis utilizing only those patients who were deemed to be ineligible candidates demonstrated shorter time to ineligibility with increased MELD (HR 1.01, 95 CI 1.00–1.02, $P<.01$), increased Child-Pugh (HR 1.04, 95 CI 1.02–1.07, $P<.01$), increased age at referral (HR 1.01, 95 CI 1.00–1.02, $P<.01$), a diagnosis of fulminant liver failure (HR 2.56, 95 CI 1.74–3.77, $P<.01$) and South Asian ethnicity (HR 2.54, 95 CI 1.32–4.89, $P<.01$) (Table S4, Supplemental Digital Content, http://links.lww.com/MD2/A550). Interestingly, diagnosis of any other etiology of liver disease excluding Wilsons was associated with longer time to ineligibility. However, it should be noted that competing risk analysis using cumulative incidence and Gray test did not reveal any significant differences between ethnicities with regards to ineligibility ($P=.91$) (Fig. 2, Table 4).

Table 3

Categorical outcomes (n%) & median times (days) for temporal outcomes.

	All patients	South Asian	Asian	First nation	Caucasian	*P*
Transpl. (n%)	1270 (25.8)	76 (34.5)	131 (31.7)	72 (30.6)	941 (34.5)	.01
W death (n%)	246 (5.0)	15 (6.8)	26 (6.3)	25 (10.6)	161 (5.9)	.03
Acu rej (n%)	505 (39.8)	24 (31.6)	43 (32.8)	29 (40.3)	393 (41.8)	<.01
Chr rej (n%)	23 (1.8)	1 (1.3)	1 (0.8)	1 (1.4)	20 (2.1)	.03
Time inelig (d)	170	97	233	236	230	<.0001
Time trans (d)	268	197	285	246	274	.48
Graft surv (d)	1845	1649	1595	1811	1937	.47

