Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Early reduction of estimated Glomerular Filtration Rate (eGFR) predicts poor outcome in acutely ill hospitalized COVID-19 patients firstly admitted to medical regular wards (eGFR-COV19 study)

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ABSTRACT

Background: Analysis of autopsy tissues obtained from patients who died from COVID-19 showed kidney tropism for SARS-COV-2, with COVID-19-related renal dysfunction representing an overlooked problem even in patients lacking previous history of chronic kidney disease. This study aimed to corroborate in a substantial sample of consecutive acutely ill COVID-19 hospitalized patients the efficacy of estimated GFR (eGFR), assessed at hospital admission, to identify acute renal function derangement and the predictive role of its association with in-hospital death and need for mechanical ventilation and admission to intensive care unit (ICU).

Methods: We retrospectively analyzed charts of 764 patients firstly admitted to regular medical wards (Division of Internal Medicine) for symptomatic COVID-19 between March 6th and May 30th, 2020 and between October 1st, 2020 and March 15th, 2021. eGFR values were calculated with the 2021 CKD-EPI formula and assessed at hospital admission and discharge. Baseline creatinine and GFR values were assessed by chart review of patients' medical records from hospital admittance data in the previous year. The primary outcome was in-hospital mortality, while ARDS development and need for non-invasive ventilation (NIV) and invasive mechanical ventilation (IMV) were the secondary outcomes.

Results: SARS-COV-2 infection was diagnosed in 764 patients admitted with COVID-19 symptoms. A total of 682 patients (age range 23–100 years) were considered for statistical analysis, 310 needed mechanical ventilation and 137 died. An eGFR value <60 mL/min/1.73 m^2 was found in 208 patients, 181 met KDIGO AKI criteria; eGFR values at hospital admission were significantly lower with respect to both hospital discharge and baseline values ($p < 0.001$). In multivariate analysis, an eGFR value <60 mL/min/1.73 m^2 was significantly associated with in-hospital mortality (OR 2.6, 1.7–4.8, $p = 0.003$); no association was found with both ARDS and need for mechanical ventilation. eGFR was non-inferior to both IL-6 serum levels and CALL Score in predicting in-hospital death (AUC 0.71, 0.68–0.74, $p = 0.55$).

Conclusions: eGFR calculated at hospital admission correlated well with COVID-19-related kidney injury and eGFR values < 60 mL/min/1,73 m^2 were independently associated with in-hospital mortality, but not with both ARDS or need for mechanical ventilation.

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1. Introduction

Renal dysfunction associated with coronavirus disease 2019 (COVID-19) and ranging from mild proteinuria and hematuria [1] to overt acute kidney injury (AKI) [2] was significantly prevalent from the beginning of the severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) pandemic.

Multiple kidney-cell types, from proximal tubular epithelial cells to podocytes, express angiotensin-converting enzyme 2 (ACE2) receptors and SARS-COV-2 can pervasively infect renal parenchyma. This enrichment expedites viral replication and SARS-CoV-2–associated kidney injury, leading to cytonecrosis [3] and determining the anatomo-clinical pictures of tubular necrosis and glomerulonephritis [4]. Other mechanisms of kidney damage in COVID-19 included hyper-inflammation-related tubular necrosis [4], prerenal azotemia due to volume depletion [5] and disseminated intravascular coagulation (DIC) [6].

High prevalence of AKI in critically ill patients, near to 30 %, was previously documented [2].

A similar prevalence (36.6 %) was described in a successive study, showing that the peak stages were stage 1 in 46.5 %, stage 2 in 22.4 %, and stage 3 in 31.1 % of COVID-19 patients; of these, 14.3 % required renal replacement therapy (RRT) [7]. However, frequency is highly variable among the studies, ranging from 1 % [8] to 46 % [9], with age and elevated interleukin-6 (IL-6) serum levels reported as risk factors for COVID-19 related renal dysfunction [10]. AKI was also associated with an increased risk of death, severe disease, and the need for mechanical ventilation [11].

This study aimed to corroborate the predictive role of estimated glomerular filtration rate (eGFR), assessed at hospital admission (early eGFR) and its association, as renal function alteration marker, with in-hospital death and need for mechanical ventilation in acutely ill hospitalized COVID-19 patients not requiring intensive care at admission. We also explored the association between renal dysfunction and personal, clinical, and laboratory data.

2. Materials and methods

2.1. Patients and data collection

The eGFR-COV19 study was a retrospective observational cohort study. We evaluate charts of patients firstly admitted to normal therapy COVID-19 dedicated wards (Division of Internal Medicine I and II of the San Giuseppe Hospital, Empoli, Italy) between March 6th and May 30th, 2020 and between October 1st, 2020 and March 15th, 2021. All admitted patients had epidemiological, clinical, laboratory, and radiologic findings suspected for COVID-19. Diagnosis of SARS-COV-2 infection was confirmed by real-time polymerase chain reaction (RT-PCR) assay or second generation antigenic test performed on specimens collected by nasopharyngeal swab.

We included COVID-19 patients aged 18 years or older, admitted to the emergency department (ED) for symptomatic SARS-COV-2 infection (fever, cough, dyspnea, nausea and vomiting, diarrhea, thoracic pain, asthenia, myalgias, pharyngodynia, loss of smell and taste).

We excluded patients firstly admitted to the Intensive Care Unit (ICU), those admitted for other medical or surgical conditions with concomitant asymptomatic SARS-COV-2 infection, and patients treated with chronic RRT.

For all enrolled patients, we reported personal data, including age, gender, comorbidities, day of symptoms onset, home treatments, and length of stay (LOS). Comorbidities definitions and medicines taken at home specifications were reported in the Supplementary materials.

Clinical data, evaluated at admission, included mean arterial pressure, Glasgow Coma Scale (GCS), body temperature, cardiac frequency, peripheral oxygen saturation (SpO_2), and the ratio of oxygen saturation to fraction of inspired oxygen [SpO2/FiO2 (SF)] and the ratio of partial pressure of oxygen to fraction of inspired oxygen [PaO2/FiO2 (P/F)]. Laboratory data, evaluated at hospital admission included: complete blood count (CBC); prothrombin time (PT) expressed as the international normalized ratio (INR); activated partial thromboplastin time (aPTT); D-dimer value; fibrinogen; transaminases; total bilirubin; lactate dehydrogenase (LDH); C-reactive protein (CRP); procalcitonin (PCT); interleukin-6 (Il-6); brain natriuretic peptide (BNP); natriemia; kaliemia; serum glucose; arterial partial pressure of oxygen (PaO_2) and carbon dioxide ($PaCO_2$); PaO2/Fio2 ratio (P/F).

