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APRI score is not predictive of post-surgical outcomes in cholangiocarcinoma patients

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Abstract

Background Cholangiocarcinoma is an epithelial malignancy of the intrahepatic or extrahepatic biliary tree, primarily driven by chronic inflammation and fibrosis. Fibrosis has been shown to correlate with malignancy, and the aminotransferase-platelet ratio index (APRI) score, a marker for hepatic fibrosis, has proved useful in prognosticating hepatocellular carcinoma. This study aimed to assess the utility of APRI score in predicting post-surgical outcomes in cholangiocarcinoma patients.

Methods Clinical data from a total of 152 cholangiocarcinoma patients who underwent surgical resection at the Mayo Clinic were collected. The data were subsequently analyzed to determine if there was a relationship between APRI score and the demographic, laboratory, pathologic and outcome data, including overall survival. To determine the relationship between quantitative and qualitative data and the APRI score, a P-value <0.05 was considered as statistically significant.

Results No relationship between APRI score and demographic factors was identified. There were correlations between APRI score and alanine transaminase, albumin and bilirubin, but the remaining laboratory parameters showed no correlation. APRI score did not prove to be useful as a prognostic tool, as it did not correlate with tumor pathology features (tumor grade *t*-test P=0.86, N stage ANOVA P=0.94, vascular invasion *t*-test P=0.59, and perineural invasion *t*-test P=0.14), or with post-surgical recurrence (*t*-test P=0.22) and mortality (*t*-test P=0.39).

Conclusion APRI score is not a prognostic tool for post-surgical outcomes in patients with cholangiocarcinoma.

Keywords Cholangiocarcinoma, biliary tract cancer, APRI score

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Conflict of Interest: None

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Introduction

Cholangiocarcinoma is the second most common primary liver cancer. Tumors can arise at different sites (intrahepatic, extrahepatic, perihilar) and from different cells of origin, and are genomically and histologically heterogeneous [1,2]. The pathogenesis of cholangiocarcinoma is felt to be largely driven by chronic inflammation and cholestasis, which subsequently results in cellular proliferation, genetic and epigenetic changes, and eventually carcinoma [3]. Conditions that increase inflammation, such as hepatitis B, hepatitis C, liver cirrhosis, primary sclerosing cholangitis (PSC), nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, and liver flukes, are well known risk factors for cholangiocarcinoma [2,4-6].

As with many malignancies, treatment options for cholangiocarcinoma include surgical resection, chemotherapy, targeted therapies, immunotherapy and radiation therapy, with surgery/transplant being the only curative option [2,4]. However, surgical resection outcomes still leave much to be desired. Five-year survival rates remain around 20-40% [2,4,7-9]. Liver transplant is only an option in selected cases of perihilar disease or early intrahepatic disease, and can achieve 5-year survival rates of around 65-70% [2,4]. Factors that are related to 5-year mortality/survival include lymph node status, margin status, histological grade, vascular invasion and tumor size [2,5,7,8]. However, these prognostic indicators are only known after surgical resection. Unfortunately, although the utility of carcinoembryonic antigen tests and cancer antigen (CA) 19-9 levels has been investigated, studies have yielded mixed results and there are no definitive preoperative prognostic implications [5,10]. A reliable presurgical prognostic indicator for postresection outcomes could be extremely valuable in surgical decision making and postoperative prognostic guidance for these patients.

Given that the underlying disease processes of cholangiocarcinoma are related to chronic inflammation of the liver and biliary tree, indicators of liver inflammation and fibrosis could be useful in assessing cholangiocarcinoma outcomes [3]. The aminotransferase-platelet ratio index (APRI), calculated as the ratio of serum aspartate transferase (AST) to platelet count, has been shown to be a useful marker for liver fibrosis [11]. It was first implemented as a simple, noninvasive indicator of liver fibrosis and cirrhosis in patients with chronic hepatitis C [12]. However, its utility has subsequently expanded beyond hepatitis C patients [11]. For example, as a result of its utility as a useful marker for fibrosis, APRI scores have shown to correlate with postsurgical liver failure and mortality in patients undergoing resection for hepatocellular carcinoma (HCC) and for mixed HCC-cholangiocarcinoma tumors [13]. Given these findings, we hypothesized that the APRI score could potentially be a useful marker for measuring disease severity and prognosticating disease in patients with cholangiocarcinoma. Therefore, we performed a retrospective analysis of 152 cholangiocarcinoma patients who underwent surgical resection at the Mayo Clinic, to determine whether a range of patient and tumor characteristics were correlated with APRI score and whether preoperative APRI scores could be used to predict postsurgical outcomes in cholangiocarcinoma patients.

