ORIGINAL ARTICLE

Comparing various cut-offs of aspartate aminotransferase-to-platelet ratio index (APRI) in liver cirrhosis diagnosis among hepatitis C patients in Malaysia

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ABSTRACT

Introduction: A major challenge in providing hepatitis C virus (HCV) treatment at primary healthcare clinics is the lack of radiological facilities to guide the decision making of liver cirrhosis (LC). This study aimed to compare the performance of three commonly used cut-offs of the aspartate aminotransferase-to-platelet ratio index (APRI) in diagnosing LC among hepatitis C patients in Malaysia.

Methods: This cross-sectional study was based on the data collected from the Hepatitis C Elimination through Access to Diagnostics (HEAD-Start) study in 25 primary healthcare clinics across three regions of Malaysia. The findings of biochemical tests were used to calculate the APRI for each study participant. Transient elastography was used as a standard reference for the diagnosis of cirrhosis. The area under the receiver operating curve (AUROC) was used to determine the discriminative ability of APRI in both HCV mono-infected and HCV/HIV co-infected patients. The diagnostic performance of APRI at three different cutoffs (>1.0, ≥1.5 and >2.0) were also evaluated.

Results: This study included 867 HCV-RNA-positive patients, 158 (16.1%) were co-infected with HIV. For the HCV mono-infected patients, the sensitivity, specificity, positive predictive value (PPV) and negative predictive values (NPV) for the cut-off of >1.0 were 61.8%, 88.7%, 73.8% and 81.9%, and for the cut-off of ≥1.5, 45.6%, 97.0%, 88.7% and 77.6%, respectively. A much lower sensitivity (29.9%) was observed for the cut-off of >2.0. The diagnostic accuracy of APRI at the cut-off of ≥1.5 in the HCV/HIV co-infected patients was relatively suboptimal.

Conclusion: APRI, with a cut-off of ≥1.5, can more accurately predict LC among hepatitis C patients in Malaysia. However, additional physical examination and laboratory assessment are likely to be required to support the diagnosis, especially in those with HCV/HIV co-infection.

KEYWORDS:
Aspartate aminotransferase-to-platelet ratio index, cirrhosis, hepatitis C, transient elastography

INTRODUCTION

Liver cirrhosis (LC) is the advanced stage of liver fibrosis. It is characterised by extensive scarring, altered microarchitecture, disruption of blood circulation, and nodularity in the liver.[1] Globally, LC is ranked thirteen among the leading causes of death in 2017.[2] Hepatitis B and C infections, alcohol-related liver disease, and non-alcoholic steatohepatitis (NASH) are among the common causes of LC. The concurrent occurrence of hepatitis C and NASH has also been shown to increase the risk of liver fibrosis.[3] Identifying LC in chronic hepatitis C (HCV) infection prior to the treatment with direct-acting antivirals (DAAs) is essential to guide the decision making of the treatment duration and follow-up intervals of patients.[4,5]

The diagnosis of LC is made through biopsy. However, the use of such an invasive method is often limited by its poor accessibility and the risk of complications following the procedure.[6,7] While the liver biopsy is the gold standard, the World Health Organization (WHO) hepatitis testing guidelines recommend non-invasive tests such as radiological imaging and biomarker testing for the assessment of liver staging.[8]

Since 2018, the Ministry of Health (MOH) Malaysia has been encouraging decentralised hepatitis C screening and treatment at primary healthcare clinics in an effort to improve access to care.[9] Both hepatitis C rapid diagnostic test (RDT) kits and DAAs are available in the health clinics. Nevertheless, one of the major challenges to providing hepatitis C treatment at health clinics is the lack of radiological facilities. As a result, the aspartate-to-platelet ratio index (APRI), a non-invasive biomarker, is recommended for the diagnosis of LC.[10]

APRI is formulated by using aspartate aminotransferase and platelet, two routinely tested parameters. These two biochemical tests are widely available in Malaysia's primary healthcare clinics and the test results were kept in each patient's note for future references. This makes the APRI a simple yet handy tool for use in resource-limited settings. Although APRI does not allow staging of fibrosis,[11] its ability to determine the status of cirrhosis enables its use in guiding hepatitis C treatment.[12,13] Many diagnostic studies confirmed

This article was accepted: 03 September 2021
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the accuracy of an APRI score in this context, reporting an AUROC ranging between 0.80 and 0.84.[12-15] Several cut-offs of the APRI score were also suggested for the diagnosis of liver cirrhosis.

