Different incidences of acute kidney injury (AKI) and outcomes in COVID-19 patients with and without non-azithromycin antibiotics: A retrospective study

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Abstract
In late December 2019, an outbreak of a novel coronavirus which caused coronavirus disease 2019 (COVID-19) was initiated. Acute kidney injury (AKI) was associated with higher severity and mortality of COVID-19. We aimed to evaluate the effects of comorbidities and medications in addition to determining the association between AKI, antibiotics against coinfections (AAC) and outcomes of patients. We conducted a retrospective study on adult patients hospitalized with COVID-19 in a tertiary center. Our primary outcomes were the incidence rate of AKI based on comorbidities and medications. The secondary outcome was to determine mortality, intensive care unit (ICU) admission, and prolonged hospitalization by AKI and AAC. Univariable and multivariable logistic regression method was used to explore predictive effects of AKI and AAC on outcomes. Out of 854 included participants, 118 patients developed AKI in whom, 57 used AAC and 61 did not. Hypertension and diabetes were the most common comorbidities in patients developed AKI. AAC, lopinavir/ritonavir, ribavirin, angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers, and corticosteroids had significant higher rate of administration in patients developed AKI. AAC were associated with higher deaths (odds ratio [OR] = 5.13; 95% confidence interval (CI): 3–8.78) and ICU admission (OR = 5.87; 95%CI: 2.81–12.27), while AKI had higher OR for prolonged hospitalization (3.37; 95%CI: 1.76–6.45). Both AKI and AAC are associated with poor prognosis of COVID-19. Defining strict criteria regarding indications and types of antibiotics would help overcoming concomitant infections and minimizing related adverse events.

KEYWORDS
2019-nCoV, acute kidney injury, acute renal failure, antibiotics, COVID-19, medications, outcomes, SARS-CoV-2
1 | INTRODUCTION

In late December 2019, a cluster of acute pneumonia of unknown etiology emerged in Wuhan City, Hubei Province, China. On January 12, 2020, the World Health Organization (WHO) stated that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), belonging to the β-coronavirus genus, caused a disease which further called coronavirus disease 2019 (COVID-19). The disease is spreading rapidly across the world and on March 11, 2020, WHO declared it as a global pandemic. As of March 16, 2021, above 120 million confirmed cases of COVID-19 and almost 2.6 million related-deaths have been reported worldwide.

COVID-19 as a multisystem disorder impacting various organs like hematological, renal, neurological, respiratory, and cardiovascular systems. Renal system has been found as one of the severely affected systems. Observational studies showed that the incidence rate of AKI in patients with COVID-19 was 3%–11%. Furthermore, it was reported that the rates of AKI increased significantly by 14.5%–50% in patients with COVID-19 admitted to intensive care units (ICUs). Elderly patients, especially those with comorbidities such as chronic kidney disease (CKD), coronary heart disease, hypertension, diabetes, or obesity are more likely to progress into severe conditions after affecting by SARS-CoV-2. Recently, AKI was described as an independent risk factor in mortality of patients with COVID-19.

In a recent study, there was a higher mortality rate among patients diagnosed with COVID-19 who received antibiotics like cefepime, ceftriaxone, vancomycin, and azithromycin compared with those who did not. In contrast, findings of another study showed no significant differences in mortality among those with COVID-19 who did or did not receive antimicrobial treatments. As a result, the effects of antibiotics used for superimposed bacterial infections and AKI on the outcomes of patients with COVID-19 still has not been described clearly. In this article, we prepared the incidence of AKI in patients with COVID-19 and determined the relationship between prescribed medications and pre-existing diseases with incidence of AKI in patients affected with SARS-CoV-2. Also, we evaluated the risk of AKI and antibiotics for bacterial coinfections on outcomes and prognosis of COVID-19.

