Original Article

The Association between Acute Cardiac Injury and Outcomes of Hospitalized Patients with COVID-19: Long-Term Follow-up Results from the Sina Hospital COVID-19 Registry, Iran

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Abstract

Background: *The present study aimed to investigate the association between acute cardiac injury (ACI) and outcomes in hospitalized patients with coronavirus disease 2019 (COVID-19) in Iran.*

Methods: *The current cohort study enrolled all consecutive hospitalized patients with COVID-19 (≥ 18 y) who had serum high-sensitivity cardiac troponin-I (hs-cTnT) measurements on admission between March 2020 and March 2021. ACI was determined as hs-cTnT levels exceeding the 99th percentile of normal values. Data on demographics, comorbidities, clinical and laboratory characteristics, and outcomes were collected from Web-based electronic health records.*

Results: *The study population consisted of 1413 hospitalized patients with COVID-19, of whom 319 patients (22.58%) presented with ACI. The patients with ACI had a significantly higher mortality rate than those without ACI (48.28% vs 15.63%; P<0.001) within a mean follow-up of 218.86 days from symptom onset. ACI on admission was independently associated with mortality (HR, 1.44; P=0.018). In multivariable logistic regression, age (OR, 1.034; P<0.001), preexisting cardiac disease (OR, 1.49; P=0.035), preexisting malignancy (OR, 2.01; P=0.030), oxygen saturation reduced to less than 90% (OR, 2.15; P<0.001), leukocytosis (OR, 1.45; P=0.043), lymphopenia (OR, 1.49; P=0.020), reduced estimated glomerular filtration rates (eGFRs) (OR, 0.99; P=0.008), and treatment with intravenous immunoglobulin during hospitalization (OR, 4.03; P=0.006) were independently associated with ACI development.*

Conclusion: *ACI occurrence on admission was associated with long-term mortality in our hospitalized patients with COVID-19. The finding further underscores the significance of evaluating ACI occurrence on admission, particularly in individuals more prone to ACI, including older individuals and those with preexisting comorbidities, reduced oxygen saturation, and increased inflammatory responses.*

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Introduction

Coronavirus disease 2019 (COVID-19) is an emerging disease with a broad spectrum of presentations, ranging from asymptomatic infection to severe illness necessitating ICU hospitalization.[1] While pulmonary damage and associated symptoms are considered prominent features of COVID-19, dysfunction of other organs (eg, the heart) appears to exacerbate the clinical condition and outcomes of this patient population.[2]

Because hospitals worldwide are overwhelmed with patients with COVID-19 and resources are scarce, optimal management and effective resource allocation require early identification and prioritization of patients with poor outcomes according to their baseline predictors.[3] Based on clinical and laboratory data, several risk scores have been developed to identify patients at higher risk.[4] These scores include biomarkers of acute cardiac injury (ACI), such as high-sensitivity cardiac troponin-I (hs-cTnT).[5] ACI, primarily defined as elevated serum hs-cTnT levels, affects 2.3% to 38% of patients with COVID-19, depending on patient characteristics and disease severity,[6, 7] and has been linked to an increased risk of severe disease and death in these patients.[6, 8-11]

The mechanisms by which infection with COVID-19 may lead to ACI could be related to increased inflammatory responses, known as cytokine storms, pneumonia-induced hypoxia, and direct viral invasion of myocardial tissue.[12] Furthermore, in hospitalized individuals with COVID-19, several patient factors, including older age, male sex, and preexisting comorbidities, appear to be linked to a higher risk of severe disease and ACI on admission.[13] A meta-analysis indicated that the association between these factors and ACI varied across different geographical regions. For instance, male sex and preexisting respiratory diseases were independent predictors of ACI in the United States and Europe but not in the Middle East.[14] Future research on this topic should, therefore, extend its scope to incorporate additional populations.