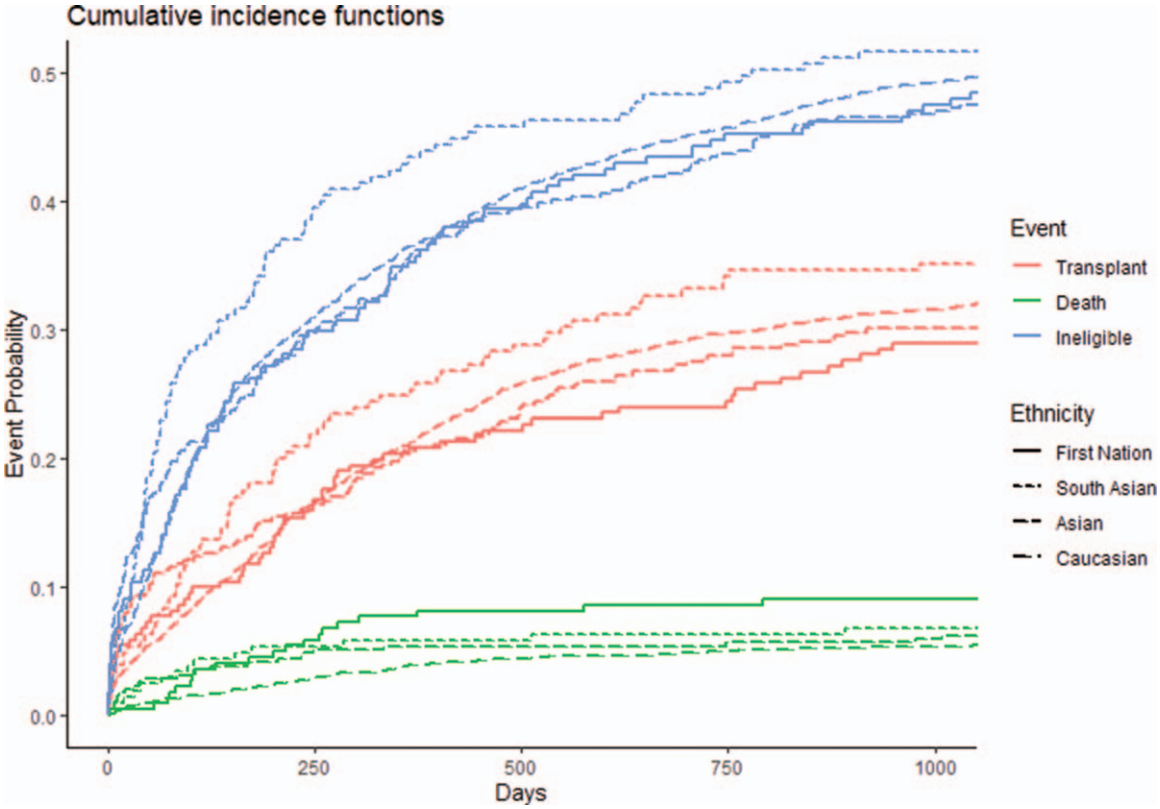

Figure 2. Competing risks analysis stratified by ethnicity. Events of interest include time to transplant (red), time to death while on waitlist (green), and time to ineligibility status (blue). Time is presented in days along the x-axis, and probability of event of interest is presented along the y-axis. Ethnicities (First nation, South Asian, Asian, Caucasian) are depicted as solid or dotted lines.

3.5. Death on waitlist

Overall, 5.0% of all referred patients died on the waitlist (Table 3). This rate was higher in First Nations patients (10.6%, $P=.03$). Frequent reasons for wait list death included acute or chronic liver failure (31.7%), multisystem organ failure (24.8%) and sepsis (16.7%) (Table S1, Supplemental Digital Content, http://links.lww.com/MD2/A547). Only liver failure as a reason for waitlist death varied between ethnicities, with South Asians having the highest rate (40.0%) and First Nations the lowest (20.0%) ($P=.04$). Multivariate regression utilizing patients who did not receive transplant, and were deemed to have died while on the wait list, demonstrated increased risk of death with higher MELD (HR 1.05, 95 CI 1.03–1.06, $P<.01$), higher Child-Pugh (HR 1.25, 95 CI 1.6–1.35, $P<.01$), and diagnosis of fulminant liver failure (HR 8.85, 95 CI 2.27–34.55, $P<.01$) (Table S5, Supplemental Digital Content, http://links.lww.com/MD2/A551). Increased death on the waitlist for First Nations patients persisted on competing risk analysis using cumulative incidence and Gray test ($P=.04$) (Fig. 2, Table 4).

Table 4

Competing risks analysis for time to transplant, time to death, and time to inelibility status suing cumulative incidence function (Gray test):.

	250 days	500 days	750 days	*P* value
Transplant:				
F. Nation	0.17	0.22	0.24	.66
S. Asian	0.22	0.29	0.34	
Asian	0.16	0.24	0.28	
Caucasian	0.17	0.26	0.30	
Death:				
F. Nation	0.06	0.08	0.09	.04
S. Asian	0.05	0.06	0.06	
Asian	0.05	0.05	0.06	
Caucasian	0.03	0.04	0.05	
Ineligible:				
F. Nation	0.30	0.40	0.45	.91
S. Asian	0.40	0.46	0.49	
Asian	0.30	0.40	0.44	
Caucasian	0.31	0.41	0.46	

3.6. Acute & chronic rejection

Of patients who were transplanted, 39.8% experienced at least 1 episode of acute rejection and 1.8% were reported as having experienced chronic rejection (Table 3). Rates of acute rejection where highest in Caucasians (41.8%) and First Nations (40.3%) when compared to Asians (32.8%) and South Asians (31.6%) ($P<.01$). Caucasians also had the highest rate of chronic rejection (2.1%, $P=.03$).

3.7. Graft survival

In transplanted patients, median graft survival was 1845 days (Table 3). Caucasians had longest graft survival (1937 days) and

Asians the shortest (1595 days), but differences between ethnicities did not reach significance ($P = .47$). Frequent reasons for graft failure included patient death with functioning graft (27.9%), recurrent disease (12.4%) and arterial or venous thrombosis (8.5%) (Table S2, Supplemental Digital Content, http://links.lww.com/MD2/A548). There was also a large proportion where reason for graft failure was unknown (26.3%). Death with a functioning graft was higher in Caucasians (29.4%) than other ethnicities ($P < .01$). Recurrence of disease was higher in South Asians (16.7%) and Caucasians (14.0%) than Asians (5.2%) or First Nations (3.4%) ($P < .01$).

