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Retrospective Cohort Study

Aspartate transferase-to-platelet ratio index-plus: A new simplified model for predicting the risk of mortality among patients with COVID-19

Madian A *et al.* APRI-plus predicts mortality among COVID-19 patients

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Abstract

BACKGROUND

Coronavirus disease 2019 (COVID-19) has a spectrum of clinical syndromes with serious involvement of the lung and frequent effectation of the liver and hemostatic system. Blood biomarkers are affordable, rapid, objective, and useful in the evaluation and prognostication of COVID-19 patients.

AIM

To investigate the association between aspartate transferase-to-platelet ratio index (APRI) and in-hospital mortality to develop a COVID-19 mortality prediction model.

METHODS

A multicenter cohort study with a retrospective design was conducted. Medical records of all consecutive adult patients admitted to Al-Azhar University Hospital (Assiut, Egypt) and Chest Hospital (Assiut, Egypt) with confirmed COVID-19 from July 1, 2020 to October 1, 2020, were retrieved and analyzed. The patient cohort was classified into the following two categories based on the aspartate transferase-to-platelet ratio index (APRI): (1) COVID-19 presenting with $APRI \leq 0.5$; and (2) COVID-19 presenting with $APRI (> 0.5 \text{ and } \leq 1.5)$. The association between APRI and all-cause in-hospital mortality was analyzed, and the new model was developed through logistic regression analyses.

RESULTS

Of the 353 patients who satisfied the inclusion criteria, 10% were admitted to the intensive care unit ($n = 36$) and 7% died during the hospital stay ($n = 25$). The median age was 40 years and 50.7% were male. On admission, 49% had aspartate transferase-dominant liver injury. On admission, $APRI (> 0.5 \text{ and } \leq 1.5)$ was independently associated with all-cause in-hospital mortality in unadjusted regression analysis and after adjustment for age and sex; after stepwise adjustment for several clinically

relevant confounders, APRI was still significantly associated with all-cause in-hospital mortality. On admission, APRI (> 0.5 and ≤ 1.5) increased the odds of mortality by five-times ($P < 0.006$). From these results, we developed a new predictive model, the APRI-plus, which includes the four predictors of age, aspartate transferase, platelets, and serum ferritin. Performance for mortality was very good, with an area under the receiver operating curve of 0.90.

CONCLUSION

APRI-plus is an accurate and simplified prediction model for mortality among patients with COVID-19 and is associated with in-hospital mortality, independent of other relevant predictors.

Key Words: COVID-19; Aspartate transferase-to-platelet ratio index, APRI; Aspartate transferase; All-cause in-hospital mortality; Serum ferritin; Severe acute respiratory syndrome coronavirus 2; SARS-CoV-2

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Core Tip: Aspartate transferase-to-platelet ratio index-plus (APRI-plus) can be used to predict the severity of coronavirus disease 2019 (COVID-19). The performance of the model for mortality was very good, with an area under the receiver operating curve of 0.90. This new prediction model could help in estimating the risk of mortality and may, therefore, assist in triaging patients. Moreover, our study confirmed that an aspartate transferase-dominant pattern, diabetes mellites, leukocytosis, and increased ferritin levels are associated with fatal outcomes.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has prompted a global race to develop a variety of vaccine platforms. As a result, the first vaccine had been approved for emergency use by approximately 1 year from the beginning of the outbreak^[1]. However, the ongoing limited availability of vaccines, particularly in low-income countries, means that the approach will not be sufficient to achieve global herd immunity. Therefore, effective and efficient allocation of health care resources is essential during the management of COVID-19 patients.

Blood biomarkers are affordable, rapid, readily available, and objective. It has been proven that blood biomarkers are useful in the evaluation and prognostication of COVID-19 patients. Many studies have demonstrated lymphopenia and thrombocytopenia among COVID-19 patients on hospital admission^[2,3]. Furthermore, both lymphopenia^[3,4] and thrombocytopenia^[5] have been shown as predictive of COVID-19 severity and mortality.

Previously, many reports have cited hepatocellular injury with an aspartate aminotransferase (AST)-dominant pattern at hospital admission^[6,7]. In addition, it has been demonstrated that AST elevation at admission is associated with severe COVID-19 disease status and poor outcomes, including intensive care admission, need for mechanical ventilation^[7], and all-cause in-hospital mortality^[6]. It has also been reported that elevated serum ferritin on admission is associated with fatal outcomes in patients with COVID-19^[8,9].