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Patients and methods

Data collection

This study entailed a retrospective analysis of 152 patients at the Mayo Clinic who had cholangiocarcinoma and underwent surgical resection between 2010 and 2020. Patient demographic data, laboratory parameters prior to surgery, tumor pathology and outcome data were obtained. Demographic data included age, sex, race, tumor type and fibrosis etiology. Laboratory data included CA19-9, albumin, bilirubin, international normalized ratio (INR), alkaline phosphatase, alanine aminotransferase (ALT), AST, and platelet count. Child-Pugh and APRI scores were calculated using the laboratory parameters listed, together with clinical data for ascites and encephalopathy for Child-Pugh score. Pathology data included tumor size, status of vascular and/or perineural invasion, tumor grade, tumor stage, tumor margin status and margin width. Outcome data included recurrence status, time to recurrence, vital status and survival from time of surgery. The data were subsequently analyzed to determine if there was a relationship between APRI score and the demographic, laboratory, pathology and outcome data. Approval from the Mayo Clinic institutional review board was obtained prior to data collection for this study (IRB: 21-007102).

Statistical analysis

The data were analyzed using the SciPy stats package (Enthought, Inc. Austin, Texas, USA) and figures were generated using the MatPlotLib package for Python (The MatPlotLib Development Team, Salt Lake City, Utah, USA) [14,15]. To determine the relationship between quantitative laboratory, pathology and outcome data, datapoints for each measure and the associated APRI score were plotted on a scatter plot. Then, using the SciPy stats package, the Pearson correlation coefficient, P-value (with $P<0.05$ being considered as statistically significant), line of best fit, and slope were determined. For qualitative demographic and pathology data, box plots were generated to illustrate how APRI score varied in each category. Then, depending on the number of variables, a 2-sample *t*-test or a 1-way ANOVA test were done using the SciPy package to determine whether the APRI score differed significantly in relation to the different variables ($P<0.05$ being statistically significant). During the analysis, if a specific datum was not available for a particular patient, that patient was excluded from that specific group analysis. For example, if tumor grade was unavailable for a patient, that patient was not included when analyzing the relationship between tumor grade and APRI score. However, that patient was still included in the analysis of the remaining variables. In addition, outliers were excluded from the analysis of the laboratory parameters alkaline phosphatase, bilirubin, CA19-9 and INR, outliers being defined as 5 times above the median for alkaline phosphatase, CA19-9, and INR, and 30 times

above the median for bilirubin. This led to the exclusion of 5 values for alkaline phosphatase, 1 value for bilirubin, 16 values for CA19-9, and 1 value for INR.

Results

Demographic data and APRI score

In this study, we examined the association between APRI score and age, sex, race, tumor type, and fibrosis etiology. As regards age, APRI score decreased at a rate of 0.01 with each additional year in age (r=-0.19, P=0.02) (Fig. 1A). However, given the small rate of change, this relationship between APRI score and age is not clinically significant.

There was no relationship between sex and APRI score. The median APRI score was 0.41 for males and 0.38 for females, with a 2-sample *t*-test P-value of 0.16 (Table 1, Fig. 1B). There was also no relationship between race and APRI score. The median APRI score was 0.40 for white patients, 0.43 for African American patients, 0.20 for Asian patients, 0.90 for Hispanic patients, and 0.29 for patients in other categories, with an ANOVA-test P-value of 0.81 (Table 1, Fig. 1C). It should be noted, however, that most of the patients in our study were white; thus, broader conclusions regarding the impact of race on APRI score cannot be drawn from this dataset.

With regard to tumor type, 140 of the 152 patients analyzed had intrahepatic cholangiocarcinoma; these patients had a median APRI score of 0.38 (Table 1, Fig. 1D). The remaining tumor types had no more than 3 patients in each category; thus, meaningful conclusions could not be drawn regarding how tumor type affects APRI score. Regarding fibrosis etiology, the 20 patients with inflammatory bowel disease (IBD: ulcerative colitis or Crohn's disease) or primary sclerosing cholangitis had a median APRI score of 0.65, higher than that of patients with other or no underlying etiologies. Among the remaining etiologies, the 14 patients with hepatitis (alcoholic, nonalcoholic, or viral) or steatosis had a median APRI score of 0.51, the 5 patients with liver cirrhosis or focal nodular hyperplasia had a median APRI score of 0.27, and the 12 patients with other causes of fibrosis had a median APRI score of 0.37 (Table 1, Fig. 1E). Most patients analyzed (100 of 152) had no underlying fibrosis etiology, and these patients had a median APRI score of 0.38 (mean 0.48). When all patients with fibrosis etiologies were considered collectively (n=51), we found that those with

