Kidney Dysfunction And COVID-19: Characteristics, Predictive Factors, And Influence Of Age

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Abstract

**Background** COVID-19 severity and mortality are strongly influenced by age and comorbidities. Among comorbidities, kidney dysfunction seems to play a crucial role. Indeed, acute kidney injury (AKI) is a frequent finding in hospitalized COVID-19 patients and seems to be associated to mortality and severity. On the other hand, the role of chronic kidney disease (CKD) in COVID-19 is more debated.

**Aims and Methods** We performed a retrospective study in a cohort of 174 hospitalized COVID-19 patients in Italy from March 3rd to May 21st 2020, to investigate the role of kidney dysfunction on COVID-19 severity and mortality. Moreover, we examined in depth the relationship between kidney function, age, and progression of COVID-19, also using different equations to estimate the glomerular filtration rate (GFR). Hazard ratios (HR) and odds ratios (OR) were obtained by logistic regression, while a predictive analysis was made through a machine learning approach.

**Results** AKI and death occurred in 10.2% and 19.5% respectively, in our population. Serum creatinine, blood urea nitrogen, neutrophils, lymphocytes, c-reactive protein and procalcitonin were significantly correlated to mortality and severity of the disease. The major risk factors for mortality in our cohort were age [adjusted HR, 6.2; 95% confidence interval (CI) 1.8-21.4] and AKI [3.36 (1.44-7.87)], while, in these relationships, GFR at the baseline mitigated the role of age. The occurrence of AKI was influenced by baseline kidney function, D-dimer and procalcitonin and hypertension. Our predictive analysis for AKI and mortality reached an accuracy ≥ of 94% and 91%, respectively. In patients ≥ 70 years, MDRD and CKD-EPI showed a better performance in the prediction of AKI and mortality, compared to BIS-1 formula.

**Discussion** Our study confirms the importance of AKI as a risk factor in COVID-19 disease, while it scales down the role of CKD, especially in elderly patients. BIS-1 formula demonstrated a worse performance to predict the outcomes in COVID-19 patients when compared to MDRD and CKD-EPI.

**Introduction**

Coronavirus disease 2019 (COVID-19), caused by Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has rapidly spread all around the world after its outbreak in Whuan, Hubei, China in December 2019.

COVID-19 infection can quickly progress from the severe to critical stage with the need for intensive care; in addition, the infection causes a high rate of ARDS (Acute Respiratory Distress Syndrome) often followed by death. In this clinical outlook, several studies have also reported the impact of age and comorbidity on the progression of COVID-19 infection [1].

In several studies, kidney dysfunction has been associated with COVID-19 infection, severe and critical COVID-19, and mortality [2–3]. However, despite a variety of evidence from observational studies and metanalysis, the real impact of Acute Kidney Injury (AKI) as a clinical risk factor is still lacking [4]. The incidence of Chronic Kidney Disease (CKD) in COVID-19 hospitalized patients is also not clearly defined,
and it is probably influenced by demographic and epidemiologic characteristics [5]. The role of CKD in COVID-19 severity is even more debated, probably as a result of the difficulty in differentiating CKD from AKI in patients hospitalized during a pandemic outbreak [6]. Recent studies and metaanalysis showed an increased risk only for CKD stage 4–5, with a lack of evidence for the impact of the disease at the earlier stages. Moreover, CKD prevalence is higher among the elderly and patients with comorbidities such as diabetes, arterial hypertension and cardiovascular disease, which are also associated with severe COVID-19 and represent possible confounding factors.

Many variables are probably implicated in COVID-19 mortality and severity and, among them, CKD could be particularly relevant, due also to its growing prevalence [7].

Moreover, the role of eGFR in the elderly is debated among nephrologists [8], and different eGFR formulas have been developed specifically for elderly patients [9].

The aim of this retrospective study is to evaluate the role of kidney dysfunctions in the progression and severity of COVID-19 infection, also analyzing the relationship between age and kidney dysfunction on clinical outcomes, and evaluating the performance of specific eGFR equations to predict the outcomes in this setting.

