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Coronavirus Pandemic

Is it possible to predict persistent acute kidney injury in critically ill patients with COVID-19 infection?

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Abstract

Introduction: Critically ill patients with coronavirus disease 2019 (COVID-19) often face a heightened risk of morbidity and mortality, particularly due to complications such as acute kidney injury (AKI). While the persistent acute kidney injury risk index (PARI) has shown promise in predicting the risk of persistent AKI (pAKI) in non-COVID patients, its effectiveness in critically ill COVID-19 patients remains to be explored. We aimed to evaluate the predictive power of the PARI in identifying pAKI and its prognostic significance in terms of clinical outcomes.

Methodology: This was a single-center retrospective study of patients with COVID-19 admitted at our 36-bed tertiary intensive care unit between April and December 2020.

Results: There were 152 patients who fulfilled our inclusion criteria. Fifty-seven (37.5%) had developed AKI and 16 (10.25%) had developed pAKI. Vasopressor, mechanical ventilation and renal replacement therapy (RRT) requirement, sequential organ failure assessment (SOFA), and PARI were significantly higher in patients who developed pAKI than those who did not. The PARI were significantly higher in patients with short-term mortality compared to survivors. The area under the receiver operating characteristic (ROC) curve (AUC) of the PARI score for predicting pAKI was 0.66 (95% CI: 0.53–0.79), whereas short-term mortality was 0.733 (95% CI, 0.65–0.81).

Conclusions: The PARI score was evaluated as simple, useful, and reliable in predicting pAKI in severe cases with COVID-19; and therefore, pAKI and its related RRT complications can be prevented with protective interventions. Further comprehensive studies are warranted to deepen our understanding of this relationship.

Key words: COVID-19; persistent acute kidney injury; intensive care.

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Introduction

Critically ill patients with acute kidney injury (AKI) face a heightened risk of morbidity and mortality. Between 5.5% and 46% of severely ill coronavirus disease 2019 (COVID-19) patients have been reported to develop AKI, and the risk of mortality was found to be approximately 3 times higher compared to those who have not been infected with COVID-19 [1–3]. At the beginning of the pandemic, the detection of renal damage in autopsy samples of 26 patients who lost their lives due to COVID-19 infection in China, led to the focus on underlying pathologies of renal injury associated with COVID-19 [4]. Dehydration, hypoxemia, pre-existing kidney damage and accompanying comorbidities, and nephrotoxic drug use were suspected as underlying reasons [1,4]. The fact that the mechanism of AKI development in patients with COVID-19 is not clear until now has made it more important to prevent the development of AKI.

There is no successful and reliable treatment for AKI. Therefore, measures before AKI develops are recommended, including avoidance of nephrotoxic medications and stabilizing hemodynamic instability. Persistent AKI (pAKI) for at least three consecutive days has been described as the development of stage 2/3 AKI in the Kidney Disease Improving Global Outcomes (KDIGO) guidelines [5]. AKI and pAKI are important risk factors for in-hospital mortality [2]. Physicians need a simple and reliable scoring system for predicting the development of AKI and pAKI. As far as we know a straightforward and dependable risk scoring system that predicts the risk of pAKI in critically ill patients with COVID-19 has not yet been established. It has been reported that the persistent acute kidney injury risk index (PARI) has the ability to

forecast the likelihood of pAKI in non-COVID-19 patients [6].

Our aim was to demonstrate the effectiveness of PARI scoring in the prediction of pAKI in severely ill COVID-19 patients and its prognostic value in terms of clinical outcomes.

Methodology

Study design

We conducted a single-center retrospective study of patients with COVID-19 infection admitted to a 36-bed tertiary intensive care unit (ICU) of the Gülhane Training and Research Hospital, between April and December 2020 which was the beginning of the pandemic in our country. The study was approved by the Gülhane Ethics Committee (08.04.2021- 2021/171).

