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Novel non-invasive score to predict cirrhosis in the era of hepatitis C elimination: A population study of ex-substance users in Singapore

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ABSTRACT

Background: Chronic hepatitis C infection is common among people with history of substance use. Liver fibrosis assessment is a barrier to linkage to care, particularly among those with history of substance users. The use of non-invasive scores can be helpful in predicting liver cirrhosis in the era of HCV elimination, especially in countries where transient elastography (TE) is not available. We compared the commonly used non-invasive scores with a novel non-invasive score in predicting liver cirrhosis in this population.

Methods: HCV patients with history of substance use between 2011 and 2016 were analyzed. All patients had TE for liver fibrosis assessment. Clinical performance of established non-invasive scores for fibrosis assessment and novel score were compared. Youden's index was used to determine optimal cut-off of the novel score.

Results: A total of 579 patients were included. In multivariate logistic regression, cirrhosis on TE was associated with age ($P=0.002$), aspartate aminotransferase (AST) ($P=0.004$), and platelet count ($P<0.001$), but not alanine aminotransferase (ALT) ($P=0.896$). These form the components of modified AST-to-platelet ratio index (APRI) score. Modified APRI was superior to APRI in predicting cirrhosis (AUROC, 0.796 vs. 0.770, $P=0.007$), but not fibrosis-4 score (FIB-4) ($P=1.00$). Modified APRI at cut-off of 4 has sensitivity, specificity and negative predictive value (NPV) of 94.4%, 26.9% and 92.6%, respectively, and at 19, has sensitivity, specificity and positive predictive value (PPV) of 33.3%, 96.2% and 77.1%, respectively. FIB-4 has a NPV and PPV of 88.6%, 41.8% and 78.5%, 77.6%, at cut-off of 1.45 and 3.25, respectively. Using the cut-off of 4 and 14 for modified APRI, 32.5% of patients can be correctly classified and misses out only 5.6% of cirrhosis patients.

Conclusions: Modified APRI score is superior in predicting cirrhosis in HCV population, with 32.5% of the population being correctly classified using cut-off of 4 and 14. Further studies are required to validate the findings.

Introduction

Hepatitis C is a major public health problem globally, with 71 million people estimated to be infected worldwide with a prevalence around 1% in the Western population [1]. Chronic HCV had been the commonest indication for liver transplantation in the Western world in the last decade, and it remains an important contributor to the burden of liver disease globally [2,3]. The Global Burden of Disease Study showed that viral hepatitis accounted for 1.45 million deaths in 2013, a 63% increase compared with the 0.89 million deaths in 1990. The biggest increase was seen amongst HCV infections, with a rise in the proportion of attributable deaths from 33.8% in 1990 to 48.4% in 2013 [4].

Former and active substance users form a major proportion of HCV-infected individuals. The seroprevalence of HCV amongst those with a history of intravenous drug use, is much higher than that of the general population and is estimated at 40–60% [5]. Despite the availability of highly potent direct-acting antiviral treatment for HCV elimination programs, linkage to care of HCV patients to receive curative antiviral therapy is still poor, particularly among people who inject drugs [6,7]. In countries like Australia, the universal reimbursement of direct-acting antiviralvastly improved patients' access to treatment and improved the model of HCV care to allow primary care physicians to treat HCV [8].

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Despite this, there are still barriers to HCV treatment delivery, particularly in the area of liver fibrosis assessment; where liver biopsy is invasive and not well tolerated, and the availability of transient elastography (TE) is limited to public hospitals in metropolitan cities [9,10]. Liver fibrosis assessment is a foreseeable barrier if scale-up treatment and population elimination of HCV is desired, particularly among those with substance use [11]. The unique population of ex-substance users and people who inject drugs with HCV infection, tend to have poorer access to health care, lower socioeconomic status [12], and thus have limited access to specialist assessment and TE [7].