Recent meta-analyses have demonstrated the association between ACI and outcomes in patients with COVID-19. Most of these studies have clearly shown that ACI is independently associated with poor outcomes in patients with COVID-19.[12, 14, 15] Notably, the studies included in these meta-analyses had small sample sizes and short follow-ups and were conducted predominantly in China, the United States, and Italy. The non-uniform characteristics of populations and the disparities in hospital facilities and health-care access across regions warrant more large-sample studies with long-term follow-ups in other countries.[15]

Our previous work showed associations between ACI and preexisting cardiovascular diseases, malignancies, reduced oxygen saturation, leukocytosis, and lymphopenia, which could increase the likelihood of in-hospital mortality by nearly 80%.[16]

In the present extended follow-up study, we sought to investigate the association between ACI and outcomes in hospitalized patients with COVID-19 during a longer follow-up.

Methods

The present retrospective cohort study used data on 1413 patients with COVID-19 hospitalized between March 2020 and March 2021 and registered in the Sina Hospital COVID-19 Registry (SHCo-19R). The SHCo-19R is a dynamic, single-center, hospital-based registry that prospectively gathers data on clinical characteristics, management, and short- and long-term outcomes (Talebpour M, Hadadi A, Oraii A, Ashraf H. Rationale and design of a registry in a referral and educational medical center in Tehran, Iran: Sina Hospital Covid-19 Registry (SHCo-19R). Front Emerg Med 2020;4(2s):e53-e).[17] The study protocol was reviewed and approved by the COVID-19 Research Committee of Sina Hospital and the Ethics Committee of Tehran University of Medical Sciences. All the participants signed written informed consent for participation in the registry.

This study included all consecutive hospitalized patients with the following characteristics: 1) age 18 years and over; 2) COVID-19 diagnosis confirmed by the reverse-transcriptase polymerase chain reaction test of the oropharyngeal or endotracheal samples according to the WHO statement[17] or highly suspicious patients with compatible chest computed tomography scan features;[18, 19] and 3) serum hs-cTnT measurements during the admission.

Necessary data regarding the patients' demographic characteristics; clinical, laboratory, and imaging findings; and treatment patterns were collected from electronic health sheets recorded as a part of the SHCo-19R project. Details pertaining to the methods of clinical and laboratory assessments were reported in the study protocol. Patients with elevated baseline cardiac enzymes underwent at least 2 serial evaluations of serum hs-cTnT and an electrocardiogram to identify probable acute coronary syndromes.

Follow-up was done by phone for the study population concerning any adverse events or poor outcomes until death or study end. The primary outcome was all-cause mortality, and the secondary outcomes consisted of cardiac injury, ICU admission, mechanical ventilation, acute respiratory distress syndrome (ARDS), and acute kidney injury (AKI). ACI was defined based on hs-cTnT levels exceeding the 99th percentile of normal values regardless of electrocardiographic or echocardiographic findings. According to this definition and standards of our laboratory kits, any patient with hs-cTnT above 26 ng/mL for men and 11 ng/mL for women was considered a case of ACI. ARDS and AKI were defined based on definitions by Berlin and Kidney Disease: Improving Global Outcomes, respectively (Kellum JA, Lameire N, Aspelin P, Barsoum RS, Burdmann EA, Goldstein SL, Herzog CA, Joannidis, M, Kribben A, Levey AS, MacLeod AM, Mehta RL, Murray PT, Naicker S, Opal SM, Schaefer F, Schetz M, Uchino S. Kidney disease: Improving global outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. Kidney International Supplements 2012;2:1-138.).[20]

Statistical analysis was conducted with the SPSS software, version 14.0. The normality of distribution was checked using the Shapiro-Wilk test. Scale variables were shown as means±standard deviations or medians (interquartile ranges) and compared using the independent Student *t* or Mann-Whitney *U* test, where appropriate. Nominal variables were shown as frequencies and compared using the Fisher exact or χ^2 test, where appropriate. Kaplan-Meier survival curves of patients with and without ACI were constructed, and the statistical difference between the curves was assessed with the log-rank test. A multivariable Cox regression analysis encompassing all variables with a P value of less than 0.05 in the univariable analysis was conducted to determine the independent association between mortality and ACI and other risk factors and estimate the hazard ratio (HR) and the 95% confidence interval (CI). The proportional-hazards assumption was visually tested by plotting the survival function and its log (-log) against time. A multivariate logistic regression analysis was utilized to find variables independently associated with ACI and estimate the odds ratio (OR) and the 95% CI. Variables significant in the univariable model, except those with high collinearity, were selected and included in the multivariable model. A *P* value of less than 0.05 was considered statistically significant.

