To the Editor:

The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a global pandemic (1). France and Spain occupy the top positions in the European league of death together with Italy and the United Kingdom (1, 2). Patients with SARS-CoV-2 infection can develop interstitial pneumonia that evolves to acute respiratory distress syndrome (ARDS) (3). Almost 5% of patients infected with SARS-CoV-2 require ICU admission (4). The most critically ill patients may develop multiorgan failure including severe acute kidney injury (AKI). Available data initially suggested that the prevalence of AKI in patients infected with SARS-CoV-2 was as low as 0.5% (4), but these figures seemed higher in a recent report from New York City (5).

We aimed at assessing the incidence and mortality associated with severe AKI (stage 3 of Kidney Disease Improving Global Outcomes [KDIGO] classification) in patients with coronavirus disease (COVID-19) and ARDS treated with invasive mechanical ventilation.

We performed a European multicenter, retrospective observational study in nine ICUs located in four university hospitals (Avicenne Hospital, Louis Mourier Hospital, Bicêtre Hospital in France, and Bellvitge Hospital in Spain) from March 1 to March 31, 2020. We included adult patients with ARDS (according to the Berlin definition) (6) receiving invasive mechanical ventilation and testing positive for SARS-CoV-2 by real-time RT-PCR in respiratory fluids. Patients with end-stage renal disease or who had sustained cardiac arrest before ICU admission were not included. We reviewed clinical electronic medical records, nursing records, and laboratory findings. We collected demographic data, comorbidities, exposition to nephrotoxic agents (nonsteroidal antiinflammatory drugs, intravenous contrast agent, aminoglycoside, and vancomycin), Sequential Organ Failure Assessment score at ICU admission, respiratory parameters in the first 24 hours of invasive mechanical ventilation, inflammatory biomarkers, need for vasopressors infusion, antiviral and immunomodulator treatments received in the first 72 hours, and survival outcome 28 days after ICU admission. We also collected the occurrence of KDIGO stage 3 AKI in the first 7 days after ICU admission and the need for renal replacement therapy. Stage 3 AKI is defined by at least one of the following criteria: serum creatinine concentration of more than 4 mg/dL (354 μmol/L) or greater than three times the baseline creatinine concentration, anuria (urine output of 100 mL/d or less) for more than 12 hours, and oliguria (urine output below 0.5 mL/kg/h or below 500 mL/d) for more than 24 hours.

Bivariate analyses were conducted to explore the association between death at 28 days after ICU admission and each of the predefined risk factors. Continuous variables were compared using a sample t test and Mann-Whitney U test. Categorical data were compared using the χ² test or Fisher’s exact test. The independent predictors of death at Day 28 were identified using logistic regression including the factors with a P value < 0.10 in the univariate analysis. The association measures were calculated (adjusted odds ratio) with a confidence interval of 95%.

The study was approved by the medical ethics committee of Avicenne University Hospital (CLEA-2020–115).

From March 1 to March 31, 302 patients with SARS-CoV-2 infection were admitted in the participating ICUs. Eighty-two patients did not receive invasive mechanical ventilation, six already had end-stage renal disease before infection, and three had cardiac arrest before admission. The remaining 211 patients fulfilled the Berlin definition of ARDS and received invasive mechanical ventilation. Among these 211 patients, 55 (26%) developed KDIGO stage 3 AKI within 7 days after ICU admission (36 patients met the serum creatinine KDIGO criteria, 7 met the urine output KDIGO criteria, and 12 met both criteria). Of the remaining 156 patients, 24 (15%) developed KDIGO stage 2 AKI and 26 (17%) KDIGO stage 1 AKI within 7 days after ICU admission. The median (interquartile range) time from ICU admission to KDIGO stage 3 AKI criteria fulfillment was 3 (2–5) days. Table 1 shows the demographic data, clinical characteristics, and outcomes of these 211 patients according to their KDIGO stage 3 AKI status. Patients who developed KDIGO stage 3 AKI were more likely to have chronic kidney disease, a higher body mass index, and a higher Sequential Organ Failure Assessment score; they received higher positive end-expiratory pressure (PEEP), and they received nitric oxide therapy or vasopressor support more frequently. A total of 30 (54%) patients with KDIGO stage 3 AKI within 7 days after ICU admission required renal replacement therapy during the ICU stay. Among them, 13 (43%) were alive and still renal replacement therapy–dependent at Day 28.