4. Discussion

Canada in general, and BC specifically, has a diverse multi-ethnic, multi-cultural population, including those of Asian, South Asian and First Nations descent. Studies from the United States have highlighted differences in disease etiology and transplantation referral outcomes between minorities and the larger Caucasian population, however, the demographic composition of BC differs markedly from the USA. Major ethnic groups in the United States, such as those of Latin and African descent, are not well represented in Canada. Asians and South Asians are very dominant demographic minorities in BC. Furthermore, the majority of South Asians in BC hail from the Punjab region of Northern India, which is not the case in the United States. As such, we thought it important to analyze our local population in a similar manner and noted several important findings.

4.1. Disease etiologies in Asians & Caucasians

There were striking demographic and etiologic differences between ethnicities. Asian patients were the oldest and had the lowest BMI. Corresponding with low BMI, they had the lowest burden of NASH. They had the highest burden of hepatitis B, as well as malignancy, which was likely driven by hepatitis B induced HCC. Hepatitis B and malignancy are known to be widely prevalent in this population.[9] Caucasian patients had the highest burden of hepatitis C. This correlates somewhat with American data, which shows higher prevalence of hepatitis C in non-Hispanic whites but also African Americans.[10] Caucasians are more likely to be screened for hepatitis C compared to minorities, and likely make up the majority of 1945 to 1965 birth cohort in our local population.[11] Caucasians were the only ethnicity with diagnoses of Alpha-1 Antitrypsin deficiency and hemochromatosis, both diseases known to occur much more frequently in those of European descent.

4.2. Disease etiologies in first nations

First Nations patients were youngest and had the highest BMI. Furthermore, almost 70% of First Nations patients were female, much higher than other ethnicities. Remarkably, 1/3rd of all First Nations patients had been referred for PBC, more than 5 times that of any other ethnicity. This explains the high rate of female patients, given PBC's strong female preponderance.[12] First Nations also had the most AIH. The First Nations population of BC has been noted to have very high burdens of PBC and AIH,[6] and our data appears to confirm this. It is interesting to note that our current study reproduces the findings of our PBC database review of 20 years ago[13] and AIH review of 13 years ago[14] suggesting that predisposition towards these 2 autoimmune liver diseases is both real and continues to the present day. Familial whole genome linkage studies in this population have identified unique candidate genes that could be explored in further studies.[15]

Interestingly, we also noted a relative paucity of PSC in this population. This rarity of PSC in the First Nations population of Canada has been seen previously in BC as well as other provinces.[6,16] PSC is a chronic inflammatory disease which leads to multifocal biliary strictures and is very commonly associated with inflammatory bowel disease (IBD).[17] In fact, it is suggested that leakage of pro-inflammatory agents from the colon into portal circulation may trigger an antigenic, inflammatory response in the biliary ducts. First Nations patients in Canada have a very low prevalence of IBD,[6,16,18] possibly explaining the paucity of PSC in this population. It should be noted that the prevalence of IBD in First Nations does appear to be increasing, and it will be interesting to see if this also results in an increase of PSC prevalence in the future.[19]

We did not witness high rates of alcohol related liver disease in First Nations patients previously noted throughout Canada.[20] It is possible that our local BC population differs in alcohol use, or that perhaps such patients are not receiving sufficient addictions help, although this is speculative at this point.

4.3. Disease etiologies in South Asians

Analysis of the South Asian population revealed several important findings, including higher MELD. Association of higher MELD with ethnicity has been noted before.[21] South Asians had the highest burden of alcohol related cirrhosis, which may explain higher MELD scores, as these patients would have lower rate of HCC than patients with viral disease and therefore referred for transplant later. Alcohol cirrhosis in this population was almost entirely limited to males, and prior data also suggests higher rates of substance abuse in South Asian males compared to females.[22] Additional factors that may contribute to alcohol related cirrhosis include binge drinking and genetic polymorphisms.[23] It should be noted that despite the increased burden of alcoholic liver disease, multivariate analysis revealed no differences with regards to transplant decisions or time to ineligibility. Our findings strongly suggest that appropriate public health measures regarding alcohol consumption, including public education, are needed in this large community within BC. Given that policies regarding timing of liver transplantation for alcohol related liver disease are rapidly changing,[24] such public health measures will also be needed to prevent relapse after transplantation. These measures will have to be designed in a culturally appropriate manner, to maximize engagement.