Results

Baseline Variables, over a mean follow-up of 218.86 days (±127.013), 1413 hospitalized patients with COVID-19 were enrolled in the final analysis. The baseline variables of the patients, categorized by the presence or absence of ACI, are shown in Table 1 and Figure 1. In brief, the mean age of the patients was 59.35±16.62 years, and 60.4% were men. The most commonly reported clinical presentations were cough (62%), dyspnea (60.2%), fever (54.3%), and myalgia (47.8%) (Figure. 1A). As shown in Figure 1B, hypertension (45.22%), diabetes mellitus (30%), and cardiac disease (23.07%) were the most frequent preexisting comorbidities in the patients. The patients with ACI had a lower oxygen saturation level (P<0.001) and a higher respiratory rate (P=0.001) than those without ACI. Hydroxychloroquine, interferon, lopinavir/ritonavir, and favipiravir were the most regularly administered medications for the patients (Figure. 1C).

Regarding the serum levels of inflammatory markers, the white blood cell count (P<0.001), high-sensitivity C-reactive protein (P<0.001), lactate dehydrogenase (P<0.001), aspartate aminotransferase (P<0.001), and potassium (P=0.003) were significantly higher and lymphocytes (P<0.001) and hemoglobin (P<0.001) were markedly lower in the ACI group than in the non-ACI group. The mean value of eGFR in the whole study population was 62.96±23.96, with the value being lower in the ACI group (P<0.001).

Concerning complications and outcomes, the rates of ICU admission, mechanical ventilation, ARDS, AKI, acute lung injury, multi-organ damage, and mortality were 15.64%, 11.96%, 27.20%, 12.53%, 10.69%, 18.82%, and 23%, respectively, all of which were significantly higher in the ACI group than in the non-ACI group (P<0.001 for all variables) (Figure 1D).

Impact of ACI and Other Variables on Mortality, Figure 2 depicts the subjects' survival curves classified based on the presence or absence of ACI. The mean survival time (95% CI) for patients with and without ACI was 195.913 (176.804-215.023) days and 316.267 (308.858- 323.677) days, respectively (the log-rank test <0.001). The mortality rate was at least 3 times higher in the ACI group than in the non-ACI group (48.28 vs 15.63; P<0.001). The results of univariate Cox regression analyses are presented in Supplementary Table 1. The variables found to be associated with an increased likelihood of mortality (P<0.05) in the univariate analysis, namely age; preexisting diabetes mellitus, hypertension, cardiac disease, malignancy, chronic lung disease, chronic kidney disease, and cerebrovascular events; previous use of angiotensin-converting enzymes, angiotensin receptor blockers, and β-blockers; ICU admission; and the occurrence of ARDS, AKI, acute lung injury, ACI, and multi-organ damage, were considered confounding factors and entered into a multivariate analysis. According to the multivariate Cox regression analyses (Table 2), older age (per 1 year: HR, 1.035; 95% CI, 1.026 to 1.044;

Table 1. Demographic and Baseline Data According to the Presence or Absence of Acute Cardiac Injury