2 | METHODS

2.1 | Study design and participants

We conducted a retrospective, single-center study on adult patients with COVID-19 admitted to Baharloo Hospital in Tehran, Iran, from February 22 to April 19, 2020. The inclusion criteria were: (1) age of at least 18 years old and (2) confirmed diagnosis of COVID-19 based on clinical presentations, radiographic features, or a positive real-time reverse transcription-polymerase chain reaction (rRT-PCR). Clinical presentations consisted of fever, cough, dyspnea, myalgia and fatigue, hyposmia or anosmia, or ageusia or hypogeusia. Radiographic features included multifocal bilateral or unilateral infiltration in chest radiograph or ground-glass opacity (GGO) of lung computed tomography (CT) scan. The exclusion criteria were: (1) underlying immunodeficiency diseases, human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS), or active cancer and (2) incomplete data on medical records. A Danish cohort study of incident patients with cancer showed that 1-year and 5-year risk for AKI development are 17.5% and 27.0%, respectively. The results have been confirmed by different studies. Moreover, due to volume depletion, septicemia, nephrotoxic medications, and antiretroviral medications, HIV-infected patients are more at risk of AKI development. As a result, we did not include these two known interfering factors in our study.

The study was approved by Tehran University of Medical Sciences. The study was explained to patients and written informed consents were obtained.

2.2 | Measurements and data collection

Demographic and radiologic characteristics in addition to data on received treatments, underlying diseases, and renal outcomes were obtained from their electronic medical records.

2.3 | Definitions

AKI was identified according to the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 clinical practice guideline. According to KDIGO 2012, it was defined as any of the followings:

- Increasing in serum creatinine (Scr) to more than or equal to 0.3 mg/dL within 48 h; or
- Increasing in Scr to more than or equal to 1.5 times compared with baseline, which is known or presumed to have occurred within the prior 7 days.

Antibiotics, including linezolid, vancomycin, carbapenem, piperacillin/tazobactam (Tazocin), and cephalosporin were considered as antibiotics used for superimposed bacterial infections which we called them antibiotics against coinfections (AAC). Scr values at admission were used as a baseline Scr level. Prolonged hospitalization was defined as duration higher than median. Definition of other terms is available in Table 1.

2.4 | Statistical analysis

Continuous and categorical variables were expressed as median (± standard deviation (SD)) and percentages, respectively. Independent sample t-test and χ² test were used for continuous and categorical variables, respectively.

We utilized univariable and multivariable logistic regression on variables to determine predictive effects of AKI and AAC on outcomes, including death, ICU admission, and prolonged hospitalization. Variables
with \( p < 0.05 \) and missing data less than 30% in univariable analysis were included in multivariable analysis. Age, sex, baseline creatinine, hypertension, lopinavir/ritonavir (Kaletra), ribavirin, favipiravir, angiotensin II receptor blockers (ARBs), and angiotensin-converting enzyme inhibitors (ACEIs) were finally included in multivariable analysis. The results were represented as odds ratios (ORs), 95% confidence intervals (CIs), and \( p \) value.

To determine survival rates by AKI and AAC, Kaplan–Meier survival method was used by the log-rank. The level of significance for \( p \) value was considered 0.05. All analyses were performed by using IBM SPSS version 24.0 software (IBM Corp.).

### TABLE 1 Definition of terms used in the study

| Term       | Definition                                                                 | Reference                |
|------------|---------------------------------------------------------------------------|--------------------------|
| BMI        | “A person’s weight in kilograms divided by the square of height in meters” | Prevention CDC\(^{30}\)  |
| Heart failure | “A complex clinical syndrome in which abnormal heart function results in, or increases the subsequent risk of, clinical symptoms and signs of reduced cardiac output and/or pulmonary or systemic congestion at rest or with stress” | Ezekowitz et al.\(^{31}\) |
| Hypertension | “A person’s systolic blood pressure (SBP) in the office or clinic is \( \geq 140 \) mmHg and/or their diastolic blood pressure (DBP) is \( \geq 90 \) mmHg following repeated examination” | Unger et al.\(^{32}\) |
| Diabetes   | “A chronic, metabolic disease characterized by elevated levels of blood glucose (or blood sugar)” | WHO\(^{33}\) |

Abbreviation: BMI, body mass index.

