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BRIEF REPORT

Validation of the aMAP score to predict hepatocellular carcinoma development in a cohort of alcohol-related cirrhosis patients

Abstract

Background and Aims: The aMAP score was recently devised to predict hepatocellular carcinoma (HCC) development. However, its performance was not tested in alcohol-related cirrhosis (ALC). We aimed to validate the aMAP score in a cohort of ALC patients.

Method: Study participants with ALC from a prior genome-wide association study were included. All participants had a history of high alcohol consumption. Cirrhosis was defined clinically, using fibroscan and/or histology. Patients were followed until the last liver imaging, HCC, liver transplantation (LT) or death with the latter two adjusted as competing risks.

Results: A total of 269 ALC patients were included: male (72.5%), Caucasian (98.9%), median age 56 years, and median Child-Pugh score 7. The median aMAP score was 60: 12.3% low-risk, 35.3% medium-risk and 52.4% high-risk. After a median follow-up of 41 months, 14 patients developed HCC, 27 received LT and 104 died. The aMAP score predicted HCC development (hazard ratio 1.12 per point increase, $P < .001$) with good separation of cumulative incidence function between risk groups. The area under the time-dependent receiver operating characteristics curve for predicting HCC development was 0.83 at 1 year and 0.82 at 5 years which was similar to ADRESS-HCC and Veterans Affairs Healthcare System scores respectively.

Conclusions: We validated the excellent performance of the aMAP score in ALC and affirm its applicability across wider aetiologies.

1 | INTRODUCTION

Primary liver cancer is the fifth most common malignancy and second most common cause of cancer death globally and hepatocellular carcinoma (HCC) accounts for 90% of these cases.[1] Several clinical risk calculators have been derived and validated to identify patients at high risk of developing HCC, especially for those with chronic hepatitis B (CHB) infection.[2] Alcohol-related cirrhosis (ALC) contributes to 30% of HCCs and associated deaths overall worldwide but up to 50%-60% in some regions.[3] Therefore, HCC risk prediction in ALC is as important as in viral hepatitis. Although alcohol-mediated hepatocarcinogenesis (and thus HCC risk) is distinct from that of other aetiologies,[4] very few HCC risk scores exist specifically for ALC. Instead, most non-viral hepatitis HCC risk scores are applicable to cirrhosis of all aetiologies without validation in ALC patients.

The most recent of these scores is the aMAP score (consisting of age, male sex, ALBI [albumin-bilirubin] grade and platelet count) developed for predicting the risk of incident HCC in chronic hepatitis from over 17 000 patients across 11 global cohorts.[5] Whilst age, sex and platelet count feature in most previous HCC prediction scores, the incorporation of ALBI grade is novel. Traditionally used as an objective measure of liver function in HCC patients, ALBI grade has been shown to correlate with survival, time to relapse and tolerability of HCC treatments.[6,7] Nonetheless, albumin and bilirubin (and hence ALBI grade) also carry predictive value for HCC development.[8]

The aMAP score developers demonstrated this simple-to-use and objective prognostic tool had excellent performance irrespective of aetiology and ethnicity.[5] However, the derivation cohort and all but one of the validation cohorts used in the study were patients with chronic viral hepatitis. The only non-viral hepatitis cohort included 720 Japanese patients with mostly non-alcoholic fatty liver disease. Although excessive alcohol was an additional risk factor in 11% of these cases, those with ALC were not specifically studied. In their discussion, the authors acknowledged the performance of the aMAP

score in patients not covered in their study (eg, Caucasians with ALC) required further investigation. Therefore, we aimed to validate the utility of the aMAP score in predicting HCC development in a subcohort of ALC patients from our recently published study by the multicentre GenomALC consortium evaluating genetic predictors for ALC amongst heavy drinkers.[9]

Key Points

- The aMAP score has excellent performance for HCC risk prediction in alcohol-related cirrhosis (ALC) patients.
- The aMAP score has similar predictive value to other HCC risk scores that can be used in ALC: ADRESS-HCC and the Veterans Affairs Healthcare System score.
- In this small cohort, the addition of genetic variants data did not improve the predictive value of the aMAP score.

