Original Article

Estimation of hepatocellular carcinoma mortality using aspartate aminotransferase to platelet ratio index

Kelvin Allenson, David Roife, Lillian S. Kao, Tien C. Ko, Curtis J. Wray

Department of Surgery, McGovern Medical School at the University of Texas Health Science Center at Houston, Houston, Texas, USA

Contributions: (I) Conception and design: K Allenson, CJ Wray; (II) Administrative support: TC Ko; (III) Provision of study materials or patients: TC Ko, CJ Wray; (IV) Collection and assembly of data: D Roife, CJ Wray; (V) Data analysis and interpretation: K Allenson, LS Kao, CJ Wray; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Curtis J. Wray, MD, MS. Department of Surgery, Lyndon B. Johnson General Hospital, 5656 Kelley Street, Suite 30S62008, Houston, Texas 77026, USA. Email: Curtis.J.Wray@uth.tmc.edu.

Background: Hepatocellular carcinoma (HCC) patients with cirrhosis are high-risk for invasive procedures. Identification of those at risk may prevent complications and allow more informed decision-making. The aspartate aminotransferase (AST) to platelet ratio index (APRI) is a measure of cirrhosis that we hypothesize predicts survival and may estimate HCC mortality.

Methods: Institutional retrospective study of all HCC patients. Demographics and labs [bilirubin, international normalized ratio (INR), creatinine, AST and platelets] were recorded at the date-of-diagnosis to calculate APRI and the Model for End-Stage Liver Disease score (MELD). Poor survival was defined as death within 30-days from diagnosis. Models were created to determine predictors of death within 30-days and overall survival.

Results: A total of 829 patients comprised this study and <30-day death was observed in 111 patients (17%). Mean APRI and MELD scores were higher in the <30-day death group. APRI [odds ratio (OR) 1.45, 95% confidence interval (CI): 1.07–1.96] and MELD (OR 1.21, 95% CI: 1.14–1.28) were predictive of <30-day death. Stratified by stage, APRI [hazard ratio (HR) 1.12, 95% CI: 1.01–1.24] and MELD (HR 1.07, 95% CI: 1.05–1.09) were associated with overall survival. Inclusion of APRI and MELD components in the Cox regression resulted in the best fit (c-index =0.67).

Conclusions: The APRI is an innovative marker of cirrhosis and survival for HCC patients. APRI provides additional prognostic information regarding the severity of cirrhosis and external validation is needed to determine clinical utility.

Keywords: Cirrhosis; liver cancer; survival estimation

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Introduction

Hepatocellular carcinoma (HCC) is the fifth leading cause of cancer death in the United States (1). Furthermore, the preponderance of hepatitis C-related HCC is unique to the United States and represents the fastest growing cause of cancer-related death in the country (2). Given that cirrhosis of any cause is present in 80–90% of HCC patients, ample time and opportunity exists to identify patients during the progression from fibrosis to cirrhosis and surveil this high-risk group for development of malignancy. In addition, for patients who have progressed to HCC, any means of risk-stratification for invasive procedures has the potential to reduce procedure-related morbidity and mortality. The incidence of major complication following an invasive procedure, including liver biopsy, ablation, trans-arterial chemoembolization (TACE), or resection in the treatment of HCC patients has been observed between 1.3–50% of

$$\frac{\left(\frac{\text{AST level}}{\text{AST (upper limit of normal)}}\right)}{\text{Platelet count } (10^9/\text{L})}$$

Figure 1 Mathematical equation to calculate the APRI. AST, aspartate aminotransferase; APRI, AST to platelet ratio index.

cases (3-6). In this context, non-invasive measures of liver function and cirrhosis have the ability to augment clinical decision making while sparing the risk and cost of biopsy.

At present, core needle biopsy is the gold standard assessment for liver fibrosis and cirrhosis (7,8). Recent investigators have criticized the utility of biopsy as the tissue sampled is miniscule relative to the mass of the organ (9), the procedure is invasive in patients at risk for complications (4), and the histologic grade of the tissue sampled may not accurately reflect the more clinically relevant liver function (10). Alternatively, many surrogates exist for the noninvasive assessment of liver fibrosis. Fibrotest, Hepascore, Fibrometer, and the enhanced liver fibrosis (ELF) scores exploit the molecular intermediates of liver extracellular matrix turnover (10). Application is limited in that particular molecular targets as lab markers are not routinely clinically assessed. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), platelet count, bilirubin, international normalized ratio (INR), and creatinine have traditionally been used to assess organ function in patients with liver disease and share the advantage of being routinely assessed lab metrics. These labs compose the AST to platelet ratio index (APRI), Fibrosis-4 (FIB-4) and Model for End-Stage Liver Disease (MELD) and have been widely studied in hepatitis B and C cohorts (10-20). Transient elastography, acoustic radiation force impulse and magnetic resonance elastography are different imaging modalities but all utilize the physical propagation of kinetic energy across the diseased, "stiff" liver (21,22). Ability to detect cirrhosis is excellent but cost may be prohibitive and the widespread availability of these platforms is limited. Combination of the various scoring systems has been shown to improve the performance of predictive models, yet the clinical utility of detecting and measuring cirrhosis remains inconsistent.

