

The Current State of Liver Transplantation in Canada

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INTRODUCTION & BACKGROUND

- Liver transplantation is the second most common transplant procedure in Canada,¹ and is associated with significant economic and quality of life burden.^{2,3}
- There are new and highly efficacious treatment options for several leading causes for liver transplants, including hepatitis C (HCV), which has curative intent,^{4,5} and primary biliary cholangitis (PBC), where new treatment options address an unmet need.^{6,9}
- In contrast, there are several diagnoses among the top reasons for liver transplant where patients have limited treatment options including alcoholic cirrhosis (AL-LC), hepatocellular carcinoma (HCC), and primary sclerosing cholangitis (PSC).
- Furthermore, non-alcoholic steatohepatitis (NASH) has been identified as a growing healthcare concern, and is expected to become the number one reason for liver transplant by 2020 in the USA¹⁰⁻¹⁹
- We therefore, undertook this study to characterize patients that received liver transplants in Canada, and to perform a focused assessment of HCV, PBC, PSC, AL-LC, HCC, and NASH where we expect the largest change in transplantation trends.

STUDY OBJECTIVES

Objective 1: Understand the liver transplant landscape in Canada, and segment the top ten most predominant diagnoses for the following metrics:

- Liver transplant demographic and clinical characteristics
- 6-year national prevalence

Objective 2: Provide a targeted assessment of HCV, PBC, PSC, AL-LC, HCC and NASH for the following metrics:

- Liver transplant annual trend
- Liver transplant regional distribution
- Wait-time and survival analysis

METHODS

Data Source

- Our study used patient-level records for liver transplants for the study period of March 2010 to April 2015.
- The data source is managed by the Canadian Institute for Health Information, and is held in the Canadian Organ Replacement Register.
- Quebec and British Columbia data were not available for this study.
- There were 144 patients where the primary diagnosis was not reported, and this data was excluded from the analysis.

Study Design

- This study used a cross-sectional design, and patients were categorized using the primary diagnosis associated with the liver transplant, as recorded by the treating physician.
- Wait-time was defined as the amount of time from when the patient was placed on the transplant list to when the liver transplant took place.
- Survival was defined as the amount of time from the liver transplant to when the patient died. Patients that died while on the waiting list were not included in analysis.

Statistical Analysis

- The 6-year prevalence estimate was age and sex adjusted to 2013, which is the median year of the study period (2010-2015).
- Temporal trends were tested using the Mann-Kendall and Spearman Rank Test, and the Kaplan-Meier method was used to assess wait-time and survival.

REFERENCES

¹CIHI, 2015; ²Sullivan, P., 2003; ³Taylor MC, et al., 2002; ⁴Jang, J. Y. et al., 2010; ⁵Corouge, M. et al., 2011; ⁶Rodriguez, E. A. et al., 2007; ⁷Boonstra, K., et al., 2012; ⁸Williamson, K. D. et al., 2016; ⁹Ali, A. H. et al., 2016; ¹⁰Carey, E. J. 2015; ¹¹Lindor, K. D. et al., 2009; ¹²Ali, A. H. et al., 2016; ¹³Fosby, B. et al. 2015; ¹⁴Haque, H. et al., 2010; ¹⁵Susca, M. et al. 2001; ¹⁶Zantout, H. et al., 1999; ¹⁷Sorrell, M. F., et al., 1999; ¹⁸Day, C. P. et al., 2002; ¹⁹Manton, N. D. et al., 2000; ²⁰Evans, C. D. et al., 2002; ²¹Minervini, M. I. et al., 2009; ²²Wree, A. et al., 2013; ²³Angulo, P. et al., 1999