In the recent years, there has been the development of several non-invasive fibrosis scores to predict cirrhosis (F4), which is an important predictor of liver complications and mortality [13,14]. The two most commonly used non-invasive scores in HCV population are the fibrosis-4 (FIB-4) and AST-to-platelet ratio index (APRI). Recently, APRI score has been proposed as a non-invasive tool for fibrosis prediction, but it has limited supporting evidence so far [15,16]. At the cut-off of 1.0, meta-analysis has shown APRI has sensitivity of 76% and specificity of 72% for cirrhosis [15]. Non-invasive fibrosis scores have the potential to improve the care cascade of fibrosis assessment by enabling the exclusion of cirrhosis with a high degree of confidence such that patients can be rapidly staged and linked to treatment without referral to specialist clinics and TE. Currently, there is limited data to support the utility of non-invasive fibrosis scores in place of TE, particularly in Asia. Therefore, we examine the performance of these non-invasive scores in the prediction of cirrhosis. Such scores may be clinically useful to triage HCV positive patients in primary care or correctional facilities, to facilitate cirrhosis management and allow earlier treatment of the individual with HCV, in countries where treatment access may already be limited.

Methods

Patient selection and data collection

Between 2011 and 2016, all HCV viremic patients seen at Changi General Hospital, Singapore, with a history of sharing drug paraphernalia and intravenous drug use were reviewed. All patient had TE performed to stage for liver disease and to help prioritize HCV treatment and the subsequent decision on cirrhosis management. None of the patients received HCV treatment prior to the fibrosis assessment. A total of 1054 cases were reviewed, 311 patients were excluded as they had no history of intravenous drug use. A further 136 patients were excluded as their blood test results were beyond 3-month window from the time of the TE. Twenty-eight patients were excluded because they had more than one TE readings during the study period. A total of 579 patients were included into the study (Fig. 1). This study was reviewed and approved by the Institutional Review Board (IRB) of SingHealth Services, Singapore.

Demographics data, liver stiffness measurement (LSM) results, biochemical profile such as liver function test, platelet count, and HCV viral characteristics were reviewed. The LSM cut-offs used to define liver fibrosis in the population of interest were F3, LSM $\geq$ 9.6 kPa, and F4, LSM $\geq$ 12.6 kPa as previously described [17]. All TEs were performed two hours after fasting using the standard protocol [18], and ten valid measurements with interquartile range/median ratio $\leq$ 30% were considered reliable results as previously described [19]. XL probe was used for patients who failed M probe [20]. In this study, only 1.6% (9 of 579) required XL probe to obtain LSM. Cirrhosis was of interest because of the more urgent need for treatment, and benefits from surveillance and monitoring of liver-related complications. The three non-invasive clinical scores, namely FIB-4, APRI and modified APRI were calculated based on the clinical data collected.

$$\text{FIB-4}: \frac{Age \times AST}{Platelet\ count \times \sqrt{ALT}}$$

$$\text{APRI}: \frac{\frac{AST}{40}}{Platelet\ count} \times 100$$

$$\text{Modified APRI}: \frac{Age \times \left(\frac{AST}{40}\right)}{Albumin \times platelet} \times 100$$

(upper limit of AST being 40 IU/L, albumin in g/dL, platelet expressed as platelet $\times 10^9$/L)

Statistical analysis

Categorical data were presented as frequency (percentage). Numeric data were presented as mean $\pm$ standard deviation (SD) for parametric distribution and median (interquartile range, IQR) for non-parametric distribution. Chi-square test or Fisher's exact test were used for categorical variables, and 2-sample *t* test or Mann-Whitney *U* test for continuous variables, where appropriate.

Clinical variables were evaluated to determine if they were significant predictors of cirrhosis, using logistic regression. Factors with $P < 0.05$ were entered into a multivariate regression model. Receiver operating characteristic (ROC) curve and its area under the ROC curve (AUROC) was used to evaluate the diagnostic performance of the non-invasive scores. The clinical performance of the non-invasive scores was analyzed by the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). Cut-offs for the clinical scores were first obtained from previously published studies [21,22]. Youden's index was also used to find out the optimal cut-off in our study to exclude and predict cirrhosis. In addition, the differences between the AUROCs of the non-invasive scores were compared using the DeLong test. In case of significance of DeLong test was detected, Bonferroni correction was applied for post-hoc multiple comparisons of AUROCs. Data were analyzed using SPSS version 23 (IBM, Armonk, New York, USA) with statistical significance defined as $P < 0.05$.