### 3 | RESULTS

#### 3.1 Baseline characteristics

A total of 854 patients (55.3% were male) with a mean age of 55.66 (SD = 17.63) years were enrolled in the study (Figure 1). Hypertension (30.4%) and diabetes (26.5%) were the most common comorbidities among eligible participants, while heart failures (15.9%) and chronic obstructive pulmonary disease (COPD)/asthma (5.4%) had the lowest prevalence among the patients (Table 2). In the group of 243 patients administered AAC, the

![FIGURE 1 Flow diagram of study selection and outcomes.](image-url)
mean age (59.36 years), first creatinine (1.38 mg/dL), and duration of hospitalization (9.44 days) were significantly higher in comparison with the group without AAC ($p < 0.0001$). Also, there was a significant sex difference ($p < 0.0001$) between the two groups with higher percent of men using AAC (65% vs. 51.4%) and greater percent of women in the group without AAC (48.6% vs. 35%). However, mean body mass index (BMI) between the groups was not significant ($p = 0.34$) (Table 2).

### TABLE 2 Clinical characteristics of patients included in the study based on antibiotics against coinfections (AAC)

| Variables                        | All patients (N = 854) | Without AAC (n = 611) | With AAC (n = 243) | $p$ value |
|----------------------------------|------------------------|-----------------------|--------------------|-----------|
| Age, mean years ± SD             | 55.66 ± 17.63          | 54.18 ± 16.94         | 59.36 ± 18.81      | $< 0.0001$|
| Mean BMI, mean kg/m² ± SD        | 27.14 ± 4.66           | 27.28 ± 4.94          | 26.85 ± 4.05       | 0.339     |
| First creatinine, mean mg/dL ± SD| 1.21 ± 0.71            | 1.14 ± 0.57           | 1.38 ± 0.95        | $< 0.0001$|
| Hospital stay, mean day ± SD     | 7.18 ± 7.12            | 6.29 ± 5.90           | 9.44 ± 9.14        | $< 0.0001$|

| Gender                           |                        |                       |                    |           |
|----------------------------------|------------------------|-----------------------|--------------------|-----------|
| Women                            | 382 (44.7)             | 297 (48.6)            | 85 (35)            | $< 0.0001$|
| Men                              | 472 (55.3)             | 314 (51.4)            | 158 (65)           |           |

| Comorbidities                    |                        |                       |                    |           |
|----------------------------------|------------------------|-----------------------|--------------------|-----------|
| Heart failure                    | 136 (15.9)             | 84 (13.7)             | 52 (21.4)          | 0.006     |
| Hypertension                     | 260 (30.4)             | 162 (26.5)            | 98 (40.3)          | $< 0.0001$|
| Diabetes                         | 226 (26.5)             | 145 (23.7)            | 81 (33.3)          | 0.004     |
| COPD/asthma                      | 46 (5.4)               | 22 (3.6)              | 24 (9.9)           | $< 0.0001$|
| Smoking or drug abuse            | 95 (11.1)              | 56 (9.2)              | 39 (16)            | 0.004     |
| AKI incidence (%)                | 118 (13.8)             | 61 (10)               | 57 (23.5)          | $< 0.0001$|

Note: The definition of AKI is based on Kidney Disease: Improving Global Outcomes (KDIGO) 2012 clinical practice guideline.

Abbreviations: AKI, acute kidney injury; AAC, antibiotics against coinfections; BMI, body mass index; COPD, chronic obstructive pulmonary disease; SD, standard deviation.

### TABLE 3 Clinical characteristics of patients included in the study based on antibiotics against coinfections (AAC) and incidence of AKI

| Variables                        | With AAC (n = 243) | Without AAC (n = 611) | $p$ value |
|----------------------------------|--------------------|-----------------------|-----------|
| Age, years ± SD                  | 58.29 ± 19.03      | 62.87 ± 17.79         | 0.107     |
| Mean BMI, kg/m² ± SD             | 26.77 ± 3.66       | 27.06 ± 4.95          | 0.679     |
| First creatinine, mg/dL ± SD     | 1.30 ± 0.95        | 1.64 ± 0.90           | 0.017     |
| Hospital stay, day ± SD          | 8.61 ± 9.47        | 12.15 ± 7.44          | 0.010     |