Creatinine was assessed at hospital admission and discharge. Baseline creatinine values were estimated computing the means of values found in chart review of patients' medical records from data of hospital admissions in the previous year. At admission (early eGFR), at discharge and baseline eGFRs values were calculated with the creatinine-based 2021 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. AKI and its stages were defined by the Kidney Disease: Improving Global Outcome (KDIGO) criteria [12] as any of the following: increase in serum creatinine by $\geq$ 0.3 mg/dl ($\geq$ 26.5 μmol/l) within 48 h; or increase in serum creatinine to $\geq$1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or urine volume <0.5 mL/kg/h for 6 h. Stage I was defined as a creatinine increase between 1.5 and 1.9 times baseline value, Stage II as an increase between 2.0 and 2.9 times, stage III as an increase over 3.0 times or over an absolute value of 4.0 mg/dl or the need of RRT.

We calculated the difference between baseline GFR values and GFR values assessed at hospital admission (GFR decline, deltaGFR) to evaluate the decline of GFR due to COVID-19; we calculated the difference between GFR assessed at hospital admission and discharge to evaluate worsening or improvement of kidney function; we also calculated the difference between baseline GFR values and GFR values assessed at hospital discharge to estimate the eventual persistence of abnormal renal function at hospital discharge.

Radiology findings acquired by computer tomography (CT) or conventional radiology scans included the presence of interstitial pneumonia.

Acute respiratory distress syndrome (ARDS) was defined by Berlin Criteria [13] and evaluated at admission; criteria were: beginning of the symptoms in the last seven days or worsening in the last seven days; presence of bilateral opacities confirmed by conventional radiology or CT; respiratory distress not supportively explained by cardiac failure or fluid overload; a PaO2/FiO2 (P/F) ratio below 300. The severity of the disease was also evaluated with the CALL Score [14].

Noninvasive ventilation (NIV), including both helmet-continuous positive airway pressure (hCPAP) and BiLevel positive airway pressure (BLPAP), was delivered when oxygen supply with Venturi masks (VM) at 50 % of FiO2 failed to maintain target SpO2 (94–98 %) and respiratory rate (<24 acts per minute), alternated to high flow nasal cannula (HFNC) at the same FiO2 or non-rebreathing reservoir masks. ICU admission decisions involved collaboration between internists and intensivists, but the decision to intubate the patient pertained to the intensivists.

The primary outcome was in-hospital mortality. Secondary outcomes were the development of ARDS and the need for non-invasive ventilation (NIV) and invasive mechanical ventilation (IMV).

We also analyzed differences in personal and laboratory data between patients with eGFR values <60 mL/min/1.73 m^2 and those with eGFR values $\geq$60 mL/min/1.73 m^2.

We retrospectively collected patients' data by review of paper and digital medical records (ARGOS version 4.2422820 and GALILEO version 1.5.3.14.2787 by Dedalus Italy S.p.A., via di Collodi 6/C, 50141 Florence, Italy). A structured web-based data collection form was developed for the retrospective chart review and for collecting clinical and personal data.

Data were collected by the medical staff of the Division of Internal Medicine I and II of the San Giuseppe Hospital, Empoli, Italy. Retrospective chart review studies relying on previously collected data may

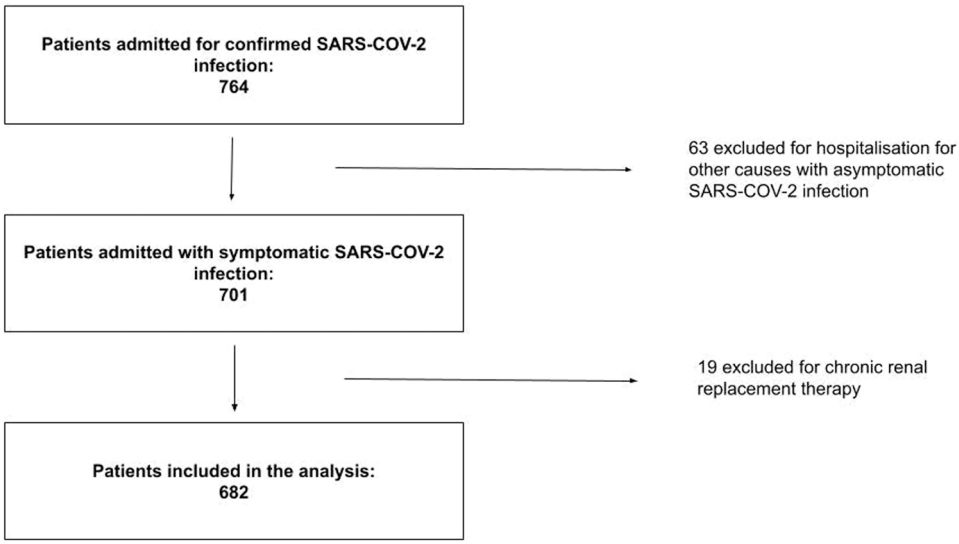

Fig. 1. Flow chart of the patient selection process. Data extraction performed between March 6th and May 30th, 2020 and between October 1st, 2020 and March 15th, 2021.

be wronged by biases due to the study operations, data collection, data entry, and data quality declaration, causing loss of information or approximation. To minimize this possibility, the first author comprehensively and carefully revised data collection, verifying also the sources in case of missing data, to curtail errors and biases. Data were analyzed after anonymization.

The sample size was calculated considering an expected incidence of renal dysfunction of 30 %, with a ratio between non-exposed and exposed of 2:1. Considering alfa = 0.05 and power = 80 %, with a difference in the incidence of the primary outcome of at least 10 %, we estimated need of a sample of 594 patients, using a sample size calculator [15].

The study was carried out and is reported according to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines for observational studies [16].

The study was approved by the local Ethical Committee (BIGCOVID, num. 2161 date 6.9.2021).

Patients gave their written informed consent to participate. For patients unable to give their consent or deceased patients, only the collection of data from clinical records was allowed. The study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

2.2. Statistical analysis

We reported continuous variables as means and their 95th percentile confidence intervals (CIs) if normally distributed, as medians and interquartile ranges (IQRs) if non-normally distributed. Normal distribution was tested with the D'Agostino-Pearson normality test. Categorical variables were reported as absolute counts and percentages.