Inclusion and exclusion criteria

We included patients who were at least 18 years old and had confirmed severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection. SARS-CoV-2 infection was confirmed by detecting presence of the virus-specific gene in a nasopharyngeal sample through a positive polymerase chain reaction (PCR) test.

The exclusion criteria of our study were: (1) patients with negative COVID-19 PCR test; (2) patients who had already required renal replacement therapy (RRT) before hospitalization in ICU; (3) patients who were hospitalized in ICU for less than 24 hours; and (4) patients with creatinine level ≥ 4 mg/dL.

Data collection

The data were collected from the hospital's records and patient files. The data on following variables were collected: patient demographic characteristics, comorbidities, acute physiology and chronic health evaluation II (APACHE-II) and sequential organ failure assessment (SOFA) scores measured within the first 24 hours of admission to the ICU, history of nephrotoxic drug use, daily serum creatinine level and urine output volume in the first week of ICU stay, laboratory values [total bilirubin, platelet, glomerular filtration rate (GFR) level], necessity for mechanical ventilation (MV), vasopressors/inotropes use and RRT during ICU stay, length of stay (LOS) in ICU, and mortality.

Definitions and calculations

AKI was defined according to the KDIGO criteria by considering both serum creatinine and urine output. Persistent AKI was described as the development of stage 2/3 AKI according to the KDIGO guidelines for at least three consecutive days [5]. Baseline serum creatinine level was obtained as the most recent serum creatinine level within 8 to 365 days prior to hospital admission.

The PARI score consists of two components [6]: "ΔCr (creatinine change) score", was calculated as the difference between the creatinine values measured at ICU admission and at the 24th hour of hospitalization; "status score" was calculated based on bilirubin value, presence of sepsis, vasopressors/inotropes, and MV requirement. The PARI Score was obtained by multiplying these two scores.

The ΔCr score was assigned based on the value of ΔCr as follows: 10 points for ΔCr ≥ 0.4 mg/dL; 4 points for ΔCr ≥ 0.3mg/dL; 2 points for ΔCr ≥ 0.2mg/dL; and 1 point for ΔCr < 0.2mg/dL.

The "status score", which was the other component of the PARI Score, was obtained by evaluating the status of the patient and was assigned according to the following criteria: 2 points if the bilirubin value ≥ 2 mg/dL; 2 points to those assessed as having sepsis; 4 points for those who needed vasopressors and/or ventilator.

If none of these risk factors are present, the patient's score in this section was recorded as 1. Then, ΔCr score and status score were multiplied to obtain the PARI Score.

Outcomes

The primary outcome of our study was pAKI development within one week of admission to the ICU. Secondary outcomes were the requirement for RRT within the two-week period following admission and mortality.

Statistical analyses

Non-normally distributed variables were described as the median with interquartile ranges (IQR), whereas normally distributed variables were described as the mean ± standard deviation. The Student's t-test was used to compare normally distributed data, while the Mann-Whitney U test was used to compare non-normally distributed data. Categorical variables were compared using the Chi square test. Spearman's or Pearson's correlation test were used to determine the relationship between the two variables. Receiver operating characteristic (ROC) analysis was conducted to assess the sensitivity and reliability of the PARI score in the early detection of pAKI, and the corresponding area under the curve (AUC) was reported. Statistical significance was defined at p value < 0.05 for all the tests conducted.

Table 1. Comparison of demographic, clinical, and laboratory characteristics between persistent acute kidney injury + (pAKI(+)) and persistent acute kidney injury - (pAKI(-)) groups.