In Malaysia, the Clinical Practice Guidelines on the management of adult hepatitis C patients indicate that an APRI score of 1.5 and above is indicative of LC.[16] However, a higher score of 2.0, the cut-off recommended by WHO, could help keep the discriminative ability of APRI above 80%.[10] A lower APRI cut-off of 1.0 has also been used in several studies.[13,17] Given the discrepancy in recommendations and the limited local evidence regarding the external validity of APRI, this study compared the above-mentioned cut-offs for diagnosis of LC among hepatitis C patients in Malaysia.

MATERIALS AND METHODS

Ethics, study design and participants

This cross-sectional study was approved by the Medical Research and Ethics Committee of the Ministry of Health Malaysia (NMRR-18-2282-43132) and was based on the data collected in a study for the Hepatitis C Elimination through Access to Diagnostics (HEAD-Start) Malaysia. HEAD-Start Malaysia was a collaborative study between the Foundation for Innovative New Diagnostics (FIND), the Drugs for Neglected Diseases initiative (DNDi), the MOH and the Clinical Research Malaysia (CRM).

In brief, the HEAD-Start Malaysia study took place between December 2018 and December 2019 with the aim to improve access to hepatitis C screening services in all the 25 primary healthcare clinics across three regions (States of Kedah, Kelantan and the Region of Kuala Lumpur/Putrajaya/State of Selangor). Adult individuals aged between 18 and 70, who had a positive HCV serological rapid diagnostic test (RDT) results were referred to one of the five nearby tertiary care centres for an HCV RNA test, which was performed using the reverse transcription polymerase chain reaction technique, and an assessment of their status of cirrhosis through transient elastography (Fibroscan®, EchoSens, Paris). They also received biochemical assessments enabling the calculation of APRI. Those who had the HCV infection confirmed and were fit for treatment were subsequently offered DAAs, either under standard hospital care or by participating in a clinical trial. Information regarding their socio-demographics, laboratory test results and radiological findings was collected using a standardized data collection form.

Transient elastography

Transient elastography (TE), the reference standard used for the diagnosis of LC in this study, is a rapid, painless, and reproducible method to measure liver stiffness. The measurement is based on the estimated velocity of a shear wave through liver tissue.[18] The procedure was performed by a trained operator in each of the tertiary care centres. The median values of a minimum ten valid readings were taken for each patient and expressed in kilopascals (kPa). Liver stiffness was then categorised as either cirrhosis (≥12.5 kPa) or non-cirrhosis (<12.5 kPa).[18,19] This approach is shown to be highly reliable in the assessment of liver fibrosis in patients with chronic hepatitis C.[20,21] Using liver biopsy as a reference, a meta-analysis of 38 studies indicated that TE can be performed with excellent accuracy to differentiate cirrhosis and non-cirrhosis, with a mean AUROC of 94%.[22]

Data collection and APRI calculation

We retrieved the data of 981 patients who received an assessment regarding the individual socio-demographics, HCV RNA test results, HIV status, TE findings, and levels of AST and platelets from the database of the HEAD-Start Malaysia study. The APRI score was calculated using the following formula: [(AST level / ULN) / platelet count (10^9/L)] x100.[23] The upper limit of normal AST varied across the participating sites, ranging between 34IU/L to 50IU/L. This value varied depending on laboratory use at each site defined reference populations therein to establish their own reference ranges for AST test.

Statistical analysis

All patients were grouped into either HCV mono-infection or HCV/HIV co-infection, as the latter group has a higher risk of developing LC.[24] Categorical variables were presented as numbers and percentages, and numerical variables as the mean or standard deviation. Receiver operating curves (ROCs) were used to determine the discriminative performance of APRI in the diagnosis of liver cirrhosis. An AUROC of 1.0 could be judged as a perfect discrimination, ≥0.90 as excellent, a ≥0.80 as good, ≥0.70 as fair, and <0.70 as poor.[25] The diagnostic accuracy of APRI test was evaluated based on the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) at different cut-offs (>1.0, ≥1.5 and >2.0). All the data was analysed using the R statistical software version 3.5.2.[26]

