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Kidney dysfunction is associated with adverse outcomes in internal medicine COVID-19 hospitalized patients

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Abstract. – OBJECTIVE: In this study, we aimed to evaluate the kidney involvement assessed by estimated glomerular filtration rate (eGFR), the associations with specific clinical disease variables and laboratory findings, and the predictive role of eGFR on clinical outcomes of patients admitted with COVID-19 in Internal Medicine ward in the first wave.

PATIENTS AND METHODS: Clinical data of 162 consecutive patients hospitalized in the University Hospital Policlinico Umberto I in Rome, Italy, between December 2020 to May 2021 were collected and retrospectively analyzed.

RESULTS: The median eGFR was significantly lower in patients with worse outcomes than in patients with favorable outcomes [56.64 ml/min/1.73 m² (IQR 32.27-89.73) *vs.* 83.39 ml/min/1.73 m² (IQR 69.59-97.08), *p*<0.001]. Patients with eGFR < 60 ml/min/1.73 m² (n=38) were significantly older compared to patients with normal eGFR [82 years (IQR 74-90) *vs.* 61 years (IQR 53-74), *p*<0.001] and they had fever less frequently [39.5% *vs.* 64.2%, *p*<0.01]. Kaplan-Meier curves demonstrated that overall survival was significantly shorter in patients with eGFR < 60 ml/min/1.73 m² (*p*<0.001). In multivariate analysis, only eGFR < 60 ml/min/1.73 m² [HR=2.915 (95% CI=1.110-7.659), *p*<0.05] and platelet to lymphocyte ratio [HR=1.004 (95% CI=1.002-1.007), *p*<0.01] showed a significant predictive value for death or transfer to intensive care unit (ICU).

CONCLUSIONS: Kidney involvement on admission was an independent predictor for death or transfer to ICU among hospitalized COVID-19 patients. The presence of chronic kidney disease could be regarded as a relevant factor in risk stratification for COVID-19.

Key Words:
COVID-19, Infection, Kidney dysfunction, Clinical outcomes.

Introduction

The infection from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread worldwide causing devastating consequences on global health[1]. The course of coronavirus disease 2019 (COVID-19) is markedly influenced by age and comorbidities. Among comorbidities, the actual incidence of chronic kidney disease (CKD) in COVID-19 hospitalized patients is not reported, probably due to the difficulty in differentiating CKD from acute kidney injury (AKI) in hospitalized patients during the pandemic outbreak[2].

Renal impairment seems to be a frequent finding in COVID-19 patients and correlate to mortality and severity[3,4], although its role on infection risk and disease prognosis is still debated. Some studies[5,6] showed a >3-fold increased rate of infection with SARS-CoV-2/COVID-19 amongst patients with estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m², with a 60-day risk of death or requirement of intensive care of >20%. Identifying and eliminating factors predicting a negative outcome is a key to improving survival from COVID-19.

The aims of this retrospective study were to evaluate the kidney involvement assessed by eGFR in COVID-19 consecutive hospitalized patients in Internal Medicine ward in the first wave, to assess associations with specific clinical disease variables and laboratory findings, and to evaluate the predictive role of eGFR on clinical outcomes.

Patients and Methods

Study Population and Data Collection

In this study we analyzed consecutive adult patients with a diagnosis of COVID-19 who were admitted to Internal Medicine (IM) ward in the University Hospital Policlinico Umberto I

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in Rome, Italy, between December 2020 to May 2021, during the first wave of the pandemic. The hospital was partially converted to COVID-19 management during the pandemic outbreak. The hospital facility was divided into three different levels of care: mild disease, severe disease (Pneumology Unit/ intensive care unit), critical care and IM was organized for mild disease. For each patient, data were acquired from paper charts including demographic and clinical variables (age, gender), early symptoms of COVID-19 and coexisting comorbidities (hypertension, diabetes mellitus, coronary artery disease, cerebrovascular disease, heart failure, chronic obstructive pulmonary disease, obstructive sleep apnea, chronic kidney disease) and medications.