RESULTS

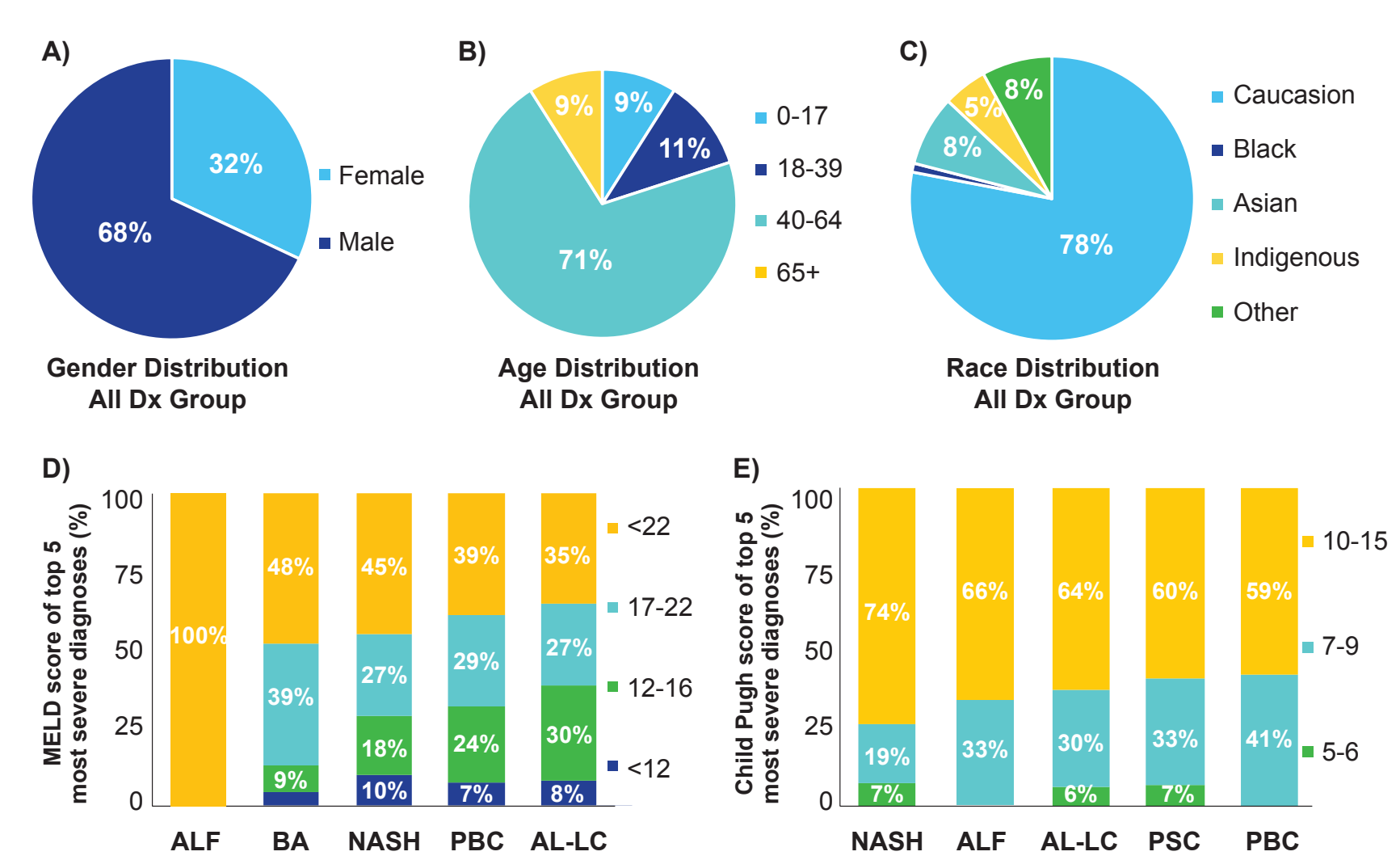
ASSESSMENT OF THE CANADIAN LIVER TRANSPLANT LANDSCAPE

Table 1: Clinical and Demographic Characteristics of Liver Transplant Patients in Canada

