AKI in hospitalized patients with COVID-19: a single-center experience

Lettera all'Editore

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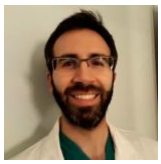
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Dear Editor,

since December 2019, the COVID-19 pandemic is straining hospitals and nephrology services worldwide. Although this disease manifests mostly with pneumonia, acute kidney injury (AKI) is recognized as a common complication in patients with severe manifestations of COVID-19. The pathogenesis of COVID-19 is still unclear but recent evidence supports a multifactorial etiology [1]. Generally, kidney involvement following SARS-CoV-2 infection is proportionate to the gravity of the infection and is commonly diagnosed in hospitalized patients with lung involvement [2]. As in another clinical scenarios, kidney injury is independently associated with morbidity and mortality in patients with SARS-CoV-2 infection [3,4].

The distribution of AKI in patients with COVID-19 is extremely variable across countries [5]. The first reports from China described a low prevalence of AKI in hospitalized patients [6] but subsequent evidence, coming from the USA and Europe, suggested a higher kidney involvement, especially in the intensive care setting [7] and among vulnerable patients [8]. Few studies have estimated the rate of AKI in hospitalized patients admitted to non-intensive care units in Italy. It ranges between 13.7-22.6% [9–11] and is similar to the prevalence detected in other European countries (4.5-22%) [12–14]. In order to broaden the knowledge of this phenomenon, we report the data on the prevalence and clinical characteristics of AKI in COVID-19 patients.

We evaluated a cohort of 792 COVID-19 patients hospitalized at the University Hospital of Modena, Italy, between February 25 and December 14, 2020 for severe symptoms of COVID-19. The diagnosis of COVID-19 was performed through reverse transcriptase-polymerase chain reaction (RT-PCR). We excluded patients aged <18 years (n=2), patients on dialysis (n=5), and patients without serum creatinine on admission (n=19). The diagnosis of AKI was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria [15], without considering the urine output criteria. Baseline serum creatinine (sCr) coincided with sCr at admission. All the enrolled patients were discharged or died at the end of the follow-up.

According to the Istituto Superiore di Sanità (ISS), the coronavirus pandemic in Italy can be subdivided in three waves during 2020: first wave (February-May), transitional period (June-August) and second wave (September- December) [16]. As a result, the study population was subdivided into three groups: wave-1 (n=389), transitional period (n=57) and wave-2 (n=346).

Data are expressed as mean ± standard deviation or a percentage (%). Statistical differences were tested using Student's t-test or Chi-square as appropriate. Cox regression analysis evaluated the influence of AKI on the hazard of death. The study was approved by the regional ethical committee of Emilia Romagna (n. 0013376/20).

In a cohort of 792 hospitalized patients, 122 cases (15.4%) of AKI were diagnosed. Patients with AKI were older (77.4 vs 64.3 years; P=<0.001) and had a higher baseline sCr (1.37 vs 0.96 mg/dl; P=0.004) than non-AKI patients (Table I). As expected, patients with AKI showed increased levels of inflammatory markers (CRP; P=0.001), tissue damage (LDH; P=0.01) and hypoxia ($PO_2/Fi0_2$;P=<0.001). We detected a higher burden of morbidity and comorbidity compared to non-AKI patients, as indicated by a higher SOFA (P=<0.001) and Charlson score (P=<0.001), respectively. In particular, AKI patients had a high rate of non-invasive ventilation (NIV; P=0.001), high flow nasal oxygen (HFNO; P=<0.001), mechanical ventilation (P=0.001) and, consequently, ICU admission (P=0.01). Given the burden of multiorgan dysfunction, AKI patients experienced a prolonged hospital stay (22.4 vs 13.2 days; P=0.008).

AKI stage 1 was the most frequent event (n=82; 67.2%) followed by AKI stage 2 (n=15; 12.2%) and AKI stage 3 (n=25; 20.4%). In this latter group, renal replacement therapy was necessary for 11 patients (44%). The overall mortality rate was 19.1% and it increased up to 61.5% in patients with an acute worsening of kidney function (Figure 1). AKI was an independent risk factor for death after adjustment for age, sex, PO2/FiO2, baseline creatinine, BMI, LDH, CRP, diabetes and cardiovascular disease (HR, 3.39; CI95% 1.032-11.1; P=0.04). Of the survivors with AKI, 40.4% did not recover kidney function at discharge.