Results

Patient characteristics

The demographics, clinical and viral characteristics of 579 patients with HCV infection were shown in Table 1. The majority of patients were male (92.7%). The median age of the cohort is 48.0 years old. Genotype 3 (77.7%) was the most prevalent HCV genotype, followed by genotype 1 (20.8%). Most of the patients were Malay (59.9%), followed by Chinese (23.1%) and Indian (13.5%) ethnicity. Overall, TE showed that 46.5% of the cohort has advanced fibrosis and 28.0% have cirrhosis.

Clinical predictors of cirrhosis

The clinical predictors associated with cirrhosis are shown in Table 2. In multivariate analysis, age (adjusted Odds ratio (aOR): 1.04, 95% CI: 1.02–1.07), AST (aOR: 1.01, 95% CI: 1.01–1.02), platelet count (aOR: 0.99, 95% CI: 0.98–0.99), and albumin (aOR: 0.90, 95% CI: 0.85–0.96) were significant predictors for cirrhosis, while ALT (aOR: 1.00, 95% CI: 0.99–1.01) was not a predictor of cirrhosis. As albumin is an important predictor of cirrhosis and this variable is part of modified APRI, modified APRI was further compared with the known non-invasive scores.

Performance of non-invasive scores

The ROC curves of all three non-invasive scores in detecting cirrhosis are shown in Fig. 2. The AUROC for FIB-4, APRI and

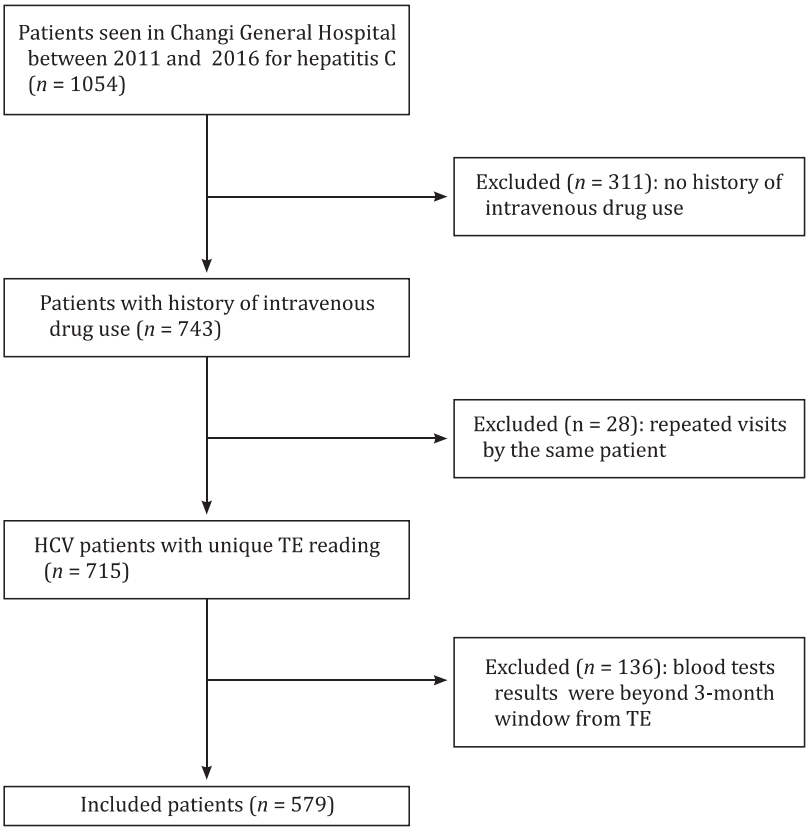

Fig. 1. Patient recruitment flowchart.