Variable	Total (n=1413)	Cardiac Injury (+) (n=319)	Cardiac Injury (-) (n=1094)	*P*
Age (y)	59.35 (16.62)	67.85 (15.71)	56.87 (16.05)	<0.001
Male (%)	854 (60.4)	188 (58.9)	666 (60.9)	0.532
Systolic blood pressure (mmHg)	126.39 (21.26)	128.23 (26.29)	125.83 (19.43)	0.153
Blood oxygen saturation (%)	89.29 (8.05)	86.31 (9.83)	90.16 (7.23)	<0.001
Respiratory rate (n/min)	20.98 (5.69)	22.25 (6.34)	20.61 (5.43)	0.001
Heart rate (bpm)	91.16 (23.52)	91.16 (19.28)	91.16 (24.66)	0.997
Laboratory Findings				
White blood cell count (10^9/L)*	10.130 (3.78)	8.40 (5.32)	6.70 (3.99)	<0.001
Lymphocytes (10^9/L)	19.02 (10.82)	15.42 (9.79)	20.24 (10.89)	<0.001
Platelets (10^9/L)	220.96 (103.96)	215.13 (111.16)	222.95 (101.37)	0.247
Hemoglobin (g/L)	13.34 (2.21)	12.81 (2.48)	13.52 (2.08)	<0.001
CRP (mg/L)	69.24 (52.11)	79.32 (56.03)	65.77 (50.26)	<0.001
ESR (mm/h)*	97.50 (59.25)	50.50 (58.25)	53.00 (52.00)	0.402
eGFR (ml/min/1.73 m2)	62.96 (23.96)	53.12 (27.57)	66.35 (21.57)	<0.001
Sodium (mmol/L)	136.28 (5.68)	136.63 (7.36)	136.16 (4.97)	0.289
Potassium (mmol/L)	4.37 (0.60)	4.46 (0.66)	4.34 (0.57)	0.003
Alanine aminotransferase (U/L)*	55.50 (86.50)	40.50 (32.25)	39.00 (26.00)	0.065
Aspartate aminotransferase (U/L)	63.33 (68.97)	73.44 (53.14)	59.45 (73.82)	<0.001
Lactate dehydrogenase (U/L)	671.87 (319.98)	777.23 (422.80)	635.13 (265.94)	<0.001
Venous Blood Gas				
pH	7.41 (0.08)	7.39 (0.09)	7.41 (0.83)	0.002
PCO2 (mmHg)*	35.45 (15.05)	37.35 (12.05)	38.65 (10.48)	0.149
HCO3 (mmol/L)	24.50 (5.50)	22.84 (5.68)	24.46 (4.49)	<0.001
Radiographic Lung Involvement				
Unilateral	484 (34.25)	101 (31.66)	383 (35.00)	0.268
Bilateral	929 (65.75)	218 (68.34)	711 (64.99)	

*Non-normally distributed variables
Continuous data are shown as means (standard deviations) or medians (interquartile ranges).
Nominal data are shown as frequencies (percentages).
CRP, C-reactive protein; ESR, Erythrocyte sedimentation rate; eGFR, Estimated glomerular filtration rate; PCO_2, Partial pressure of carbon dioxide; HCO_3, Bicarbonate

P<0.001), preexisting malignancy (HR, 2.414; 95% CI, 1.643 to 3.547; *P*<0.001) and cerebrovascular events (HR, 1.740; 95% CI, 1.165 to 2.599; *P*=0.007), ICU admission (HR, 3.719; 95% CI, 2.676 to 5.170; *P*<0.001), and the occurrence of ARDS (HR, 1.931; 95% CI, 1.364 to 2.734; *P*<0.001), AKI (HR, 2.194; 95% CI, 1.583 to 3.040; *P*<0.001), and ACI (HR, 1.441; 95% CI, 1.064 to 1.952; *P*=0.018) were independently associated with higher mortality in our hospitalized patients with COVID-19. Survival function curves (Figure. 2) and related log (-log) curves (not shown in the article) all followed a similar trend without crossing, indicating a lack of a discernible proportional hazard violation.

Factors Associated with ACI, The 20 variables shown to be significant in the univariate logistic regression analysis (P<0.05) (Supplementary Table 2) were entered into a multivariate model. According to the multivariate logistic regression (Table 3), older age (per 1 year: OR, 1.034; 95% CI, 1.023 to 1.046; *P*<0.001), preexisting cardiac disease (OR, 1.489; 95% CI, 1.028 to 2.158; *P*=0.035) and malignancy (OR, 2.014; 95% CI, 1.070 to 3.792; *P*= 0.030), oxygen saturation levels below 90% (OR, 2.152; 95% CI, 1.593 to 2.906; *P*<0.001), leukocytosis (OR, 1.447; 95% CI, 1.013 to 1.067; *P*=0.043), lymphopenia (OR, 1.493; 95% CI, 1.065 to 2.094; *P*=0.020), eGFR (OR, 0.990; 95% CI, 0.982 to 0.997; *P*=0.008), and treatment with intravenous immunoglobulin during hospitalization (OR, 4.026; 95% CI, 1.490 to 10.881; *P*=0.006) were associated with ACI development.