RESULTS

Demographic and clinical characteristics

Of the 981 patients who received an assessment of their cirrhosis status through TE and a APRI score in the HEAD-Start Malaysia study, 114 had unknown HIV infection status and were excluded from our study analysis. Finally, findings from a total of 867 patients were analysed. 709 patients included in this study were mono-infected with HCV. This mono-infected group was mainly males (95.8%) and in the age group of 40-49 years (40.1%). Their mean AST levels and platelet counts were 65.3±45.46IU/L and 223.2±78.80x10^9/L, respectively. The HCV/HIV co-infection group consisted of 158 patients, predominantly males (96.8%), and more than half were 40-49 years in age (51.3%). The mean AST levels and platelet counts were 62.6±47.97IU/L and 237.0±86.98 x10^9/L, respectively. The TE scores indicated that 34.2% of the HCV mono-infected and 21.5% of the HCV/HIV co-infected patients had cirrhosis. The demographic characteristics, laboratory test results, and radiological findings of all the patient are presented in Table I.

Discriminative ability of APRI

Figure 1 shows the AUROC of the APRI for HCV mono-infected patients and Figure 2 for HCV/HIV-co-infected patients. Applying APRI in all HCV mono-infected patients showed good discrimination between cirrhotic and non-cirrhotic cases, indicated by an AUROC above 0.8. However,

Table I. Demographic characteristics, laboratory test results and radiological findings of HCV mono-infected and HCV/HIV co-infected patients

Characteristic	HCV mono-infected	(%)	HCV/HIV co-infected	(%)
Total	709		158	
Age (year), mean (SD)	45.9	(9.74)	43.5	(6.94)
Age group				
20-29	26	(3.7)	2	(1.3)
30-39	153	(21.6)	45	(28.5)
40-49	284	(40.1)	81	(51.3)
50-59	174	(24.5)	25	(15.8)
60+	72	(10.2)	5	(3.2)
Gender				
Male	679	(95.8)	153	(96.8)
Female	30	(4.2)	5	(3.2)
Aspartate Aminotransaminase (IU/L), Mean (SD)	65.3	(45.46)	62.6	(47.97)
Platelet (109/L), Mean (SD)	223.2	(78.80)	237.0	(86.98)
Fibrosis grading by TE				
F0-F1	220	(31.0)	66	(41.8)
F2	152	(21.4)	31	(19.6)
F3	95	(13.4)	27	(17.1)
F4 / Cirrhosis	242	(34.2)	34	(21.5)

SD, standard deviation; TE, transient elastography.

Table II: Diagnostic accuracy of the APRI to diagnose liver cirrhosis among HCV infected individuals at different cut-offs using transient elastography as reference standard (n=709)

	HCV mono-infected patients		
	APRI >1.0	APRI ≥1.5	APRI >2.0
Sensitivity, % (95% CI)	61.8 (55.4, 68.0)	45.6 (39.2, 52.2)	29.9 (24.2, 36.1)
Specificity, % (95%CI)	88.7 (85.5, 91.4)	97.0 (95.0, 98.4)	98.5 (96.9, 99.4)
PPV, % (95%CI)	73.8 (68.2, 78.7)	88.7 (82.2, 93.1)	91.1 (82.8, 95.7)
NPV, % (95%CI)	81.9 (79.3, 84.2)	77.6 (75.5, 79.6)	73.2 (71.5, 74.8)
No. of patients matched the finding of TE, n(%)	564 (79.6)	564 (79.6)	533 (75.2)
False positive cases, n(%)	53 (7.4)	14 (2.0)	7 (1.0)
False negative cases, n(%)	92 (13.0)	131 (18.5)	169 (23.8)

HCV, hepatitis C virus; HIV, human immunodeficiency virus; APRI, aspartate aminotransferase-to-platelet ratio index; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; TE, transient elastography; 95%CI, 95% Confidence Interval

Table III: Diagnostic accuracy of the APRI to diagnose liver cirrhosis among HCV/HIV co-infected individuals at different cut-offs using transient elastography as reference standard (n=158)

	HCV/HIV co-infected patients		
	APRI >1.0	APRI ≥1.5	APRI >2.0
Sensitivity, % (95%CI)	32.4 (17.4, 50.5)	26.5 (12.9, 44.4)	20.6 (8.7, 37.9)
Specificity, % (95%CI)	87.1 (79.9, 92.4)	94.4 (88.7, 97.7)	96.8 (92.0, 99.1)
PPV, % (95%CI)	40.7 (26.1, 57.3)	56.3 (34.1, 76.2)	63.6 (35.2, 84.9)
NPV, % (95%CI)	82.4 (78.7, 85.7)	82.4 (79.2, 85.2)	81.6 (78.9, 84.1)
No. of patients matched the finding of TE, n (%)	119 (75.3)	126 (79.7)	127 (80.4)
False positive cases, n (%)	16 (10.1)	7 (4.4)	4 (2.5)
False negative cases, n (%)	23 (14.6)	25 (15.8)	27 (17.1)

HCV, hepatitis C virus; HIV, human immunodeficiency virus; APRI, aspartate aminotransferase-to-platelet ratio index; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; TE, transient elastography; 95%CI, 95% Confidence Interval

a slightly lower AUROC of the APRI for HCV/HIV co-infected patients (0.762) was observed.