Variables	All Dx	Other Dx	Top 10 Diagnosis									
			HCV	HCC*	AL-LC	PSC	NASH*	PBC	BA	FLC	HBV	ALF
Distribution, n (% relative to all Dx)	1,800, (100%)	372, (21%)	318, (18%)	279, (16%)	210, (12%)	161, (9%)	140, (8%)	92, (5%)	74, (4%)	61, (3%)	58, (3%)	35, (2%)
Sex, n (% within group)												
Male	1,223, (68%)	204, (55%)	250, (79%)	232, (83%)	169, (80%)	114, (71%)	90, (64%)	22, (24%)	33, (45%)	48, (79%)	49, (84%)	12, (34%)
Female	577, (32%)	168, (45%)	68, (21%)	47, (17%)	41, (20%)	47, (29%)	50, (36%)	70, (76%)	41, (55%)	13, (21%)	9, (16%)	23, (66%)
Age, n (% within group)												
0-17	166, (9%)	77, (21%)	---	<5, (1%)	---	10, (6%)	<5, (1%)	<5, (1%)	67, (91%)	---	---	5, (14%)
18-39	199, (11%)	76, (20%)	<5, (1%)	<5, (1%)	5, (2%)	64, (40%)	8, (6%)	8, (9%)	<5, (1%)	---	14, (24%)	16, (46%)
40-64	1,273, (71%)	201, (53%)	300, (94%)	217, (78%)	185, (88%)	80, (50%)	113, (81%)	71, (77%)	5, (7%)	48, (79%)	40, (69%)	13, (37%)
65+	162, (9%)	18, (5%)	14, (4%)	55, (20%)	20, (10%)	7, (4%)	17, (12%)	12, (13%)	<5, (1%)	13, (21%)	<5, (7%)	<5, (3%)
Race, n (% within group)												
Caucasian	388, (78%)	84, (72%)	100, (86%)	25, (61%)	41, (93%)	49, (88%)	29, (81%)	30, (91%)	18, (72%)	<5, (100%)	7, (27%)	<5, (50%)
Black	6, (1%)	<5, (2%)	<5, (1%)	---	---	---	---	---	---	---	<5, (8%)	<5, (17%)
Asian	42, (8%)	8, (7%)	<5, (3%)	12, (29%)	---	---	<5, (3%)	---	<5, (16%)	---	12, (46%)	<5, (17%)
Indigenous population	23, (5%)	9, (8%)	5, (4%)	<5, (2%)	<5, (7%)	<5, (2%)	<5, (6%)	<5, (3%)	---	---	---	<5, (17%)
Other	42, (8%)	13, (11%)	6, (5%)	<5, (7%)	<5, (11%)	<5, (6%)	<5, (6%)	<5, (12%)	<5, (1%)	13, (21%)	<5, (19%)	<5, (17%)
Not reported	1,299	256	202	238	166	105	104	59	49	59	32	29
MELD Score, n (% within group)												
<12	141, (22%)	27, (22%)	48, (31%)	37, (47%)	5, (8%)	<5, (6%)	5, (10%)	<5, (7%)	<5, (4%)	---	11, (33%)	---
12-16	135, (21%)	13, (11%)	37, (24%)	24, (31%)	18, (30%)	16, (23%)	9, (18%)	10, (24%)	<5, (9%)	---	6, (18%)	---
17-22	145, (23%)	25, (21%)	27, (18%)	11, (14%)	16, (27%)	27, (38%)	13, (27%)	12, (29%)	9, (39%)	---	5, (15%)	---
>22	220, (34%)	57, (47%)	42, (27%)	6, (8%)	21, (35%)	22, (32%)	22, (45%)	16, (39%)	11, (48%)	---	11, (33%)	12, (100%)
Not reported	1,159	250	164	201	150	92	91	51	51	61	25	23
Child Pugh Score, n (% within group)												
5-6	64, (17%)	18, (21%)	20, (20%)	7, (37%)	<5, (6%)	<5, (7%)	<5, (7%)	---	<5, (5%)	---	11, (52%)	---
7-9	111, (29%)	15, (18%)	35, (34%)	8, (42%)	10, (30%)	15, (33%)	5, (19%)	12, (41%)	8, (38%)	---	<5, (10%)	<5, (33%)
10-15	210, (55%)	52, (61%)	47, (46%)	<5, (21%)	21, (64%)	27, 60%	20, (74%)	17, (59%)	12, (57%)	---	8, (38%)	<5, (66%)
Not reported	1,415	287	216	260	177	116	113	63	53	61	37	32