Differences of continuous variables between groups were tested with the T-test in normally distributed variables, with the Mann-Whitney-test in non-normally distributed variables. Differences over time were tested with paired sample T-test or Wilcoxon test.

Categorical variables were tested with the Chi-square (χ^2) probability distribution test and the Chi-square (χ^2) test for trend (Cochran-Armitage test for trend).

We calculated Odds Ratios (ORs) and their 95th percentile CIs in both univariate and multivariate logistic regression models, with prespecified thresholds for eGFR of 60 and 30 mL/min/1.73 m^2. In multivariate analysis we used the enter method, the simultaneous standard method of entry, as variable selection approach for the multivariable regression model and included only the variables that resulted significant in univariate analysis. For the continuous variables that resulted statistically significant in univariate analysis, we calculated ORs at values associated with the best of their sensitivity and specificity according to the Youden's index for the primary outcome.

This study was conducted retrospectively and based on datasets with plausible missing laboratory results. Listwise deletion of missing values was performed. In univariate analysis we reported data for all the variables included in the study and we excluded those with a loss of data over 10 %. Similarly, we excluded in the multivariate analysis those with a loss of data over 10 %. To cope with this possibility, we included in the retrospective chart review a number of patients far beyond the prespecified sample size to safeguard the strength of the statistical analysis for a loss of data of about 10 %.

The association between low eGFR values and personal and clinical data was tested in a multivariate analysis considering patients without CKD.

We tested the ability of eGFR values computed at admission to predict in-hospital mortality by calculating the area under the curve (AUC) of the receiver operating characteristic (ROC) curves and tested the non-inferiority with both Call Score and IL-6 serum levels. We estimated both sensibility and specificity.

For all the analyses a p-value below 0.05 was considered statistically significant.

All the statistical analyses were performed using MedCalc statistical software (MedCalc Software, Acacialaan 22, Ostend, 8400, Belgium).

3. Results

Of 764 acutely ill hospitalized COVID-19 patients admitted to hospital, 63 were excluded for hospitalization due to other medical or surgical illnesses and 19 for chronic RRT; 682 patients (age range 23–100 years) were included in the analysis (Fig. 1), and 400 were males (58.7 %). The median time since symptom onset was 5 (2−7) days. ARDS occurred in 449 (65.8 %) patients, 310 (45.5 %) required NIV and 44 (6.5 %) IMV; 75 (11 %) were transferred to the ICU. The primary outcome occurred in 137 (20.1 %) patients, median LOS was 11 (IQR 7–17) days.

Median serum creatinine values at hospital admission were 0.91 mg/dL (IQR 0.74–1.18), median eGFR values 77 mL/min/1.73 m^2 (IQR 54–91); eGFR values <60 mL/min/1.73 m^2 were found in 208 (30.5 %) patients, and a serum creatinine value over 1.2 mg/dl was found in 200

Table 1
Baseline characteristics of the study population.

Vital Parameters at admission	
Glasgow Coma Scale	15 (15-15)
Body temperature (°C)	37 (36-38)
Mean arterial pressure (mmHg)	93 (83-101)
Heart rate (bpm)	86 (77-98)
SpO_2/FiO_2	433 (333-446)
Comorbidities	540 (78.9%)
Hypertension	329 (61.2%)
Cardiovascular disease	210 (39%)
Diabetes	137 (25.5%)
Respiratory diseases	112 (20.8%)
Chronic Kidney Disease	93 (17.3%)
Solid or Hematologic Neoplasm	65 (12.1%)
Severe Obesity (Body Mass Index > 35 kg/m^2)	84 (15.6%)
Neuropsychiatric disorders	134 (24.9%)
Chronic pharmacologic treatment	502 (73.6%)
ACE Inhibitors or angiotensin receptor blockers	272 (54.2%)
Anticoagulants	68 (13.5%)
Antiplatelets	155 (30.9%)
Beta-Blockers	147 (29.3%)
Calcium Channel Blockers	84 (16.7%)
Diuretics	107 (21.3%)
Statins	124 (24.7%)
Neuroactive agents	125 (24.9%)
Antidiabetics	101 (20.1%)
Proton Pump Inhibitors	115 (22.9%)
Laboratory findings	
Hemoglobin (g/dl)	13.7 (12.4-14.9)
Platelets (units/L)	207000 (163000-260000)
Leucocyte count (units/L)	8500 (6000-15000)
Neutrophils (units/L)	5500 (3780-8100)
Lymphocytes (units/L)	880 (600-1200)
INR	1.2 (1.1-1.3)
aPTT (sec)	30 (28-33)
D-dimer (μg/mL)	870 (530-1530)
Fibrinogen (mg/dL)	720 (600-850)
Aspartate aminotransferase (U/L)	36 (26-51)
Alanine aminotransferase (U/L)	27 (17-44)
Total bilirubin (mg/dL)	0.6 (0.5-0.8)
CRP (mg/dL)	6.6 (3-12)
PCT (ng/ml)	0.1 (0.06-0.23)
IL-6 (pg/mL)	43 (22-88)
LDH (U/L)	540 (430-700)
BNP (pg/mL)	73 (34-160)
Natriemia (mEq/L)	135 (134-139)
Kaliemia (mEq)	3.9 (3.6-4.2)
Serum Glucose (mg/dl)	127 (107-161)
Renal function tests	
Admission creatinine (mg/dl)	0.91 (0.74-1.18)
Admission creatinine > 1.15 mg/dl	200 (29.3%)
Admission GFR (mL/min/1.73 m^2)	77 (54-91)
Admission GFR between 30- 60 mL/min/1.73 m^2	170 (24.9%)
Admission GFR below 30 mL/min /1.73 m^2	38 (5.6%)
Discharge creatinine (mg/dl)	0.79 (0.65-0.9)
Discharge GFR	88 (70-101)
Baseline creatinine	0.8 (0.7-0.85)
Baseline GFR	86 (71-97)
deltaGFR	7 (0-19)
AKI prevalence	181 (26.5%)
AKI stage I	125 (69%)
AKI stage II	27 (14.9%)
AKI stage III	29 (16%)
Confirmed bilateral interstitial pneumonia	584 (85.6%)
Arterial blood gasses analysis	
pO_2	63 (55-72)
pCO_2	35 (32-39)
PaO2/FiO2	242 (95-300)
CALL Score	11 (10-12)

(29 %) patients. For the majority of patients (658, 96.4 %), we were able to retrieve previous serum creatinine values, so baseline creatinine and GFR values were estimated (for 221 patients, 33.5 %, only one creatinine value was retrieved and used as baseline value), 181 patients (26.5 %) developed AKI and 14 patients (2.1 %) required RRT.