Table 1
Patient characteristics.

Characteristics	Frequency ($n = 579$)
Sex	
Male	537 (92.7%)
Female	42 (7.3%)
Ethnicity	
Chinese	134 (23.1%)
Indian	78 (13.5%)
Malay	347 (59.9%)
Others	20 (3.5%)
Age (yr)	48.0 (42.0–54.3)
HIV coinfection ($n = 455$)*	
Positive	9 (2.0%)
Negative	446 (98.0%)
Hepatitis B coinfection ($n = 527$)*	
Positive	6 (1.1%)
Negative	521 (98.9%)
HCV genotype ($n = 538$)*	
Type 1	112 (20.8%)
Type 2	5 (0.9%)
Type 3	418 (77.7%)
Type 4	2 (0.4%)
Type 6	1 (0.2%)
HCV viral load (log IU/mL)	6.07 (5.43–6.46)
Severity of liver fibrosis (liver stiffness measure)	
F0-F1 (< 7.1 kPa)	180 (31.1%)
F2 (≥ 7.1 kPa, < 9.6 kPa)	130 (22.5%)
F3 (≥ 9.6 kPa, < 12.6 kPa)	107 (18.5%)
F4 (≥ 12.6 kPa)	162 (28.0%)

* Per protocol analysis of available results.

Table 2
Clinical predictors of cirrhosis (liver stiffness measurement ≥ 12.6 kPa).

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P* value	aOR (95% CI)	*P* value
Sex	2.03 (0.88–4.67)	0.10	NA	NA
Age	1.06 (1.04–1.08)	<**0.001**	1.04 (1.02–1.07)	**0.002**
Ethnicity		0.76	NA	NA
Chinese	1			
Indian	1.07 (0.89–1.95)			
Malay	0.84 (0.54–1.31)			
Others	1.07 (0.35–3.27)			
ALT	1.01 (1.00–1.01)	<**0.001**	1.00 (0.99–1.01)	0.896
AST	1.02 (1.01–1.02)	<**0.001**	1.01 (1.01–1.02)	**0.004**
Platelet	0.99 (0.98–0.99)	<**0.001**	0.99 (0.98–0.992)	<**0.001**
Albumin	0.88 (0.83–0.92)	<**0.001**	0.90 (0.85–0.96)	<**0.001**
Bilirubin	1.03 (1.01–1.05)	**0.002**	1.00 (0.98–1.02)	0.893

ALT: alanine aminotransferase; AST: aspartate aminotransferase; OR: Odds ratio; aOR: adjusted Odds ratio; NA: not available.

modified APRI are 0.789 (95% CI: 0.747–0.830), 0.770 (95% CI: 0.727–0.814) and 0.796 (95% CI: 0.754–0.838), respectively. Modified APRI has a better performance in predicting cirrhosis compared to APRI (0.026, 95% CI: 0.009–0.042, $P = 0.007$). There is no significant difference between APRI and FIB-4 ($P = 0.64$), as well as FIB-4 and modified APRI ($P = 1.00$) in predicting cirrhosis.

In excluding cirrhosis, FIB-4 established cut-off of 1.45 has sensitivity of 81.5%, specificity of 55.9%, and NPV of 88.6%. At the upper cut-off of 3.25, FIB-4 has sensitivity of 32.1%, specificity of 96.4% and PPV of 77.6% for F4. Using Youden's index, modified APRI with albumin incorporated in the equation, at the cut-off of 4, has sensitivity and NPV of 94.4% and 92.6%, respectively for the exclusion of cirrhosis. At the cut-off of 14, modified APRI has, specificity and PPV and NPV of 90.2%, 65.0% and 81.4%, respectively. At the cut-off of 19, modified APRI has specificity and PPV and NPV of 96.2%, 77.1% and 78.8%, respectively (Table 3).

A commonly used APRI cut-off of 1.0 has sensitivity, specificity and NPV of 57.4%, 82.5% and 83.3% for excluding cirrhosis,

Table 3
Performance of non-invasive scores in predicting cirrhosis in hepatitis C population.