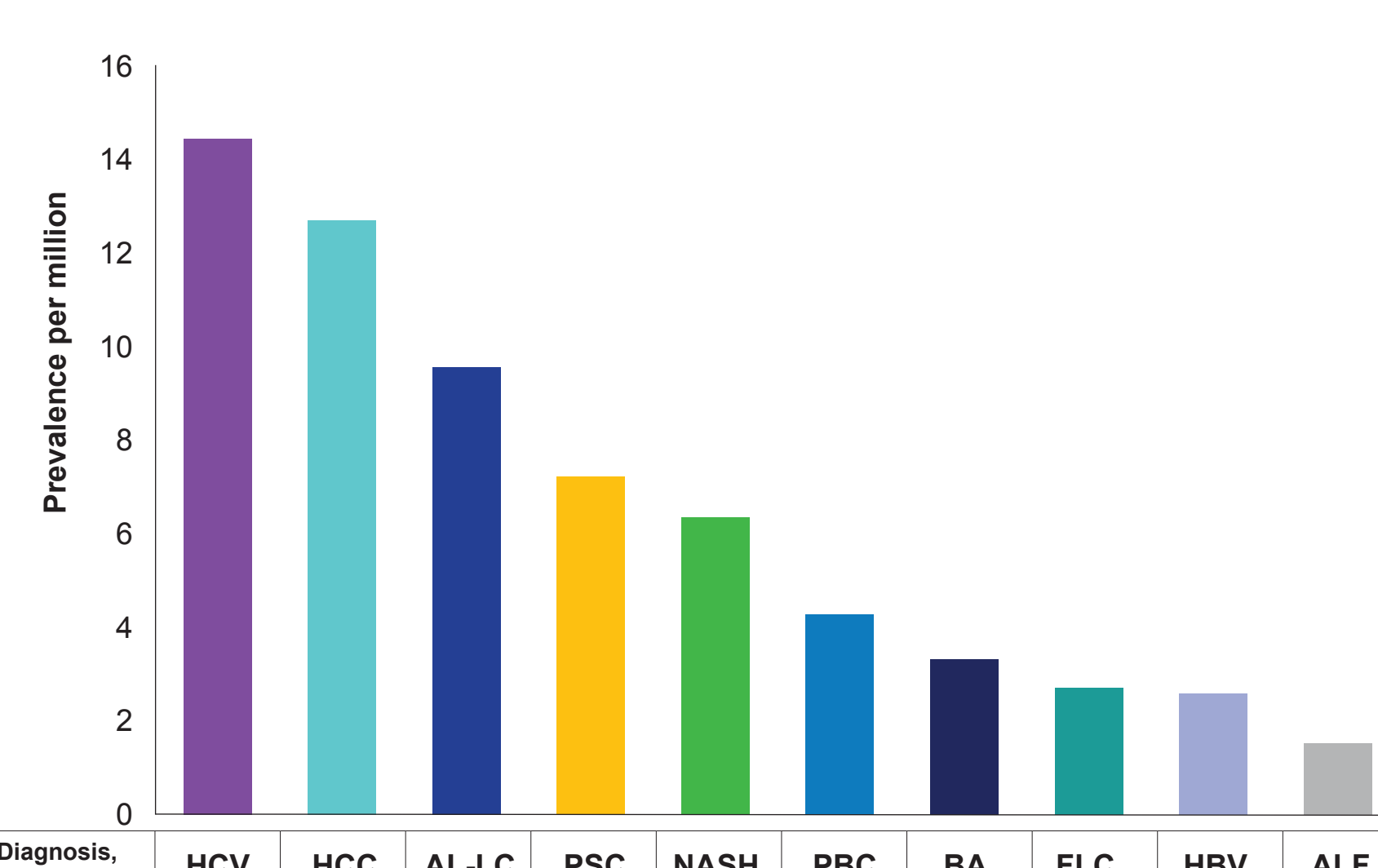
Abbreviations: ALF, Acute Liver Failure; All Dx, all liver transplants with a primary diagnosis; Other Dx, remaining diagnoses not included in the top 10; AL-LC, Alcoholic Cirrhosis; FLC, Fibrolamellar Hepatoma; HBV, Hepatitis B; HCV, Hepatitis C; HCC, Hepatocellular Carcinoma; MELD, Model for End Stage Liver Disease; NASH, Non-alcoholic Steatohepatitis; BA, Primary Biliary Atresia; PBC, Primary Biliary Cholangitis; PSC, Primary Sclerosing Cholangitis.
Note: The dashed line (---) indicates there were no patients in this category. Cell sizes <5, are not reported. MELD and Child Pugh score were recorded at the time of transplant.
* The following diagnoses were combined to form NASH and HCC groupings respectively: NASH and Cryptogenic Cirrhosis, HCC and Hepatic Tumour.