Other personal, clinical, and laboratory data were reported in Table 1.

Serum creatinine values at hospital admission were significantly higher and eGFR values at admission were significantly lower than at hospital discharge ($p < 0.001$) and baseline ($p < 0.001$). The median deltaGFR was 7 (0−19), and 288 (42 %) patients had deltaGFR over 10 mL/min/1.73 m. Among the patients who survived, 40 (7.7 %) had altered creatinine serum levels and 47 (9 %) had low GFR at hospital discharge (creatinine serum level at hospital discharge was missing in 25 patients).

Creatinine serum levels at hospital admission were higher (1.14 mg/dl CI 0.84–1.5 vs 0.89 mg/dl, CI 0.72–1.1, $p < 0.001$), and eGFR values were lower (53 mL/min/1.73 m^2, CI 39–79 vs 81 mL/min/1.73 m^2, CI 62–84 $p < 0.001$) in the patients who died respect to the patients who survived. Likewise, deltaGFR values were higher in the patients who died (14 mL/min/1.73 m^2, CI 3–26 vs 5 mL/min/1.73 m^2 CI 0–18 $p < 0.001$) and AKI was more frequent in this group (71/137, 51.8 % vs 110/545, 13 % $p < 0.001$). Other differences between the patients who died respect to the patients who survived are reported in Table 2.

In the univariate analysis, an eGFR value between 60 and 30 mL/min/m^2 had an OR for primary outcome of 3.9 (CI 2.6–5.9, $p < 0.001$) and a value below 30 had an OR of 7.10 (CI 3.6–14, $p < 0.001$). Similar ORs were found for both a deltaGFR >10 mL/min/m^2 (OR 2.2, CI 1.5–3.3 $p < 0.001$) and AKI (OR 4.3, CI 2.9–6.4, $p < 0.001$).

In the multivariate logistic regression models, an eGFR value <60 mL/min/m^2 was independently associated with risk of mortality (OR 2.6, CI 1.7–4.8, $p = 0.003$), as well as age > 73 years (OR 4.3, CI 2–9, $p < 0.001$), lymphocyte count below 460 u/L (OR 3, CI 1.4–6.4, $p = 0.004$) and platelet count below 177000 (OR 2.2, CI 1.2–4.2, $p = 0.017$). As shown in Table 2 and Fig. 2, comorbidities, IL-6 serum level over 75 pg/mL and PaO2/FiO2 below 250 were associated with an increased risk of death (nearly significant). AKI also correlated with a significant increase in the risk of death (OR 3.1, CI 1.6–6 $p < 0.001$), while deltaGFR over 10 mL/min/m^2 was not associated with a significant increase in the risk of death (OR 1.6, CI 0.9–2.9, $p = 0.135$); as detailed in Table 6 in Supplementary material, IL-6 serum levels over 75 pg/mL, PaO_2/FiO_2 below 250 and comorbidities in the last two models were associated with a significant increase of the risk of death, as well as older age, and low platelet and lymphocyte count.

eGFR values were just about but not significantly different between ARDS and non-ARDS patients ($p = 0.06$); the deltaGFR values were significantly higher in ARDS patients (OR 7.3, CI 0.1–20 vs 4.5, 1–15, $p = 0.037$) but without a significant increment of the risk of death (OR 1.3, CI 0.94–1.8, $p = 0.10$). No association between ARDS and AKI was found ($p = 0.55$) (Table 3).

Similar findings were found for ventilated patients, as eGFR values were not different ($p = 0.37$), but deltaGFR values were higher in ventilated patients (7.4 mL/min/m^2, CI 0.14–22 vs 5.4, 0–16, $p = 0.031$) with a modest increment of the risk of death (OR 1.4, CI 1.02–1.9 $p = 0.04$); differences are detailed in Table 7 in Supplementary materials.

The statistical significance of the correlation between deltaGFR and need for mechanical ventilation was not confirmed in multivariate analysis (Table 2); factors independently associated with increased risk of mechanical ventilation were: LDH values over 580 u/L (OR 2.2, CI 1.4–3.5, $p = 0.001$) and a PaO_2/FiO_2 below 250 (OR 2.9, 1.8–4.6, $p < 0.001$), while IL-6 serum levels over 75 pg/mL correlated with an increased risk of mechanical ventilation (nearly significant); age <73 years was associated with a reduction of risk of mechanical ventilation (OR 0.5, CI 0.3–0.79, $p = 0.002$). AKI was not associated with an increased risk of mechanical ventilation ($p = 0.27$).

The values of eGFR showed good reliability in predicting in-hospital mortality (AUC 0.71, CI 0.68–0.74, $p < 0.001$), with a sensibility of 60 % and specificity of 77 % for a reference value < 60 mL/min/1.73 m^2. It

Table 2
Differences between acutely ill hospitalized COVID-19 patients who died or survived.