Assessment of the 55 patients with KDIGO stage 3 AKI at 28 days after ICU admission showed that 31 (56%) died, 12 (22%) were still hospitalized in the ICU, and 12 (22%) were discharged alive from the ICU. These figures were, respectively, 38 (24%), 38 (24%), and 80 (51%) for patients without KDIGO stage 3 AKI.

Multivariable analysis (Table 2) showed that KDIGO stage 3 AKI was highly associated with 28-day mortality (odds ratio, 3.54; 95% confidence interval, 1.74–7.37).

A recent large, multicenter epidemiological study (BAKIT [Beijing Acute Kidney Injury Trial] study) conducted in the ICU showed that KDIGO stage 3 AKI accounted for 16% of critically ill patients (7). This incidence was 15% in a secondary analysis of the LUNG SAFE (Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure) study (8). In a group of critically ill patients with COVID-19 requiring invasive mechanical ventilation, our study shows a higher incidence of KDIGO stage 3 AKI (26%). Whether the AKI of COVID-19 is caused by a coronavirus-induced cytopathic effect or the cytokine storm remains unclear (9). However, other causes of generic critical illness that promote AKI, such as hypotension, shock, hemodynamic alterations worsened by mechanical ventilation and/or high PEEP, ischemia, or drug side effects, can coexist, and AKI in patients with COVID-19 might be a combination of all these mechanisms.

Severe AKI is associated with significant short-term mortality in critically ill patients (10). Furthermore, AKI is a major risk factor for...
the development of chronic kidney disease that worsens the long-term outcome of the patients. In the BAKIT study, KDIGO stage 3 AKI was associated with a 28-day mortality of 45%. Our study shows that critically ill patients with COVID-19 and KDIGO stage 3 AKI have a 28-day mortality of 56%. Moreover, in this population, 22% remained hospitalized in ICU after 28 days.

Despite the inherent limitation of its retrospective design, our study has the noticeable strength to describe a very homogeneous population of patients with the same underlying disease receiving invasive mechanical ventilation.

In summary, this European multicenter study suggests that severe AKI is frequent in patients with COVID-19 and ARDS and is associated with high short-term mortality.