Figure 1: Demographic and Clinical Insights from the Canadian Liver Transplant Landscape



a) Gender distribution of all Dx group b) Age distribution of all Dx group c) Race distribution of all Dx group
d) MELD Score of the top five most severe diagnoses e) Child Pugh Score of the top five most severe diagnoses
Abbreviations: ALF, Acute Liver Failure; All Dx, all liver transplants with a primary diagnosis; AL-LC, Alcoholic Cirrhosis; NASH, Non-alcoholic Steatohepatitis; PSC, Primary Sclerosing Cholangitis; PBC, Primary Biliary Cholangitis; BA, Primary Biliary Atresia

Figure 2: 6-Year National Prevalence of Top 10 Most Common Primary Diagnoses for Liver Transplant



Abbreviations: ALF, Acute Liver Failure; AL-LC, Alcoholic Cirrhosis; FLC, Fibrolamellar Hepatoma; HBV, Hepatitis B; HCV, Hepatitis C; HCC, Hepatocellular Carcinoma; NASH, Non-alcoholic Steatohepatitis; BA, Primary Biliary Atresia; PBC, Primary Biliary Cholangitis; PSC, Primary Sclerosing Cholangitis

SUMMARY OF RESULTS

Summary of the Canadian Liver Transplant Landscape:

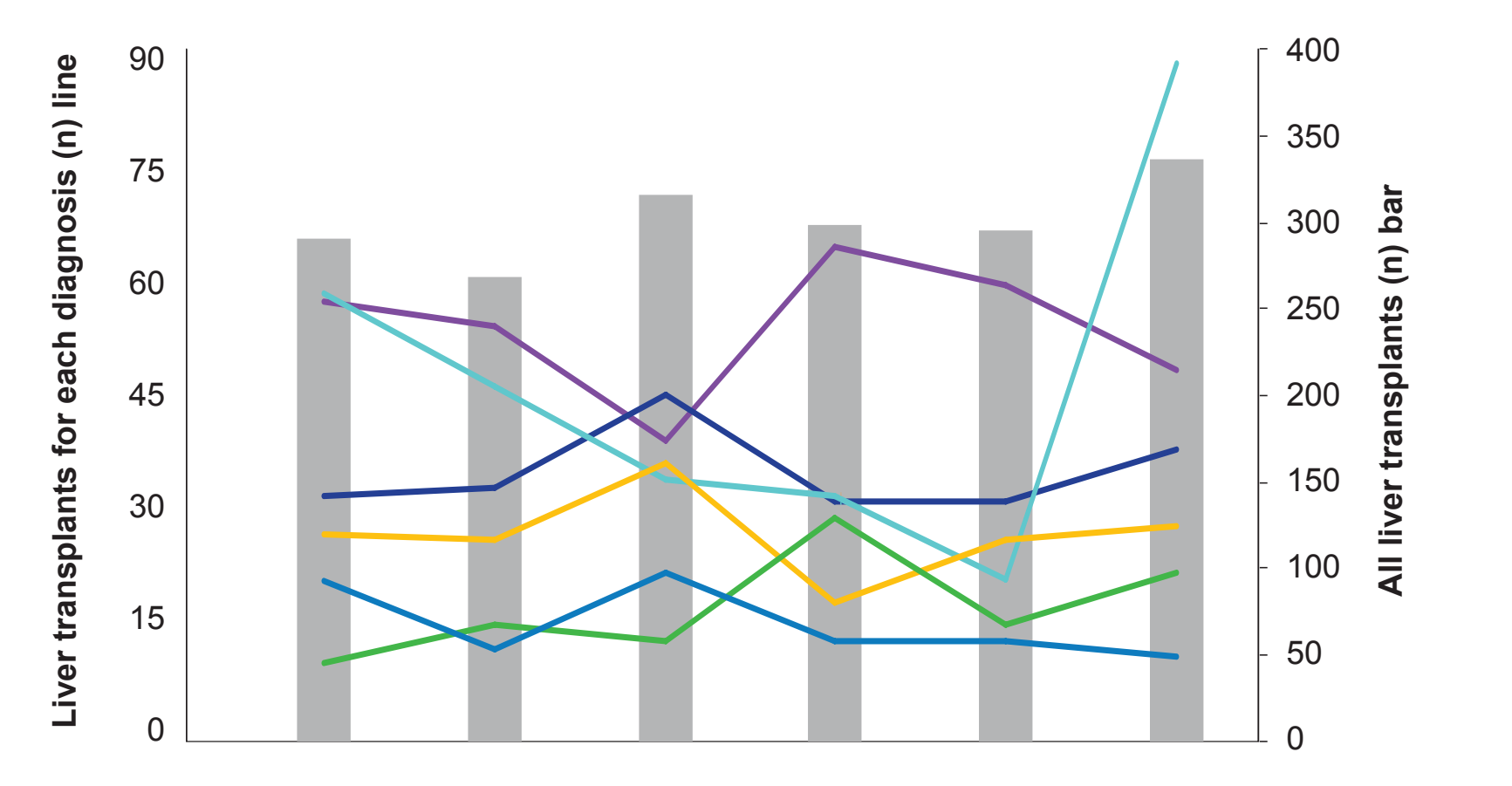
- Liver transplant patients were mostly male (68%), and between the age of 40-64 (71%).
- The number one reason for liver transplant in females was PBC (12%), while for men it was HCV (20%).
- The most common ethnicity for liver transplant in Canada was Caucasian (78%); while the Indigenous population made up 5% of the transplants, and a high proportion of HBV (46%) and HCC (29%) patients were of Asian descent.
- The most severe diagnoses within the top 10 reasons for liver transplant as indicated by MELD and Child Pugh score were: ALF, NASH, BA, PBC, AL-LC, and PSC.