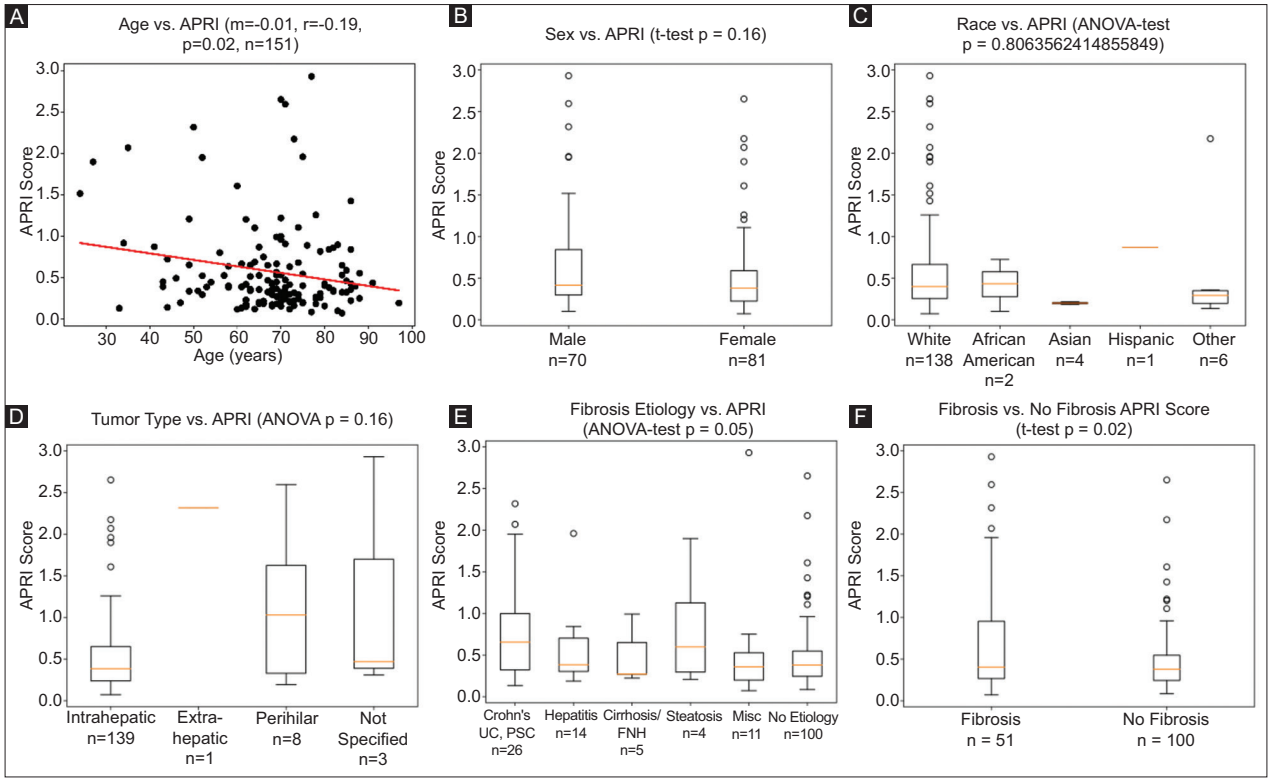

Figure 1 Clinical characteristics and correlation with APRI score. (A) Scatter plot with line of best fit illustrating relationship between age and APRI Score. (B) Boxplot illustrating variations in APRI score in relation to sex (male vs. female). (C) Boxplot illustrating variations in APRI score in relation to race. (D) Boxplot illustrating variations in APRI score among various tumor types. (E) Boxplot illustrating variations in APRI score among various fibrosis etiologies. (F) Boxplot illustrating differences in APRI scores between patients with underlying liver fibrosis etiologies versus those without fibrosis etiologies

APRI, aminotransferase-platelet ratio index; PSC, primary sclerosing cholangitis

Table 1 Sex, race, tumor type, fibrosis etiology, presence of fibrosis, and relationship to APRI score

Demographic	Mean APRI	Median APRI	95% Confidence interval	Statistical test (2-sample *t*-test or ANOVA)
Sex				
Male (n=70)	0.64	0.41	0.50-0.78	2-sample *t*-test
Female (n=81)	0.52	0.38	0.41-0.62	P=0.16
Race				
White (n=138)	0.58	0.39	0.49-0.67	ANOVA
African American (n=2)	0.20	0.20	0.18-0.22	P=0.81
Asian (n=4)	0.42	0.43	0.20-0.65	
Hispanic (n=1)	0.87	0.87	-	
Other (n=6)	0.57	0.29	-0.006-1.147	
Tumor type				
Intrahepatic (n=140)	0.52	0.38	0.44-0.59	ANOVA
Extrahepatic (n=1)	2.32	2.32	-	P=0.16
Perihilar (n=8)	1.11	1.03	0.54-1.70	
Not specified (n=3)	1.24	0.47	-0.12-2.59	
Fibrosis etiologies				
Crohn's, ulcerative colitis, and PSC (n=20)	0.83	0.65	0.54-1.12	ANOVA
Hepatitis (alcoholic, nonalcoholic, and viral)/steatosis (n=14)	0.71	0.51	0.41-1.01	P=0.04
Liver cirrhosis and focal nodular hyperplasia (n=5)	0.48	0.27	0.22-0.74	
Other* (n=12)	0.75	0.37	0.23-1.27	
No etiology identified (n=100)	0.48	0.38	0.40-0.56	
Fibrosis vs. no- fibrosis etiologies				
Fibrosis etiologies present (as listed above) (n=51)	0.74	0.40	0.55-0.93	2-sample *t*-test
No-fibrosis etiologies present (n=100)	0.48	0.38	0.40-0.56	P=0.02