The APRI amplifies the aberrations in the AST and platelet values that accompany cirrhosis (*Figure 1*). The AST to platelet ratio index amplifies the physiologic derangements reflected by AST and platelet count inherent to liver fibrosis and cirrhosis. As liver fibrosis proceeds, increasing liver inflammation is reflected by elevations in the AST level. This value is normalized according to the processing lab's normal to account for inter-lab variability. With compromised liver function, the liver's production of thrombopoietin declines and there is a subsequent decrease in platelet count. Therefore, as the AST numerator increases, and the platelet denominator decreases, higher APRI values will be obtained signifying a greater degree of liver cirrhosis. APRI has been shown to reliably identify cirrhotic from non-cirrhotic patients in the context of viral liver disease, and can predict the risk of developing viral-related HCC (23). Perhaps most compelling is that APRI has been shown to predict liver-related mortality independent of the well-established MELD or Child-Pugh scores arguing that additional clinical data exists but is underutilized in the evaluation of such patients (24). Furthermore, patients with HCC and advanced cirrhosis are predisposed to poor survival and the APRI may allow for risk-stratification in order to prevent complications and allow for more informed and shared decision making (25). In this study we analyzed 829 patients in order to ascertain the predictive value of APRI for short term mortality as a means of risk-stratification prior to consideration for invasive procedure or surgery. We examined 30-day mortality as an estimate of procedure-related mortality (26).

Methods

Patients

We conducted an institutional review board approved retrospective study of all HCC patients diagnosed in a safety-net hospital system from 1998–2014. Standard demographics included age, stage at diagnosis, race, treatment (type of surgery, chemotherapy and radiation therapy), and mortality. In addition, laboratory values (bilirubin, INR, creatinine, albumin, AST and platelets) were recorded at the date of diagnosis to calculate APRI and MELD scores. The seventh version American Joint Committee on Cancer staging system was used to classify extent of disease.

Statistical analyses

Poor survival was defined as death within 30 days from the date of HCC diagnosis. Death within 30 days was recorded as a binary variable. A logistic regression model was created to determine predictors of 30-day death. Univariate analyses were completed with Student's *t*-test for continuous variables and chi-square analysis for categorical variables. Univariate

logistic and multivariate logistic regression analyses were performed to determine predictors of <30-day survival. Receiver operating characteristic (ROC) curves were used to calculate the area under the curve (AUC) for the logistic regression models and compare the predictive power.

Overall survival was estimated using a multivariate Cox proportional hazards model. The final multivariate, multinomial model was created using the backward, stepwise method of covariate selection. The backward stepwise method was used to include only significant covariates (P value of <0.05) in the final model. Significance of the exploratory model was tested using the Likelihood Ratio test to determine if the model is significantly better with additional predictor variables. Standard tests for regression diagnostics and assumptions, including tests of collinearity and interactions were performed. A covariate that did not meet the proportional hazards assumption was tested for possible inclusion as a time-varying covariate. This specifies a variable that varies continuously with respect to time. Confirming that a coefficient is time invariant is a way of testing the proportional hazards assumption. Proportional hazards imply that the relative hazard is fixed over time and this assumption would be violated if a time interaction proved significant. Iterations of the Cox proportional hazards model were compared for goodness of fit using Harrell's c-index. All statistical analyses were performed using Stata 14 (StataCorp, College Station, TX, USA).

Results

During the study period, 877 patients were diagnosed with HCC. A total of 48 patients (5.4%) were excluded due to incomplete data. The remaining 829 HCC patients (78% male) were included in this study. A total of 145 patients (17.5%) survived less than 30 days. Mean age at diagnosis was 55.9 years [standard deviation (SD) 8.8] and there was no age difference between survival <30 and ≥30 days (*Table 1*). There was no difference in hepatitis B virus (HBV) or hepatitis C virus (HCV) status between groups. Patients who died <30 days had liver dysfunction evidenced by increased APRI, MELD score, and alpha-fetoprotein (AFP) and decreased albumin.

A multivariate logistic regression model was created to identify factors associated with <30-day survival. APRI, creatinine, bilirubin, lower albumin values, higher AFP, advanced stage and no treatment were associated with <30-day survival (*Table 2*). The AUC of this model was 0.88 with APRI and 0.80 without the inclusion of APRI.