	Patients who died	Patients who survived	Younden's index	p value
Age	82 (74–87)	68 (56–78)	>73	p < 0.001
Male sex	85/137 (62 %)	315/545 (58 %)		p = 0.42
Comorbidities	133/137 (97 %)	4/545 (0.7 %)		p < 0.001
Polypharmacy (> 3 medicines)	97/137 (70.8 %)	228 (41.8 %)		p < 0.001
Admission creatinine (mg/dl)	1.14 (0.84–1.5)	0.89 (0.73–1.10)	>1.13	p < 0.001
Admission GFR (mL/min/1.73 m^2)	53 (39–79)	81 (62–84)	<60	p < 0.001
deltaGFR (mL/min/1.73 m^2)	14.6 (3–26)	5 (0–18)	>10	p < 0.001
AKI	71/137 (51.1 %)	110/545 (13 %)		p < 0.001
Body temperature (°C)	37.4 (36–38)	37 (36–38)		p = 0.17
Mean arterial pressure (mmHg)	91 (82–101)	93 (85–101)		p = 0.15
Heart rate (bpm)	86 (75–98)	87 (77–98)		p = 0.82
SpO_2/FiO_2	371 (220–428)	438 (395–448)	<414	p < 0.001
Haemoglobin (g/dl)	13.3 (11.8–14.7)	13.8 (12.5–15)	<12.6	p = 0.024
Lymphocyte count (units/L)	800 (455–1100)	900 (640–1250)	<460	p = 0.001
Neutrophils (units/L)	6100 (4600–9500)	5340 (3700–7840)	>5000	p = 0.004
Platelets (units/L)	177000 (137000–249000)	210000 (168500–256750)	<177 000	p < 0.001
INR	1.2 (1.1–1.4)	1.2 (1.1–1.3)	>1.2	p = 0.006
aPTT (sec)	31 (28–34)	30 (28–32)	>33	p = 0.015
D-dimer (μg/mL)	1190 (740–2000)	830 (480–1400)	>1040	p < 0.001
Fibrinogen (mg/dl)	680 (550–820)	735 (620–870)	<620	p = 0.009
Aspartate aminotransferase (U/L)	40 (28–62)	34 (26–50)	>37	p = 0.011
Alanine aminotransferase (U/L)	27 (16–43)	27 (18–44)		p = 0.38
Total bilirubin (mg/dL)	0.7 (0.5–0.9)	0.6 (0.5–0.8)	>0.7	p = 0.013
C-reactive protein (mg/dL)	10 (5–15)	5.7 (2.7–11)	>9	p < 0.001
Procalcitonin (ng/mL)	0.21 (0.1–0.5)	0.01 (0.05–0.18)	>0.12	p < 0.001
Interleukin-6 (pg/mL)	85 (41–164)	39 (19–72)	>75	p < 0.001
LDH (U/L)	601 (470–790)	530 (410–670)	>580	p < 0.001
BNP (pg/mL)	140 (81–350)	61 (32–135)	>81	p < 0.001
Natriemia (mEq/L)	136 (134–139)	136 (133–139)		p = 0.6
Kaliemia (mEq/L)	4 (3.8–4.5)	3.9 (3.5–4.2)	>3.9	p < 0.001
Serum glucose	137 (108–176)	125 (107–156)		p = 0.072
PaO2/FiO2	190 (73–250)	260 (110–304)	<250	p < 0.001
Bilateral pneumonia	127/137 (92.7 %)	457/536 (85.5 %)		p = 0.021
ARDS	125/137 (91 %)	324/545 (59 %)		p < 0.001

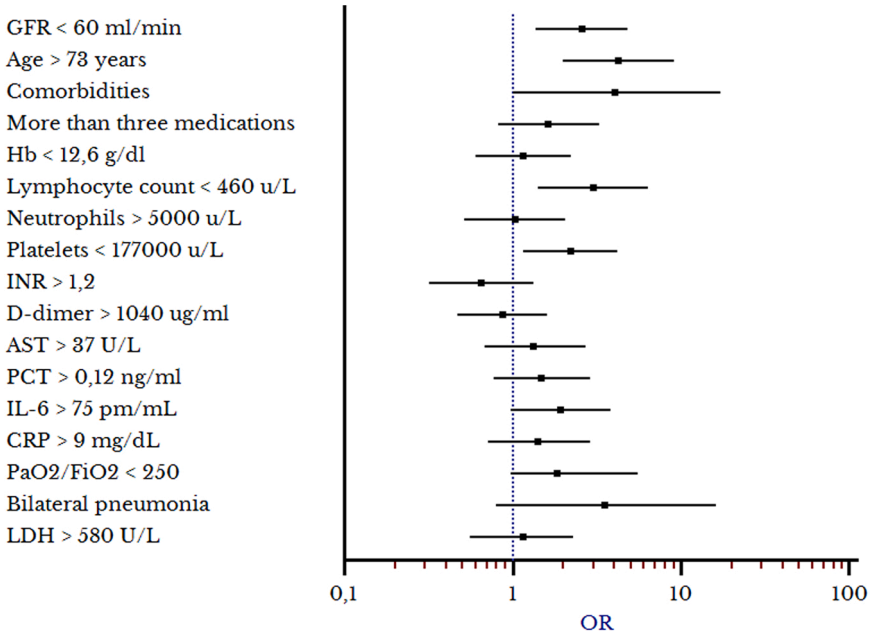

Fig. 2. Multivariacoutcome.

resulted superior to both deltaGFR (AUC 0.62, CI 0.58–0.65, p < 0.001) and creatinine serum levels (AUC 0.66, 0.63–07, p < 0.001). Creatinine serum levels showed lower sensibility (51 %) and similar specificity (78 %), as deltaGFR showed both lower sensibility (57 %) and specificity (62 %).

As shown in Fig. 3, eGFR resulted non-inferior to both CALL Score (AUC 0.70, CI 0.66–0.74, p = 0.54) and IL-6 serum levels (AUC 0.71, CI 0.67–0.75, p = 0.66), assessed at admission, in predicting in-hospital death. CALL Score over 10 showed better sensibility (82 %) and lower specificity (49 %); IL-6 serum levels had both sensibility (57 %) and specificity (76 %) values similar to eGFR.

Differences between patients with and without decrease of eGFR

Table 3
Multivariate analysis for eGFR and primary outcome and for deltaGFR class and secondary outcome.

Variables	ORs	p value
eGFR for in-hospital mortality		
eGFR < 60 mL/min/1.73 m²	2.6 (1.7-4.8)	0.003
Age > 73 years	4.26 (2-9)	< 0.001
Comorbidities	4.1 (1-17)	0.051
Polypharmacy (> 3 medicines)	1.6 (0.82-3.25)	0.15
Hb > 12.6 g/dl	1.15 (0.6-2.4)	0.68
LDH > 580 u/L	1.15 (0.55-2.4)	0.7
Lymphocytes < 460 u/L	3 (1.4-6.3)	0.004
Neutrophils > 5000 u/L	1.03 (0.5-2)	0.93
Platelets < 177000 u/l	2.2 (1.2-4.2)	0.017
INR > 1.2	0.65 (0.32-1.3)	0.24
D-dimer > 1040	0.9 (0.46-1.6)	0.65
AST > 37 u/L	1.3 (0.7-2.6)	0.4
PCT > ng/mL	1.5 (0.8-2.9)	0.23
CRP > 9 mg/dl	1.4 (0.7-2.9)	0.31
IL-6 > 75 pg/ml	1.9 (0.97-3.5)	0.062
pO_2/Fio_2 < 250	1.9 (0.98-3.5)	0.059
Bilateral pneumonia	3.5 (0.8-16)	0.106
deltaGFR for ventilation		
deltaGFR> 10 mL/min/1.73 m²	1.4 (0.9-2.1)	0.114
Age > 73 years	0.5 (0.3-0.8)	0.002
Hb > 12.6 g/dl	0.7 (0.4-1.2)	0.166
LDH > 580 u/L	2.2 (1.4-3.5)	0.001
Lymphocytes < 460 u/L	1.6 (0.9-2.9)	0.12
Neutrophils > 5000 u/L	1.2 (0.8-1.9)	0.316
INR > 1.2	1.1 (0.7-1.8)	0.778
AST > 37 u/L	1.2 (0.8-1.8)	0.403
PCT > ng/mL	1.1 (0.7-1.7)	0.728
CRP > 9 mg/dl	0.9 (0.5-1.4)	0.619
IL-6 > 75 pg/ml	1.6 (1-2.6)	0.063
pO_2/Fio_2 < 250	2.9 (1.8-4.5)	< 0.001