Materials And Methods

Study design

This was a retrospective study conducted at the Ospedale Evangelico Internazionale of Genova (Italy) approved by the Ligurian Ethical Committee on 02/07/2020 (registry number: 257/2020). Study population included 174 patients admitted to the hospital with Sars-Cov2 positive RT-PCR nasopharyngeal swab, from March 3rd, 2020 to May 21st, 2020.

For each patient, data were acquired from paper charts and electronic medical records and anonymized before analyses. Due to the emergency scenario, the high biological hazard, and the need for improving scientific knowledge on COVID-19, the Ethical Committee approved this retrospective research without requirement of a study-specific consent by the patients.

Inclusion and exclusion criteria

The analysis included all COVID-19 patients aged ≥ 18 years who had at least 2 Sars-Cov2 positive RT-PCR nasopharyngeal swabs, radiological findings documenting pulmonary disease (via either x-ray or CT scan), and blood oxygen saturation < 95% evidenced with arterial blood gas analysis.

The exclusion criteria were age < 18 years and death in the first 24 h after admission. Moreover, we excluded patients with less than 2 serum creatinine examinations and with unknown medical history. Of the 182 patients admitted to the hospital, 174 constituted the study group after the application of inclusion and exclusion criteria.
Data collection
Variables collected were age, gender, blood pressure, comorbidities including cardiovascular disease (CVD), diabetes, hypertension, chronic obstructive pulmonary disease (COPD), malignancies, CKD, medications (dexamethasone, oseltamivir, ritonavir/darunavir, hydroxychloroquine, heparin, tocilizumab), and biohumoral laboratory: serum creatinine (sCr), blood urea nitrogen, ferritine, c-reactive protein (CRP), procalcitonin, lactate dehydrogenase (LDH), transaminase, blood cells count. CVD was defined as any of the following: previous episodes of myocardial infarction, revascularization procedures, strokes, acute heart failure, peripheral vascular disease or LVEF < 55%. Serum creatinine and blood urea nitrogen values were collected for 7 days since hospital admission. Glomerular filtration rate (GFR) was estimated based on sCr at the admission.

Definitions
eGFR: was calculated using different equations: CKD EPI, MDRD, and in patients over 70 or 80 years the CKD BIS 1 was used [10]; Thus, 4 different variables were generated for the analysis: MDRD for the whole population, CKD-EPI for the whole population, CKD-EPI for patients < 70 years and BIS-1 for patients ≥ 70 years (BIS-1 over 70), and CKD-EPI for patients < 80 years and BIS-1 for patients ≥ 80 years (BIS-1 over 80);

- CKD was defined according to KDIGO 2012 Clinical Practice Guideline (KDIGO, Kidney Int Suppl. 3, 2013,19–62);
- AKI were defined according to KDIGO criteria (KDIGO, Kidney Int Suppl.2, 2012, 1-138) i.e. increase in serum creatinine at least of 0.3 mg/dL within 48 h or at least 1.5 times baseline creatinine within 7 days. Urine criteria were not used in this analysis.

Study Endpoints
a. Primary endpoints were AKI and mortality;
b. Secondary endpoints were severe or critical diseases defined as the need for high oxygen fluxes (FiO$_2$ ≥ 60%), continuous positive airway pressure (CPAP) or mechanical ventilation after endotracheal intubation (ETI,) and were evaluated as a composite endpoint.

Statistical analysis
Patients’ characteristics are expressed as frequency (n) and percentage (%) for qualitative variables; quantitative variables are expressed as mean ± standard deviation, or median and Interquartile Range (IQR, i.e. difference between 75 and 25 percentiles) for non-normally distributed variables.

Univariate analysis was carried out for baseline characteristics of different AKI endpoints and for non-kidney short-term clinical outcomes. Continuous variables were compared by unpaired Student’s t test or Mann Whitney U test whenever required. Categorical variables were compared by χ2 test and odds ratios (OR) with 95% Confidence Intervals (95%CI) were reported. A two-sided p-value < 0.05 was considered significant. Kaplan-Meyer curves were performed in order to model survival time and Logrank test was
applied to assess comparisons between curves. Cox analysis with a stepwise approach was carried out to evaluate the effect of age (cut-off set at 70 years, being 70 years the median of the distribution) and AKI (yes/no) and other kidney dysfunction variables (creatinine and eGRF) on the survival. Crude and adjusted Hazard ratios (HR) and relative 95% CI were also estimated.