| Gender                           |                       |                       |           |
|----------------------------------|------------------------|-----------------------|-----------|
| Women                            | 70 (37.6)              | 15 (26.3)             | 277 (50.4)| 20 (32.8) |
| Men                              | 116 (62.4)             | 42 (73.7)             | 273 (49.6)| 41 (67.2) |

| Comorbidities                    |                       |                       |           |
|----------------------------------|------------------------|-----------------------|-----------|
| Heart failure                    | 44 (23.7)              | 8 (14)                | 0.121     |
| Hypertension                     | 71 (38.2)              | 27 (47.4)             | 0.216     |
| Diabetes                         | 58 (31.2)              | 23 (40.4)             | 0.199     |
| COPD/asthma                      | 19 (10.2)              | 5 (8.8)               | 0.749     |
| Smoking or drug abuse            | 26 (14)                | 13 (22.8)             | 0.112     |

Note: The definition of AKI is based on Kidney Disease: Improving Global Outcomes (KDIGO) 2012 clinical practice guideline.

Abbreviations: AKI, acute kidney injury; AAC, antibiotics against coinfections; BMI, body mass index; COPD, chronic obstructive pulmonary disease; SD, standard deviation.
3.2 | Characteristics and incidence of AKI

AKI was developed in 57 (23.46%) and 61 (9.98%) patients in groups with and without AAC, respectively (Figure 1). In the group using AAC, patients who developed AKI had significantly higher values for their first creatinine ($p = 0.02$) and duration of hospital stay ($p = 0.01$). Moreover, patients with AKI in non-AAC group had longer duration of hospitalization ($p < 0.0001$), greater baseline serum creatinine values ($p < 0.0001$), and were older ($p = 0.002$) (Table 3).

3.3 | Comorbidities

All evaluated comorbidities, including heart failures, hypertension, diabetes, COPD/asthma, and smoking or drug abuse had significantly greater rate among patients treated with AAC (Table 1). The incidence of AKI in patients who did not use AAC and had hypertension was significantly higher ($p = 0.007$) (Table 3).

3.4 | Medications

Among 854 patients, 28.5% used at least one antibiotics for prevention from bacterial coinfections. Linezolid and vancomycin were the most and the least common AAC in included participants (13% vs. 1.9%). Diphenhydramine and azithromycin which were prescribed in 60.5% and 52.8% of all participants were the most prescribed medications. Apparently, incidence of AKI was significantly higher in patients who had received AAC such as linezolid ($p < 0.0001$), vancomycin ($p < 0.0001$), carbapenem ($p < 0.0001$), cephalexin ($p < 0.0001$), and piperacillin/tazobactam ($p = 0.028$). Among other prescribed medications, patients who used lopinavir/ritonavir (Kaletra) ($p < 0.0001$), ribavirin ($p = 0.001$), ACEIs and ARBs ($p = 0.013$), and corticosteroids ($p = 0.013$) significantly more developed AKI, while favipiravir ($p = 0.008$) had a significant higher rate in non-AKI patients (Table 4).

3.5 | Outcomes

Rates of prolonged hospitalization, ICU admission, and mortality among all of the participants were 54.3%, 21.4%, and 13.9%, respectively. AAC and AKI were significantly associated with severity and deaths ($p < 0.0001$) (Table 5). Obviously, both development of AKI and using AAC were associated with poor prognosis compared with patients who did not use AAC and did not develop AKI (Table S1). Results of multivariable logistic regression showed that increasing OR of deaths and ICU admission in patients without AKI who used AAC in comparison with patients with AKI who did not use those medications (OR = 5.13 95% CI: 3.8–8.78 vs. 1.23 95% CI: 0.86–3.8 for deaths; OR = 5.26 95% CI: 3.34–8.26 vs. 2.39 95% CI: 1.17–4.90 for ICU admission). While AAC was a more prominent factor than AAC in prolonged hospitalization (OR = 3.37 95% CI: 1.76–6.45 multivariable analysis in the group with AKI and without