Patients with COVID-19 associated with thrombocytopenia and hepatocellular injury progress to severe disease and poor outcomes. Previously, a simple scoring system, the AST-to-platelet ratio index (APRI), was developed to predict fibrosis in patients with chronic hepatitis C, being based upon routine blood biomarkers, including AST and platelets^[10]. Using this as a premise, we hypothesized that it is possible to build a similar prediction model for patients with COVID-19 using objective, inexpensive, and readily available items.

The aim of the current study was to investigate whether APRI is associated with all-cause in-hospital mortality among patients with COVID-19 and develop a predictive model using objective and readily available factors.

MATERIALS AND METHODS

We conducted a multicenter retrospective cohort study using medical records of all consecutive adult patients admitted to Al-Azhar University Hospital in Assiut, Egypt and Chest Hospital in Assiut, Egypt with confirmed COVID-19 from July 1, 2020 to October 1, 2020, as the Egyptian Ministry of Health had allocated both hospitals for the management of COVID-19 patients. The inclusion criteria for patients were complete medical record data, hospitalized adults of ages ≥ 18 years, and COVID-19 diagnosis established by examination of nasopharyngeal swab specimens using reverse-transcriptase PCR [CerTest Viasure® SARS-CoV-2 Real Time PCR Detection Kit (CerTest; Biotec, Spain)] for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). All laboratory tests were operated in the accredited laboratories at the Clinical Pathology Departments (Microbiology and Immunology units) in Al-Azhar University Hospital and Chest Hospital. The exclusion criteria were pediatric patients of ages < 18 years, patients with known chronic liver disease or newly diagnosed with chronic liver disease at hospital admission, pregnant females, patients with incomplete data, patients with splenomegaly, splenectomy, chemotherapy, or radiotherapy within 1 mo of hospital admission, and patients on immunosuppressive therapy. In addition, we excluded any patient with marked fibrosis, as determined by both APRI and fibrosis-4 (FIB-4) scores (FIB-4 > 2.67 and APRI > 1.5). The institutional review boards approved the study protocol.

Cohort assignment

AST and platelets were measured within 24 h of hospital admission. The normal upper limit for AST was 40 U/L, and the normal upper limit and lower limit for platelets were $350 \times 10^9/L$ and $150 \times 10^9/L$, respectively. APRI was calculated according to the

following equation: $AST\ Level/ULN \div Platelet\ count \times 100$ ^[10]. We categorized our patient cohort into the following two categories based on APRI: (1) COVID-19 presenting with $APRI \leq 0.5$; and (2) COVID-19 presenting with $APRI (> 0.5 \text{ and } \leq 1.5)$.

Covariates

For every participant of our cohort, demographic criteria, including age, sex, and smoking status, comorbidities, including as diabetes mellites (DM), hypertension (HTN), chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), and Deyo-Charlson index, and laboratory biomarkers, including complete blood count, liver enzymes, serum albumin, serum total bilirubin, blood urea, and serum creatinine and creatine kinase, were retrieved and analyzed. The FIB-4 was calculated by the following equation:

$$Age(year) \times AST(U/L) \div Platelets (1000/\mu L) \times \sqrt{ALT(U/L)}^{[11]}.$$

Outcome measurement

The primary outcome of interest was all-cause in-hospital mortality. The vital status of each patient in the study cohort was confirmed from hospital records. Follow-up of outcome was ended on October 15, 2020.

Statistical analysis

We summarized continuous variables as medians and interquartile ranges, and categorical variables were summarized as absolute numbers and percentages. We utilized unadjusted binary logistic regression for analyses of group differences. We performed a stepwise analysis adjusted for age and sex, as well as for relevant confounding factors, to investigate clinical confounders. Spearman's correlation coefficients were utilized to analyze the relationships between variables. All *P* values calculated were two-tailed; values less than 0.05 were considered as indicative of statistical significance. Prediction performance was evaluated by the area under the curve of the receiver operating curve (AUROC). Overall fit of the models was evaluated

by the Hosmer-Lemeshow test and the Bayesian information criterion. We used Stata Software (Stata Statistical Software: Release 16. College Station, TX, United States: Stata Corp LP) for data visualization and analysis.

RESULTS

Out of the 396 patients considered, 353 satisfied the inclusion criteria. Among those, 10% of the study cohort was admitted to the intensive care unit ($n = 36$) and 7% of the study participants succumbed during hospitalization ($n = 25$) (Figure 1). The median age at hospital admission was 40 years [interquartile range (IQR): 28–55 years], and 50.7% were males ($n = 179$) (Table 1). The frequency of thrombocytopenia was 9.6% ($n = 34$). Thrombocytosis was reported among 15% ($n = 54$) of the study cohort. However, there was no statistically significant difference in platelet count between the survivor and death groups (Table 1). On admission, 49% of study participants had AST-dominant liver injury ($n = 174$). Study participants were grouped based on all-cause in-hospital death into survivor and nonsurvivor groups, and their features are provided in Table 1.