From an epidemiological point of view, the prevalence of AKI remained similar during the first (15.9%) and the second wave (14.7%) (P=0.89) (see Figure 2). The rate of ICU admission (P=0.42) was similar in these two groups but during the second wave AKI patients were more frequently treated with steroids (P=0.007), HFNO (P=0.001) and required less mechanical ventilation (P=0.019) compared to patients admitted during the first wave. Nevertheless, the mortality of AKI patients did not change between the first (59.7%) and the second (70.6%) wave of COVID-19 (P=0.243). The findings of this study provide new information on the epidemiology of AKI in COVID-19. We found that the overall rate of AKI in unvaccinated hospitalized patients with COVID-19 accounted for 15.4% and that the prevalence of AKI remained relatively steady (about 15%) during the three phases of the COVID-19 pandemic that hit Italy and Europe during 2020. These data are in line with the results of a recent metanalysis, reporting a comparable pooled incidence (15.4%) among 25,566 patients, enrolled in 39 studies [17]. However, the distribution of AKI is not homogeneous among the published studies, where prevalence ranged from 0.5%-60%. Multiple factors may have affected this epidemiological variability including the surge capacity of the healthcare system, how the care was delivered (publicly or privately) and the method of patients selection (e.g. criteria for hospital admission).

In our study, subjects with AKI showed different demographic and clinical characteristics compared to non-AKI patients. Kidney injury was indeed experienced by elder patients affected by a more severe disease than non-AKI patients. COVID-19 patients with kidney involvement had a higher rate of morbidity (lung involvement, ICU admission, length of stay) and a 3.4-fold increase in mortality than non-AKI patients. No clear differences were detected in terms of AKI prevalence between the first and second wave, despite some therapeutic improvements (steroids, remdesivir, immunomodulant) were made in the management of these patients.

Variable	All patients (n=792)	No AKI (n=670)	AKI patients (n=122)	*p-value*
Age	66.3±16.1	64.3±16.18	77.4±10.92	**0.012**
Males (%)	511 (64.5)	425 (63.4)	86 (70.5)	0.15
White blood cells (cell/mm^3)	8587±7170	7657.1±5696.6	9737.7±7380.5	0.053
Hemoglobin (gr/dl)	12.7±1.8	12.6±1.8	13.1±1.6	0.084
Platelets (10^3/mm^3)	253.7±116.3	261.8±111.2	207.8±133.5	0.85
CRP (mg/dl)	8.9±8.2	8.3±7.89	12.3±9.6	**0.001**
LDH (U/L)	648.9±991.9	592±283.4	950±238.9	**0.01**
Baseline sCr (mg/dl)	1±0.71	0.96±0.25	1.37±0.08	**0.004**
sCr peak (mg/dl)	1.2±1.1	1.01±0.65	2.72±1.76	**<0.001**
sCr at discharge (mg/dl)	1±0.89	0.84±0.44	2.23±1.57	**<0.001**
MAP	90.3±13.2	88.8±12.2	95.5±14.2	0.12
PO_2/FO_2	250.6±105.2	261.11±101.3	184.87±106	**<0.001**
SOFA score	2±2	1.7±1.6	3.5±2.7	**<0.001**
Charston score	3.4±2.9	3 ±2.8	5.1±3.1	**<0.001**
Comorbidities§ (%)				
COPD (%)	32 (14.5)	22 (12.1)	10 (26.3)	**0.04**
Diabetes (%)	75 (31.9)	61 (31.1)	14 (35.9)	0.576
Hypertension (%)	182 (65.9)	150 (64.7)	32 (72.6)	0.386
CVD (%)	50 (22.5)	30 (16.5)	20 (50)	**<0.001**
CKD (%)	35 (15.8)	24 (13.1)	11 (28.9)	**0.025**
BMI>30 (%)	113 (32.2)	99 (33.6)	14 (25)	0.275
ACE inibitors (%)	102 (12.9)	90 (13.4)	12 (9.8)	0.307
FANS (%)	21 (2.7)	17 (2.5)	4 (3.3)	0.550
Nephrotoxic antibiotic (%)	20 (2.5)	15 (2.2)	5 (4.1)	0.216
Use of chonic diuretic therapy (pre-AKI) (%)	259 (32.7)	182 (27.2)	77 (63.1)	**0.001**
Antiviral (%)	253 (31.9)	215 (32.1)	38 (31.1)	0.91
IV hydratation with cystalloids pre-AKI (%)	233 (29.4)	189 (28.2)	44 (36.1)	0.085
Steroid (%)	287 (38.5)	232 (36.7)	55 (48.7)	**0.021**
Immunotherapy (%)	326 (43.4)	275 (43.4)	326 (43.7)	0.758
O_2 therapy (%)	537 (67.8)	454 (67.8)	83 (68)	1
HFNO (%)	101 (18.5)	71 (15.4)	30 (35.7)	**<0.001**
NIV (%)	172 (31.3)	128 (27.8)	44 (49.4)	**0.001**
Mechanical ventilation (%)	91 (12.2)	59 (9.3)	32 (28.3)	**0.001**
ICU admission (%)	153 (20.5)	111 (7.5)	42 (37.2)	**0.001**
BMI	28.5±5.3	28.5±5.1	28.1±6.2	0.109
Time elapsed from admission to AKI (day)	11.8±9.34	NA	11.8±9.34	0.063
Hospitalization (day)	14.7±13.7	13.28±11.3	22.45±21.38	**0.008**
Death (%)	151 (19.1)	76 (11.3)	75 (61.5)	**<0.001**

Legend: CRP, C-reactive protein; LDH, lactate dehydrogenase; MAP, mean arterial pressure; sCr, serum creatinine; SOFA, Sequential Organ Failure Assessment; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; CKD, chronic kidney disease; BMI, body mass index; HFNO, high-flow nasal oxygen; NIV, noninvasive ventilation; AKI, acute kidney injury; ICU, intensive care unit.