Figure 1. The images present the frequencies of baseline characteristics, complications, and outcomes.
1A) Demonstrates the frequencies of the most commonly reported clinical manifestations by patients.
1B) Shows the frequencies of the most common preexisting comorbidities among patients.
1C) Illustrates the frequencies of the most commonly administered medications.
1D) Shows the frequencies of complications and outcomes during hospitalization and follow-up.
*Indicates significant differences between the study groups.

Table 2. Multivariate Analysis to Identify Factors Associated With Mortality

	Hazard Ratio	95% Confidence Interval	*P*
Age (per 1-year increase)	1.035	1.026-1.044	<0.001
Diabetes mellitus	1.049	0.827-1.329	0.694
Hypertension	1.097	0.825-1.458	0.526
Cardiac disease*	0.923	0.706-1.208	0.562
Malignancy	2.414	1.643-3.547	<0.001
Chronic lung disease	0.977	0.662-1.441	0.905
Chronic kidney disease	1.158	0.760-1.764	0.495
Cerebrovascular events	1.740	1.165-2.599	0.007
Previous ACEI/ARB use	0.780	0.578-1.053	0.105
Previous β-blocker use	1.017	0.736-1.406	0.918
ICU admission	3.719	2.676-5.170	<0.001
Acute respiratory distress syndrome	1.931	1.364-2.734	<0.001
Acute kidney injury	2.194	1.583-3.040	<0.001
Acute liver injury	1.307	0.956-1.786	0.093
Acute cardiac injury	1.441	1.064-1.952	0.018
Multi-organ damage	0.886	0.552-1.423	0.617

*Includes ischemic heart disease and heart failure
ACEI, Angiotensin-converting enzyme inhibitor; ARB, Angiotensin receptor blocker

Table 3. Multivariate Analysis to Identify Factors Associated With Acute Cardiac Injury

	Odds Ratio	95% Confidence Interval	*P*
Age (per 1-year increase)	1.034	1.023-1.046	<0.001
Hypertension	1.099	0.754-1.600	0.624
Cardiac disease*	1.489	1.028-2.158	0.035
Malignancy	2.014	1.070-3.792	0.030
Chronic kidney disease	1.756	0.933-3.307	0.081
Cerebrovascular events	0.723	0.376-1.392	0.333
Previous statin use	0.959	0.610-1.508	0.856
Previous angiotensin-converting enzyme inhibitor/angiotensin receptor blockers use	0.868	0.565-1.333	0.518
Previous β-blocker use	0.916	0.592-1.417	0.693
Previous Aspirin use	1.316	0.828- 2.093	0.245
Blood oxygen saturation < 90%	2.152	1.593-2.906	<0.001
White blood cell > 10000 × 10^9/L	1.447	1.013-1.067	0.043
Lymphocytes < 1000 × 10^9/L	1.493	1.065-2.094	0.020
Estimated glomerular filtration rate	0.990	0.982-0.997	0.008
High-sensitivity C-reactive protein	1.00	0.997-1.003	0.846
Potassium	1.037	0.812-1.324	0.774
Treatment with hydroxychloroquine	0.753	0.535-1.060	0.104
Treatment with interferon β-1a	0.915	0.631-1.327	0.640
Treatment with remdesivir	1.246	0.757-2.050	0.386
Treatment with intravenous immunoglobulin	4.026	1.490-10.881	0.006