*Other: includes chronic inflammation, hemochromatosis, iron overload, radiation, biliary impairment, pancreatic pathologies, cholecystitis, α-1-antitrypsin, CREST, Ehrlichiosis

APRI, aminotransferase-platelet ratio index; PSC, primary sclerosing cholangitis

fibrosis etiologies had a median APRI score of 0.4 (mean 0.74). When compared to those without fibrosis etiologies, although the median APRI scores were similar, the mean APRI score was significantly higher in patients with fibrosis etiologies, and the overall distribution suggested that these patients tend to have higher APRI scores (2-sample *t*-test P=0.02) (Table 1, Fig. 1F).

Laboratory data and APRI score

The relationships between APRI score and laboratory parameters, including albumin, bilirubin, ALT, alkaline phosphatase, CA19-9 and INR, were also determined.

After outliers had been excluded, assessment of the 144 patients with a recorded albumin level showed that the APRI score decreased at a rate of 0.35 for every 1 unit increase in albumin (r=0.35, P<0.01) (Fig. 2A). Among the 145 patients with a recorded bilirubin level, APRI score went up by 0.13 for every 1 unit increase in bilirubin (r=0.23, P=0.01) (Fig. 2B). For the 129 patients with a recorded ALT, we found that APRI score went up by 0.1 for every 10 unit increase in ALT (r=0.47, P<0.01) (Fig. 2C). Among the 145 patients with a recorded alkaline phosphatase level, there was a 0.18 increase in APRI score for every 100 unit increase in alkaline phosphatase (r=0.41, P<0.01).

A total of 134 patients had a recorded CA19-9 level, from which 16 outliers were excluded. For the remaining patients, CA19-9 did not correlate with APRI score in patients (m<0.01, r=0.01, P=0.90). Similarly, there was no significant relationship between APRI score and INR among the 148 patients with a recorded INR (m=0.17, r=0.06, P=0.46) (Fig. 2D, 2E).

We also analyzed the association of APRI score with AST and platelet count. As would be expected, there was a strong correlation between AST and APRI (m=0.013, r=0.77, P<0.01) and platelet count and APRI (m=-0.002, r=-0.46, P<0.01) (Fig. 2F, 2G). These findings provide internal confirmation for the validity of the APRI score, given that platelet count and AST are components of the APRI score determination.

Tumor pathology and APRI score

The relationship between APRI score and tumor grade, N stage, T stage, presence of vascular invasion, presence of perineural invasion, tumor size, margin status and margin width were also assessed.

For tumor grade, the median APRI score was 0.36 in patients with grade G1 or G2, and 0.40 in those with G3 or G4, with a 2-sample *t*-test P=0.86, meaning there was no relationship between APRI score and grade (Table 2, Fig. 3A).