### Table 4: Prescribed medications in patients with and without AKI

| Medications during hospitalization | Total (N = 854) | Non-AKI (N = 736) | AKI (N = 118) | p value |
|-----------------------------------|----------------|-----------------|---------------|---------|
| **With AAC**                      |                |                 |               |         |
| Linezolid                         | 111 (13)       | 82 (11.1)       | 29 (24.9)     | <0.0001 |
| Vancomycin                        | 16 (1.9)       | 9 (1.2)         | 7 (5.9)       | <0.0001 |
| Carbapenem                        | 72 (8.4)       | 52 (7.1)        | 20 (16.9)     | <0.0001 |
| Piperacillin/tazobactam (Tazocin) | 39 (4.6)       | 29 (3.9)        | 10 (8.5)      | 0.028   |
| Cephalosporin                     | 100 (11.7)     | 74 (10.1)       | 26 (22)       | <0.0001 |
| At least one of AAC               | 243 (28.5)     | 186 (25.3)      | 57 (48.3)     | <0.0001 |
| **Without AAC**                   |                |                 |               |         |
| Lopinavir/ritonavir (Kaletra)     | 373 (43.7)     | 301 (40.9)      | 72 (61)       | <0.0001 |
| Ribavirin                         | 135 (15.8)     | 104 (14.1)      | 31 (26.3)     | 0.001   |
| Favipiravir                       | 66 (7.7)       | 64 (8.7)        | 2 (1.7)       | 0.008   |
| Oseltamivir                       | 300 (35.1)     | 253 (34.4)      | 47 (39.8)     | 0.249   |
| Hydroxy                           | 140 (16.4)     | 120 (16.3)      | 98 (83.1)     | 0.861   |
| Chloroquine                       | 451 (52.8)     | 350 (47.6)      | 53 (44.9)     | 0.594   |
| Azithromycin                      | 325 (38.1)     | 274 (37.2)      | 67 (56.8)     | 0.431   |
| Naproxen                          | 83 (9.7)       | 76 (10.3)       | 7 (5.9)       | 0.135   |
| Indomethacin                      | 517 (60.5)     | 446 (60.6)      | 71 (60.2)     | 0.930   |
| Diphenhydramine                   | 390 (45.7)     | 332 (45.1)      | 58 (49.2)     | 0.175   |
| PPIs                              | 138 (16.2)     | 113 (15.4)      | 93 (78.8)     | 0.111   |
| ACEIs, ARBs                       | 86 (10.1)      | 70 (9.5)        | 16 (13.6)     | 0.013   |
| Corticosteroids                   | 95 (11.1)      | 74 (10.1)       | 21 (17.8)     | 0.013   |

Abbreviations: AAC, antibiotics against coinfections; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; AKI, acute kidney injury; PPIs, proton-pump inhibitors.

### Table 5: Incidence of AKI

| Characteristic                      | Non-AKI (N = 736) | AKI (N = 118) | p value |
|-------------------------------------|-----------------|---------------|---------|
| Diabetes                            | 52 (6.7)        | 57 (48.3)     | <0.0001 |
| COPD/asthma                         | 30 (4.1)        | 57 (48.3)     | <0.0001 |
| Smoking/drug abuse                  | 35 (4.8)        | 57 (48.3)     | <0.0001 |
| Heart failures                      | 34 (4.6)        | 57 (48.3)     | <0.0001 |
| Hypertension                        | 165 (22.5)      | 61 (52.1)     | <0.0001 |
| AKI and AAC                         | 16 (2.2)        | 61 (52.1)     | <0.0001 |
| All evaluated comorbidities         | 157 (21.3)      | 61 (52.1)     | <0.0001 |

AAC vs. 1.31 95% CI: 0.89–1.89 in the group without AKI and with AAC (Table 6). Figures 2 and 3 show Kaplan-Maier survival curve and percentage of each outcome, respectively, which are categorized in four groups by AAC and AKI.