Characteristics	pAKI(+) (n = 16)	pAKI(-) (n = 136)	*p* value
Age (years)	68 (50-90)	72 (22-94)	0.753[u]
Gender (Female) n (%)	7 (43.7)	53 (38.9)	0.669 [α2]
Comorbidities n (%)			
Diabetes mellitus	6 (37.5)	55 (40.4)	0.82 [α2]
Hypertension	6 (37.5)	80 (58.8)	0.104 [α2]
Cardiovascular disease	5 (31.2)	47 (34.5)	0.792 [α2]
Cerebrovascular disease	0	18 (13.2)	0.219[β]
Clinical characteristics n(%)			
Vasopressors/inotropes	9 (56.2)	41 (30.1)	**0.036** [α2]
Mechanical ventilation	13 (81.2)	72 (52.9)	**0.031** [α2]
RRT in 14 days	3 (18.7)	6 (4.4)	0.055 [α2]
Mortality in 7 days	3 (18.7)	34 (25)	0.762 [β]
Clinical and laboratory characteristics: med (min–max)			
Baseline creatinine	1.17 (0.78–1.44)	1.01 (0.33–3.76)	0.488[u]
Basaline GFR	63 (37–107)	70 (10–241)	0.372[u]
APACHE-II Score	23.5 (13–45)	20 (5–57)	0.161[u]
Glasgow coma scale	11 (3–15)	14 (3–15)	**0.043**[u]
SOFA score	7 (5–11)	5 (1–14)	**0.001**[u]
PARI score	7 (2–70)	6 (1–70)	**0.028**[u]

APACHE II: acute physiology and chronic health evaluation II; GFR: glomerular filtration rate; pAKI: persistent acute kidney injury; PARI: persistent acute kidney ınjury risk ındex; RRT: renal replacement therapy; SOFA: sequential organ failure assessment. α^2: Chi-squared test; [β]: Fisher's exact test; [u]: Mann-Whitney U test. Statistically significant data are highlighted in bold.

Results

There were 152 patients who fulfilled our inclusion criteria. The mean (± SD) age was 69.3 ± 14.4 years and 93 (61.2%) of them were male. Eighty six (56.6%) patients were hypertensive, 61 (40.1%) diabetic, 52 (34.2%) had cardiovascular disease, and 18 (11.8%) had cerebrovascular disease. The mean (± SD) APACHE-II Score was 21.74 ± 8.7, the mean (± SD) SOFA score was 5.79 ± 2.07, and mean (± SD) PARI score was 11.67 ± 18.89. Eighty five patients (55.9%) required MV and 50 patients (32.9%) required vasopressors/inotropes administration. Fifty seven (37.5%) had developed AKI (stage 1: 36 patients, stage 2: 14 patients, stage 3: 7 patients). Additionally, 16 (10.25%) had developed pAKI. Short term (7 days) all cause mortality was observed in 37 (24.3%) patients. A significant increase in AKI was observed in patients who had short-term mortality (64.9% vs 28.7%, $p < 0.001$). The median (min–max) ICU LOS was 9 (1–56) days. Vasopressors/inotropes use, MV/RRT requirement, SOFA and PARI scores were significantly higher in patients who developed pAKI than those who did not ($p = 0.036$, $p = 0.031$, $p = 0.055$, $p < 0.001$, and $p = 0.028$, respectively). Glasgow coma scale (GCS) was significantly lower in patients with pAKI than those without ($p = 0.043$). Nine (5.92%) patients had required RRT. The PARI scores did not differ significantly between those who required RRT in the first 14 days and those who did not ($p = 0.494$). The comparison of patients in terms of pAKI development is presented in Table 1.

Table 2. Comparison of demographic and baseline characteristics between survival and non-survival groups.