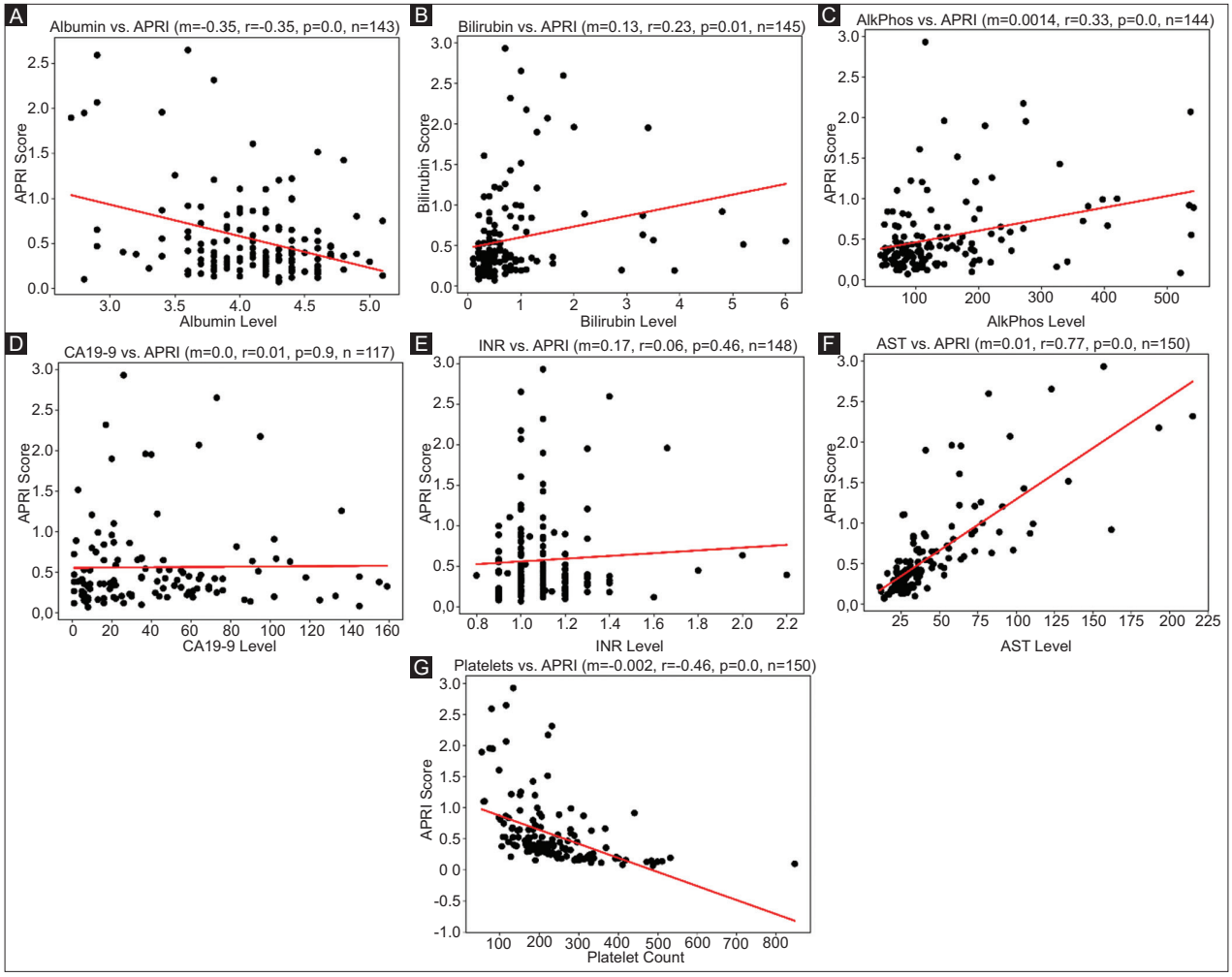

Figure 2 Laboratory values and correlations with APRI score (A) Albumin. (B) Bilirubin. (C) Alkaline phosphatase. (D) CA19-9. (E) INR. (F) AST. (G) Platelet count

APRI, aminotransferase-platelet ratio index; CA, cancer antigen; INR, international normalized ratio; AST, aspartate aminotransferase

Regarding T stage, T3 and T4 had a slightly higher median APRI score of 0.52 when compared to the median APRI score for T1 and T2, which was 0.38 (2-sample *t*-test P=0.01) (Table 2, Fig. 3B). However, only 19 patients in the cohort had either stage T3 or T4, compared to the 122 patients with either stage T1 or T2. Thus, a larger sample size for T3 and T4 stage would be needed to draw more definitive conclusions about the relationship between T stage and APRI score. For N stage, the patient cohort consisted of tumors with either NX, N0 or N1. The median APRI score was 0.36 for NX, 0.38 for N0 and 0.40 for N1 (1-way ANOVA P=0.94) (Table 2, Fig. 3C).

APRI score also had no relationship with vascular invasion or perineural invasion. The median APRI score was 0.44 for patients with vascular invasion and 0.36 for those without (2-sample *t*-test P=0.59) (Table 2, Fig. 3D). Similarly, the median APRI score was 0.47 for patients with perineural invasion and 0.36 for those without (2-sample *t*-test P=0.14) (Table 2, Fig. 3E). There was also no relationship between margin status and APRI score. Of the 152 patients with a margin status of R0, 126 had a median APRI score of 0.37, while the 18 patients with a margin status of R1 had an APRI score of 0.53 (2-sample *t*-test P=0.17). The remaining 8 patients did not have a reported margin status.

Pathological tumor size and margin width were also not related to APRI score. Pathology size showed no significant correlation with APRI score (m=-0.01, r=0.12, and P=0.61; Table 2, Fig. 3F). The same applied to margin width (m=0.01, r=0.12, P=0.16; Table 2, Fig. 3G).