2 | METHODS

2.1 | Study population

GenomALC study participants with ALC from centres in Australia (Royal Prince Alfred Hospital, Sydney) and UK (Nottingham University Hospitals NHS Trust, Nottingham and Freeman Hospital, Newcastle upon Tyne) where data on HCC development were available were included in the analysis. All participants had a history of high alcohol consumption of ≥80 g/d (males) and ≥ 50 g/d (females) for ≥10 years and no other cause of the liver disease.[9] Cirrhosis was defined by clinically evident portal hypertension or decompensation, FibroScan (liver stiffness measurement >22 kPa if aspartate aminotransferase [AST] < 100 IU/L, >32 kPa if AST = 100-200 IU/L), and/or liver histology (METAVIR F4) as described previously.[9] ALC patients were recommended to undergo 6-monthly HCC surveillance using abdominal ultrasound with or without alpha-foetoprotein at each site. The study was approved by the ethics committee or institutional review board at each site (X15-0153 and 2019/ETH07479 for Sydney and 12/LO/0071 for both Nottingham and Newcastle).

2.2 | Clinical data

The baseline date was defined as the date of enrolment into the GenomALC study. The aMAP score, ADRESS-HCC score by Flemming et al. and Veterans Affairs Healthcare System (VAHS) score by Ioannou et al. were calculated from patient demographics and baseline laboratory values as previously described.[5,10,11] The diagnosis of HCC was made radiologically based on the American Association for the Study of Liver Diseases (AASLD) imaging criteria[12] and/or tumour histology. Those with current or previously diagnosed HCC were excluded as were patients with HCC diagnosed within 6 months of the baseline date unless they had cross-sectional imaging with dynamic contrast at baseline showing no liver lesions. Patients were followed until the date of last liver imaging, development of HCC, liver transplantation (LT), or death.

2.3 | Genetics

The genetic information used in this study was derived from our recent GenomALC genome-wide association study (GWAS) and larger meta-GWAS.[9] To determine the impact of the single nucleotide polymorphisms (SNPs), we used meta-GWA-significant risk-increasing alleles showing greatest effect size in our cohort (*PNPLA3*:rs2294915, *TM6SF2*:rs10401969, *HSD17B13*:rs10433937, *FAF2*:rs11134977, *SERPINA1*:rs28929474) and those reported previously as associated with ALC (*MBOAT7*:rs641738, *MARC1*:rs2642438, *HNRNPUL1*:rs15052).[13,14] A three-gene (*PNPLA3*, *TM6SF2*, *HSD17B13*) and eight-gene risk score (all genes listed above) was calculated using the sum of these risk alleles (where scores of 0, 1, and 2 were assigned for noncarriers, heterozygous, and homozygous carriers respectively) as described[15] and analysed.

2.4 | Statistical analysis

Continuous variables were expressed in mean ± standard deviation or median (25th percentile [P25]-75th percentile [P75]) as appropriate. Gray's method was used to estimate the cumulative probability of study endpoints with a 95% confidence interval (CI). The Gray's test was used to compare time-to-event curves between aMAP risk groups; death and LT were considered as competing risks. Fine-Gray model was performed to determine the association between variables, including gene scores, and HCC development with competing risks. The time-dependent receiver operating characteristic curve was used to evaluate and compare the prediction accuracy of each model with competing risks. All statistical tests were two-sided. Statistical significance was taken as $P < .05$. Statistical analysis was performed by R software (4.1.0; R Foundation for Statistical Computing) and Statistical Package for Social Science (SPSS version 22.0).

3 | RESULTS

3.1 | Patient characteristics and outcomes

From a total of 405 GenomALC study participants with ALC across the study centres, 136 were excluded because of previous HCC (n = 27) or LT (n = 75) before the baseline date, or not undergoing any abdominal imaging after enrolment (n = 34). Therefore, 269 patients met the inclusion criteria for analysis (Table 1). Patients were predominantly male (72.5%), Caucasian (98.9%), with a median age

of 56 years (P25-P75 49-62), median body mass index of 24 kg/m^2 (P25-P75 27-31) and median Child-Pugh score of 7 [P25-P75 5-9]). Diabetes mellitus was present in 49 patients (18.2%). The median aMAP score was 60 (P25-P75 54-66) with 12.3% classified as low-risk (score 0-50), 35.3% medium-risk (score 50-60) and 52.4% high-risk (score > 60). After a median follow-up period of 41 months (P25-P75 12-66), 14 patients (5.2%) developed de novo HCC, 27 (10.0%) received LT and 104 (38.7%) died.

TABLE 1 Baseline patient characteristics of ALC patients

Characteristic	n (%) or median (P25-P75)
Male	195 (72.5)
Caucasian	265 (98.9)
Age (y)	56 (49-62)
BMI (kg/m^2)	24 (27-31)
Diabetes	49 (18.2)
Platelet count (x10^9/L)	128 (88-182)
ALT (U/L)	28 (19-39)
Albumin (g/L)	38 (33-42)
Bilirubin (umol/L)	26 (13-53)
INR	1.3 (1.1-1.6)
Child-Pugh score	7 (5-9)
aMAP score	60 (54-66)

Abbreviations: ALC, alcohol-related cirrhosis; ALT, alanine aminotransferase; BMI, body mass index; INR, international normalised ratio.

