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EVIDENCE BRIEF

Should Clinical Guidelines Continue to Require Fibrosis Assessments Prior to Initiating Hepatitis C Treatment in British Columbia?

Marion Selfridge, Kiffer G. Card, Tamara Barnett, Fiona Boothman, Chris Fraser, Karen Lundgren, Kellie Guarasci

Cool Aid Community Health Centre

ABSTRACT

Background. Pre-treatment fibrosis levels are used to monitor for liver damage prior to initiating treatment for hepatitis C Virus and required to access provincial reimbursement for treatment. However, given that modern hepatitis C therapies are considerably safer and that early treatment is recommended, some have raised question of the value of fibrosis assessments – particularly among younger people with hepatitis C.

Objectives. The present study was conducted to examine the levels of fibrosis among patients initiating DAA treatment over time and by age in order to inform discussions regarding the role of pre-treatment fibrosis assessments.

Methods. This study examined longitudinal trends in pre-treatment fibrosis level among people living with hepatitis C using a clinical cohort of participants in a nurse-led hepatitis C treatment program. A chart review was conducted, extracting client information, including age, year of treatment initiation, and pre-treatment fibrosis level. A multivariable model examined factors associated with pre-treatment fibrosis level.

Results. Results show that fibrosis levels at treatment have dropped considerably over the study period and that among those 35 years of age or younger, fibrosis levels are particularly low.

Conclusions. These findings raise questions about whether fibrosis screenings among people who are aged 35 or younger and without a history of severe alcohol use are warranted. Removing these fibrosis screenings for treatment reimbursement could help flatten the care cascade for people living with hepatitis C.

Victoria Cool Aid Society respectfully acknowledges the Lekwungen and W̱SÁNEĆ peoples, on whose traditional territories we build homes and deliver our programs and services. Hay'sxw'qa. HÍSW̱ḴE. We also want to acknowledge and thank people who use drugs, our clients, who teach us so much in our work and the entire team at the health centre for their continued work and dedication.

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Introduction

Hepatitis C is a global public health concern that affects more than 56.8 million people around the world, accounting for at least 399,000 deaths globally (Blach et al., 2022). Over 200,000 people are estimated to be living with chronic Hepatitis C infection in Canada, 16,000 people in British Columbia (BC). Hepatitis C is a contagious virus that primarily affects the liver. Hepatitis C is most commonly transmitted through sharing equipment for injecting, smoking or snorting drugs or re-using tattooing or piercing equipment that was not sterilized properly.

Hepatitis C is readily treatable with antiviral medication, and with new simple 8-12 week treatments, the virus can be eliminated from the body. The drugs used to treat hepatitis C are called direct-acting antivirals (DAAs) and they work by targeting specific proteins in the virus to prevent it from replicating.

Treatments for hepatitis C have improved markedly over the years. In the past, the standard treatment for hepatitis C involved a combination of drugs called interferon and ribavirin, which had severe side effects and a low cure rate. However, the development of DAAs has revolutionized the treatment of hepatitis C, with over 95% cure rates and virtually no side effects.

BC's Ministry of Health has recently affirmed its' commitment to the WHO's goal of eliminating hepatitis C by 2030. However, policies that complicate, delay, or prevent treatment initiation still persist.

Clinical guidelines recommend that all individuals with chronic hepatitis C infection receive treatment with DAAs, regardless of the severity of liver damage or symptoms. This is because early treatment can prevent or reduce the risk of serious complications, such as liver cirrhosis, failure and liver cancer.

The APRI (AST to Platelet Ratio Index) is a non-invasive blood test used to assess liver fibrosis in patients with hepatitis C. It is calculated using the levels of the liver enzyme AST (aspartate aminotransferase) and platelet count. The APRI score is obtained by dividing a patient's AST by the normal AST number, dividing that number by the patient's platelet count, and then multiplying the result by 100.

The APRI score is one of the standard assessments recommended in clinical guidelines to help determine the severity of liver fibrosis in patients with hepatitis C. The score has been found to correlate with liver biopsy results, which is the gold standard for assessing liver fibrosis. In some clinical guidelines, an APRI score greater than 1.5 is used to indicate significant fibrosis or cirrhosis and may prompt further investigation of the liver (such as ultrasound or CT scan).