Postsurgical outcomes and APRI score

The postsurgical outcomes analyzed included recurrence and death. For tumor recurrence, the median APRI score was 0.39 for patients with recurrent disease within 5 years and 0.38

Table 2 Tumor pathology and relationship to APRI score

Tumor pathology metric	Mean APRI	Median APRI	95% Confidence interval	Statistical test (2-sample *t*-test or ANOVA)
Grade				
G1+G2 (n=94)	0.51	0.36	0.41-0.60	2 sample *t*-test
G3+G4 (n=47)	0.59	0.40	0.43-0.75	P=0.86
T stage				
T1+T2 (n=122)	0.51	0.38	0.43-0.59	2-sample *t*-test
T3+T4 (n=19)	0.82	0.52	0.49-1.15	P=0.01
N stage				
NX (n=27)	0.54	0.36	0.32-0.75	ANOVA
N0 (n=78)	0.56	0.38	0.44-0.68	P=0.94
N1 (n=37)	0.53	0.40	0.40-0.66	
Vascular invasion				
Yes (n=40)	0.58	0.44	0.44-0.71	2-sample *t*-test
No (n=106)	0.53	0.36	0.43-0.63	P=0.59
Perineural invasion				
Yes (n=30)	0.68	0.47	0.47-0.88	2-sample *t*-test
No (n=89)	0.50	0.36	0.40-0.60	P=0.14
Margin status				
R0 (n=126)	0.52	0.37	0.43-0.60	R0 vs. R1
R1 (n=18)	0.70	0.53	0.42-0.98	2-sample *t*-test
Not specified (n=8)	1.15	1.08	0.68-1.63	P=0.17
5-year recurrence				
Yes (n=73)	0.52	0.39	0.43-0.61	2-sample *t*-test
No (n=68)	0.63	0.38	0.48-0.79	P=0.22
5-year mortality				
Yes (n=54)	0.54	0.39	0.43-0.64	2-sample *t*-test
No (n=92)	0.61	0.39	0.48-0.73	P=0.39

APRI, aminotransferase-platelet ratio index

for those without (2-sample *t*-test P=0.22) (Table 2, Fig. 4A). Among patients with recurrent disease, there was no correlation between the days to recurrence and their APRI score (m<0.01, r=0.05, P=0.67) (Table 2, Fig. 4B).

As regards death, the median APRI score was 0.39 for patients who died within 5 years of surgery and also 0.39 for patients who did not die during that period (2-sample *t*-test P=0.39) (Table 2, Fig. 4C). Among the patients who died, there was no correlation between days to death and APRI score (m<-0.01, r=-0.04, P=0.80) (Table 2, Fig. 4D).

Discussion

Given that one of the most common drivers of cholangiocarcinoma pathogenesis is chronic inflammation of the liver and biliary tree, we hypothesized that a marker of liver fibrosis, such as the APRI score, might be a useful marker for predicting postsurgical outcomes [3]. However, the results of our study illustrate that this is not the case.

In our analysis, we found no relationship between the APRI score and an array of demographic factors, including age, sex, race and tumor type. However, this may have been be due to the lack of diversity in our patient cohort. This is especially true for race, as most of the patients in our study were white.

As regards the underlying fibrosis etiologies, patients with IBD or PSC had a higher APRI score when compared to other etiologies. This is probably because IBD and PSC are inflammatory processes that lead to increased liver fibrosis, and thus a higher APRI score. However, it should be noted that only 26 of the 152 patients we analyzed had IBD or PSC; thus, no meaningful conclusions can be drawn in view of the limited sample size.

We did find a relationship between APRI score and laboratory parameters, including ALT, bilirubin and alkaline phosphatase. However, although these findings may suggest a relationship between APRI score and liver function/inflammation, it does not make the case for its use as a prognostic tool in cholangiocarcinoma patients.

We ascertained that APRI score did not correlate with tumor pathology or postsurgical outcomes. We found no relationship between APRI score and tumor grade, stage, presence of vascular invasion or presence of perineural invasion—all characteristics that have been shown to be related to patient outcomes [2,5,7,8]. Moreover, we found that APRI score was related to neither postsurgical disease recurrence nor mortality. There may be several reasons for this discrepancy. Although chronic inflammation is thought to be a potential underlying