Summary of Liver Transplant Trends in Targeted Diagnoses:

- An increase in liver transplants were observed for NASH, while HCV, AL-LC, and PSC remained neutral, and PBC and HCC are decreasing; however, these trends did not reach significance.
- In terms of regional distribution, we observed a large proportion of liver transplants in Alberta are related to HCV (28%) compared to between 11-18% in other provinces.
- In Ontario, 20% of the transplants are dedicated to HCC patients, compared to between 3-15% in other provinces.
- While, in the Maritime Provinces, we observed a larger proportion of liver transplants for NASH (14%) and PBC (10%) patients, which ranged from 6-8% and 4-7% respectively in other provinces.
- In terms of wait-time, HCC patients had the shortest wait at an average of 5.80 months, whereas PSC patients experienced the longest wait-time being on average 8.88 months.

TARGETED ASSESSMENT OF LIVER TRANSPLANT TRENDS IN CANADA

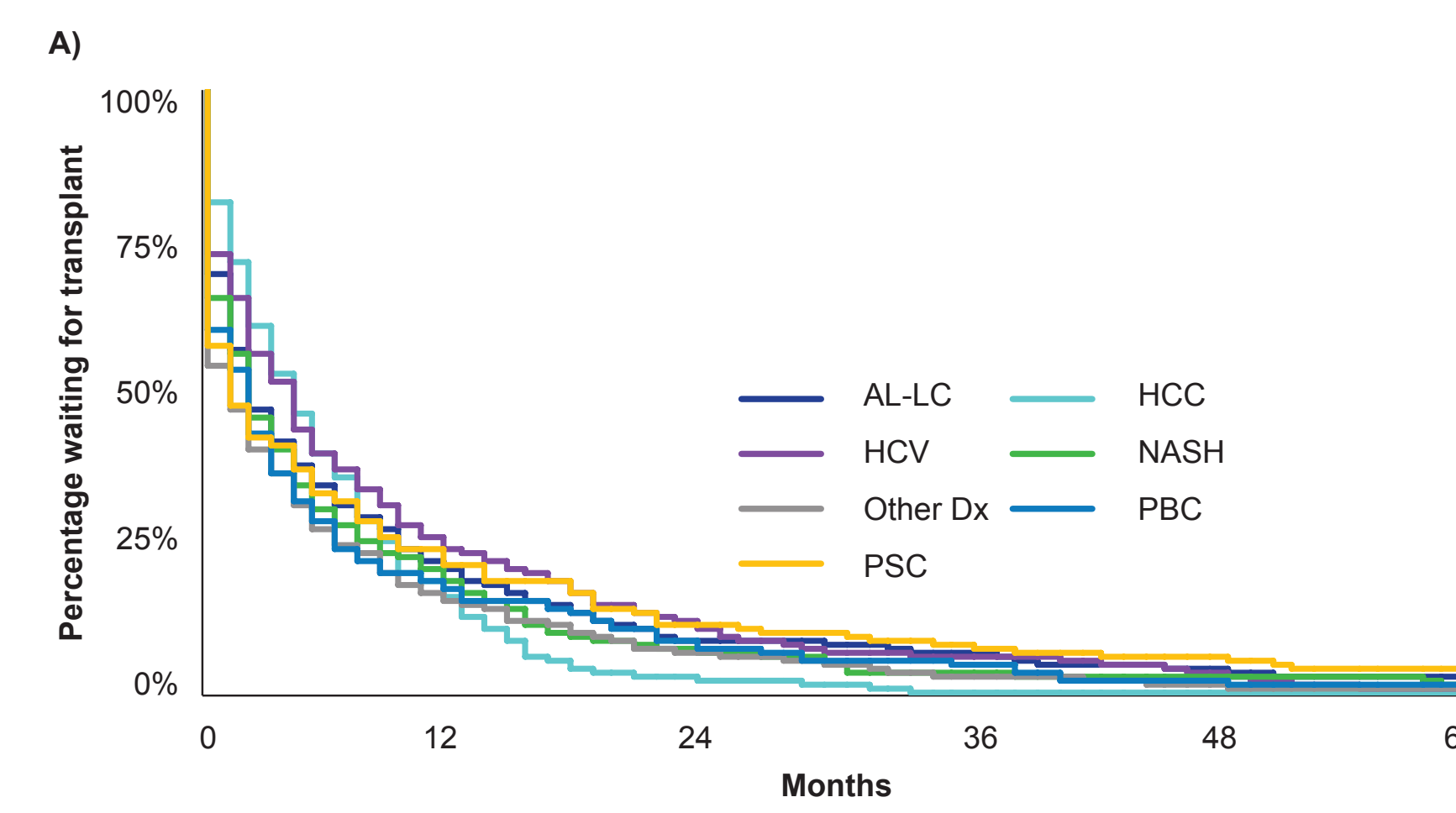
Figure 3: Annual Trend in Liver Transplant by Diagnosis