While APRI score alone should not be used to make treatment decisions and should be considered alongside other factors such as patient history, blood work, clinical examination, and imaging studies, some jurisdictions, including British Columbia, require an assessment of fibrosis level before beginning treatment as a requirement of medication reimbursement. This requirement can be a barrier to treatment because it may require extra blood work and additional visits that can delay or stall treatment initiation, increasing the number of steps required before care can be initiated.

Over time, the standard of care for treating hepatitis C has shifted towards earlier and more aggressive treatment with safer drugs. In the past, treatment options for hepatitis C were limited and often had serious side effects, which led to a focus on treating individuals with advanced liver disease or fibrosis levels to prevent further liver damage. However, with the introduction of new, highly effective and safer

DAA drugs, the standard of care for treating hepatitis C has encouraged the treatment of individuals as early as possible, even before significant liver damage or fibrosis has occurred.

As a result, there is now a growing debate among experienced healthcare professionals regarding the value of measuring fibrosis levels before initiating hepatitis C treatment with DAAs. In particular, Noel et al. (2022) have demonstrated that fibrosis assessment is unnecessary for individuals under the age of 35 with hepatitis C to initiate treatment.

While fibrosis level assessment can provide valuable information about the extent of liver damage, the current standard of care is to provide treatment with these safer drugs that would not harm liver function, regardless of fibrosis levels. These assessments could be delayed until after treatment is initiated to maximize patient outcomes or they could be eliminated for some age groups not likely to have liver damage.

Consistent with this information, the present study was conducted to examine the levels of fibrosis among patients initiating DAA treatment over time and by age to inform discussions regarding the role of pre-treatment fibrosis assessments. We hypothesized that fibrosis levels would be increasingly lower over the course of our study period and that this would be especially true for individuals younger than age 35.

Methods

Participants were individuals accessing nurse-led hepatitis C treatment through the Cool Aid Community Health Centre (CACHC) in Victoria British Columbia between November 2014 (beginning of DAA treatment at the clinic) until end of December 2022. The Victoria Cool Aid Society's CACHC provides low-barrier health services to inner-city populations that are economically vulnerable, have complex medical needs, and face multiple barriers to accessing care. Clients of CACHC experience homelessness, mental health issues, infectious disease, problematic substance use, and chronic illnesses. DAA treatments were first available through CACHC in November 2014, and reimbursement restrictions requiring high fibrosis level of an F2 or above for treatment were lifted in 2018.

A chart review of patient records was conducted. Data were extracted from patient charts, including their age, sex, HIV status, recent drug use history, fibrosis level at time of DAA initiation, and other details about their hepatitis C clinical care.

Data analyses were conducted in R and were primarily descriptive in nature. A multivariable regression model was fit identifying factors associated with fibrosis level. The primary explanatory variables in this model were age and year of treatment. Additional covariates included sex, Opioid Agonist Treatment (OAT) use, recent drug use and HIV status.

Results

A total of 760 participants were included in our chart review. **Table 1** provides an overview of the clinic sample. The mean age was 49.6, 68.3% were men, 13.3% were living with HIV, and 54.0% were receiving opioid agonist therapy.

		N(%) / M(SD)
Age (mean (SD))		49.64 (11.05)
Age group (%)	29 years or younger	35 (5.1)
	30 to 39	95 (13.9)
	40 to 49	189 (27.6)
	50 to 59	219 (32.0)
	60+	146 (21.3)
Sex (%)	F	240 (31.6)
	M	519 (68.3)
	Transgender	1 (0.1)
Living with HIV (%)	No	659 (86.7)
	Yes	101 (13.3)
Opioid Agonist Treatment (%)	No	347 (45.7)
	Unknown	2 (0.3)
	Yes	41 (54.0)
Recent drug use (last 6 months) (%)	No	235 (30.9)
	Unknown	5 (0.7)
	Yes	520 (68.4)

Figure 1 shows the age of participants initiating treatment, by year.