4 | DISCUSSION

We conducted a retrospective, single-center analysis on 854 patients with COVID-19 categorized into four groups in terms of administration of AAC and incidence of AKI in a tertiary hospital. AKI was
developed in 118 (13.8%) participants among all patients. We observed that the incidence of AKI in patients with COVID-19 received AAC was more than two times higher compared with whom did not. In addition, it was higher in males and elderly patients in both groups. About 28% of all participants used at least one AAC, which linezolid was the most common one. The effects of AAC were greater on deaths and ICU admission, whereas AKI was associated with prolonged hospitalization.

Our study showed that the incidence of AKI among hospitalized patients with COVID-19 was 13.8% and different studies have reported rates with a range from 0.5% to 29%. Also, a systematic review and meta-analysis included 6945 patients from China, Italy, the United Kingdom (UK) and the United States revealed that prevalence rate of AKI in patients with COVID-19 is 8.9% (95% CI: 4.6%-14.5%). The difference in AKI development in patients with COVID-19 can be due to lacking a specific treatment for COVID-19, differences in SARS-CoV-2 species, and race variations.

Our study shows that AAC itself is not useful for COVID-19 treatment. Other studies also confirm it and represent the potential biological mechanisms of antimicrobial-induced nephrotoxicity. For instance, direct proximal tubule cytotoxicity in vancomycin and daptomycin, direct proximal and distal tubule cytotoxicity in aminoglycosides, glomerular injuries in beta-lactams, impaired creatinine secretion and epithelial sodium channels (ENaC) in trimethoprim/sulfamethoxazole.

### TABLE 5
Mortality, ICU admission, and prolong hospitalization of patients included in the study based on antibiotics against coinfections (AAC) and incidence of AKI

|                          | All patients (N = 854) | Without AAC (n = 611) | With AAC (n = 243) | p value |
|--------------------------|------------------------|-----------------------|--------------------|---------|
| Mortality                | 119 (13.9)             | 40 (6.5)              | 79 (32.5)          | <0.0001 |
| ICU admission            | 183 (21.4)             | 63 (10.3)             | 120 (49.4)         | <0.0001 |
| Prolonged hospitalization (higher than median = 6 days) | 464 (54.3) | 306 (50.1) | 158 (65) | <0.0001 |
|                          |                        | Non-AKI (N = 736)     | AKI (N = 118)      | p value |
| Mortality                | 86 (11.7)              | 33 (28)               | 54 (45.8)          | <0.0001 |
| ICU admission            | 129 (17.5)             | 54 (45.8)             | 75 (52.4)          | <0.0001 |
| Prolonged hospitalization (higher than median = 6 days) | 369 (50.1) | 95 (80.5) | 274 (69) | <0.0001 |

Abbreviations: AAC, antibiotics against coinfections; AKI, acute kidney injury; ICU, intensive care unit.

### TABLE 6
Logistic regression and odds ratio for different category of antibiotics against coinfections (AAC) and incidence of AKI and mortality, ICU Admission, and prolong hospitalization

|                        | Outcome: Death | Age and sex adjusted odds ratio (CI 95%) | p value | Multivariate adjusted odds ratio (CI 95%)* | p value |
|------------------------|----------------|----------------------------------------|---------|-------------------------------------------|---------|
|                        |                |                                        |         |                                           |         |
| Without AAC and without AKI | 1              | 1                                      | 1       |                                           | 1       |
| Without AAC and with AKI   | 2.61 (1.17–5.79) | <0.0001  | 1.23 (0.86–3.80) | 0.105  |
| With AAC and without AKI     | 6.62 (4.01–10.91) | <0.0001  | 5.13 (3–8.78)   | <0.0001 |
| With AAC and with AKI       | 9.12 (4.62–17.99) | <0.0001  | 5.87 (2.81–12.27) | <0.0001 |
| Outcome: ICU Admission      |                |                                        |         |                                           |         |
| Without AAC and without AKI | 1              | 1                                      | 1       |                                           | 1       |
| Without AAC and with AKI     | 2.99 (1.53–5.82) | 0.001  | 2.39 (1.17–4.90) | 0.017  |
| With AAC and without AKI      | 7.60 (4.98–11.60) | <0.0001  | 5.26 (3.34–8.26) | <0.0001 |
| With AAC and with AKI        | 20.14 (10.53)   | <0.0001  | 12.67 (6.31–25.47) | <0.0001 |
| Outcome: Prolonged hospitalization (higher than median) |                |                                        |         |                                           |         |
| Without AAC and without AKI | 1              | 1                                      | 1       |                                           | 1       |
| Without AAC and with AKI      | 3.51 (1.88–6.56) | <0.0001  | 3.37 (1.76–6.45) | <0.0001 |
| With AAC and without AKI       | 1.54 (1.10–2.17) | 0.102  | 1.31 (0.89–1.89) | 0.168  |
| With AAC and with AKI        | 5.45 (2.61–11.42) | <0.0001  | 4.95 (2.26–10.81) | <0.0001 |