We were also interested in the prediction of some binary outcomes such as mortality (yes/no), composite endpoint (yes/no), and AKI (yes/no) via a well-known Machine Learning tool: using the above-listed variables or predictors, a 10-fold cross-validation was applied to calculate the accuracy (%) of prediction by the MATLAB® Classification Learner application (method: Fine Tree, where all default settings were unchanged; The MathWorks, Inc., Natick, MA). In particular, we assumed that the choice of only a single indicator of kidney functionality (serum creatinine, or the estimated CKD-EPI, BIS-1 over-70, BIS-1 over-80, MDRD) together with the remaining and above-listed variables could give a good performance in predicting the binary outcomes (mortality, composite endpoint, AKI).

**Results**

**Characteristics of patients with COVID-19**

Characteristics of the 174 patients are shown in Table 1. The mean age of study participants was 69.1 ± 15.7 years with a male preponderance (63.2 %). The most common comorbidities were hypertension (48.9 %), CVD (24.1 %) diabetes (12.6 %) and CKD (16.6% with MDRD, 19.5% with CKD-EPI, 27.6% with BIS-1 over 80 and, 28.7% over 70, respectively). GFR at baseline was 88.9 ± 33.4 with MDRD, 79.8 ± 23.9 with CKD-EPI, and 75.5 ± 25.8 mL/min with CKD-EPI and BIS-1 (for patients 70 years older). The median creatinine at baseline was 82.68 (IQR = 28.3 micromol/L). The median duration of hospitalization was 19 (IQR = 21 days).

**Variables associated with AKI in COVID-19 patients**

The occurrence of AKI in our population was 10.2%. Compared to patients that did not develop AKI, patients with AKI showed significantly increased creatinine, and blood urea nitrogen values at the baseline: 113.67 ± 72.05 vs 78.96 ± 26.27 micromol/L, and 52 ± 27 vs 39 ± 22 mg/dL, respectively. Moreover, eGFR measured with all the different equations was significantly lower in AKI patients at the baseline. Other biochemical variables correlated to AKI were: procalcitonin (3.36 ± 9.45 vs 0.57 ± 2.39 ng/mL, p = 0.008), and D-dimer (4479 ± 4857 vs 2269 ± 5173 ng/mL, p = 0.002). Hypertension represents a risk factor for AKI (OR 6.14; 95% CI 1.71–22.1), but not diabetes or CVD.

(Supplementary materials Tables 1–2)

**Variables associated with mortality in COVID-19 patients**

The overall mortality was 19.5%. The average time between disease onset and death was 19 ± 12.8 days, whereas median time to discharge was 27.1 ± 16.6 days. Compared to survivors, non-survivors were older (80.2 ± 7.8 vs 66.5 ± 16.0 years p < 0.001), presented higher baseline values of creatinine (1.14 ± 0.41 vs 0.9 ± 0.39 mg/dL or 100.02 ± 35.51 vs 78.79 ± 34.55 micromol/L p = 0.002), and blood urea nitrogen
Moreover, in non-survivors, neutrophils, GOT, PCR, procalcitonin were higher, while lymphocytes and diastolic blood pressure were lower (Supplementary material Table 3). Creatinine and blood urea nitrogen were also significantly higher between 48 hours and 7 days, in the non-survivors group. No differences were found for gender and LDH values. Univariate analyses identified the following other risk factors for mortality: AKI (OR 5.16 95% CI 1.86–14.3), arterial hypertension (OR 3.12; 95% CI 1.39–7.02), diabetes (OR 3.46 95% CI 1.34–8.97), COPD (OR 3.45; 95% CI 1.20–9.89), CVD (OR 4.52; 95% CI 2.03–10.06).

The use of antiviral drugs was also associated with increased risk of mortality, oseltamivir (OR 3.62; 95% CI 1.61–8.16), ritonavir/darunavir (OR 3.40; 95% CI 1.48–7.83), while dexamethasone seemed to be protective with an association with the outcome close to statistical significance (OR 0.45; 95% IC 0.19–1.07) and no differences were found for hydroxychloroquine, heparin, and tocilizumab (Supplementary materials Table 4).