That many South Asians in BC hail from Northern India, may explain their high hepatitis C burden. This region has high hepatitis C prevalence due to unsterile procedures and growing opioid use.[25] Many immigrants forego screening and those born in Canada may acquire the virus through household contact.[26] The discovery of an 8th genotype of hepatitis C, occurring exclusively in Canadian immigrants from Punjab, India, may complicate management.[27] South Asians also had highest burden of cryptogenic cirrhosis. It is possible that these cases represent undiagnosed NASH, as South Asians have higher rates of metabolic syndrome.[28] Lastly, the finding of high PSC prevalence in this population is surprising. Very few studies have profiled PSC specifically in South Asians, and there are no large epidemiologic studies highlighting this association. Previous data

highlighted an increased incidence of IBD in the pediatric South Asian population of BC, which suggests an evolving correlation.[29] Findings regarding disease etiology and higher MELD in this population will have important ramifications for preventative and management strategies.

4.4. Lower transplant rates & higher waitlist death in first nations

Rates of transplantation were similar between ethnicities but was lowest for First Nations patients, a trend that has been observed before.[13] Disparate geographic distribution of many First Nations in BC may also contribute to this trend, as has been observed in other populations.[30] Additionally, death whilst on the waitlist occurred most frequently for First Nations patients. Interestingly, waitlist death has previously been noted to be higher in certain minorities with PBC.[31] First Nations patients in our study had high burden of PBC, and also a higher rate of GI bleeding as cause of death (Table S1, Supplemental Digital Content, http://links.lww.com/MD2/A547), suggesting that perhaps pre-sinusoidal portal hypertension contributes to catastrophic events in these patients. This may also partially explain why, even though First Nations patients had highest waitlist deaths, they did not have highest MELD. It should also be noted that despite the lower transplant rate in First Nations, those who were deemed appropriate candidates (i.e., Placed on the waitlist) did not differ in their time to transplantation compared to other ethnicities. First Nations patients throughout Canada have relatively worse outcomes in other areas as well, for example, cancer survival.[32] Perhaps our findings of lower transplant rate and higher waitlist death for this population reflect larger, systemic issues not accounted for by MELD score or other conventional transplant measures and warrant further investigation.

4.5. Similar graft survival despite differences in rejection & disease recurrence

Rates of rejection in our overall cohort were somewhat higher than the literature. This may reflect the wide time frame of our study as rejection rates have decreased overtime with advances in immunosuppression. We are also unsure why Caucasians had the highest burden of rejection, as this trend has only been observed in minorities before.[33] Difference in follow-up, as well as changes in immunosuppression over time and medical non-compliance may play roles, but this data was unavailable to us. Graft survival times after transplant did not differ between ethnicities. However, disease recurrence after transplant was higher in South Asians and Caucasians. We believe this may be due to the higher burden of disease etiologies that are prone to recurrence in these populations. For example, hepatitis C viremia, pre-direct acting antiviral therapy, was common post-transplant, and greater than 20% of patients with alcohol related liver disease will relapse after transplant.[34] PSC, which was higher in these populations, is also prone to recurrence.[35] Overall, this data suggests that graft survival is similar among ethnicities despite differences in rates of rejection episodes and disease recurrence.

5. Limitations

Our study has several limitations to take note of. Firstly, this is a retrospective analysis and encompasses the entirety of BCs liver transplant program. As such, it is possible that certain trends we noted may already be changing. Additionally, data regarding why a candidate was deemed ineligible for transplantation was not available. Specific data regarding immunosuppression was also not available. Lastly, although data regarding how many patients had died were available, date of death was not available. As such, survival curves for overall and post-transplant survival could not be calculated. Regardless, we have highlighted key differences in disease etiology and transplantation referral outcomes between major ethnicities within our province.

6. Conclusion

We have confirmed known epidemiologic patterns for certain ethnicities such as hepatitis B in Asian patients but have also made note of evolving trends such as alcohol related liver disease and PSC within the South Asian population. Additionally, we have confirmed that First Nations patients have an increased predisposition to autoimmune liver disease, specifically PBC and AIH but not PSC, and may have lower transplantation rates. We have discovered that South Asian patients may be deemed ineligible for transplantation at an earlier stage of assessment. These data have significance for designing preventative and management strategies, as well as public and health care professional education, tailored towards specific ethnic communities, not only for BC, but Canada as a whole.

Author contributions

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