Variables	Non-survival group (n = 37)	Survival group (n = 115)	*p* value
Age (years)	70 (35-91)	72 (22-94)	0.926[u]
Gender (female) n (%)	17 (45.9)	42 (36.5)	0.306 [α2]
Baseline creatinine	1.0 (0.33-3.54)	1.03 (0.6-3.76)	0.807[u]
Basaline GFR	73 (17-241)	70 (10-138)	0.842[u]
Glasgow coma scale	12 (3-15)	14 (3-15)	**0.009**[u]
SOFA score	6 (2-14)	5 (1-12)	0.145[u]
PARI score	7 (2-70)	6 (1-70)	**0.001**[u]
APACHE-II score	24 (8-57)	19 (5-48)	**0.007**[u]
Diabetes mellitus	20 (54.1%)	41 (35.7)	**0.047** [α2]
Hypertension	22 (59%)	64 (55.7%)	0.684 [α2]
Cardiovascular disease	15 (40.5%)	37 (32.2)	0.351[α2]
Cerebrovascular disease	3 (8.1%)	15 (13%)	0.564 [β]
Vasopressor	18 (48.6)	32 (27.8)	**0.019** [α2]
Mechanical ventilation	32 (86.5%)	53 (46.1%)	**< 0.001** [α2]
AKI			
pAKI	3 (8.1%)	13 (11.3)	0.762 [β]

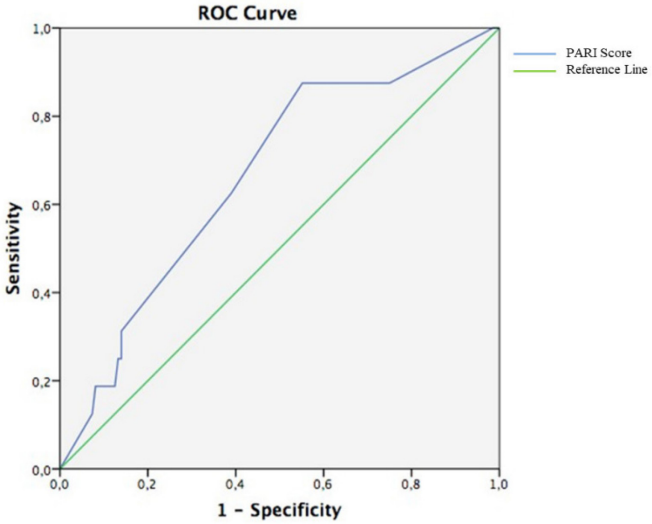
AKI: acute kidney injury; APACHE II: acute physiology and chronic health evaluation II; GFR: glomerular filtration rate; pAKI: persistent acute kidney injury; PARI: persistent acute kidney ınjury risk ındex; SOFA: sequential organ failure assessment; α^2= Chi-squared test, [β]= Fisher's exact test, [u]= Mann-Whitney U test. Statistically significant data are highlighted in bold.

Demographic and baseline characteristics of survival and non-survival groups are listed in Table 2. Vasopressors/MV requirement, PARI score, APACHE-II score, and diabetes mellitus (DM) frequency were significantly higher in the non-survival group, while GCS was significantly lower ($p = 0.019$, $p < 0.001$, $p = 0.001$, $p = 0.007$, $p = 0.047$, and $p = 0.009$, respectively). According to the regression analysis, short-term mortality was associated with PARI Score (OR 1.02, CI 1.001–1.039, $p = 0.043$) and MV requirement (OR 0.165, CI 0.058–0.467, $p = 0.01$). The patients who did not survive had significantly higher PARI Scores compared to the survivors [OR 7.0 CI (2.0–70.0) vs OR 6.0 CI (1.0–70.0); $p = 0.001$]. The survival and non-survival groups showed notable difference regarding the GCS, APACHE-II score, presence of DM, use of vasopressors/inotropes, and mechanical ventilation ($p = 0.009$, $p = 0.007$, $p = 0.047$, $p = 0.019$, and $p < 0.001$ respectively). There was a significant correlation between the PARI score, and the APACHE-2 and SOFA score (Spearman $\rho = 0.298$, $p < 0.001$; Spearman $\rho = 0.313$, $p < 0.001$ respectively). Figure 1 shows that the ROC curves of the PARI score for predicting persistent AKI was 0.66 (95%CI, 0.53–0.79).