The detection of SARS-CoV-2 nucleic acid was obtained by reverse-transcriptase polymerase chain reaction (RT-PCR) test in nasopharyngeal swab/other biological specimens performed in the emergency department in association with a chest imaging (computed tomography or radiography).

At baseline, eGFR was estimated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, expressed as a single equation: GFR = 141 min (sCr/k, 1)$^{\alpha}$x max (sCr/k, 1)$^{-1.209}$ x 0.993^{Age} x 1.018 (if female) x 1.159 (if Afro-American), in which k is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of sCr/k or 1, and max indicates the maximum of sCr/k or 1[7]. CKD is defined with eGFR according to Kidney Disease Improving Global Outcomes (KDIGO)[8]. Five stages of CKD are defined by value of GFR estimated by CKD-EPI creatinine equation: 1 stage: eGFR>90 ml/min/1.73 m^2; 2 stage: eGFR 60-89 mL/min/1.73 m^2; 3a stage: eGFR 45-59 mL/min/1.73 m^2; 3b stage: eGFR 30-44 mL/min/1.73 m^2; 4 stage: eGFR 15-29 mL/min/1.73 m^2; 5 stage: eGFR<15 mL/min/1.73 m^2. Stages 3a and 3b were grouped. CKD is defined as abnormalities of kidney function with estimated eGFR <60 ml/min/1.73 m^2 present over 3 months. Urine criteria were not used in this analysis. Complete blood cell counts, which included total white blood cells, neutrophils, lymphocytes, and platelets, were obtained at the time of admission. The neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) were calculated as the ratio of neutrophil count to lymphocyte count and as the ratio of platelet count to lymphocyte count, respectively.

The study was conducted in accordance with the Declaration of Helsinki and informed consent was obtained from all individual participants included in the study. The Ethics Committee of Policlinico Umberto I approved the study with number 109/2020.

Statistical Analysis

The coefficient of kurtosis was used to evaluate normal distribution of data. All the results are expressed as median and interquartile range (IQR). Group comparisons were made by Kruskal-Wallis' test. Spearman's rank correlation coefficient was used to test for an association between numerical variables. The Chi-square test or Fisher's exact test, as appropriate, were used to compare categorical variables. Kaplan-Meier curves with the log-rank test were used to evaluate free survival from bad outcome (death or transfer to ICU) in hospitalized patients with normal or reduced eGFR. In univariate and multivariate analysis, Cox regression with Hazard Ratio (HR) and 95% confidence intervals (CI) was applied to evaluate the predictive role of independent variables for poor outcome. *p*-values <0.05 were considered significant. SPSS version 26.0 software (IBM Corp., Armonk, NY, USA) was used for statistical analysis.

Results

Clinical data of 162 consecutive patients hospitalized in IM ward in the University Hospital "Policlinico Umberto I" in Rome, Italy, between December 2020 to May 2021, in the first wave, were collected and retrospectively analyzed in this study. The most frequent symptoms of SARS-CoV-2 infection were fever (58%), dyspnea (42%) and cough (34.6%) and the median from onset of these symptoms to hospitalization was 8 days (IQR 5-17). Among concomitant comorbidities, the most frequent were systemic arterial hypertension (56.8%), cardiac diseases (31.5%), dyslipidemia (22.2%) and diabetes mellitus (17.3%). Moreover, 38 patients (23.4%) had eGFR < 60 ml/min/1.73 m^2 at the admission. Table I shows the clinical features of the patients. In 135 patients the outcome was favorable: 70 (43.2%) patients were discharged into home isolation with positive test result for coronavirus and 65 (40.1%) were discharged after complete recovery and test negativization. Twenty-seven patients had a worse

Table I. Clinical characteristics of 162 consecutive patients.