Survival analysis identified two major predictors for mortality, age and AKI. Kaplan-Meier plots (Fig. 1) pointed out significantly shorter onset of mortality for the older old and the AKI groups in comparison to young group and no-AKI (Logrank test: p < 0.001). Among other kidney dysfunction variables, eGFR showed an effect on mortality by mitigating the role of age but not that of AKI (see table 2).

Variables associated with COVID-19 severity
When considering the need for CPAP, ETI, FiO$_2$ ≥ 60% or mortality, 44.8% of the patients presented at least one of the mentioned conditions (composite endpoint).

Variables significantly associated with the composite endpoint were: serum creatinine at baseline (1.05 ± 0.52 vs 0.85 ± 0.25 mg/dL p = 0.002), blood urea nitrogen at baseline (47.73 ± 29.0 vs 33.78 ± 13.04 mg/dL p < 0.001), blood urea nitrogen at 48h (53.61 ± 34.11 vs 32.71 ± 14.69 mg/dL p < 0.001). Also, neutrophils, lymphocytes, LDH, PCR and procalcitonin were significantly associated with the composite endpoint (Supplementary material Table 5). Interestingly, age, AKI and comorbidities were not significantly associated with composite endpoint. Conversely, drugs administrated for COVID-19 disease (oseltamivir, ritonavir/darunavir, hydroxychloroquine, and tocilizumab) were associated with composite endpoint, just as dexamethasone (OR 3.52 95% IC 1.84–6.71), but not for heparin (Supplementary materials Table 6).

The effect of age on mortality (OR 9.71 95% IC 3.24–7.83) but not on composite endpoint was also confirmed after dichotomization of the variable (under and over 70 years). Analyzing all the individual components of the endpoint that expresses disease severity we found an inverse correlation for ETI (OR 0.34 95% IC 0.12–0.92), and CPAP (OR 0.37 95% IC 0.18–0.78) and a positive, but not significant, correlation FiO$_2$ ≥ 60%. (Table 3)

Predictive analysis
We identified the following most valuable variables to build the predictive model and to achieve the best accuracy: Age, sCr or eGFR (using different equations), blood urea nitrogen, leucocytes, neutrophils, and
lymphocytes count, LDH, PCR, ferritin, procalcitonin. All the variables abovementioned were selected on the basis of their correlation with the development of AKI, mortality, and/or severity of COVID-19 disease.

The prediction performance of our cross-validated model is reported in the following tables. (Table 4)

For the overall population and for the subset with age < 70 years, the accuracy reached higher values in predicting AKI than the other two binary outcomes (mortality, composite). On the other hand, the model gave a better prediction in the population with age < 70 years. For the patients < 70 years, the eGFR formulas enabled a good prediction of AKI and mortality with accuracies > 90%, and a slightly better performance to predict AKI of CKD-EPI, compared to the others. Interestingly, in the population > 70 years, the accuracy of our model was globally low, but BIS-1 formulas showed a worse performance to predict the outcomes, compared to CKD-EPI and MDRD.

Discussion

In our study, we added new information and insights on the contribution of kidney dysfunction in COVID-19. We investigated and characterized several risk factors in COVID-19, with a specific focus on the relationship between age and kidney dysfunction on progression and severity of the disease. The most interesting results of our study, in a population of COVID-19 hospitalized patients, are the importance of AKI as independent risk factor for mortality, the identification of key variables for risk assessment of patients, and the evidence that the influence of baseline GFR on the clinical outcomes decreases with age, and it seems to not represent a major risk factor for elderly patients.

AKI occurred in one-third of hospitalized COVID-19 patients with a wide range among different studies, probably due to differences in study populations examined [11–14]. Based on the literature, incidence of AKI seems to be higher in COVID-19 patients compared to SARS-CoV2 negative patients [15–16] confirming that it is not an epiphenomenon in severe or critical disease. CKD is a well-known risk factor for AKI and poor outcomes in different clinical settings and is frequently observed in the elderly that appear to be at higher risk of developing severe or critical COVID-19 disease as do other patients affected by comorbidities associated with kidney dysfunction (diabetes, CVD, and hypertension) [17]. This is why it is challenging to discriminate between association and causality of CKD and poor outcome in COVID-19.