<60 mL/min/1.73 m^2 were reported in Table 4. For patients without CKD, in the multivariate analysis an association with increased risk of in-hospital death was found for the chronic use of ACE (angiotensin-converting enzyme) inhibitors and angiotensin receptor blockers (ARBs) (OR 2.3, IC 1.9–4.6, p = 0.014), hemoglobin below 12.6 g/dL (OR 3.8, CI 1.9–7.5, p < 0.001), platelet count below 177000 u/L (OR 2.2, CI 1.2–4.3, p = 0.017), INR over 1.2 (OR 2.2, CI 1.03–4.6, p = 0.043) and PaO_2/FiO_2 below 250 (OR 2.1, CI 1.04–4.1, p = 0.039).

Use of beta-blockers, age over 73 years, and a D-dimer value over 1040 μg/mL were associated with increased risk of in-hospital death (nearly significant), as detailed in Table 5 and Fig. 4.

4. Discussion

Defining alteration in renal function in acute settings is often challenging and a direct measurement of the GFR in acute settings is often unpractical, as it requires specific or radioactive substances and a constant infusion of them to reach a steady state [17]. Over the last two decades, many equations were developed for estimating the GFR using endogenous biomarkers such as serum creatinine and cystatin C, and they are actually adopted for staging CKD [18].

However, estimation of GFR (eGFR), usually based on creatinine serum levels, is widely used even in acute care settings as a marker of renal function. Dosing of some medications, such as antibiotics, requires the evaluation of GFR even in critically ill patients [19]. The previous Risk, Injury, Failure, Loss, and End-Stage Renal Disease (RIFLE) criteria included the reduction of GFR to define and stage AKI [20]; the subsequent KDIGO (Kidney Disease: Improving Global Outcomes) guidelines removed the GFR-based favoring the creatinine-based and the urinary output-based criteria, as many studies reported errors in staging AKI [21].

Anyway, the significance of an increase in serum creatinine levels is influenced by the baseline GFR. Creatinine serum level augmentation of as little as 0.3 mg/dL could correspond to a great decrease in GFR, so that creatinine serum levels in the normal range or with minor changes could mask sever GFR alteration. Consequently, measuring and reporting both eGFR and creatinine serum level changes was strongly suggested for assessing AKI [22].

In this study, the use of GFR assessed at hospital admission and estimated with the last CKD-EPI formula showed good capability to identify alterations in renal function due to COVID-19. In fact, eGFR values were significantly lower with respect to both hospital discharge and baseline values, and the low eGFR-based incidence was similar to creatinine-based AKI incidence. Moreover, a high proportion of patients showed deltaGFR over 10 mL/min/1.73 m^2, so that eGFR variations could reliably detect subclinical kidney damage in the early phases of SARS-COV-2 infection. A recent meta-analysis reported an incidence of AKI of 19.45 %, which is slightly lower with respect to our findings; however, the meta-analysis included both inpatient and outpatient [23].

A very high proportion of the hospitalized COVD-19 patient recovered renal function and only 9 % of the patients maintained a GFR <60 mL/min/1.73 m^2. The recovery rate was greater than recently reported [24], with a recovery rate of 74.8 % reported in our study. However, in our analysis, a significantly lesser proportion of ICU

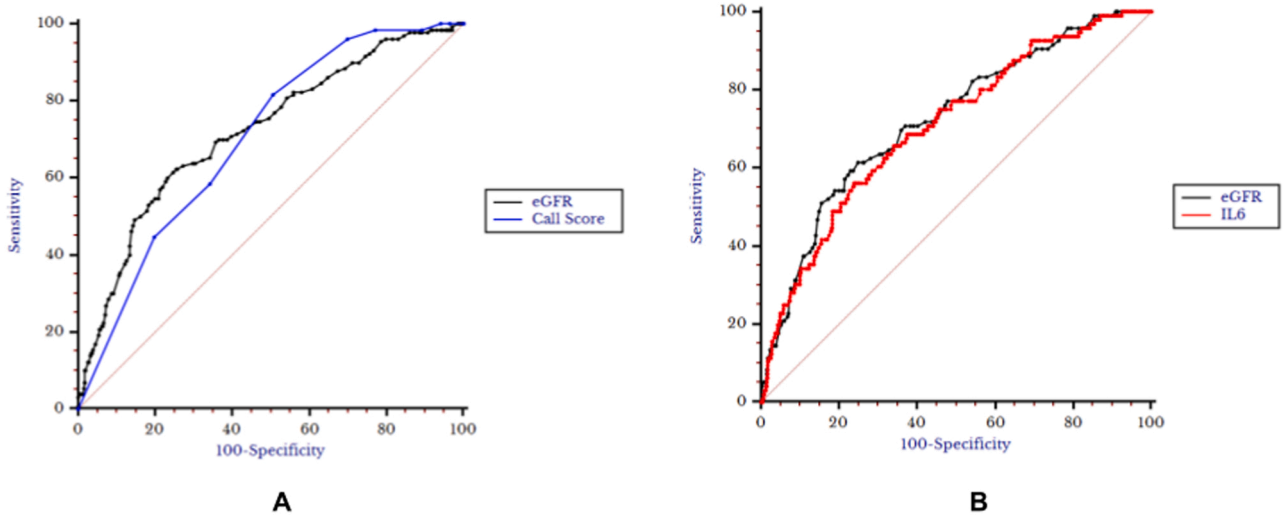

Fig. 3. Comparison of ROC curves for eGFR and Call Score (A) and IL-6 (B) respectively.

Table 4
Differences between patients with and without eGFR value below 60 mL/min/1.73 m^2.