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| Characteristics                                      | All Patients (n = 211) | Patients with Severe AKI* (n = 55) | Patients without Severe AKI (n = 156) | P Value |
|-------------------------------------------------------|-----------------------|------------------------------------|--------------------------------------|---------|
| Age, yr, mean (SD)                                    | 60 (11)               | 63 (10)                            | 60 (11)                              | 0.11    |
| Sex, M, n (%)                                         | 163 (77)              | 45 (82)                            | 118 (76)                             | 0.35    |
| Body mass index, kg/m², mean (SD)                    | 29.8 (5.7)            | 31.1 (6.1)                         | 29.2 (5.5)                           | 0.046   |
| Delay between initial symptoms and ICU admission, d, mean (SD) | 8.7 (3.9)            | 8.3 (3.5)                         | 8.9 (4.0)                            | 0.95    |
| Coexisting condition, n (%)                          |                       |                                    |                                      |         |
| Chronic kidney disease                               | 18 (9)                | 11 (20)                            | 7 (4)                                | <0.001  |
| Hypertension                                          | 107 (51)              | 32 (58)                            | 75 (48)                              | 0.20    |
| Diabetes mellitus                                     | 78 (37)               | 23 (42)                            | 55 (35)                              | 0.38    |
| Congestive heart failure                              | 9 (4)                 | 4 (7)                              | 5 (3)                                | 0.24    |
| Ischemic heart disease                                | 19 (9)                | 8 (14)                             | 11 (7)                               | 0.11    |
| Exposure to at least one nephrotoxic agent in past 2 d, n (%) | 15 (7)               | 5 (9)                              | 10 (6)                               | 0.51    |
| NSAID                                                 | 9 (4)                 | 3 (5)                              | 6 (4)                                | 0.51    |
| Intraosmotic contrast                                 | 1 (0)                 | 0 (0)                              | 1 (0)                                | 0.55    |
| Vancomycin                                            | 2 (0)                 | 0 (0)                              | 2 (1)                                | 0.40    |
| SOFA, mean (SD)                                       | 6.5 (2.3)             | 8.3 (2.3)                          | 5.8 (1.9)                            | <0.001  |
| C-reactive protein, mg/L, mean (SD)                  | 218 (126)             | 239 (154)                          | 211 (114)                            | 0.18    |
| Respiratory parameters*                               |                       |                                    |                                      |         |
| PEEP, mean (SD)                                       | 12.9 (2.0)            | 13.4 (2.0)                         | 12.6 (2.0)                           | 0.02    |
| Prone positioning, n (%)                             | 137 (65)              | 41 (74)                            | 96 (61)                              | 0.08    |
| PaO₂/FIO₂ ratio, mean (SD)                           | 131 (66)              | 123 (65)                           | 134 (65)                             | 0.27    |
| Inhaled nitric oxide, n (%)                           | 15 (7)                | 8 (14)                             | 7 (4)                                | 0.01    |
| Use of ECMO in the first 72 h, n (%)                  | 4 (2)                 | 1 (2)                              | 3 (2)                                | 0.96    |
| Antiviral therapy, n (%)                              |                       |                                    |                                      |         |
| Lopinavir/ritonavir                                    | 85 (40)               | 18 (33)                            | 67 (42)                              | 0.17    |
| Remdesivir                                            | 10 (5)                | 0 (0)                              | 10 (6)                               | 0.07    |
| Hydroxychloroquine                                    | 142 (67)              | 34 (62)                            | 108 (69)                             | 0.32    |
| Immunomodulator therapy, n (%)                        |                       |                                    |                                      |         |
| Systemic glucocorticoids                              | 73 (35)               | 14 (25)                            | 59 (38)                              | 0.10    |
| Tocilizumab                                           | 33 (16)               | 6 (11)                             | 27 (17)                              | 0.26    |
| Supportive therapy                                    |                       |                                    |                                      |         |
| Vasopressors, n (%)                                   | 155 (74)              | 46 (84)                            | 109 (70)                             | 0.047   |
| Total amount of i.v. fluids (first 72 h), ml, mean (SD) | 4,474 (2,200)       | 4,629 (2,621)                      | 4,386 (1,964)                        | 0.72    |
| Diuretics therapy (first 72 h), n (%)                 | 99 (47)               | 21 (38)                            | 78 (50)                              | 0.13    |
| Serum creatinine, µmol/L, mean (SD)                   |                       |                                    |                                      |         |
| Baseline                                              | 78 (28)               | 96 (38)                            | 72 (20)                              | <0.001  |
| At ICU admission                                      | 101 (92)              | 162 (160)                          | 79 (27)                              | <0.001  |
| Highest in the first 7 d                              | 187 (178)             | 415 (208)                          | 106 (62)                             | <0.001  |
| Renal replacement therapy, n (%)                      | 41 (19)               | 30 (54)                            | 11 (7)                               | <0.001  |
| Day-28 outcomes, n (%)                                |                       |                                    |                                      |         |
| Discharged alive from ICU                             | 92 (43)               | 12 (22)                            | 80 (51)                              | <0.001  |
| Death                                                 | 69 (33)               | 31 (56)                            | 38 (24)                              | <0.001  |
| Day-28 survivors                                      | 50 (24)               | 12 (22)                            | 38 (24)                              | 0.70    |

Definition of abbreviations: AKI = acute kidney injury; ARDS = acute respiratory distress syndrome; COVID-19 = coronavirus disease; ECMO = extracorporeal membrane oxygenation; NSAID = nonsteroidal antiinflammatory drugs; PEEP = positive end-expiratory pressure; SOFA = Sequential Organ Failure Assessment.

*In the first 24 hours of invasive mechanical ventilation.

†These patients received renal replacement therapy because they developed late (>7 d) severe AKI.

In summary, this European multicenter study suggests that severe AKI is frequent in patients with COVID-19 and ARDS and is associated with high short-term mortality.
Table 2. Multivariable Logistic Regression of Factors Associated with 28-Day Mortality

|                          | OR      | 95% CI       | P Value |
|--------------------------|---------|--------------|---------|
| KDIGO stage 3 AKI        | 3.539   | 1.737–7.374  | <0.001  |
| Congestive heart failure | 2.738   | 0.582–16.100 | 0.11    |
| Respiratory SOFA (0–4)   | 1.663   | 1.039–2.741  | 0.02    |
| Age, yr                  | 1.082   | 1.044–1.126  | <0.001  |
| Diabetes mellitus        | 0.936   | 0.441–1.949  | 0.87    |

Definition of abbreviations: AKI = acute kidney injury; CI = confidence interval; KDIGO = Kidney Disease Improving Global Outcomes; OR = odds ratio; SOFA = Sequential Organ Failure Assessment.

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COVID-19– versus non–COVID-19–related Acute Respiratory Distress Syndrome: Differences and Similarities

To the Editor:

The current pandemic of coronavirus disease (COVID-19) is responsible for a massive influx of patients with acute respiratory...