Age, years, median (IQR)	68 (56-80)
M/F, n (%)	77 (47.5)/85 (52.5)
RT-PCR test Covid-19, days, median (IQR)	7 (1-15)
Symptom onset, days, median (IQR)	8 (5-17)
Ground glass at HRCT, n (%)	130 (80.2)
Symptoms of SARS-CoV2 infection	
Asthenia, n (%)	38 (23.5)
Dyspnea, n (%)	68 (42)
Fever, n (%)	94 (58)
Ageusia, n (%)	7 (4.3)
Anosmia, n (%)	6 (3.7)
Cough, n (%)	56 (34.6)
Pharyngodynia, n (%)	8 (5)
Comorbidities	
Systemic arterial hypertension, n (%)	92 (56.8)
Diabetes mellitus, n (%)	28 (17.3)
Dyslipidemia, n (%)	36 (22.2)
Cardiac diseases, n (%)	51 (31.5)
Chronic obstructive pulmonary disease, n (%)	17 (10.5)
Cancer, n (%)	27 (16.7)
Others, n (%)†	28 (17.3)
Hb, g/dl, median (IQR)	12.55 (11.15-13.85)
NLR, median (IQR)	3.52 (2.04-6.23)
PLR, median (IQR)	183.87 (124.47-283.76)
Creatinine, mg/dl, median (IQR)	0.88 (0.7-1.07)
eGFR, ml/min/1.73 m^2, median (IQR)	81.68 (60.24-95.07)
eGFR < 60 ml/min/1.73 m^2, n (%)	38 (23.4)
Stages of CKD according to eGFR, n (%)†	
1	53 (33.5)
2	67 (42.4)
3a	19 (12)
3b	12 (7.6)
4	7 (4.4)
C-reactive protein, mg/l,	15,400 (4,750-42,950)
D dimer, ng/mL median (IQR) median (IQR)	837 (491-1437)
Therapies	
O_2 therapy, n (%)	110 (67.9)
Corticosteroids, n (%)	125 (77.2)
Antiviral, n (%)	45 (27.8)
Antibiotic, n (%)	77 (47.5)
Heparin, n (%)	137 (84.6)
Outcome of hospitalization, n (%)	
Death	7 (4.3)
Transfer to ICU	20 (12.3)
Home isolation	70 (43.2)
Negativization with discharge	65 (40.1)

†Others: 19 patients with Hashimoto's disease, 7 patients with autoimmune diseases and 2 patients with hepatic diseases. †The analysis was performed in 158 patients due to missing data. HRCT: high resolution computed tomography; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; eGFR: estimated glomerular filtration rate; CKD: chronic kidney disease; ICU: intensive care unit.

outcome, died or will be transferred to intensive care unit (ICU) during hospitalization: 15 (55.6%) patients had eGFR < 60 ml/min/1.73m^2. The median days from hospitalization to any outcome was 13 days (IQR 8-21). Median age was higher in patients with worse outcome compared to patients with favorable outcome [79 years (IQR 64-85) *vs.* 66 years (IQR 54-77), $p<0.01$] and they had fever less frequently [33.3% *vs.* 61.5%, $p<0.01$]. Moreover, diabetes mellitus [44.4% *vs.* 11.8%, $p<0.001$] and cardiac diseases [48.1% *vs.* 26.7%, $p<0.05$] were more frequent in patients with worse outcome compared to patients with favorable outcome. Moreover, the median eGFR was significantly lower in patients with worse outcome than patients with favorable outcome [56.64 ml/min/1.73 m^2 (IQR 32.27-89.73) *vs.* 83.39 ml/min/1.73 m^2 (IQR 69.59-97.08), $p<0.001$]. The comparative analysis of clinical characteristics between patients with poor outcome (death or transfer to ICU) and patients with good outcome (home isolation or discharged after complete recovery and test negativization) is summarized in Table II.