Since both stage and treatment are known to influence survival, the Cox proportional hazards model was stratified by these covariates. This demonstrated that higher APRI values [hazard ratio (HR) 1.15, 95% confidence interval (CI): 1.03–1.30] were associated with worse overall survival. In addition, higher values of bilirubin, INR, creatinine and AFP were also predictors of poor survival (*Table 3*). There is a relatively weak direct relationship between APRI and MELD score (coefficient 0.32, P value <0.05, 95% CI: 0.21–0.43), however, there was no interaction or evidence of collinearity in the Cox regression model. Inclusion of both APRI and MELD score components resulted in the highest c-index score (0.67).

Discussion

We investigated the relationship between APRI and clinical outcomes, <30-day survival as well as overall survival. In this study of 829 HCC patients, a lower APRI is associated with improved survival. Since APRI has previously been shown to correlate with the degree of cirrhosis, in this study it provided additional prognostic information, independent of variables that comprise the widely utilized MELD score. This noninvasive measure of cirrhosis may help clinicians estimate both cirrhosis and survival when considering different treatment options.

APRI was first proposed by Wai and colleagues as a biochemical surrogate for the diagnosis of advanced fibrosis and cirrhosis in patients with chronic hepatitis C (9). Since that time, the utility of the metric has further been explored with regard to concomitant HIV coinfection, and also hepatitis B cohorts with continued favorable performance at identifying cirrhotics from non-cirrhotics (20,24). More recently, APRI has been shown to be predictive of the risk of developing HCC in the setting of established cirrhosis and additionally can predict liver-related mortality after hepatic resection for HCC (11-13). The current study adds to the body of APRI literature since this study cohort is significant larger and more diverse than those described in earlier reports.

In our study we explored the ability of APRI to predict the risk of early mortality in HCC patients. We believe such an application to be appropriate as the majority of the patients in our cohort exhibited viral hepatitis, with 66.2% HCV positive, and 16.2% HBV positive. Whereas the majority of APRI studies focused on the diagnosis of cirrhosis, we explored the association between APRI and early mortality. It is important to assess short term mortality

Table 1 Standard patient cohort demographics (N=829)

Patient demographics (N=829)	Mortality <30 days	Mortality >30 days	P value
Age (SD)	55.9 (9.3) yrs	55.9 (8.7) yrs	0.98
Gender			0.004
Male	126 (86.9%)	519 (75.8%)	
Female	19 (13.1%)	165 (24.1%)	
Race			0.463
Caucasian	48 (33.1%)	199 (29.1%)	
African-American	49 (33.7%)	210 (30.7%)	
Hispanic	34 (23.4%)	193 (28.2%)	
Asian	14 (9.7%)	82 (12%)	
HBV			0.940
Positive	23 (15.9%)	111 (16.2%)	
Negative	110 (75.9%)	541 (79%)	
HCV			0.918
Positive	96 (66.2%)	457 (70.1%)	
Negative	43 (29.7%)	209 (30.6%)	
AFP (SD)	80,597.01 (182,220.9)	15,241.62 (77,195.21)	<0.0001
Total bilirubin (SD)	5.48 (6.83)	1.99 (2.95)	<0.0001
INR (SD)	1.67 (0.75)	1.34 (0.7)	<0.0001
Albumin (SD)	2.34 (0.68)	2.85 (0.71)	<0.0001
AST (SD)	331.4 (342.6)	153.8 (295.7)	<0.0001
Platelets (SD)	193.5 (127.3)	181.7 (129.3)	0.33
Creatinine (SD)	1.43 (1.03)	0.97 (0.48)	<0.0001
APRI (SD)	6.38 (7.22)	3.52 (9.75)	0.002
MELD (SD)	19.0 (8.2)	11.7 (4.5)	<0.0001
Stage			<0.0001
I	9 (6.2%)	143 (20.9%)	
II	11 (7.6%)	125 (18.3%)	
III	38 (26.2%)	182 (26.6%)	
IV	75 (51.7%)	200 (29.2%)	
Unknown	12 (8.3%)	33 (4.8%)	
Treatment			<0.0001
Yes	12 (8.3%)	364 (53.2%)	
No	122 (84.1%)	283 (41.4%)	
Surgery			0.011
Yes	4 (2.8%)	63 (9.2%)	
No	130 (89.7%)	581 (84.9%)	
Chemotherapy			<0.0001
Yes	5 (3.4%)	204 (29.8%)	
No	129 (89%)	440 (64.3%)	
Radiotherapy			0.065
Yes	1 (0.7%)	25 (3.7%)	
No	133 (91.7%)	616 (90.1%)	

HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, alpha-fetoprotein; INR, international normalized ratio; AST, aspartate aminotransferase; APRI, AST to platelet ratio index; MELD, model for end stage liver disease.