3.2 | Predictive value of aMAP score vs other scores

The aMAP score was a significant predictor of HCC development (hazard ratio 1.12 per point increase, 95% CI 1.06-1.20, $P < .001$). Accordingly, the cumulative probability of HCC development increased significantly with increasing aMAP risk category (Figure 1). The HCC incidence per year (95% CI) was 0% in the low-risk group, 0.5% (0.1%-2.2%) in the medium-risk group and 2.9% (1.6%-5.0%) in the high-risk group.

The area under the time-dependent receiver operating characteristics curve (AUROC) for the aMAP score for predicting HCC development was 0.83 (95% CI 0.78-0.88) at 1 year, 0.80 (95% CI 0.69-0.91) at 3 years and 0.82 (95% CI 0.72-0.91) at 5 years. The 5-year AUROC was comparable to that reported overall in the original Fan et al. study (0.82-0.87) but numerically superior to that shown in the Japanese non-viral hepatitis cirrhosis cohort (0.61, 95% CI 0.49-0.73). We then compared the performance of the aMAP score to the

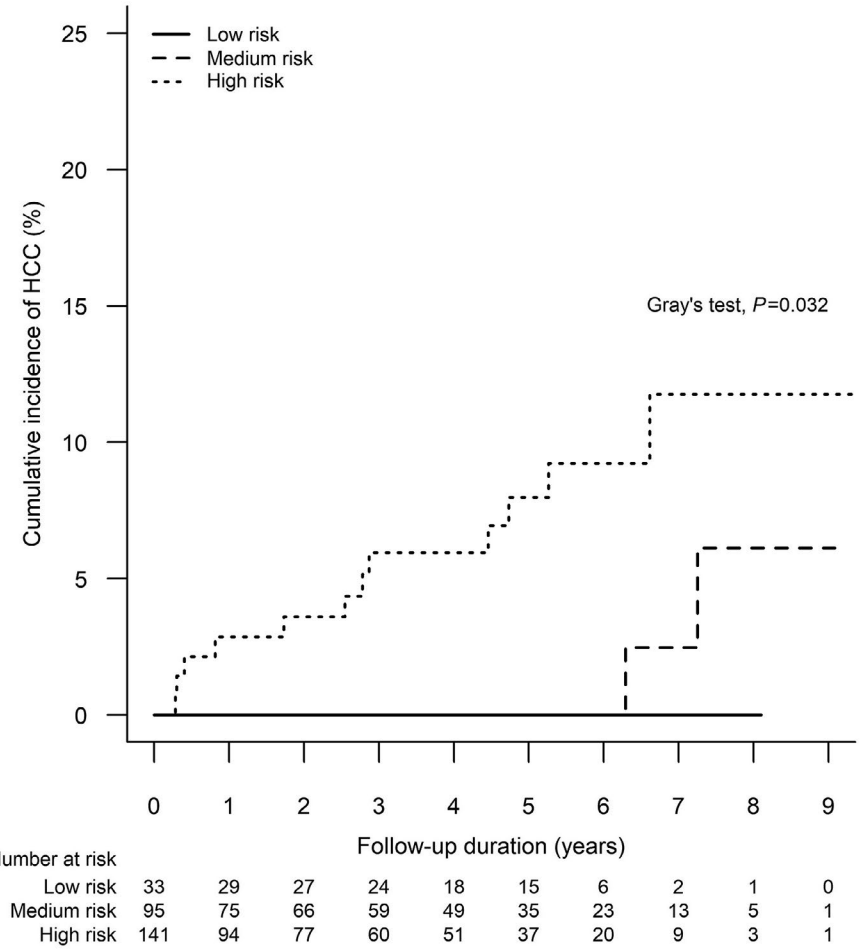

FIGURE 1 The cumulative probability of HCC development amongst the three different aMAP risk categories by Gray's method. HCC, hepatocellular carcinoma

ADRESS-HCC score (for patients with cirrhosis of any cause) and VAHS score (for ALC patients). The aMAP score had similar AUROCs for the ADRESS-HCC score at 1 year and the VAHS score at 3 and 5 years (Figure 2).