Predictors of the primary outcome

Variables associated with in-hospital mortality were first assessed by univariate analysis. Significant variables from univariate analysis ($P < 0.05$) or clinically relevant variables were then utilized for multivariate analysis by forward logistic regression to identify independent predictors associated with in-hospital death among patients with COVID-19.

Regression analysis: (1) Binary logistic regression analysis. Age, Deyo-Charlson index, CKD, DM, and HTN were the clinical predictors significantly associated with hospital mortality. Additionally, the unadjusted regression demonstrated that APRI, serum ferritin, total leukocytic count, serum total bilirubin, serum creatinine, serum AST, and serum albumin levels were significant biochemical markers associated with hospital

death. There was no association between hospital mortality and sex, COPD, hemoglobin, platelets, serum alanine transferase (ALT), C-reactive protein (CRP), creatine kinase, or D-dimer levels (Table 1). (2) Multivariable logistic regression analysis. The APRI ($> 0.5 - \leq 1.5$) at admission was significantly associated with hospital mortality in the unadjusted binary logistic regression analysis and remained a significant predictor of the odds of hospital mortality in model 1 adjusted for age and sex (Table 2). In addition, in model 2, after adjustment for several covariates, APRI was still a significant predictor of hospital mortality and associated with increased odds of hospital mortality by five times ($P < 0.005$) (Table 2).

Variables in the best model (full model) for the prediction of death among patients with COVID-19 included APRI, age, CKD, DM, total leukocytic count, and serum ferritin. The AUROC for the prediction of death among patients with COVID-19 was 0.94 [95% confidence interval (CI): 0.90–0.98]. When the prediction model comprised APRI alone (APRI model), the AUROC for the prediction of mortality was 0.66 (95%CI: 0.56–0.76). The model with APRI, age, and serum ferritin (APRI-plus model) had better accuracy than the APRI model, and the AUROC became 0.90 (95%CI: 0.86–0.95) ($P < 0.0001$) (Figure 2). In addition, the APRI-plus model showed good calibration (Hosmer-Lemeshow χ^2 1.7, $P = 0.97$) and was a better-fitting model than the full model (Bayesian information criterion 148.4) (Table 3).

The adjusted equation for the APRI-plus in patients with COVID-19 was P (in-hospital mortality) = $-0.18 + 0.06 \times (\text{APRI} > 0.5 \text{ and } \leq 1.5) (\text{yes} = 1, \text{no} = 0) + 0.004 \times \text{age} + 0.00013 \times \text{ferritin}$.

Comparison with FIB-4

The AUROC for FIB-4 score was 0.72 (95%CI: 0.61–0.82). Upon comparison of the APRI-plus with FIB-4, the AUROC was significantly higher for APRI-plus, at 0.92 (95%CI: 0.86–0.98) ($P < 0.0001$) (Figure 3).

Association of D-dimer with inflammatory markers

D-dimer was examined as a marker of thrombosis. On admission, platelets, serum ferritin, CRP, total leukocytic count, and AST were correlated with D-dimer ($r = 0.1$; $P < 0.03$, $r = 0.4$; $P < 0.0001$, $r = 0.4$; $P < 0.0001$, $r = 0.1$; $P < 0.01$, and $r = 0.1$; $P < 0.03$, respectively).

Association of APRI components with markers of inflammation

Serum ferritin, CRP, and total leukocytic count were investigated as inflammatory markers. Serum levels of AST were correlated with serum ferritin ($r = 0.2$; $P < 0.0001$), CRP ($r = 0.2$; $P < 0.0001$), and total leukocytic count ($r = 0.1$; $P < 0.007$). Platelets were correlated with serum ferritin ($r = 0.1$; $P = 0.04$), CRP ($r = 0.07$; $P = 0.1$), and total leukocytic count ($r = 0.1$; $P = 0.05$).

DISCUSSION

In the current study, we developed APRI-plus, a new, simple, inexpensive, and objective clinical score that is significantly associated with mortality among patients with COVID-19. APRI (> 0.5 and ≤ 1.5) increased the odds of mortality by five-fold. Since patients with chronic liver disease were excluded from participation in our analysis, this association is likely due to inflammation related to COVID-19 and the direct impact of SARS-Cov-2 on the liver and hemostatic system.