Year, n	2010	2011	2012	2013	2014	2015	Trend analysis (slope, p value)
PBC	21	12	22	13	13	11	Negative, (p<0.05)
NASH	20	24	15	34	22	25	Positive, (p<0.05)
PSC	27	26	36	18	26	28	Neutral, (p>0.05)
HCC	58	46	34	32	21	88	Negative, (p<0.05)
AL-LC	32	33	45	31	31	38	Neutral, (p>0.05)
HCV	57	54	39	63	58	47	Neutral, (p>0.05)
Other Dx (not depicted)	74	73	124	106	124	99	Positive, (p<0.05)
All Dx	289	268	315	297	295	336	Positive, (p<0.05)

Abbreviations: AL-LC, Alcoholic Cirrhosis; HCC, Hepatocellular Carcinoma; HCV, Hepatitis C; NASH, Non-alcoholic Steatohepatitis; PBC, Primary Biliary Cholangitis; PSC, Primary Sclerosing Cholangitis; All Dx, all transplants with a diagnosis code; Other Dx, all other transplant diagnosis not listed in the table

Figure 5: Survival Post-transplant and Patient Wait-time Analysis

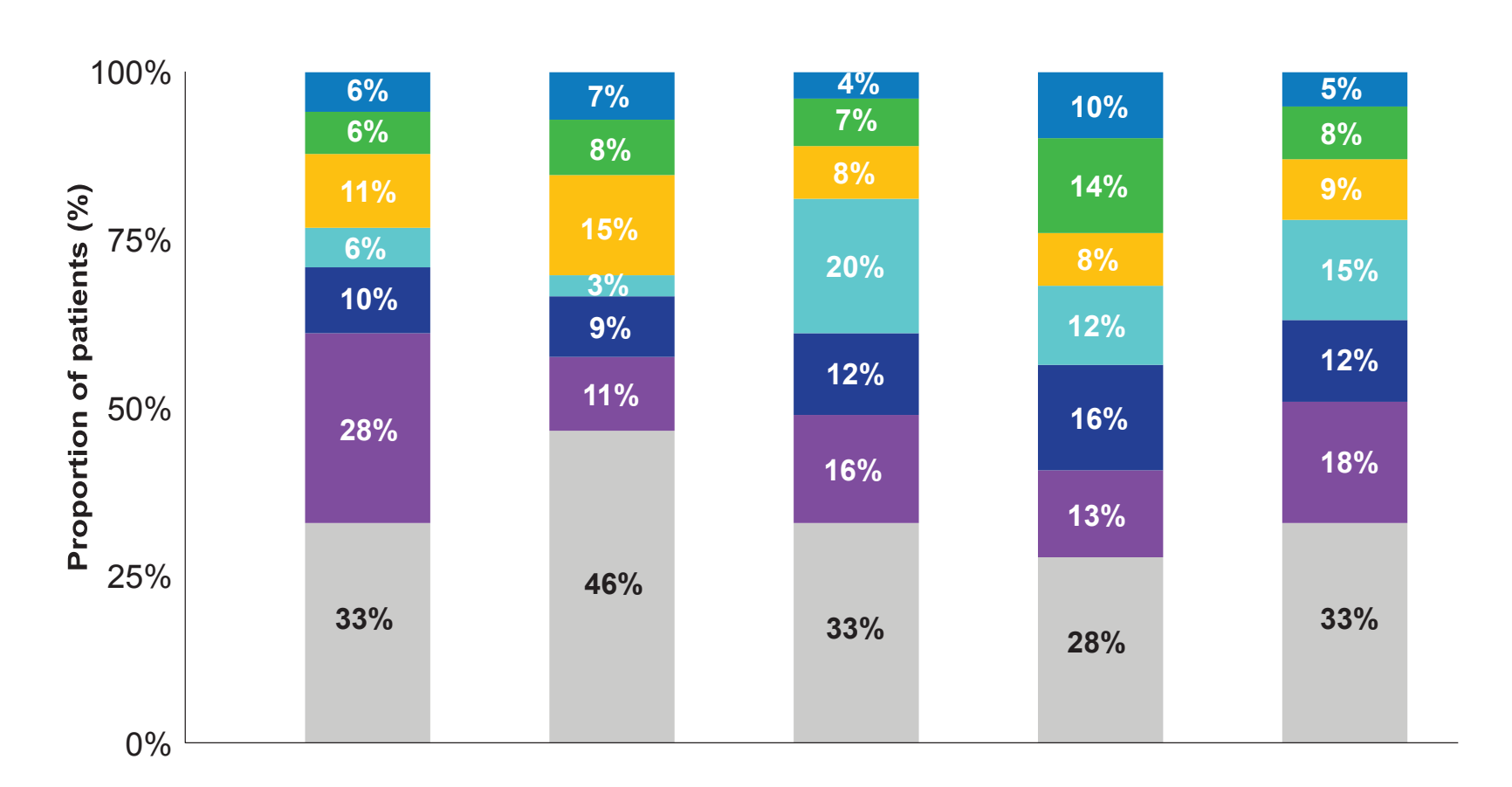


Diagnosis	HCC	PBC	NASH	AL-LC	HCV	PSC	Other Dx
6-month wait, proportion	35%	24%	28%	31%	37%	32%	24%
Average wait, months	5.80	6.44	6.61	8.27	8.72	8.88	6.96

a) Wait-time analysis b) Survival post-transplant

Abbreviations: AL-LC, Alcoholic Cirrhosis; HCC, Hepatocellular Carcinoma; HCV, Hepatitis C; NASH, Non-alcoholic Steatohepatitis; PBC, Primary Biliary Cholangitis; PSC, Primary Sclerosing Cholangitis; All Dx, all transplants with a diagnosis code; Other Dx, all other transplant diagnosis not listed in the table

Figure 4: 6-year Regional Distribution in Liver Transplant by Diagnosis



Region, n	Alberta	Prairie Provinces	Ontario	Maritime Provinces	Provinces Combined