We stratified the population based on normal or reduced eGFR; due to missing data we performed statistical analysis in 158 out of the 162 considered patients. Patients with eGFR < 60 ml/min/1.73 m^2 (n=38) were significantly older compared to patients with normal eGFR [82 years (IQR 74-90) *vs.* 61 years (IQR 53-74), $p<0.001$] and they had fever less frequently [39.5% *vs.* 64.2%, $p<0.01$]. Moreover, systemic arterial hypertension [81.6% *vs.* 47.5%, $p<0.001$], diabetes mellitus [39.5% *vs.* 10.8%, $p<0.001$], dyslipidemia [39.5% *vs.* 16.7%, $p<0.01$] and cardiac diseases [65.8% *vs.* 20%, $p<0.001$] were more frequent in patients with reduced eGFR compared to patients with normal eGFR. The comparative analysis of clinical characteristics between patients with eGFR < 60 ml/min/1.73 m^2 and patients with normal eGFR is summarized in Table III. Figure 1 shows the significant differences in clinical characteristics according to CKD defined with eGFR according to KDIGO. Kaplan-Meier curves demonstrated that overall survival was significantly shorter in patients with eGFR < 60 ml/min/1.73 m^2 ($p<0.001$) (Figure 2). In univariate analysis, age [HR=1.031 (95% CI=1.004-1.058), $p<0.05$], diabetes mellitus [HR=3.474 (95% CI=1.622-7.438), $p<0.001$], cardiac diseases [HR=2.126 (95% CI=0.998-4.528), $p<0.05$], NLR [HR=1.040 (95% CI=1.009-1.073), $p<0.05$], PLR [HR=1.004 (95% CI=1.002-1.006), $p<0.001$] and eGFR < 60 ml/min/1.73

Table II. Comparative analysis between patients with good outcome (home isolation or negativization with discharge) and patients with poor outcome (death or transfer to ICU) (n = 162).

	Good outcome (n = 135)	Poor outcome (n = 27)	p
Age, years, median (IQR)	66 (54-77)	79 (64-85)	< 0.01
M/F, n (%)	64 (47.4)/71 (52.6)	16 (59.3)/11 (40.7)	> 0.05
RT-PCR test Covid-19, days, median (IQR)	8 (2-16)	3 (1-12)	> 0.05
Symptoms onset, days, median (IQR)	9 (5-18)	5 (2-10)	< 0.05
Ground glass at HRCT, n (%)	105 (77.8)	22 (81.5)	> 0.05
Symptoms of SARS-CoV2 infection			
Asthenia, n (%)	31 (23)	7 (25.9)	> 0.05
Dyspnea, n (%)	52 (38.5)	13 (48.1)	> 0.05
Fever, n (%)	83 (61.5)	9 (33.3)	< 0.01
Ageusia, n (%)	7 (5.2)	0 (0)	> 0.05
Anosmia, n (%)	6 (4.4)	0 (0)	> 0.05
Cough, n (%)	51 (37.8)	2 (7.4)	>0.05
Pharyngodynia, n (%)	8 (5.9)	0 (0)	>0.05
Comorbidities			
Systemic arterial hypertension, n (%)	74 (54.8)	14 (51.9)	> 0.05
Diabetes mellitus, n (%)	16 (11.8)	12 (44.4)	< 0.001
Dyslipidemia, n (%)	27 (20)	8 (29.6)	> 0.05
Cardiac diseases, n (%)	36 (26.7)	13 (48.1)	< 0.05
Chronic obstructive pulmonary disease, n (%)	14 (10.4)	3 (11.1)	> 0.05
Cancer, n (%)	19 (14.1)	6 (22.2)	> 0.05
Others, n (%)†	24 (17.8)	4 (14.8)	> 0.05
Hb, g/dl, median (IQR)	12.8 (11.4-14)	12.1 (9.6-12.7)	< 0.05
NLR, median (IQR)	3.31 (1.82-5.38)	6.17 (3.09-12.99)	< 0.001
PLR, median (IQR)	180 (119.61-277.78)	217.91 (135.89-298.39)	> 0.05
Creatinine, mg/dl, median (IQR)	0.86 (0.69-1.03)	1.16 (0.75-1.6)	< 0.01
eGFR, ml/min/1.73 m^2, median (IQR)	83.39 (69.59-97.08)	56.64 (32.27-89.73)	< 0.001
eGFR < 60 ml/min/1.73 m^2, n (%)	23 (17)	15 (55.6)	< 0.001
Stages of CKD according to eGFR, n (%)†			< 0.001
1	47 (34.8)	6 (22.2)	
2	61 (45.2)	6 (22.2)	
3a	15 (11.1)	4 (14.8)	
3b	5 (3.7)	7 (25.9)	
4	3 (2.2)	4 (14.8)	
C-reactive protein, mg/l, median (IQR)	1,200 (4,300-37,500)	38,450 (21,300-82,100)	< 0.001
D dimer, ng/mL, median (IQR)	835 (469-1,233)	1,134 (592-2,428)	> 0.05
Therapies			
O2 therapy, n (%)	88 (65.2)	19 (70.4)	> 0.05
Corticosteroids, n (%)	105 (77.8)	17 (63)	> 0.05
Antiviral, n (%)	40 (29.6)	5 (18.5)	> 0.05
Antibiotic, n (%)	63 (46.7)	12 (44.4)	> 0.05
Heparin, n (%)	113 (83.7)	20 (74.1)	> 0.05