Diagnostic performance of APRI

The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the APRI at different cut-offs for the 709 HCV mono-infected patients is shown in Table II. Generally, using a cut-off of >1.0 yielded a sensitivity, specificity, PPV and NPV of 61.8%, 88.7%, 73.8% and 81.9%, respectively. The cut-off ≥1.5 showed a sensitivity of 45.6%, specificity of 97.0%, PPV of 88.7% and NPV of 77.6%. Using a cut-off of >2.0 made the APRI slightly more specific (98.5%) but much less sensitive (29.9%). It was also found that the lower cut-off resulted in a greater NPV. An APRI cut-off of >1.0 and ≥1.5 resulted in a similar number of patients that matched the finding of TE (564 patients, 79.6%), as compared to using cut-off >2.0 (533 patients, 75.2%).

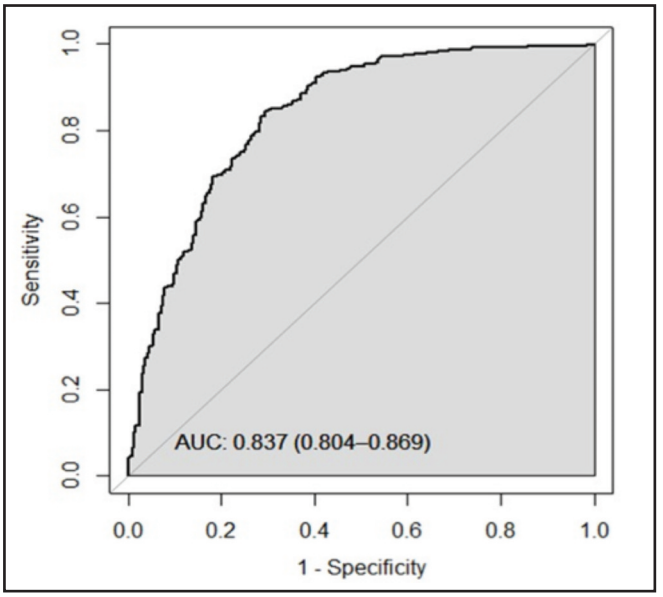

Fig. 1: Receiver operating characteristic analysis for the accuracy of APRI to diagnose cirrhosis (transient elastography ≥12.5kPa) in patients with chronic hepatitis C mono-infection (n=709).

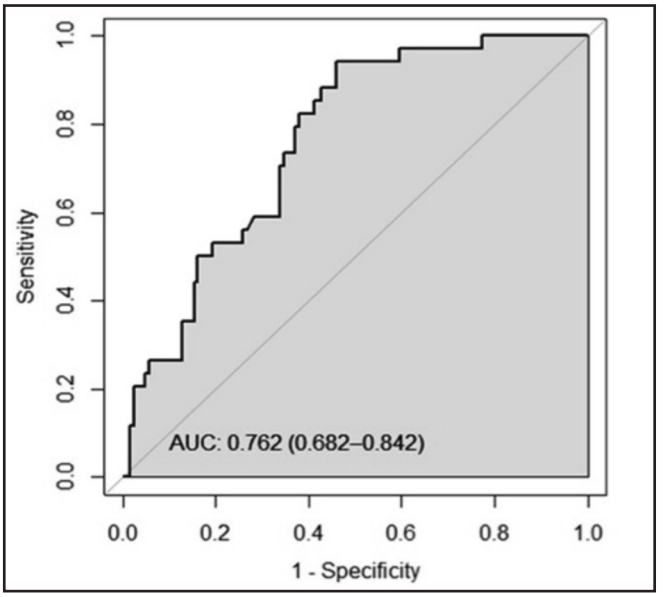

Fig. 2: Receiver operating characteristic analysis for the accuracy of APRI to diagnose cirrhosis (transient elastography ≥12.5kPa) in patients with HCV/HIV co-infection (n=158).