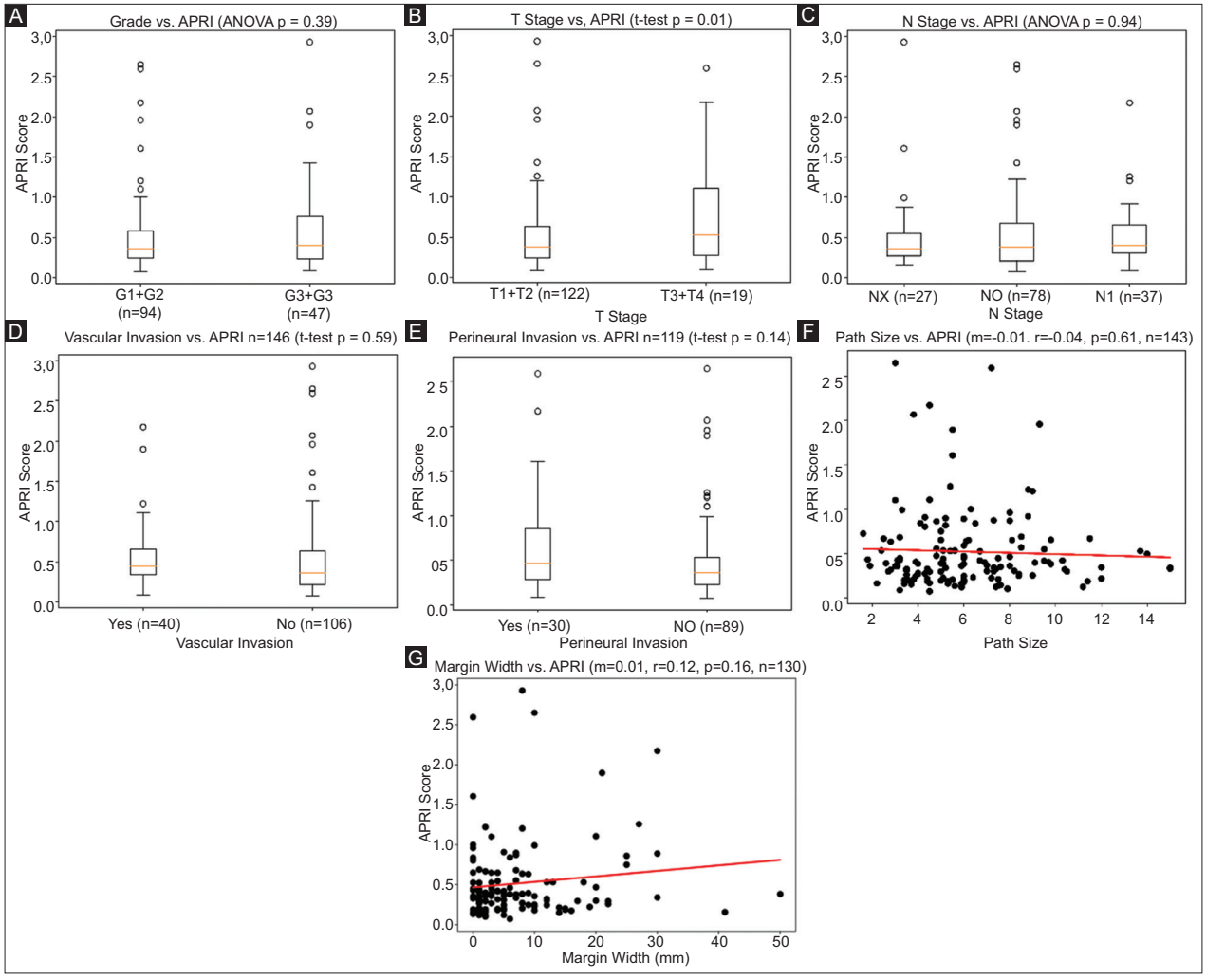

Figure 3 Tumor grade, stage, vascular invasion, and perineural invasion related to APRI score. (A) Grade. (B) T Stage. (C) N Stage. (D) Vascular invasion. (E) Perineural invasion. (F) Pathology size. (G) Margin width
APRI, aminotransferase-platelet ratio index

driver of the development of cholangiocarcinoma, it may not be the sole driver of disease [3,16]. Other causes, such as genetic and epigenetic factors, or aberrant signaling pathways, may play a larger role in disease pathogenesis compared to chronic inflammation [16]. Thus, if chronic inflammation is not the primary driver of disease, then measures like the APRI score would not be effective in predicting disease, as we noted in our study.

However, this understanding of the pathogenesis of cholangiocarcinoma does not rule out the utility of APRI score in other settings, as has been shown in prior studies. On the contrary, the APRI score may still be useful in patients with underlying inflammatory etiologies of cholangiocarcinoma, such as PSC, hepatitis virus and liver cirrhosis, especially given that we found IBD and PSC patients to have higher APRI scores when compared to other groups in our cohort. Moreover, this has also been found to be the case in studies looking at the utility of APRI score in prognosticating HCC [17]. A study conducted by Mai *et al* showed that a combination of APRI and albumin-bilirubin scores was correlated with postsurgical liver failure in patients with HCC related to hepatitis B virus [17]. This would make sense, given that APRI score has shown to be a marker for liver fibrosis: since this type of HCC is largely driven by inflammation, more severe fibrosis should relate to worse outcomes.