Also, a precise risk assessment in COVID-19 patients is essential to allocate health resources during the pandemic emergency.

A recent study performed on the Danish population [5], which differentiated between pre-existing CKD and AKI through national healthcare registries, showed an increasing risk for severe disease in CKD population. Although these findings appear in contrast with our data, the mean age in this study was significantly lower compared to our sample (57.6 y vs. 69.1 y), which shows this could be due to demographic differences of the populations studied. However, the risk for severe disease or death was weak for early stages of CKD and when the variable “age” was included in the regressive model [5]. Previous studies have reported a significant influence of age on the association between CKD and
disease progression. The same influence was not found for mortality, but this may be due to a markedly younger median age, compared to our sample [18].

Beyond COVID-19, various studies investigated the relationship between eGFR and clinical outcomes in the elderly, and the role of reduced GFR in this population is still debated among nephrologists [8]. Some studies demonstrated that in elderly patients a GFR < 60 mL/min is not associated with increased risk for mortality or progression to end stage kidney disease (ESKD) [19–20], while a meta-analysis found a U shape curve in the relationship between GFR and mortality for older age group (> 65 years) with a higher risk for GFR > 115 mL/min [21].

Thus, a lower limit for CKD definition in the elderly has been proposed (e.g. eGFR < 45 mL/min) [15], and different GFR equations have been developed and validated in this population. Recent studies evaluated the performance of different and more used equations for eGFR and found various pitfalls, limitations, and conflicting results in the association with short- and long-term hard outcomes [9, 22–23].

To investigate the correlation between age and kidney dysfunction, we firstly analysed age as a dichotomous variable, and we showed that it influences mortality but not the composite endpoint, performed to evaluate the severity of the disease. However, analysing the single outcomes of the composite endpoint, we found a positive, but not significant, correlation with the need for high flux oxygen therapy (FiO₂ > 60%; OR 1.83 95% IC 0.96–3.5). Conversely, we demonstrated an inverse correlation between age and C-PAP and age and EIT. A speculative reason for this evidence could be that elderly patients experiment a higher rate of mortality despite a slightly increased risk for severe or critical disease. This could partially be due to a minor eligibility of elderly patients to more invasive therapeutic approaches, and maybe to a reduced availability of medical resources during the pandemic outbreak. The non-randomized nature of this study, however, does allow us to clarify the reasons.

Age and AKI confirmed their important role as independent risk factors for COVID-19 mortality. In this relationship, eGFR acted as possible confounder with an effect of diminishing the hazard risk of death in patients over 70 years.

We did not show a significant impact of pharmacologic treatment on disease progression or mortality, with the exception of steroids. Indeed, all the drugs used were positively correlated with the severity of disease, probably because patients affected by pauci-symptomatic diseases were not referred to pharmacologic treatment. Steroid treatment, on the other hand, seemed to have a beneficial effect (OR 0.45 95% IC 0.19–1.07), consistent with previous reports [24].

We also developed a predictive analysis with a very high accuracy for AKI and mortality in the subset of patients < 70 years. Interestingly, in patients ≥ 70 years the model showed a worse accuracy, and a worse accuracy of BIS-1 formula compared to CKD-EPI and MDRD. Although BIS-1 formula has been specifically developed in the elderly population, the diagnostic and predictive performance of this equation did not show significant superiority compared to CKD-EPI and/or MDRD[17]. In our population, MDRD showed the best predictive value, for AKI, severity of the disease and mortality, while BIS-1, which
identifies almost twice the amount of CKD compared to other formula (28.7 % vs 16.6 %) showed the worst performance compared to MDRD and CKD-EPI.

The worse accuracy of our predictive analysis in patients ≥ 70 years could be due to a lack of variables of interest in the older population, such as albuminuria and BMI, and the reduced influence of our variables in the elderly, including GFR.