For the 158 HCV/HIV co-infected patients, the cut-off >1.0 showed a sensitivity of 32.4%, a specificity of 87.1%, a PPV of 40.7%, and a NPV of 82.4%, with 119 patients (75.3%) matching TE findings. A ≥1.5 cut-off matched TE findings in 126 patients (79.7%). The sensitivity, specificity, PPV and NPV were 26.5%, 94.4%, 56.3% and 82.4%, respectively (Table III). The number of patients that matched TE findings was 127 (80.4%), when considering the cut-off of >2.0 giving sensitivity, specificity, PPV and NPV of 20.6%, 96.8%, 63.6% and 81.6%, respectively.

DISCUSSION

Although this study presents the findings of an external validation on APRI using a local HCV-infected population as in most of the previous studies, our focus was on the evaluation of commonly used cut-off points used to diagnose LC using TE as the standard reference rather than suggesting a new one. A cut-off giving a good diagnostic accuracy to APRI would facilitate the treatment of HCV infection in primary health clinics without needing to refer patients to hospitals for further investigation. In addition, this would enable full-scale decentralised treatment of the disease.

The current study findings on the AUROC of APRI for discriminating between cirrhosis and non-cirrhosis cases among HCV mono-infected patients were consistent with those in a meta-analysis of 26 studies (>80%).[13] The meta-analysis also showed that AUROC of APRI for the HCV/HIV co-infection group was lower (0.79), but still better than the current study findings on similar groups of patients (0.76). Nevertheless, all studies included in the meta-analysis used liver biopsy as the standard reference to determine the status of the cirrhosis.[12]

In HCV mono-infected patients, our study shows that all three cut-off points yielded a good specificity (range 88.7-98.5%) but a relatively low sensitivity. However, the cut-off of >2.0 recorded the lowest sensitivity (29.9%), as well as the largest number of false negative cases. Although the cut-offs of >1.0 and ≥1.5 produced findings which agreed with those of TE for the same number of patients, the latter cut-off led to a smaller number of false positive cases. Therefore, as far as overtreatment of non-cirrhotic patients is concerned, 1.5 is the most clinically acceptable cut-off for LC screening in HCV mono-infected patients.

A similar observation was made when APRI was used on HCV/HIV co-infected patients. The use of 1.0 and 2.0 as the cut-offs were, respectively, limited by the high number of false positive and the high number of false negative cases. Even though APRI with a cut-off of ≥1.5 also seems to have a fair discriminative ability in detecting liver cirrhosis, this result should be interpreted with caution. A value of APRI below the threshold 1.5 could accurately indicate the absence of cirrhosis (NPV of 82.4% HCV/HIV co-infected patients). However, due to its relatively low sensitivity, additional physical examination and laboratory assessments are recommended to support the diagnosis of LC. The presence of chronic liver disease stigmata on physical examination, and low serum albumin or high bilirubin, were among the abnormal parameters that indicate LC.[1] Other non-invasive biomarkers, such FIB-4 index, can also be used along with APRI to enhance the accuracy of diagnosis.[27] A recent study suggests that the combined use of both biomarkers could increase the sensitivity, specificity, PPV and NPV up to 82.0%, 89.5%, 87.0% and 85.5%, respectively.[28]

The strengths of this study include the large study population, its multi-center design, as well as the high proportion of cirrhotic patients in the study. Nevertheless, the results from this study may not applicable to other HCV-infected populations such as patients co-infected with hepatitis B virus or have concomitant NASH. Another

limitation is that each participating centre had a different upper limit normal (ULN) value for AST. This could contribute to a lower diagnostic capacity for the APRI score.

CONCLUSION

In conclusion, APRI showed a fair to good discriminative ability in the diagnosis of liver cirrhosis among HCV mono-infected and HCV/HIV co-infected patients in Malaysia. The findings of this study favour a cut-off of 1.5, yet further assessment is likely to be required when the tool is used for diagnosing liver cirrhosis in HCV/HIV co-infected patients.

ACKNOWLEDGEMENTS

We would like to thank the Director General of Health, Malaysia, for his permission to publish the study findings. We would also like to thank Unitaid, the Foundation for Innovative New Diagnostics (FIND), the Drugs for Neglected Diseases initiative (DNDi), the Ministry of Health Malaysia and the Clinical Research Malaysia (CRM) for their support and backing of this study. We would like to acknowledge all staff from the participating sites for their invaluable roles in this study.

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