Scores	AUROC	Cut-off value	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Youden's Index
FIB-4	0.789	1.45	81.5	55.9	41.8	88.6	0.374
		3.25	32.1	96.4	77.6	78.5	0.285
APRI	0.770	0.5	85.8	39.8	35.6	87.8	0.256
		1.0	57.4	82.5	56.0	83.3	0.399
		1.5	35.8	93.5	68.2	78.9	0.293
		2.0	20.4	97.1	73.3	75.8	0.175
Modified APRI	0.796	4	94.4	26.9	33.4	92.6	0.213
		14	46.9	90.2	65.0	81.4	0.371
		19	33.3	96.2	77.1	78.8	0.295

Cirrhosis is defined using transient elastography as reference.
FIB-4: fibrosis-4 score; APRI: AST-to-platelet ratio index; AUROC: area under the ROC curve.

Table 4
Performance of combination algorithm of non-invasive scores in excluding cirrhosis.

Non-invasive score with low/high cut-offs	Overall correctly classified (non-cirrhosis/ cirrhosis)	Correctly classified	Number of cirrhosis misclassified, at the low cut-off (cirrhosis, $n = 162$)	Number in the indeterminate range	Number of correctly classified cirrhosis / number of patients at the high cut-off
FIB-4 < 1.45 & FIB-4 > 3.25	233 / 52	49.2%	30 (18.5%)	249 (43.0%)	52 / 67 (77.6%)
FIB-4 < 1.45 & Modified APRI > 14	233 / 76	53.4%	30 (18.5%)	199 (34.4%)	76 / 117 (65.0%)
FIB-4 < 1.45 & Modified APRI > 19	233 / 54	49.6%	30 (18.5%)	246 (42.5%)	54 / 70 (77.1%)
Modified APRI < 4 & FIB-4 > 3.25	112 / 52	28.3%	9 (5.6%)	391 (67.5%)	52 / 67 (77.6%)
Modified APRI < 4 & Modified APRI > 14	112 / 76	32.5%	9 (5.6%)	341 (58.9%)	76 / 117 (65.0%)
Modified APRI < 4 & Modified APRI > 19	112 / 54	28.7%	9 (5.6%)	388 (67.0%)	54 / 70 (77.1%)

Cirrhosis defined by liver stiffness measurement ≥ 12.6 kPa.
FIB-4: fibrosis-4 score; APRI: AST-to-platelet ratio index.

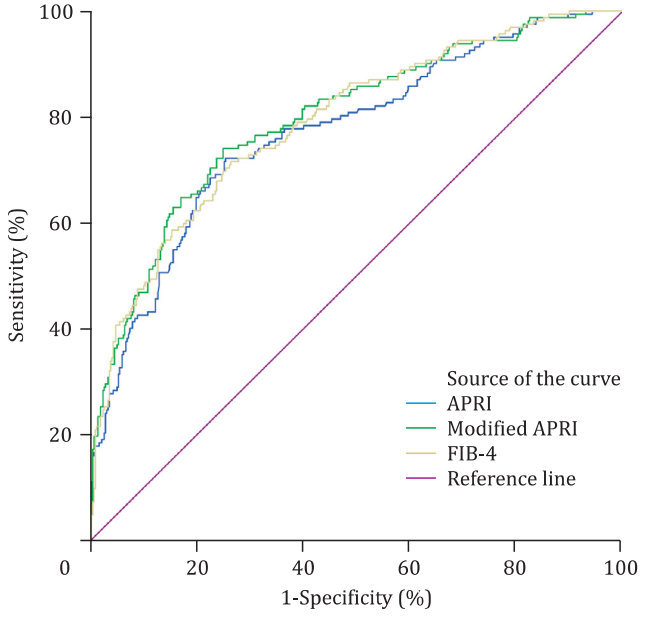

Fig. 2. AUROC curve for three clinical non-invasive scores in predicting liver cirrhosis.
APRI: AST-to-platelet ratio index; FIB-4: fibrosis-4 score; AUROC: area under the ROC curve