Table I: Demographics and clinical manifestation of COVID-19 patients

Since AKI is an independent risk factor in COVID-19, many efforts should be made to identify and correct predisposing factors for kidney injury. From a practical point of view, the prevention measures that we put in place were not different from those we follow for AKI from other causes in critically ill patients [15,16]. These were based mainly on surveillance of kidney function, maintenance of normovolemia and avoidance of nephrotoxic agents.

In conclusion, our study confirms that AKI is a common event (15.4%) in COVID-19 and its prevalence was stable through 2020. AKI was more common in older patients who experienced a severe COVID-19. The outcome of patients with AKI was poor, as more than half died at the end of the follow-up and 40% of survivors had not recovered kidney function at hospital discharge. The heterogeneity of COVID-19-associated AKI in terms of incidence and etiology presents many challenges to its prevention and management. Further studies are required to investigate the effects of new virulent SARS-CoV-2 variants on the development of AKI, the impact of vaccination in the prevention of kidney involvement and the long term consequences of AKI.

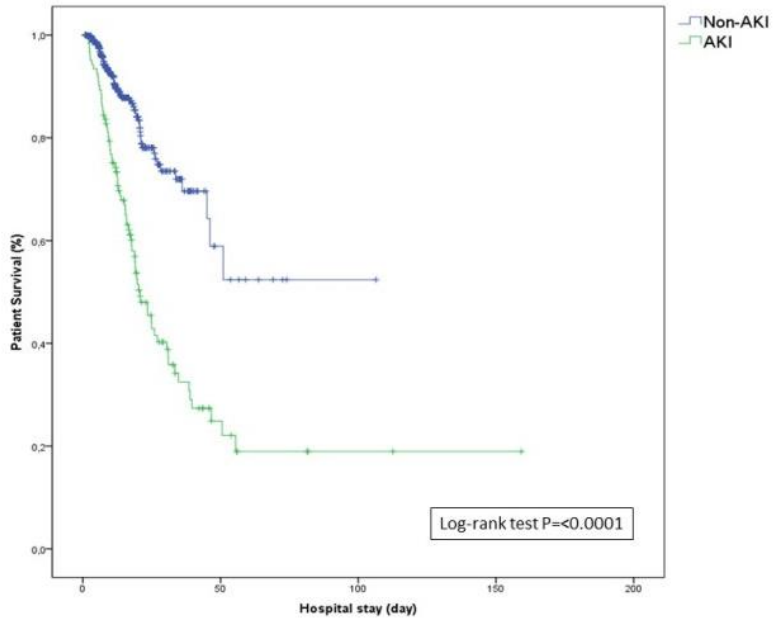

Figure 1: Kaplan Mayer curves showing survival of AKI and non-AKI patients with COVID-19

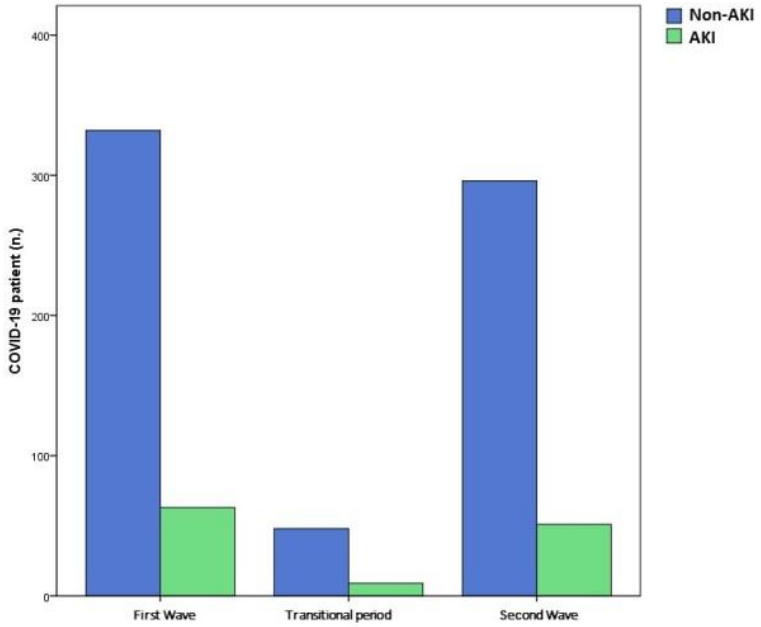

Figure 2: AKI prevalence during the first wave, the trasitional period and the second wave

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