PBC	22	7	46	15	90
NASH	22	8	87	21	138
PSC	38	14	94	12	158
HCC	19	3	233	19	274
AL-LC	33	9	141	25	208
HCV	95	10	190	20	315
Other Dx	112	44	390	43	589
All Dx (not depicted)	341	95	1,181	155	1,772

Note: There were 28 patients where the province details were not reported
Abbreviations: AL-LC, Alcoholic Cirrhosis; HCC, Hepatocellular Carcinoma; HCV, Hepatitis C; NASH, Non-alcoholic Steatohepatitis; PBC, Primary Biliary Cholangitis; PSC, Primary Sclerosing Cholangitis; All Dx, all transplants with a diagnosis code; Other Dx, all other transplant diagnosis not listed in the table

CONCLUSIONS & FUTURE DIRECTIONS

- Our findings show in 2015 there was an increase in the number of HCC liver transplants. We believe this is a result of the use of MELD exemption points for patients with HCC, which prioritizes HCC patients on the wait-list.^{20,22}
- Our study did not observe a reduction in HCV liver transplants as a result of the new directly acting antivirals introduced in 2014. It is likely that the benefit will impact the wait-list in future years.
- We did not observe dramatic growth in NASH liver transplants in Canada, although forecasts suggest it will be the number one reason for liver transplants in 2020 in the US.¹⁰⁻¹⁹ Obesity is less of a healthcare concern in Canada compared to the USA.²³
- Given, the diversity of insights observed in this study, we propose to re-evaluate the Canadian liver transplant landscape in the next 5 years.