respectively. At the lower cut-off of 0.5, APRI has sensitivity, specificity of 85.8%, 39.8% and PPV, NPV of 35.6%, 87.8%, respectively. At the cut-offs of 1.0, 1.5 and 2.0, APRI improved the PPV at 56.0%, 68.2% and 73.3%, respectively. These values were still lower than the PPV for FIB-4 and modified APRI at the higher cut-off. Modified APRI and FIB-4 have the highest AUROCs, therefore these two scores were examined in different combination to evaluate the utility in predicting cirrhosis patients (Table 4). With the combination of modified APRI cut-off of 4 and 14, 32.5% of the patients would be accurately predicted while misclassifying 5.6% (9 of 162) of cirrhosis patients as non-cirrhosis. The commonly used FIB-4 and its cut-offs of 1.45 and 3.25 would accurately predict 49.2% of the patients but misses 18.5% of cirrhosis patients at the lower cut-off. Using the cut-off of 4 and 14 for modified APRI, 58.9% (341) of the patients would be in the 'gray zone', of these only 77 (22.6%) had cirrhosis by TE criteria. For FIB-4, 43.0% of the patients fall into the gray zone, between 1.45 and 3.25. However, modified APRI had lower percentage of cirrhosis misclassified at the low cut-off as non-cirrhosis (5.6%) compared to FIB-4 (18.5%) at the low cut-off.

Discussion

In our study of 579 HCV patients with history of drug use, modified APRI performed better than APRI or FIB-4 score as non-invasive tool in the assessment of cirrhosis. Modified APRI which was derived using multivariate logistic regression, has high NPV for excluding cirrhosis and misclassified cirrhosis only at 5.6%. This non-invasive score could aid clinicians in triaging patients where TE may not be readily available and resources are scarce.

In line with the global HCV elimination strategy, there is an urgent need to limit the number of steps within the HCV cascade of care. Staging of liver disease has been a major obstacle within the care cascade. Within the last decade, a number of non-invasive scoring systems have been shown to be equally effective to TE, negating the need for a liver biopsy in most instances. This is particularly important if the strategy of decentralization of HCV care is to be pursued in the era of HCV elimination. The performance of three non-invasive scores for prediction of cirrhosis was assessed in a population of ex-substance users with HCV infection,

in Singapore. Within this cohort, modified APRI was found to be a superior non-invasive score in predicting cirrhosis, in order to forego the need for TE in the era of HCV elimination with population scale-up treatment. The combination of modified APRI cut-off threshold of 4 and 14 had the lowest rate of missing cirrhosis as non-cirrhosis at 5.6%, while achieving a high percentage of accurately classifying non-cirrhosis and cirrhosis in 32.5% of the population.

TE is an excellent non-invasive means of staging for liver disease but it has several limitations. It requires a trained staff to operate the device and may not be readily available in non-metropolitan based hospitals, due to its high procurement cost. In some countries, TE cannot be done on the initial visit of HCV assessment at the specialist clinic. Hence these reasons pose an impediment for linkage to care. Efforts need to be made to circumvent this step in the care cascade. Decentralization of diagnosis and staging by means of non-invasive biomarkers or composite scoring systems is an effective way to abbreviate the care cascade. Such algorithm may be useful in primary care or correctional facilities for the purpose of screening HCV patient directly for treatment abrogating the need for TE. Minimizing the need for certain aspects of HCV care cascade, such as TE, is vital to allow increasing HCV treatment coverage within areas of high HCV prevalence [23,24].

Identification of cirrhosis is important in the HCV care cascade because this group of patients warrant further management such as variceal screening and hepatocellular cancer surveillance. We demonstrated that the cut-offs of 4 and 14 had the highest NPV (92.6%) and a good PPV (65.0%) for detecting cirrhosis, making it a satisfactory non-invasive tool to rule out cirrhosis and as a surrogate for TE. The modified APRI offers an inexpensive, reliable and easy to use non-invasive fibrosis scoring system which can be used to stratify for the probability of cirrhosis. In this regards, modified APRI outperformed other fibrosis scoring systems with the best rear under the curve values. For modified APRI, 58.9% of the patients fell in the 'gray zone'. Given modified APRI has the highest AUROC, in practice applying additional non-invasive score would not improve the performance. In this group of patients, better non-invasive assessment like TE would be superior to applying an alternative non-invasive score like FIB-4 or APRI.