Abbreviations: AKI, acute kidney injury; AAC, antibiotics against coinfections; CI, confidence interval.

*Model adjusted for confounders age, sex, baseline creatinine, hypertension, lopinavir/ritonavir (Kaletra), ribavirin, favipivir, and angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs).
tubular damage and enhanced cellular immunity in fluoroquinolones are some of the proposed mechanisms for antibiotics that can lead to renal injuries such as acute tubular necrosis and acute interstitial nephritis.\textsuperscript{43}

In terms of incidence of AKI based on age and sex, we found that AKI is higher among males and the elderly. Likewise, another cohort study carried out in New York, USA on patients with COVID-19 showed that there was a statistically significant difference in the mean age of patients who developed AKI compared with those who did not (69.0 vs. 61.0; \( p < 0.001 \)) and the incidence was higher among males (63.7% vs. 59.2% males in AKI and non-AKI groups, respectively; \( p = 0.001 \)).\textsuperscript{43} The gender differences could be due to genetic factors and sex hormones.\textsuperscript{44}

Our findings showed that patients with hypertension who did not administered AAC have developed a significant higher rate of AKI (\( p = 0.007 \)). The results of abovementioned cohort study on 5449 patients with COVID-19 showed that hypertension, coronary artery disease, heart failure, and diabetes are significantly higher in patients developed AKI (\( p < 0.001 \)).\textsuperscript{43} The effects of hypertension in the development of AKI could be explained by several mechanisms, including ischemic organ damage induced by SARS-CoV-2, vascular endothelial damage, fibrinogen consumption as a result of coagulopathy and cytokine storm.\textsuperscript{45}

A systematic review and meta-analysis included 154 articles showed that the antibiotics prevalence rate was 74.6% (95% CI: 68.3%-80.0%).\textsuperscript{46} Moreover, it revealed that fluoroquinolones (20%), following by macrolides (18.9%) and beta-lactam/beta-lactamase inhibitors (15%) were the most common prescribed antibiotics.\textsuperscript{46} In addition, the prevalence rate of using antibiotics in ICUs was 86.4%, which was also correlated with deaths (OR = 1.45; 95% CI: 1.21-1.74).\textsuperscript{46} The results of a multicenter observational study in the Netherlands showed that confirmed bacterial coinfection was 1.2%, while antibiotics, especially cefuroxime and ceftriaxone were initiated for 60.1% of patients for a median duration of 2 days.\textsuperscript{47} Findings of an international survey showed that broad spectrum antibiotics like ceftriaxone/cefotaxime + macrolides and piperacillin/tazobactam were the most common used antibiotics for patients with COVID-19 in wards and ICUs, respectively.\textsuperscript{48} In our center, azithromycin, following by linezolid and cephalexin were the most frequent prescribed antibiotics. The variation might be due to differences in local guidelines. An observational study conducted in Morroco to determine the predictors of severity in COVID-19 revealed that azithromycin was the most common prescribed antibiotic in both patients in ICU and non-ICU, and third-generation cephalosporin, quinolones, aminoglycosides, and carbapenem were significantly more administered in ICUs (\( p < 0.001 \)).\textsuperscript{49} The study by Liu et al.\textsuperscript{50} on 1123 patients with COVID-19 showed that antibiotics were associated with increased in-hospital deaths (OR = 5.58; 95% CI: 1.29-24.17) and acute organ injury (OR = 1.60; 95% CI: 1.01-2.55), which were in accordance to our findings. Also, it revealed that intravenous moxifloxacin meropenem (OR = 4.26; 95% CI: 2.36-7.68) and (OR = 1.75; 95% CI: 1.02-3.00) in patients with suspected bacterial infection, and meropenem (OR = 55.77; 95% CI: 2.14-1452.51) and penicillin (OR = 20.14; 95% CI: 1.35-299.88) in patients with no evidence of bacterial infection are associated with increased mortality.\textsuperscript{50} A statistical analysis study aimed to compare antibiotic use with mortality and morbidity of COVID-19 declared a negative correlation of macrolides, cephalosporins, quinolones, sulfonates, and trimethoprim with mortality, while only tetracyclines (\( r = 0.14 \)) and penicillins (\( r = 0.35 \)) sowed a positive correlation.\textsuperscript{51} A retrospective cohort study in China showed that AKI had a significant higher rate in deceased group than survived patients with COVID-19 (\( p < 0.001 \)), while no significant difference in antibiotic treatment was observed between these two groups (\( p = 0.15 \)).\textsuperscript{14} In this regard, the article by Almazeedi et al.\textsuperscript{52} declared that antibiotics were only used for patients in non-ICU units and all of those who received antibiotics were alive, whereas 43.6% of patients in ICU developed AKI and 14.1% were expired. Furthermore, a