In conclusion, this study confirms the important role of AKI in COVID-19 progression. We believe that frequent sCr measurements should be performed in hospitalized patients to achieve an early detection of AKI, in order to identify patients at high risk for mortality and morbidity. Moreover, our study diminishes the role of a pre-existing CKD in COVID-19 patients, especially in the elderly patients, where its contribution, compared with age and AKI, results of minor relevance.

Reasons behind this evidence are partially speculative. GFR estimation based on sCr levels is actually the most feasible method in the clinical routine but it presents strong bias in specific clinical conditions. Indeed, low sCr levels could be measured in fragile and sarcopenic patients. In this specific population, GFR could be artifactually higher. CKD is a well-recognized negative prognostic factor for mortality and CVD morbidity, but also malnutrition inflammation syndrome (MIS), in which creatinine generation is very low, is a strong CVD risk factor and correlates with mortality [25].

Moreover, as we discussed above, our population was characterized by a high percentage of elderly patients and a relatively high mean GFR value, which, in this setting, became prognostically relevant when under 45 mL/min.

Our study has several limitations: first of all, we were not able to collect previous creatinine values of patients, thus causing possible overlapping of CKD and AKI. Moreover, we missed important variables such as albuminuria, proteinuria, BMI and fragile state index. In particular, nutritional status and body mass assessment is essential to further investigations into the relationship between CKD and clinical outcomes in the older old affected by COVID-19.

Finally, the evaluation of the severity, through the composite endpoint, was affected by a bias of eligibility of older patients to invasive treatments, due to clinical decision making, and probably influenced by the availability of healthcare resources during the COVID-19 outbreak in Italy.

Declarations

Conflict-of-interest statement

The authors declare no conflicts of interests

Authors contributions
ELP, MB, and GM provided the idea and the study conception, FT, IT, GT, GS collected the data, and ELP, CE, VE collected the literature and wrote the manuscript. PB, LF, and SP provided analysis and interpretation of the data. AL, GD, MP, and FL revised the manuscript.

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**Data Availability**

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request

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**Tables**

**Table 1.** Patient’s characteristics
|                                | Mean  | SD    | Median | IQR  |
|--------------------------------|-------|-------|--------|------|
| Age (years)                    | 69.06 | 15.69 |        |      |
| eGFR (MDRD)                    | 88.90 | 33.42 |        |      |
| eGFR (CKD-EPI; BIS-1 over-80 years) | 76.71 | 25.77 |        |      |
| eGFR (CKD-EPI; BIS-1 over-70 years) | 75.48 | 25.77 |        |      |
| eGFR (CKD-EPI)                 | 79.78 | 23.88 |        |      |
| Creatinine (mg/dL)             | 0.93  | 0.40  | 0.88   | 0.32 |
| Creatinine (micromol/L)        | 82.68 | 35.50 | 77.81  | 28.29|
| Creatinine 48 hours (mg/dL)    | 0.97  | 0.60  | 0.83   | 0.37 |
| Creatinine 7 days (mg/dL)      | 0.97  | 0.57  | 0.80   | 0.47 |
| Blood urea nitrogen (mg/dL)    | 40.23 | 22.92 |        |      |
| Blood urea nitrogen 48 hours (mg/dL) | 42.85 | 27.91 |        |      |
| White blood cells (n°/cc)      | 7014.77 | 6826.20 | 5590 | 3740 |
| Neutrophiles (n°/cc)           | 4957.08 | 3432.36 | 3800 | 3400 |
| Lymphocytes (n°/cc)            | 1058.78 | 560.43 |        |      |
| Platelets (n°)                 | 212.91 | 90.33 |        |      |
| LDH (IU/L)                     | 277.38 | 116.32 | 244   | 128  |
| GOT (IU/L)                     | 39.92  | 32.57 | 31     | 24   |
| GPT (IU/L)                     | 37.89  | 37.52 | 27     | 28   |
| CRP (mg/L)                     | 69.96  | 70.83 | 47.0   | 98.55|
| Procalcitonine                 | 0.90   | 4.00  | 0.10   | 0.16 |
| Ferritine                      | 832.46 | 907.65 | 573   | 723  |
| D-didimer                      | 2548.91 | 5157.41 | 948   | 1764 |
| Systolic blood pressure (mmHg) | 127.02 | 20.37 |        |      |
| Diastolic blood pressure (mmHg) | 73.60 | 12.35 |        |      |
| Length of hospitalization (days) | 25.20 | 20.36 | 19    | 21   |
| Time between the onset of symptoms and discharge/death | 25.47 | 16.12 |     |      |