	GFR < 60 (mL/min/1.73 m^2)	GFR > 60 (mL/min/1.73 m^2)	p value
Age	80 (71-86)	67 (56-78)	< 0.001
Male sex	129/203 (63.5%)	271/479 (56.6%)	P = 0.10
Comorbidities			
Hypertension	128/203 (63.1%)	191/477 (40%)	< 0.001
Cardiovascular diseases	107/203 (53%)	103/477 (21.6%)	< 0.001
Diabetes	52/203 (25.7%)	76/477 (16%)	0.01
Respiratory diseases	45/203 (22.3%)	67/477 (14%)	0.011
Chronic kidney disease	80/203 (39.6%)	13/477 (2.7%)	< 0.001
Solid or Hematologic Neoplasm	26/203 (12.8%)	39/477 (8.2%)	0.075
Severe Obesity	28/203 (13.8%)	56/477 (11.7%)	0.53
Neuropsychiatric disorders	46/203 (22.7%)	86/477 (18%)	0.011
Chronic pharmacologic treatment			
ACE-Inhibitors and ARBs	115/203 (56.7%)	147/477 (30.8%)	< 0.001
Anticoagulants	33/203 (16.3%)	34/477 (7.1%)	0.001
Antiplatelets	63/203 (31%)	88/477 (18.4%)	0.002
Beta-Blockers	73/203 (36%)	74/477 (16.1%)	< 0.001
Calcium Channel blockers	35/203 (17.3%)	49/477 (10.3%)	0.017
Diuretics	59/203 (29%)	48/477 (10%)	< 0.001
Statins	48/202 (23.8%)	76/477 (16%)	0.024
Neuroactive agents	44/203 (21.2%)	81/477 (17%)	0.19
Antidiabetic agents	44/202 (21.8%)	57/477 (11.9%)	0.004
Proton pump inhibitors	45/203 (21.2%)	70/477 (14.7%)	0.025
Laboratory parameters			
Haemoglobin (g/dl)	12.9 (11.6-14.5)	13.9 (12.8-15)	< 0.001
Platelets (units/L)	190000 (145000-243000)	212000 (170000-270000)	< 0.001
Neutrophils (units/L)	5510 (4000-8640)	5500 (3710-8000)	0.427
Lymphocytes (units/L)	810 (550-1200)	900 (640-1200)	0.057
INR	1.2 (1.1-1.3)	1.2 (1.1-1.2)	< 0.001
aPTT (sec)	30 (28-34)	30 (28-32)	0.087
D-dimer (μg/ml)	1150 (650-2020)	690 (570-830)	< 0.001
Fibrinogen (mg/dl)	38 (25-51)	740 (620-870)	0.032
Aspartate aminotransferase (U/L)	23 (16-36)	35 (27-51)	0.875
Alanine aminotransferase (U/L)	0.6 (0.5-0.8)	29 (19-49)	< 0.001
Total bilirubin (mg/dl)	8.4 (3.2-14)	0.6 (0.5-0.8)	0.572
CRP (mg/dL)	0.17 (0.1-0.43)	5.9 (2.8-11)	0.001
PCT (ng/ml)	57 (31-111)	0.09 (0.05-0.17)	< 0.001
IL-6 (pg/mL)	560 (447-745)	41 (19-73)	< 0.001
LDH (U/L)	145 (63-330)	530 (415-680)	0.016
BNP (pg/mL)	137 (133-140)	(30-112)	< 0.001
Natriemia (mEq/L)	4 (3.7-4.5)	136 (134-138)	0.227
Kaliemia (mEq)	136 (110-180)	3.8 (3.6-4.1)	< 0.001
Serum Glucose (mg/dl)	228 (93-278)	124 (107-150)	0.006
PaO2/FiO2		260 (99-300)	0.021
Bilateral pneumonia	168/203 (83.8)	416/477 (87.2%)	0.054

Table 5
Multivariate analysis for association between personal and clinical factors and low eGFR values (patients with CKD not included).

Variables	ORs	p-value
Age > 73 years	2 (0.97-4.1)	0.061
Hypertension	0.95 (0.43-2.1)	0.911
Cardiovascular disease	0.71 (0.3-1.8)	0.475
Diabetes	0.3 (0.1-1.3)	0.108
Respiratory disease	0.7 (0.2-2)	0.464
Neuropsychiatric conditions	0.5 (0.24-1.3)	0.161
ACE and ARBs	2.3 (1.2-4.6)	0.014
Antiplatelets	0.5 (0.2-1.2)	0.114
Anticoagulants	0.7 (0.3-2.4)	0.547
Beta-blockers	2.3 (0.99-6.4)	0.051
Calcium channel blockers	1.6 (0.6-4)	0.304
Diuretics	1.6 (1-3.9)	0.299
Statins	1.1 (0.46-2.6)	0.855
Antidiabetics	3.5 (0.9-13)	0.081
Proton pump inhibitors	1.4 (0.6-3.3)	0.443
Hb > 12.6 g/dl	3.7 (1.9-7.5)	< 0.001
Platelets < 177000 u/L	2.2 (1.2-4.5)	0.017
INR > 1.2	2.2 (1.03-4.6)	0.043
D-dimer > 1040 μg/ml	1.9 (0.97-3.6)	0.063
CRP > 9 mg/dL	0.9 (0.4-1.9)	0.764
PCT > 12 ng/ml	1.7 (0.86-3.4)	0.13
IL-6 > 75 pg/ml	0.9 (0.4-1.9)	0.789
LDH > 580 u/L	1 (0.5-2)	0.938
PaO_2/FiO_2 < 250	2.1 (1.04-4)	0.039

needing patients were included.

Many risk factors for death in the hospitalized COVD-19 patient were described. Age and comorbidities were reported since the initial studies [25]. Other parameters associated with grim prognosis included markers of inflammation and other laboratory parameters such as altered blood cells count values, especially in critically ill patients [26]. In our multivariable models, we confirmed that increased age, low lymphocyte and platelet counts, increased IL-6 serum levels, and renal dysfunction, expressed as both AKI and low eGFR, correlated significantly with increased risk of in-hospital death.

The efficacy of eGFR in predicting outcome in acutely ill patients is not well documented. However, a good prognostic capacity for eGFR in acute myocardial infarction and acute heart failure [27,28] and a correlation between low eGFR and in-hospital mortality in acute pancreatitis-related necrosis was also found [29].