*Included ischemic heart disease and heart failure

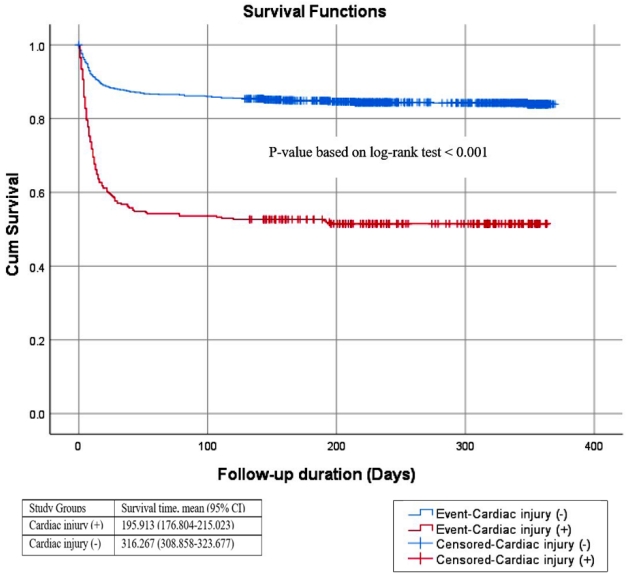

Figure 2. The Kaplan-Meier curve shows survival rates among patients suffering from COVID-19 with and without acute cardiac injury.

Discussion

The present study describes the association between ACI and COVID-19 outcomes with a follow-up of up to 1 year. We believe that our study is one of the most comprehensive studies to date evaluating the above objectives over a long-term follow-up in a single-center cohort of Iranian patients hospitalized for COVID-19.

The main findings of our research are as follows:

1) ACI, defined by high hs-cTnT levels, was a relatively common complication in hospitalized patients with COVID-19 (22.58%).

2) Poor outcomes and complications, including all-cause mortality, multi-organ damage, acute lung injury, AKI, ARDS, mechanical ventilation, and ICU admission, were more prevalent in patients with ACI than those without it.

3) The ACI group had a shorter mean survival time than the non-ACI group.

4) In addition to ACI, variables such as older age, preexisting malignancy and cerebrovascular disease, ICU admission, and the occurrence of ARDS and AKI were independently associated with mortality during follow-up.

5) Older age, a prior history of cardiac disease and malignancy, O_2 saturation reduced to below 90%, leukocytosis, lymphopenia, eGFR on admission, and treatment with intravenous immunoglobulin during hospitalization were independently associated with ACI.

Our literature review showed that the rate of ACI in hospitalized patients with COVID-19 varied from 2.3% in outpatients to up to 38% in hospitalized and severe cases. Apart from the severity of the disease, this discrepancy

in incidence rate may also be partially related to different population characteristics or various definitions of ACI.[6, 7] These studies consistently found a high mortality rate and low survival time in patients with ACI compared with those without ACI. A meta-analysis of 16 cohort studies involving 2224 hospitalized patients with COVID-19 by Zou et al[14] estimated a pooled incidence rate of 24.4% for ACI and found that the rate of all-cause mortality was nearly 5-fold higher in hospitalized patients with ACI than those without it. Our previously published work found that 29.8% of hospitalized patients with COVID-19 had ACI. Further, almost 40% of the ACI group died, a rate 3 times that in the non-ACI group.[16] It should, however, be noted that most of the included studies in the abovementioned meta-analysis and our previously published research had low sample sizes and short-term follow-ups.[14, 16] In the present long-term follow-up study, ACI occurred in more than one-fifth of cases (22.58%), similar to but slightly lower than the rates reported in studies with short-term follow-ups. Moreover, in accordance with previous studies, our patients with ACI showed an elevated mortality rate since nearly half of them died from COVID-19 infection, while this rate was only 15.63% in our patients without ACI.

Current evidence suggests that older age and preexisting comorbidities place patients with COVID-19 have a higher risk of death because of their older age and preexisting comorbidities.[21, 22] These factors also have a significant impact on the development of ACI, so there may be a confounding effect in this context. A meta-regression analysis suggested that ACI was independently associated with increased odds of mortality, and this association did not change with mediating factors.[3] Our previous study confirmed these findings in Iranian patients and specifically found that, in addition to ACI, older age, preexisting malignancy, and ARDS were independently associated with an increased risk of in-hospital mortality. In the current study, we found independent prognostic value for ACI and variables such as age, preexisting malignant disease and cerebrovascular disease, ICU admission, and the occurrence of AKI and ARDS, after accounting for the potential confounders in a multivariate regression model. The prognostic significance of age, preexisting malignancy, ARDS, and ACI was consistent with our previous work, showing an association between these factors and short- and long-term mortality rates. The preexistence of other comorbidities, such as hypertension, diabetes mellitus, cardiovascular diseases, and chronic kidney disease, has been shown to increase the risk of mortality in some studies.[21-23] In the present study, however, their association was not statistically significant.