3.3 | Addition of genetics to aMAP score

None of the individual genetic variants studied significantly predicted for incident HCC (all $P > .200$). The three-gene and eight-gene scores had AUROCs of 0.51 (95% CI 0.34-0.68) and 0.64 (95% CI 0.50-0.78), for predicting HCC development at 5 years, respectively. The addition of genotype data (either individual variants or combined gene scores) failed to improve the aMAP score performance.

4 | DISCUSSION

Hepatocellular carcinoma is an important and feared complication of chronic liver disease and cirrhosis. Numerous HCC risk prediction scores have been developed for viral hepatitis and cirrhosis of all aetiologies. However, the scores for general cirrhotic patients have

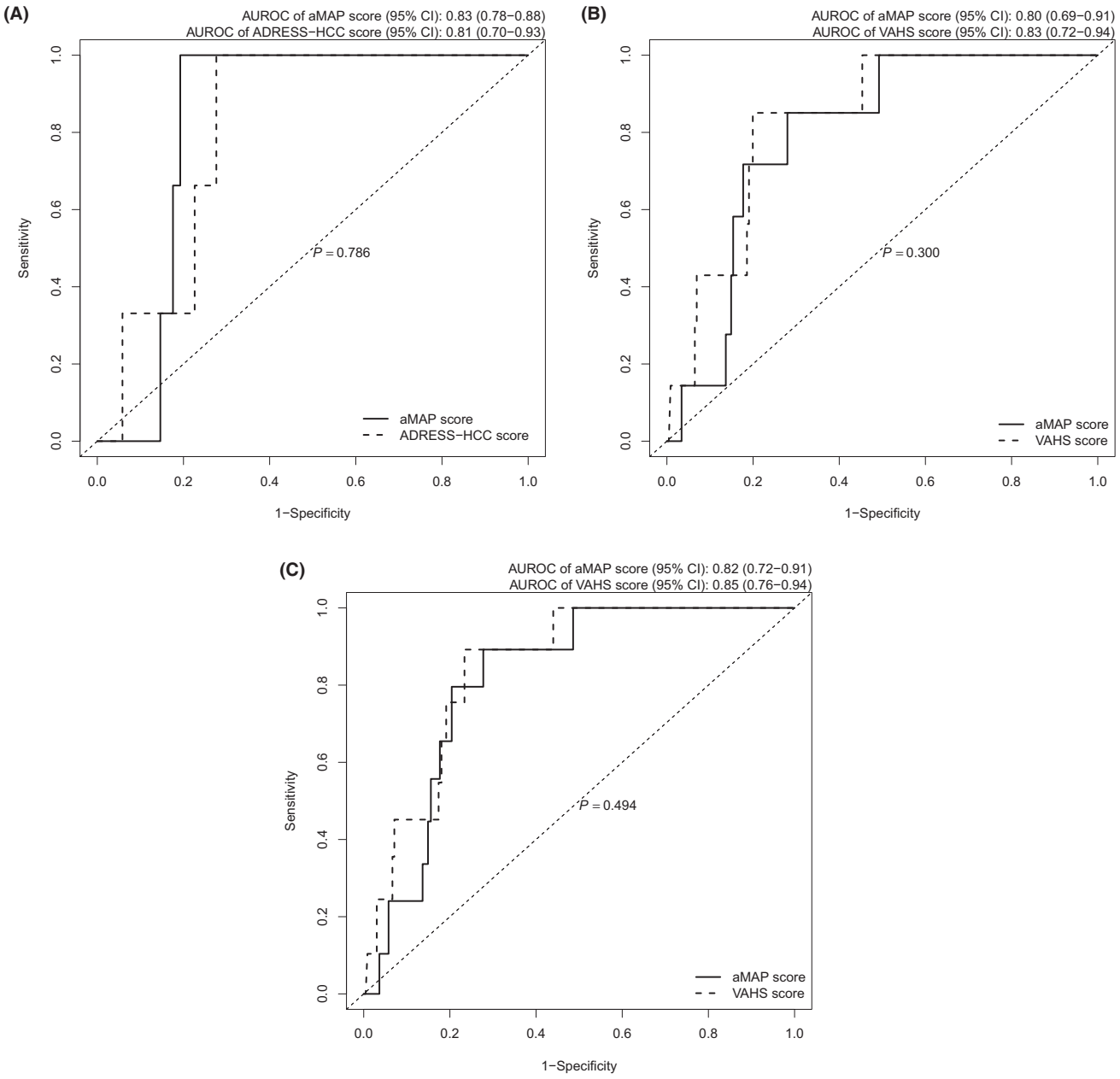

FIGURE 2 (A) Comparison of the performance of aMAP score vs ADRESS-HCC score for predicting HCC development at 1 y. (B) Comparison of the performance of aMAP score vs. VAHS score for predicting HCC development at 3 y. (C) Comparison of the performance of aMAP score vs VAHS score for predicting HCC development at 5 y. AUROC, area under the receiver operating characteristics curve; CI, confidence interval; HCC, hepatocellular carcinoma; VAHS, Veterans Affairs Healthcare System

not been validated in ALC and only one risk score (VAHS score) has studied ALC patients specifically. Barring this exception, ALC has largely been overlooked in HCC scoring systems.