Predicting prognosis in acutely ill COVID-19 patients is often challenging and frequently patients at high risk of death are hospitalized in medical regular wards. Previously, our group tested the hypothesis that both CALL Score [30] and IL-6 serum levels [31] could reliably predict clinical deterioration and in-hospital death. Differently from other reports and meta-analysis [32], our data did not confirm the association between low eGFR and ARDS; however, in univariate analysis a high deltaGFR values showed near significant association with the risk of need for mechanical ventilation. Previous comparison of risk factors of COVID-related AKI with usual AKI risk factors found that respiratory rate, altered blood cells counts and LDH correlated with AKI in COVID-19 patients [33].

In our study, eGFR values, but not creatinine serum levels at admission and deltaGFR, showed non-inferior reliability respect to both CALL Score and IL-6 serum levels in predicting in-hospital mortality. Our results corroborate the findings of two topical studies. A recent study, aiming at finding biomarkers able to stratify acutely ill COVID-19 patients requiring sub-intensive/intensive care in order to prevent poor outcome, retrospectively evaluated a small sample size (231 patients) and pinpointed to eGFR value at hospital admission as good predictor of high risk for clinical deterioration and in-hospital death [34]. The other study intentionally considered hospitalized elderly COVID-19 patients aged ≥65 years [35], whereas our study considers hospitalized COVID-19 patients aged ≥18 years, so that our study population is much more inclusive.

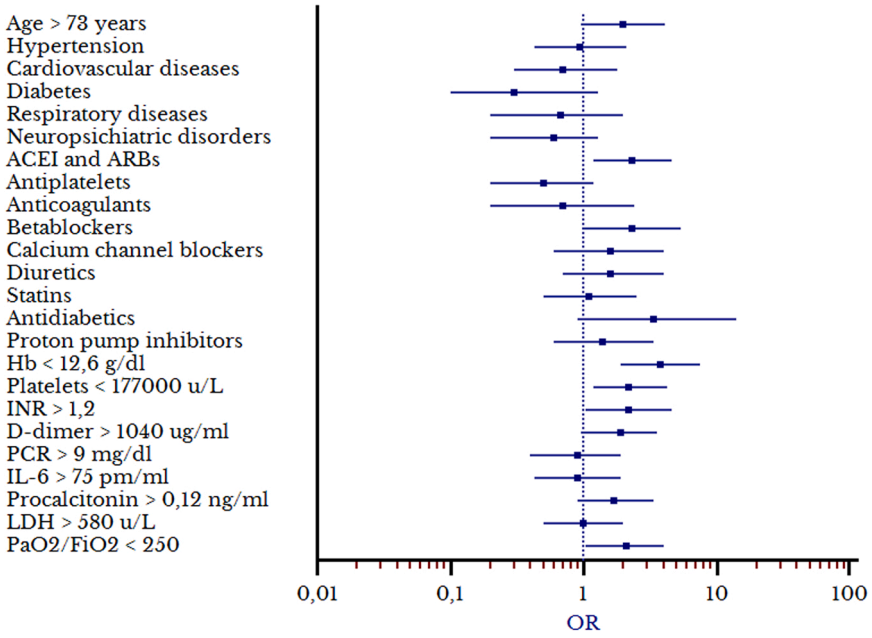

Fig. 4. Multivariate analysis for association between personal and clinical factors and low eGFR values.

On the whole, multiple easily available parameters such as eGFR, PaO_2/FiO_2 (P/F) ratio, CALL Score and IL-6 serum levels could allow to stratify acutely hill COVID-19 patients at hospital admission, in particular could consent to identify patients requiring early sub-intensive care unit and ICU admission. We also found that in acutely hill COVID-19 patients without CKD, chronic use of ACE and ARBs, low hemoglobin and platelet count, high INR, and low PaO_2/FiO_2 (P/F) ratio are associated with low eGFR values.

Our study has some limitations, mainly related to its retrospective monocenter design, while the strengths are related to the real-world setting, the large sample size evaluated and the great number of variables analyzed. Regarding good generalizability, the studied population was made up entirely of members with disease (cases) and study participants were recruited from not specialized and all-encompassing clinics (two different Divisions of Internal Medicine with completely different medical staff). Besides, the age range of enrolled patients was wide and information on the study factors and covariates were collected in a fair and equal manner for all subjects to avoid information bias (data inaccuracy).

5. Conclusions

The SARS-COV-2 pandemic represented a challenge for healthcare professionals worldwide. ARDS, as well as cytokines storm and the association with thromboembolic events, were the most frequent COVID-19 related complications, directly impacting on patient'sprognosis and management strategies. Many biomarkers and scores were tested to define prognosis in COVID-19 patients, including both respiratory and immunologic parameters, with contrasting results. Even if a role for AKI was described since the earliest clinical observational studies, its frequency, durability, and impact on prognosis appeared unclear, as many studies showed conflicting results. Moreover, renal dysfunction parameters were not typically used for the most important decision, such as inpatient transfer to the ICU or administration of antivirals or immunosuppressants. The results of our study conducted on acutely ill hospitalized COVID-19 patients strongly suggest that eGFR values assessed at hospital admission show good capability to detect clinical and subclinical renal dysfunction, similar to KDIGO-defined AKI. Low eGFR values were independently associated with in-hospital mortality and resulted non-inferior to CALL Score and IL-6 serum levels in predicting in-hospital death. Anemia, low platelet count, low PaO_2/FiO_2 P/F ratio, high INR, and chronic use of ACE and ARBs were associated with lower eGFR values. Overall, eGFR value assessed at admission is a useful and reliable renal dysfunction marker and in-hospital mortality predictor in acutely ill hospitalized COVID-19 patients initially admitted to medical regular wards.

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Institutional review board statement

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Consent

Written informed consent was obtained from all study participants or their legal representatives.

CRediT authorship contribution statement

F.C. and R.T. conceived the article, wrote the paper; G.M. reviewed the scientific literature, supervised the statistical analysis, wrote the paper; F.C. and R.T. created the database, performed the statistical analysis, reviewed data collection; L.C., S.B., M.S.M., S.D., D.D.S., S.B., I. S., V.M., M.M.G., G.V., R.L., E.C., C.M., G.P. collected the data. G.P. and G.L. administered and supervised the whole project. All authors approved the final version of the manuscript and agreed to the published version of the manuscript. F.C., R.T. and G.M. take the responsibility for the integrity of the work as a whole.

Conflict of interest statement

The author declares that there are no conflicts of interest with respect to the authorship and/or publication of this article.

Data availability

Data will be made available on request.

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We thank all the patients who voluntarily consented to participate in the study. I apologize to authors whose relevant publications were not cited due to space limitations.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.biopha.2022.113454.

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