We observed a significant difference in AST between survivors and nonsurvivors at hospital admission. The AST-dominant pattern of hepatocellular injury among patients with COVID-19 has been reported many times in previous studies^[6,7]. Likewise, the levels of serum ferritin were significantly higher among nonsurvivors. Platelets have been reported to be one of the strongest indicators of adverse outcomes and mortality among patients with COVID-19^[23]. However, in our cohort, we did not find any statistically significant difference in platelets between survivors and nonsurvivors. Thus, platelets alone are less ideal in predicting outcomes among patients with COVID-19.

APRI includes AST in the numerator and platelets in the denominator. These criteria make the APRI score a better predictor of COVID-19 outcomes than AST or platelets alone. Regarding its accuracy in predicting mortality among patients with COVID-19, the APRI has an AUROC of 0.66. However, when age and serum ferritin were incorporated in the regression model (APRI-plus model), the performance of the model had an AUROC of 0.90. In contrast, compared with another noninvasive score, FIB-4 (composed of AST, ALT, age, and platelets), we found that the AUROC was significantly lower for FIB-4 (0.72). In line with our findings, the reported AUROC in an earlier study for FIB-4 was 0.79^[11]. Using APRI-plus, it is possible to predict mortality among patients with COVID-19 with good performance.

Liver stiffness among patients with COVID-19 is likely to be multifactorial. Hepatic congestion, hepatocellular injury, and systemic inflammation may all play a role in the development of liver stiffness among patients with COVID-19. It has been reported that COVID-19 is associated with increased pressure within the right ventricle^[12]; thus, this may result in hepatic venous congestion and liver stiffness^[11].

Severe liver injury caused by SARS-CoV-2 Likely results in mitochondrial damage and defective clearance of AST, leading to an AST-dominant pattern. At the onset of severe SARS-CoV-2 infection, severe liver injury is likely associated with extensive inflammation, hepatocyte swelling, and tissue edema, especially among patients with an AST-dominant pattern. Similar to acute viral hepatitis, extensive necroinflammatory activity among patients with COVID-19 increases liver stiffness^[13].

Our cohort revealed that platelet count did not have a significant association with mortality. Interestingly, not all previous studies have found platelet counts to be a predictor of COVID-19 mortality^[14]. Inflammatory mediators associated with SARS-CoV-2 infection may result in the activation of platelets. Activated platelets have two pathways. First, enhanced platelet clearance/sequestration from circulation by the spleen results in thrombocytopenia. Second, consumptive coagulopathy, such as inflammation-mediated endothelial damage/activation in addition to platelet activation, leads to the formation of platelet aggregates through systemic circulation

and/or pulmonary circulation^[15]. Therefore, we can speculate that the early phase of SARS-CoV-2 infection results in the activation of platelets followed by thrombocytopenia. Our results support this speculation, as inflammatory markers (CRP, serum ferritin, and leukocytosis) were correlated with D-dimer. This may suggest that the mechanism and progression of platelet activation rather than platelet number were associated with worse outcomes.

The rising question is why we did not find a significant difference in D-dimer between the survivor and nonsurvivor groups. This could be explained by COVID-19-associated coagulopathy. Coagulation changes associated with COVID-19 have the following three proposed stages: stage 1 presents with raised D-dimer; stage 2 presents with raised D-dimer together with modestly increased prothrombin time/international normalization ratio, activated partial thromboplastin time, and mild thrombocytopenia; and stage 3 presents with critical illness and laboratory markers, directing towards classic disseminated intravascular coagulopathy^[14]. Therefore, our data may be retrieved early during platelet activation and before firing of stage 1 COVID-19-associated coagulopathy.

Limitations of the current study

The retrospective design of the study reflected the association between APRI-plus and risk of mortality among patients with COVID-19 but did not reflect causality. We used APRI at the time of admission for group categorization without knowing follow-up changes. Because of the lack of follow-up, we do not know whether these necroinflammatory changes were self-limiting or progressive. Moreover, we do not know the extent and duration of resolution. We did not evaluate platelet activity, fibrin degradation products, or coagulation profiles. Elastography should be evaluated in different age groups to dissect the impact of age from COVID-19 on liver stiffness. Validation of the APRI-plus is required.

CONCLUSION

The current study showed that, on admission, APRI-plus among patients with COVID-19 has good performance in predicting mortality. A prediction model could help stratify the risk of mortality. This association may be explained by the impact of SARS-CoV-2 infection on the liver and hemostatic system. Further studies are required to investigate this association.

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