There is some evidence that ACI is more common in patients suffering from COVID-19 with severe illness, older age, and comorbidities.[8, 21, 24] Inflammatory responses are seen more frequently in patients with preexisting comorbidities and severe disease.[21, 25] Our study, in concordance with previous evidence, found that older patients with preexisting cardiac disease, hypertension, malignancy, cerebrovascular disease, and chronic kidney disease and those with severe disease characterized by reduced O_2 saturation, increased inflammatory markers, or ICU admission might be more susceptible to COVID-19–induced ACI as these factors were significantly more prevalent in the ACI group than the non-ACI group. Still, among these factors, only older age, preexisting cardiac disease or malignancy, O_2 saturation reduced to below 90%, leukocytosis, and lymphopenia were independently linked to increased odds of ACI development. While it is crucial to determine whether the post-infection increased inflammatory status is a cause or consequence of ACI, it is evidently an indicator of severe disease.[21]

AKI, characterized by reduced eGFR at admission, might serve as a marker of severe disease and death in admitted patients with COVID-19.[26] As mentioned above, the present study, chiming with previous evidence, showed an independent association between AKI and mortality. Our results also indicated that reduced eGFR at admission might be independently associated with ACI development in hospitalized patients with COVID-19. Despite the uncertainty regarding the exact mechanism of the association between kidney involvement and poor outcomes in patients with COVID-19, some assumptions have been reported previously. A plausible assumption is that increased systemic inflammatory responses, called “a cytokine storm”, are preceding factors for multiple organ damage, including ARDS, ACI, and AKI. As patients enter the hyperinflammatory response phase, renal function gradually declines before other injuries, such as severe respiratory failure and ACI.[27-29] Accordingly, it should come as no surprise that impaired renal function is associated with other injuries, although further research must clarify the exact mechanism behind this association.

The present study also found that patients who received intravenous immunoglobulin were nearly 4 times more likely to develop ACI. Some studies have reported the therapeutic effects of high-dose intravenous immunoglobulin through the modulation of the immune system as a therapeutic choice for severe cases of COVID-19. On the other hand, intravenous immunoglobulin may increase blood viscosity and induce a hypercoagulative state, ultimately resulting in an increased risk of cardiac injury.[30, 31] However, there is no report regarding ACI development in the context of COVID-19, and the present study is the first to address this issue.

The salient strengths of our research are its comprehensive sample size and long-term follow-up, enabling us to provide new data regarding the association between different variables and poor outcomes in patients

with COVID-19 after discharge. Be that as it may, our study has some noteworthy limitations. Firstly, we derived our data from a single-center registry, and further multicenter studies should determine whether the results could be applied to other regions. Secondly, we had no data on some specific methods of cardiovascular evaluation, such as echocardiography, electrocardiography, and Holter monitoring. Thirdly, considering that we based our research on a cohort registry, there may be potential biases throughout the study, such as information and selection biases, threatening the internal and external validity of the results.

Conclusion

Overall, ACI was present in 22.58% of our hospitalized patients with COVID-19 and was associated with long-term mortality. This finding underscores the importance of evaluating the occurrence of ACI in hospitalized patients with COVID-19, particularly in patients who are more susceptible to developing ACI, including older individuals and patients with preexisting comorbidities, reduced oxygen saturation, and increased inflammatory responses. Given the predictive value of ACI, determination of hs-cTnT should be considered for risk stratification of hospitalized patients to improve optimal treatment and effective resource allocation.