#### FIGURE 2
Kaplan-Meier survival time of patients based on different category of antibiotics against coinfections (AAC) and incidence of acute kidney injury

#### FIGURE 3
Percent of main outcome in patients by different category of antibiotics against coinfections (AAC) and incidence of acute kidney injury (AKI) (Group 1: Without AAC and without AKI, Group 2: Without AAC and with AKI, Group 3: With AAC and without AKI, and Group 4: With AAC and with AKI)
retrospective observational study on 119 patients with COVID-19 in Wuhan, China showed that antibiotics can increase the risk of AKI. It also revealed that 16 out of 17 and 32 out of 34 patients received antibiotics developed mild and severe AKI, respectively. Therefore, the appropriate dosage of antibiotics should be administered for patients with COVID-19 and be monitored continuously to prevent from AKI.

Our study had some limitations. First, we included all patients with clinical, radiologic manifestations of COVID-19 in addition to patients with rRT-PCR positive tests. This might cause inclusion of participants without COVID-19 due to lower sensitivity of CT-scan compared with rRT-PCR test as the gold standard for diagnosis of COVID-19. Second, the data of a single tertiary hospital and on adult hospitalized patients with COVID-19 was included in this study, as a result, the findings might not be suitable for all patients with COVID-19, especially those who are asymptomatic or have mild symptoms. Third, the radiologic features of participants were not analyzed and compared with risk of AKI progression and prognosis in these participants. Fourth, results of urinary analysis were not included in this study. Fifth, participants simply divided into two groups, AKI and non-AKI, and the staging system for the severity of AKI was not implemented.

Sixth, renal biopsy was not used to determine the pathophysiologic mechanisms of SARS-CoV-2 on the kidney. Seventh, azithromycin due to some efficacy for viral elimination was added to the drug regime of the group without AAC.

### 5 CONCLUSIONS

Both AKI and AAC are associated with poor prognosis of COVID-19. The findings should be used by physicians to have a high threshold for starting additional antibiotics against possible superimposed bacterial infection for COVID-19 because of high prevalence of adverse renal effects.

### CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

### AUTHOR CONTRIBUTIONS

Seyed Majid Mousavi Movahed, Hamed Akhavizadegan, Fatemeh Dolatkhani, and Zahra Ghazi: Conceptualization and design of the study. Monireh Faghir Gangi and Faezeh Aghajani: Statistical analysis and interpretation of data. Seyed Aria Nejadghaderi and Hoomaan Ghasemi: Writing the first draft of the manuscript. Hamed Akhavizadegan, Seyed Aria Nejadghaderi, Hoomaan Ghasemi, and Faezeh Aghajani: Revised the article. All authors reviewed and approved the final manuscript.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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### PEER REVIEW

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SUPPORTING INFORMATION

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