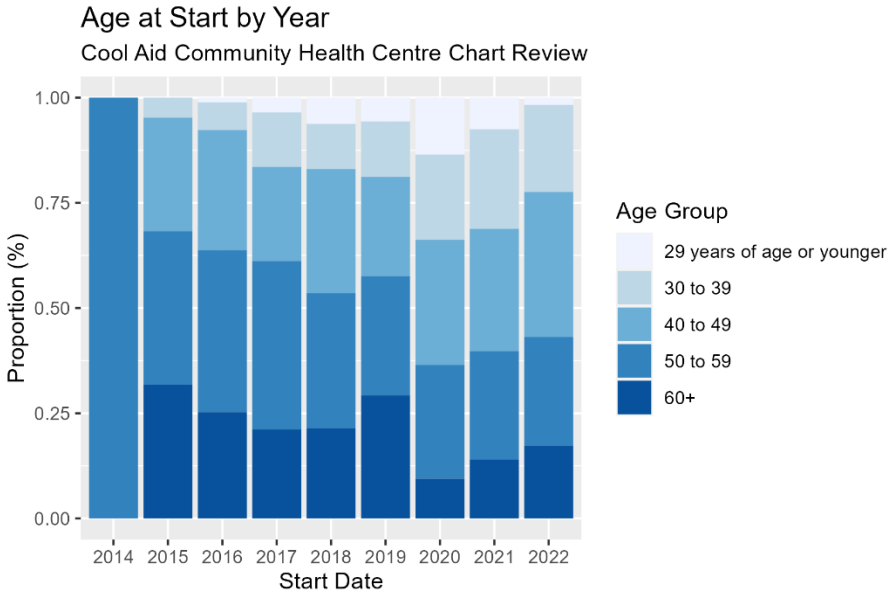


Table 2 provides an overview of their hepatitis C related treatment. The plurality had a fibrosis level of F0 or F1. Approximately equal proportions had fibrosis determined using APRI and Fibroscan. Almost all participants completed treatment, and few experienced reinfections.

		N(%) / M(SD)
Fibrosis level (%)	F0-F1	331 (43.6)
	F2	224 (29.5)
	F3	77 (10.1)
	F4	121 (15.9)
	Unknown	7 (0.9)
Method to determine fibrosis (%)	APRI	372 (48.9)
	Fibroscan	378 (49.7)
	Other (e.g., liver biopsy, ultrasound, doctor report)	4 (0.6)
	Unknown	6 (0.8)
Pegylated Interferon plus Ribavirin (PR). experienced (%)	Yes	44 (5.8)
	No	715 (94.1)
	Unknown	1 (0.1)
Direct Acting Agent (DAA) experienced (%)	Yes	53 (7.0)
	No	706 (92.9)
	Unknown	1 (0.1)
Completed Treatment (%)	No	23 (3.0)
	Yes	737 (97.0)
Sustained Virological Response (SVR) (12wk) (%)	Yes	692 (91.1)
	No	68 (8.9)
Reinfection (%)	Yes	27 (3.6)
	No	724 (95.3)
	No - Unknown + Viremic Post Treatment	7 (0.9)
	No - relapse	2 (0.3)

Figure 2 shows the baseline fibrosis level over time.