Table 2 Logistic regression model to identify variables associated with less than 30-day survival

Variables	OR	P value	95% CI
APRI	1.33	0.03	1.03–1.71
Creatinine	2.21	0.00	1.53–3.18
Total bilirubin	1.13	0.00	1.06–1.21
Albumin	0.55	0.01	0.36–0.84
INR	1.28	0.10	0.96–1.71
Stage			
2	2.22	0.17	0.71–6.96
3	2.33	0.10	0.86–6.29
4	6.50	0.00	2.47–17.13
Unknown	3.53	0.27	0.37–33.67
AFP	1.00	0.04	1.00–1.00
Treatment	0.16	0.00	0.08–0.33

OR, odds ratio; CI, confidence interval; APRI, aspartate aminotransferase to platelet ratio index; INR, international normalized ratio; AFP, alpha-fetoprotein.

Table 3 Cox proportional hazards model to identify variables associated with overall survival

Variables	HR	P value	95% CI
APRI	1.15	0.02	1.03–1.30
Albumin	0.69	0.00	0.60–0.80
Total bilirubin	1.03	0.01	1.01–1.05
INR	1.22	0.00	1.07–1.38
Creatinine	1.27	0.00	1.11–1.45
AFP	1.12	0.00	1.08–1.15
Hepatitis			
HBV	0.97	0.86	0.66–1.40
HCV	0.98	0.89	0.76–1.27
HBV/HCV	0.62	0.22	0.29–1.32
Unknown	4.13	0.00	1.59–10.72

Stratified by stage and treatment. HR, hazard ratio; CI, confidence interval; APRI, aspartate aminotransferase to platelet ratio index; INR, international normalized ratio; AFP, alpha-fetoprotein; HBV, hepatitis B virus; HCV, hepatitis C virus.

risk as means of risk stratification prior to consideration of an invasive procedure, biopsy and/or surgery (27,28). As applied, we observed a <30-day mortality of 17.5% suggesting that risk stratification should be considered in high-risk HCC patient cohorts. As previously mentioned, our regression model exhibited the best performance when combining APRI data with other available laboratory data, namely components of MELD score and serum albumin (10,24). Of note, the individual components of the MELD score (bilirubin, INR and creatinine) were included in our regression model. Using MELD score as a continuous variable would have meant inclusion of already transformed data (natural logarithm of bilirubin, INR and creatinine).

The Child-Pugh score has historically been used to assess the prognosis of cirrhotic patients undergoing surgery. More recently, the MELD score was used for further prognostication initially for cirrhotic patients undergoing transjugular intrahepatic portosystemic shunt (TIPS) procedures, and subsequently for the prioritization of liver allografts for transplantation (29). MELD has become near ubiquitous in the evaluation of liver function (30). Interestingly, both are composites scores, which mirror the attempts from recent studies to combine APRI with other available metrics to improve performance. In our study, we observed that APRI can predict mortality independent of MELD score components, suggesting that available information exists but is underutilized in assessing patients with hepatic cirrhosis and compromised liver function. Since the labs composing APRI and MELD are routinely assessed together, and the MELD score itself requires calculation, we recommend that all available data be considered in order to properly assess risk in cirrhotic HCC patients prior to intervention.

Our study included a diverse racial and ethnic composition and with a high prevalence of hepatitis C. Demographic variables more consistent with the challenges of HCV-related cirrhosis and HCC, compared to large majority-HBV cohorts that frequently have less severe cirrhosis secondary to the different mechanisms of hepatocarcinogenesis. However, our efforts are not without limitation. While our cohort is the largest to date to examine the relationship between APRI and survival outcomes, it is retrospective in nature. Although, medical management of cirrhosis and invasive treatment of HCC evolved over the survey period, accounting for this in the multivariate model did not affect the results. Additionally, since this cohort hails from a safety-net facility, liver transplantation is not included in the treatment algorithm of these patients. At present, APRI is a noninvasive measure that may aid clinicians when counseling cirrhotic HCC patients about the risks and benefits of various invasive treatments. Further study is needed to determine the clinical utility of using APRI for prognostic and treatment decisions.

Conclusions

APRI is associated with both the diagnosis of cirrhosis and HCC across multiple high-risk populations. In our study, we demonstrate that APRI is predictive of mortality in HCC patients, independent of the MELD score. APRI provides additional prognostic information in the management of HCC patients, and may be used to stratify high-risk patients when considering invasive procedures.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Retrospective collection of patient data was approved by the UT Health and Lyndon B Johnson General Hospital Institutional Review Board.

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