Epidemiologic factors also play a role when assessing the utility of APRI score. In Asian countries, such as China and South Korea, inflammatory etiologies of cholangiocarcinoma are more prevalent, because of the higher incidence of liver flukes, parasites and hepatitis B or C virus [16], whereas the prevalence of these inflammatory etiologies is much lower in western countries [16]. Since our study was conducted among patients in the United States, the APRI score did not prove useful as a prognostic tool, as most patients did not have underlying inflammatory etiologies. If the utility of APRI score were to be assessed among patients in high-risk regions where

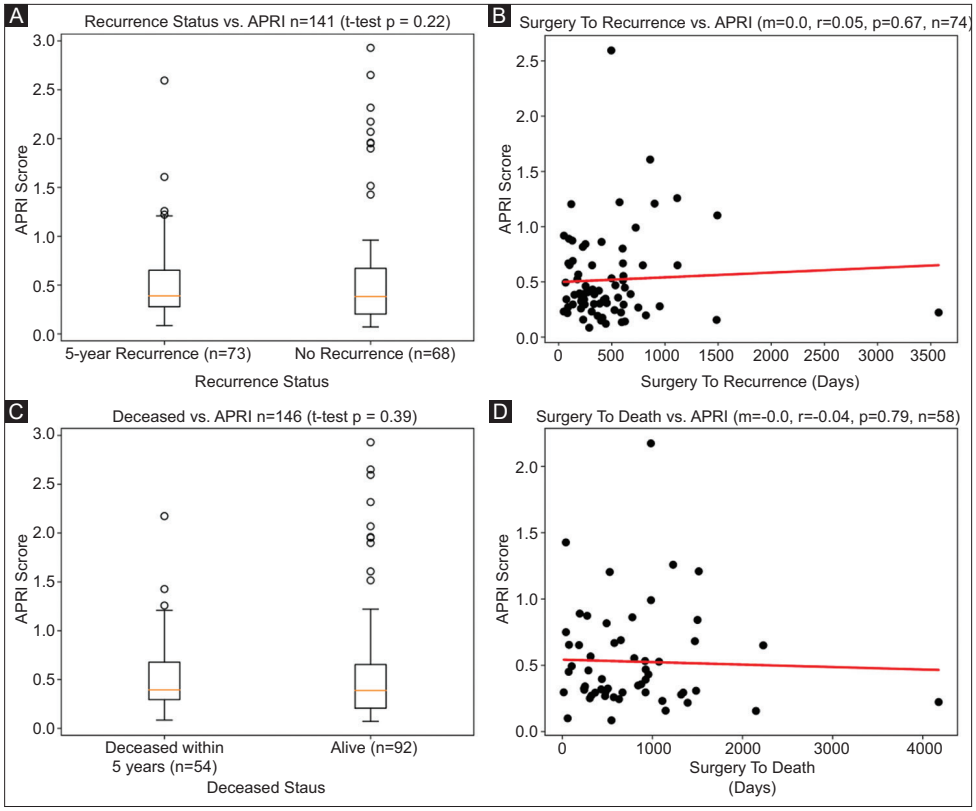

Figure 4 Post-resection tumor recurrence, death, and APRI score. (A) Recurrence status. (B) Days to recurrence. (C) Deceased status. (D) Days to death
APRI, aminotransferase-platelet ratio index

inflammatory etiologies are more common, then it might prove useful.

Our study did have some limitations. This was a retrospective analysis and therefore had the weaknesses related to such studies. It was also a single-center study, so population bias and referral bias would be factors that could influence our results. Moreover, although we were able to discern underlying etiologies of disease in some patients, most patients in our cohort had no identifiable underlying etiology of their cholangiocarcinoma, as the etiology of many cases are multifactorial and not readily discernable. Thus, we were unable to draw meaningful conclusions regarding the relationship of APRI score and outcomes among the different subgroups of etiologies for cholangiocarcinoma in this study. Future studies could look at the utility of APRI score in predicting disease in patients within these subgroups.

In conclusion, we found that the APRI score was not useful to predict postsurgical outcomes in patients with cholangiocarcinoma. These findings were contrary to our initial hypothesis that chronic inflammation could be a key driver of outcomes in cholangiocarcinoma pathogenesis [3]. However, our findings suggest that the pathogenesis of cholangiocarcinoma cannot be explained by chronic inflammation alone. Rather, a combination of causes, including genetic, epigenetic and epidemiological factors, may all influence the pathogenesis of the disease [16].

Summary Box

What is already known:

- Cholangiocarcinoma, a malignancy of the biliary tree epithelium, is largely due to chronic inflammation and fibrosis
- The aminotransferase-platelet ratio index (APRI) score has been shown to be a noninvasive marker for liver fibrosis and cirrhosis
- Although cholangiocarcinoma is driven by inflammation and fibrosis, little is known about the relationship between APRI score and postsurgical outcomes in cholangiocarcinoma patients

What the new findings are:

- There was no marked correlation between APRI score and demographic factors or laboratory parameters in cholangiocarcinoma patients
- APRI score was not correlated with postsurgical pathology features in patients with cholangiocarcinoma
- APRI score is not a useful prognostic tool in predicting postsurgical outcomes (recurrence and mortality) in patient with cholangiocarcinoma

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