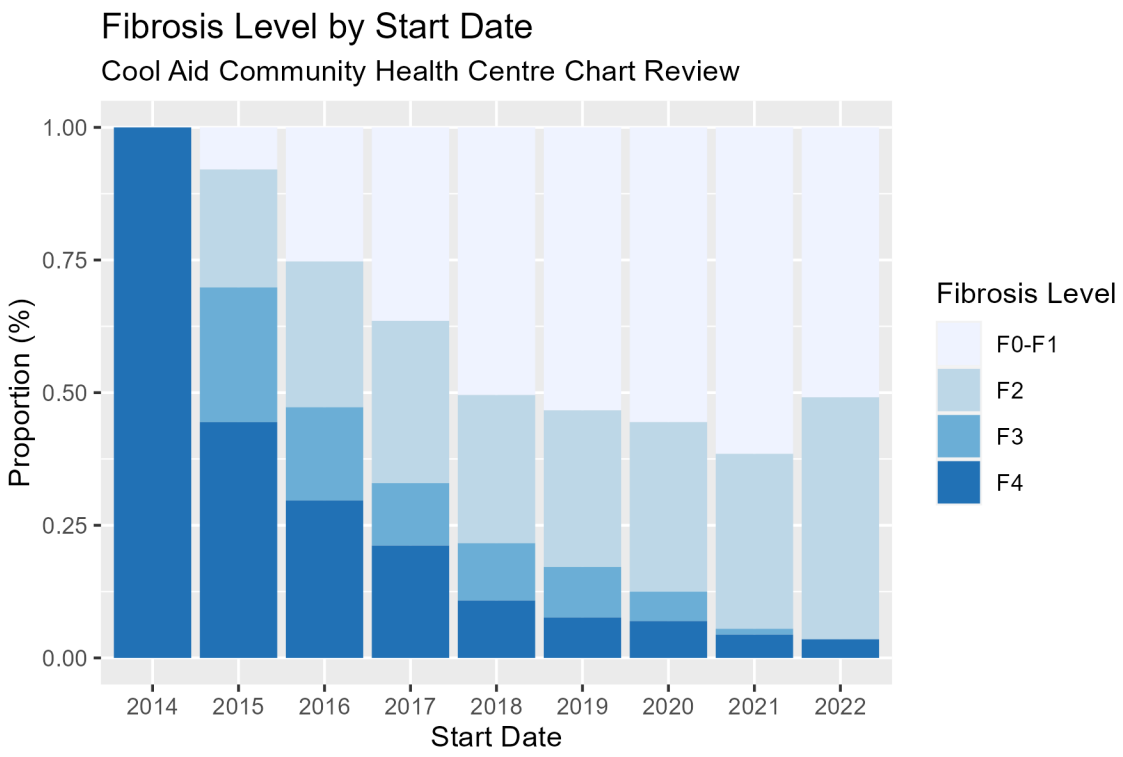


Figure 3 shows the baseline fibrosis level, stratified by individuals under and over age 35.

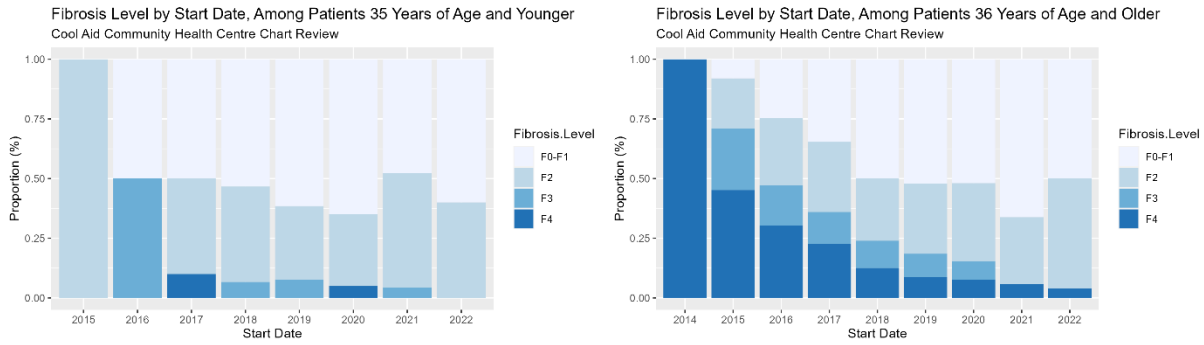


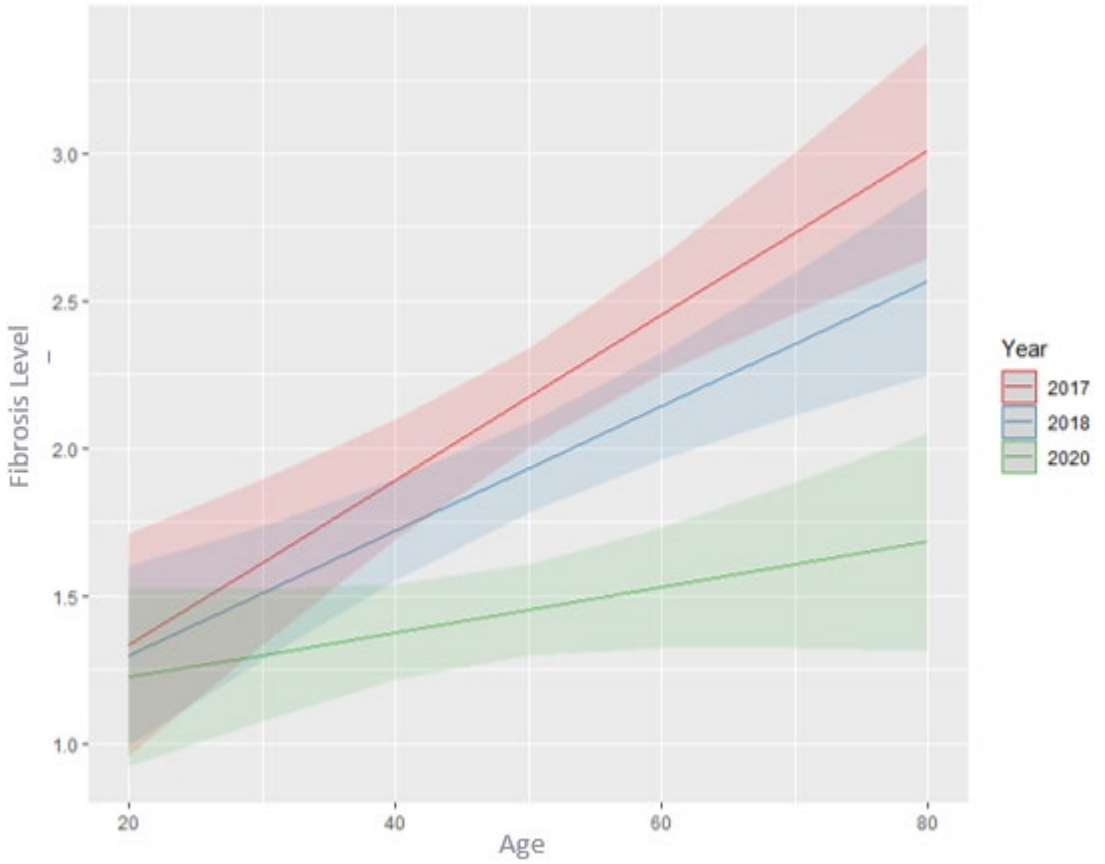
Table 3 provides results of our multivariable regression model, which showed that higher fibrosis levels were associated with older age, earlier year of treatment initiation, and recent drug use.