We demonstrated that the aMAP score was a significant predictor of incident HCC in ALC patients. Its performance was not superior to the ADRESS-HCC and VAHS scores. However, compared to these other scores, the aMAP score has the fewest variables and is a single score that can be applied to both viral and non-viral aetiologies. In contrast, the VAHS score requires the use of other variables/formulae for non-alcoholic fatty liver disease and hepatitis C and ADRESS-HCC has only been externally validated in hepatitis C patients.[5,10,11] The ADRESS-HCC cohort also had a short follow-up and thus can only estimate the 1-year probability of HCC whilst both aMAP and VAHS scores predict 5-year probability.

The practical application of the aMAP score may be in deciding HCC surveillance with abdominal ultrasound in ALC.[16] Since the recommended surveillance interval of six months is determined by tumour doubling time (rather than tumour development risk),[12] shortening intervals for patients classified as high-risk of HCC may not result in improved outcomes.[17] However, the aMAP score may identify high-risk patients in whom extra effort should be made to ensure adherence to surveillance, especially since adherence has been shown to be suboptimal in the ALC population.[4] Furthermore, if eventually validated in (non-cirrhotic) alcohol-related liver disease patients, the aMAP score may identify high-risk patients who should undergo earlier surveillance (before the development of cirrhosis), akin to non-cirrhotic CHB patients. Although abdominal ultrasound is the recommended modality for HCC surveillance,[12] cross-sectional contrast-enhanced modalities such as computed tomography (CT) or magnetic resonance imaging (MRI) have been shown to be more sensitive.[18] Despite their high diagnostic performance, CT and MRI are currently not recommended for HCC surveillance because of the paucity of data on survival benefits and cost-effectiveness.[12] However, they may be justified in the subset of patients identified as high-risk by aMAP score, especially if ultrasound visualisation of the liver is further limited by other factors such as truncal obesity, hepatic steatosis, or severe parenchymal heterogeneity from advanced cirrhosis.[12] These clinical applications all warrant further prospective study.

A particular strength of our study was that it recruited well-characterised ALC patients with genotyping data from multiple centres. Nonetheless, several limitations deserve mention. Our patient cohort was relatively small with only 14 HCCs diagnosed during the follow-up. Despite this, we were able to validate the excellent predictive value of the aMAP score. However, it may have limited our ability to assess the usefulness of genotyping data on HCC risk prediction. Indeed, a similar three-gene score was shown to be predictive of HCC in the general population cohorts of >100 000 individuals and other studies of genetic variants in ALC have involved larger cohorts than ours.[15,19] Furthermore, a large proportion of our cohort died during follow-up, thus limiting the time to develop HCC. This is a reflection of alcohol use being a leading cause of premature death via causes other than liver-related diseases such as cancers and injuries.[20] Continued alcohol use during the study period may have also contributed to excess mortality. Although alcohol was the primary liver injury in our cohort, metabolic risk factors (diabetes, obesity) in some patients may have also contributed to HCC risk, need for LT and death. In this study, we did adjust for both death and LT using competing risk analyses. These limitations could be addressed in larger prospective ALC cohorts in the future to confirm our findings.

In conclusion, we validated the excellent performance of the aMAP score in ALC and affirm its applicability across wider aetiologies.

KEYWORDS

alcohol-related cirrhosis, genetic risk score, hepatocellular carcinoma, risk prediction, single nucleotide polymorphism

ACKNOWLEDGEMENTS

None.

CONFLICT OF INTEREST

All the authors declare no conflict of interest.

ETHICS APPROVAL STATEMENT

The study was approved by the ethics committee or institutional review board at each site (X15-0153 & 2019/ETH07479 for Sydney and 12/LO/0071 for both Nottingham and Newcastle).

PATIENT CONSENT STATEMENT

All patients provided written informed consent for the original GenomALC study from which the current study cohort was derived. The need for patient consent for this current study was waived by the ethics committee.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author Devanshi Seth. The data are not publicly available due to privacy or ethical restrictions.

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