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Supplementary Material

Table 1. Univariate Cox Proportional Hazards Model for Long-Term Mortality in Hospitalized Patients with COVID-19*

	Hazard Ratio	95% Confidence Interval	P
Age (per 1-year increase)	1.048	1.040-1.056	<0.001
Male	1.090	0.870-1.364	0.454
Diabetes mellitus	1.459	1.165-1.826	0.001
Hypertension	1.896	1.520-2.365	<0.001
Cardiovascular diseases	1.627	1.288-2.055	<0.001
Malignancy	2.988	2.094-4.263	<0.001
Chronic lung disease	1.521	1.045-2.215	0.029
Chronic kidney disease	1.937	1.306-2.872	0.001
Cerebrovascular events	2.736	1.889-3.963	<0.001
Previous statin use	1.146	0.854-1.538	0.364
Previous ACEI/ARB use	1.405	1.098-1.798	0.007
Previous β-blocker use	1.525	1.144-2.035	0.004
Previous CCB use	1.341	0.904-1.988	0.145
Previous aspirin use	1.234	0.931-1.637	0.143
Previous corticosteroid use	0.635	0.327-1.232	0.179
ICU admission	9.035	7.232-11.288	<0.001
ARDS	5.117	4.099-6.389	<0.001
Acute kidney injury	6.299	5.018-7.908	<0.001
Acute liver injury	2.251	1.703-2.974	<0.001
Acute cardiac injury	3.890	3.126-4.840	<0.001
Multi-organ damage	7.107	5.701-8.860	<0.001

*Cardiovascular diseases include hypertension, coronary heart disease, and congestive heart failure.
ACEI, Angiotensin-converting enzyme inhibitor; ARB, Angiotensin receptor blocker; CCB, Calcium channel blocker; ARDS, Acute respiratory distress syndrome

Supplementary Material

Table 2. Univariate Logistic Regression Analysis of the Predictors of Cardiac Injury in Hospitalized Patients with COVID-19

	Odds Ratio	95% Confidence Interval	P
Age (per 1-year increase)	1.046	1.037-1.055	<0.001
Female	1.084	0.841-1.398	0.532
Diabetes mellitus	1.192	0.912-1.558	0.198
Hypertension	2.152	1.669-2.775	<0.001
Cardiovascular diseases*	2.314	1.760-3.042	<0.001
Malignancy	1.996	1.179-3.379	0.010
Chronic lung disease	1.228	0.757-1.990	0.406
Chronic kidney disease	2.635	1.606-4.324	<0.001
Cerebrovascular events	1.855	1.090-3.157	0.023
Previous statin use	1.702	1.231-2.354	0.001
Previous ACEI/ARB use	1.918	1.445-2.545	<0.001
Previous β-blocker use	1.609	1.136-2.277	0.007
Previous CCB use	1.488	0.932-2.377	0.096
Previous Aspirin use	2.028	1.484-2.772	<0.001
Previous corticosteroid use	0.946	0.505-1.772	0.863
SBP	1.005	0.999-1.011	0.095
Heart rate	1.000	0.994-1.006	0.997
Blood oxygen saturation <90%	2.556	1.977-3.304	<0.001
Leukocytosis	2.588	1.931-3.470	<0.001
Lymphopenia	2.785	2.106-3.684	<0.001
eGFR	0.975	0.970-0.981	<0.001
C-reactive protein	1.005	1.002-1.007	<0.001
Erythrocyte sedimentation rate	1.002	0.998-1.006	0.304
Sodium	1.015	0.992-1.038	0.202
Potassium	1.397	1.134-1.720	0.002
Hydroxychloroquine	0.666	0.518-0.856	0.002
Azithromycin	1.347	0.888-2.043	0.161
Lopinavir/Ritonavir	1.008	0.779-1.303	0.954
Atazanavir	0.969	0.666-1.411	0.870
Interferon	1.495	1.143-1.956	0.003
Remdesivir	1.647	1.098-2.472	0.016
Methylprednisolone	0.994	0.594-1.662	0.981
Dexamethasone	1.271	0.984-1.641	0.067
Favipiravir	1.008	0.683-1.488	0.968
IVIG	3.015	1.380-6.587	0.006

*Cardiovascular diseases include hypertension, coronary heart disease, and congestive heart failure.

ACEI, Angiotensin-converting enzyme inhibitor; ARB, Angiotensin receptor blocker; CCB, Calcium channel blocker; SBP, Systolic blood pressure; IVIG, Intravenous immunoglobulin; eGFR, Estimated glomerular filtration rate