Discussion

In our study, we found that the PARI score obtained by evaluating the data during the first 24 hours of ICU stay had considerable sensitivity and specificity in predicting the development of pAKI. We consider that the PARI score, which can be obtained with a very easy calculation at the bedside, will guide the clinician in a reliable way regarding pAKI and short-term mortality.

Figure 1. Receiver operating characteristic (ROC) curve of the persistent acute kidney injury risk index (PARI) score used in prediction of persistent acute kidney injury (pAKI).



In ROC analysis, when the PARI Score threshold value was ≥ 6.5, it predicted pAKI with 62.5% sensitivity and 61% specificity. AUC = 0.66 (95% CI; 0.53-0.79) (p = 0.031).

In our study, it was found that AKI developed in 57 (37.5%) patients. AKI has been reported to occur in 5.5% to 46% patients in severe cases of COVID-19 infection [1–3]. We found the incidence of AKI to be within the range reported in the literature. We evaluated the diagnosis of AKI more precisely by paying attention to urine output because the amount of urine is also a determinant in KDIGO AKI staging. This is one of the interesting aspects of our study compared to other studies in the literature. Several studies have demonstrated a correlation between severe AKI and mortality in individuals with COVID-19 [7,8]. In our study, a significant increase in AKI was observed in patients with short-term mortality.

We found the incidence of pAKI to be 10.25% in severe cases with COVID-19 infection. To the best of our knowledge, no study has so far reported the incidence and mortality rate of pAKI in severe cases with COVID-19. pAKI is an important clinical situation that should be recognized early due to its poor prognosis. A study published by Ozrazgat-Baslanti *et al.* in 2021, retrospectively analyzed a remarkable number of patients admitted to the hospital and found that the one-year mortality in patients who developed pAKI was significantly higher than those who developed rapidly reversed AKI (35% vs 15%) [9].

There are numerous published studies on the occurrence of AKI and the requirement for RRT in cases with COVID-19 infection [10,11]. In a meta-analysis evaluating 51 studies, AKI (12.3%) and requirement for RRT (5.4%) was found to be high in cases with COVID-19 [12]. Despite many studies on AKI and RRT requirement in COVID-19 patients, as far as we know, the association between pAKI and COVID-19 has not yet been evaluated in previous studies. Based on studies in severely ill COVID-19 patients, it is obvious that mortality is affected by pAKI [13,14]. We concluded that the PARI score is not useful in predicting the requirement for RRT in the short term.

In the context of our study, it is imperative to consider how the PARI score encapsulates relevant parameters, such as vasopressor use and mechanical ventilation, both separately detailed above. The incorporation of these components into the PARI score underscores its role as a comprehensive index reflective of the complex clinical scenario observed in critically ill patients with COVID-19 and AKI. This amalgamation of factors within the PARI score

contributes to its predictive ability for pAKI. We acknowledge the importance of explicitly highlighting this relationship to enhance the transparency of our methodology and the interpretation of our findings.

This study has some limitations as it was conducted retrospectively at a single center, which may have introduced biases that could impact the results. Furthermore, the limited number of patients enrolled in the study may also restrict the generalizability of our findings. We acknowledge the importance of contextual application for indices such as Renal Angina Index and PARI. Our primary focus was on evaluating the predictive ability of the PARI score in the specific clinical scenario of critically ill patients with COVID-19 and acute kidney injury. It is important to note that indices may vary in utility across different clinical contexts, and we explicitly state this as another limitation in the manuscript.

Conclusions

The PARI score was evaluated as simple, useful and reliable in predicting pAKI in severe cases with COVID-19, and therefore pAKI and its related RRT complications can be prevented with protective interventions. Further studies are needed to better understand this relation.

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Authors' contributions

Study concept and design: MY, GT, HLY; data collection: MY, SY, HS, ME, ST; data analysis and interpretation: GT, MY; manuscript draft: MY, GT; critical revision of manuscript for important intellectual content: MY, GT, HLY; statistical analysis: HS, GT, MY; supervision: MY, GT, HLY.

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