	β	SE	P-value
Age	**0.02**	**0.00**	**0.0002**
Year	**-0.24**	**0.02**	**< 0.0001**
Sex			
Female	1.00		
Male	0.07	0.10	0.4675
Other	-1.02	1.17	0.3862
OAT Use			
No	1.00		
Unknown	-0.07	0.83	0.9348
Yes	-0.02	0.10	0.8337
HIV Coinfection			
No	1.00		
Yes	-0.10	0.14	0.4518
Recent Drug Use			
No	1.00		
Unknown	**1.43**	**0.60**	**0.0164**
Yes	**0.24**	**0.11**	**0.0261**

Table 4 shows a secondary model which included an interaction term to assess whether effect of age on fibrosis levels differed across years. This interaction term was statistically significant showing that the effect of age on fibrosis level has declined over time.

	β	SE	P-value
Age	**13.57**	**4.20**	**0.0013**
Year	0.10	0.11	0.3688
Sex			
Female			
Male	0.08	0.10	0.4147
Other	-0.99	1.16	0.3966
OAT Use			
No			
Unknown	0.17	0.83	0.8411
Yes	-0.02	0.10	0.8542
HIV Coinfection			
No			
Yes	-0.08	0.14	0.5761
Recent Drug Use			
No			
Unknown	**1.41**	**0.59**	**0.0178**
Yes	**0.24**	**0.11**	**0.0249**
Age*Year Interaction	**-0.01**	**0.00**	**0.0013**

Figure 5 shows the interaction plot of the effect of age on fibrosis level for year – illustrating that the effect of increasing age on fibrosis level has decreased with time.



Conclusion

This study examined the relationship between fibrosis level, age, and year of DAA initiation for a clinical sample of people living with hepatitis C. Results show that fibrosis levels at treatment have dropped considerably over the study period. For those 35 years of age or younger, fibrosis levels are particularly low. These findings raise questions about whether fibrosis screenings among people 35 years of age or younger and without a history of severe alcohol use are warranted to access DAA treatments.

Mandel et al (2023) have highlighted that the journey towards the eradication of hepatitis C is not just about understanding the disease's clinical trajectory. The broader framework encompassing legislation, laboratory workflow optimization, treatment reimbursement structures, and the intricate interplay among healthcare providers plays a pivotal role in shaping the health outcomes of those affected.

In light of these insights, a recalibration of the current policies is required. Following policy adaptations from other provinces, British Columbia could consider doing away with mandatory fibrosis screenings as a pre-condition for treatment reimbursement. Such a move could be instrumental in streamlining the care cascade for those living with hepatitis C. By leveraging both the clinical insights and the broader healthcare ecosystem's potential, we can bolster our efforts towards eliminating hepatitis C.

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713 Johnson St
Victoria, BC
Canada, V8W 1M8

www.coolaid.org
society@coolaid.org
T: 250-385-1466