Median and Interquartile Range are shown for non normally distributed variables only
SD=Standard Deviation; IQR=Interquartile Range; eGFR=Estimated Glomerular Filtration Rate;
MDRD= Modification of Diet in Renal Disease Study; CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; BIS-1= Berlin Initiative Study 1 Equation; LDH=Lactate Dehydrogenase; GOT=Glutamic Oxaloacetic Transaminase; GPT= Glutamate Pyruvate Transaminase; CRP= C-Reactive Protein;

**Table 2.** Crude and adjusted (creatinine and eGFR) Hazard Ratios (HR) for mortality
### Table 3. Occurrence and comparison of endpoints in patients over and under 70 years old

| Risk Factor | Age <70 years | Age >=70 years | OR (95% CI)* |
|-------------|---------------|----------------|--------------|
| Inhospital mortality (0/1) | | | |
| No | 79 | 95.2 | 59 | 67.0 | 9.71 (3.24-29.1) |
| Yes | 4 | 4.8 | 29 | 33.0 | |
| Oxygen flux FiO2>60% | | | |
| No | 61 | 73.5 | 53 | 60.2 | 1.83 (0.96-3.5) |
| Yes | 22 | 26.5 | 35 | 39.8 | |
| ETI (0/1) | | | |
| No | 68 | 81.9 | 80 | 93.0 | 0.34 (0.12-0.92) |
| Yes | 15 | 18.1 | 6 | 7.0 | |
| NPPV (0/1) | | | |
| No | 54 | 65.9 | 72 | 83.7 | 0.37 (0.18-0.78) |
| Yes | 28 | 34.1 | 14 | 16.3 | |
| Composite endpoint | | | |
| No | 51 | 61.4 | 45 | 51.1 | 1.52 (0.83-2.80) |
| Yes | 32 | 38.6 | 43 | 48.9 | |

*Odds Ratio and 95% Confidence Interval. Reference category: absence of the condition or FiO2≤60
ETI=endotracheal intubation, NPPV=non-invasive positive pressure ventilation

Table 4. Predictive analysis. We calculated the accuracy (%) of prediction for mortality, composite endpoint and AKI using only a single indicator of kidney functionality (serum creatinine or a specific eGFR) together with the other variables, in the overall population, in the population with age < 70 years, and In the population with age≥70 years. The other variables are: age, blood urea nitrogen, comorbidities, leucocite, neutrophiles, LDH, CRP, procalcitonine, ferritine, drugs.

| Overall population | Accuracy (%) | Creatinine | CKD-EPI | BIS-1 over-70 | BIS-1 over-80 | MDRD |
|--------------------|--------------|------------|---------|---------------|---------------|------|
| Mortality          | 78.74        | 75.86      | 76.44   | 78.74         | 76.44         |      |
| Composite          | 59.77        | 66.09      | 64.37   | 60.92         | 66.09         |      |
| AKI                | 89.08        | 87.36      | 87.93   | 86.78         | 86.21         |      |
| Age < 70 years     | | | | | | |
| Mortality | 88.37 | 90.70 | - | - | 91.86 |
| Composite | 70.93 | 76.74 | - | - | 70.93 |
| AKI | 89.53 | 94.19 | - | - | 91.86 |
| Age ≥ 70 years     | | | | | | |
| Mortality | 69.32 | 67.05 | 67.05 | 61.36 | 71.59 |
| Composite | 69.32 | 67.05 | 72.73 | 63.64 | 75.00 |
| AKI | 81.82 | 82.95 | 72.73 | 77.27 | 84.09 |

Figures
Figure 1

Kaplan-Meier plots of mortality. Curves represent mortality in (A) = patients over and under 70 years old – Logrank test: p<0.001 (B) = patients with and without occurrence of Acute Kidney Injury (AKI) – Logrank test: p<0.001

Supplementary Files
This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarymaterials.odt