This study has to be interpreted within the context of its limitations. Ideally, the non-invasive scores should have been compared with liver histology as the gold standard for the validation of the non-invasive fibrosis scores. However, as TE is now widely used as the mainstay method of fibrosis assessment [25,26], our study offers a real-world comparison of TE and the non-invasive fibrosis scores. The diagnostic accuracies for the non-invasive scores on HCV patients in our study were not too dissimilar to diagnostic accuracies from other studies based on liver histology [25,27,28]. Furthermore, most clinical trials for hepatitis C treatment utilize TE as a reference surrogate marker of liver fibrosis. TE is also highly sensitive for detecting cirrhosis and excluding fibrosis and since non-invasive fibrosis scores are principally being used to exclude cirrhosis, its comparison with TE is justified. This cohort consists predominantly male subjects compared to other studies [21,22]. Thus, the utility of modified APRI in female population will require further validation.

The commonly used APRI score did not perform well in exclusion of cirrhosis in our study. In a recent meta-analysis, APRI cut-off of 1.0 has sensitivity of 76% and specificity of 72% for identification of cirrhosis [15], and has been suggested for use in primary care to facilitate early treatment of HCV patients without cirrhosis, or refer patients to specialists for further management of cirrhosis [29]. However, in our population, APRI > 1.0 has much lower NPV (83.3%) compared to previously published literature. This is likely due to higher proportion of advanced fibrosis (46.5%) and cirrhosis (28.0%) in our population and the lack of histological comparison. Finally, we did not have an external cohort to validate the performance of modified APRI.

There were several interesting findings in this study. First, genotype 3 infection was the most predominant genotype in this cohort of ex-substance users which is consistent with other studies in Southeast Asia [30,31]. The current study offers a different insight at the population level, into the true genotype prevalence of HCV in Singapore which has never been shown in older studies based on small sample size [32,33]. Finally, we have identified low seroprevalence of HIV (2%) and hepatitis B (1.1%) co-infection among the HCV population with history of drug use in Singapore, which has never been described previously.

A viable strategy to achieve the WHO targets of the elimination of HCV by year 2030, within the context of the Singapore health care system is micro-elimination. In this regard, both WHO and professional society guidelines recommend the use of non-invasive tools to stage liver disease. We demonstrated that modified APRI is a better scoring system for the Southeast Asian HCV population compared to APRI or FIB-4. The use of the modified APRI score would be ideal in clustered environments of HCV infection such as drug rehabilitation centers and within the penal system and would allow for a rapid assessment of patients where a test-and-treat approach of non-cirrhotics HCV patients can be adopted. Undoubtedly, this would aid efforts to scale up treatment programs.

In conclusion, non-invasive score such as modified APRI is clinically useful in the prediction of cirrhosis among high-risk HCV population, to minimize the need for liver fibrosis assessment. Modified APRI of 4 and 14 can be considered adequate in excluding cirrhosis prior to direct-acting antiviral treatment. This may be used in primary care or remand institutions with high-prevalence of HCV infection, where there is high demand for TE assessment. Further studies are required to validate modified APRI in external cohorts with HCV infection.

Contributors

ZY and HJC performed the research and data analysis, and wrote the first draft. ZY, TPH, KR, TJ, TEK and HJC collected the data. ZY, TPH, KR, TEK and HJC performed critical revision of the manuscript. All authors contributed to the design and interpretation of the study and final manuscript. HJC is the guarantor.

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Ethical approval

This study was approved by the Ethics Committee of Centralised Institutional Review Board of SingHealth, Singapore (CIRB ref no. 2017/2615).

Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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