†Others: 19 patients with Hashimoto's disease, 7 patients with autoimmune diseases and 2 patients with hepatic diseases. †The analysis was performed in 158 patients due to missing data. HRCT: high resolution computed tomography; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; eGFR: estimated glomerular filtration rate; CKD: chronic kidney disease; ICU: intensive care unit.

m^2 [HR=3.728 (95% CI=1.783-7.993), p<0.001] showed significant predictive value for death or transfer to ICU. Moreover, fever [HR=0.369 (95% CI=0.166-0.823), p<0.05] reduced the risk for death and transfer to ICU (Table IV). In multivariate analysis, only eGFR < 60 ml/min/1.73 m^2 [HR=2.915 (95% CI=1.110-7.659), p<0.05] and PLR [HR=1.004 (95% CI=1.002-1.007), p<0.01] showed a significant predictive value for death or transfer to ICU (Table IV).

Discussion

Chronic diseases such as malignancies, diabetes, hypertension, and CKD are reported as risk factors for increased severity of and mortality from COVID-19[9]. In this monocentric observational study, we found that renal function was closely related to the prognosis of hospitalized COVID-19 patients. Chronic kidney disease is a public health issue in the world and

Table III. Comparative analysis between patients with normal or reduced eGFR (n = 158).

	eGFR ≥ 60 ml/min/1.73 m² (n = 120)	eGFR <60 ml/min/1.73 m² (n = 38)	p
Age, years, median (IQR)	61 (53-74)	82 (74-90)	< 0.001
M/F, n (%)	62 (51.7) / 58 (48.3)	14 (36.8) / 24 (63.2)	> 0.05
RT-PCR test COVID-19, days, median (IQR)	7 (2-15)	7 (1-17)	> 0.05
Symptom onset, days, median (IQR)	9 (5-17)	6 (4-14)	> 0.05
Ground glass at HRCT, n (%)	98 (81.7)	29 (76.3)	> 0.05
Symptoms of SARS-CoV-2 infection			
Asthenia, n (%)	29 (24.2)	9 (23.7)	> 0.05
Dyspnea, n (%)	51 (42.5)	14 (36.8)	> 0.05
Fever, n (%)	77 (64.2)	15 (39.5)	< 0.01
Ageusia, n (%)	7 (5.8)	0 (0)	> 0.05
Anosmia, n (%)	6 (5)	0 (0)	> 0.05
Cough, n (%)	44 (36.7)	9 (23.7)	> 0.05
Pharyngodynia, n (%)	7 (5.8)	1 (2.6)	> 0.05
Comorbidities			
Systemic arterial hypertension, n (%)	57 (47.5)	31 (81.6)	< 0.001
Diabetes mellitus, n (%)	13 (10.8)	15 (39.5)	< 0.001
Dyslipidemia, n (%)	20 (16.7)	15 (39.5)	< 0.01
Cardiac diseases, n (%)	24 (20)	25 (65.8)	< 0.001
Chronic obstructive pulmonary disease, n (%)	10 (8.3)	7 (18.4)	> 0.05
Cancer, n (%)	16 (13.3)	9 (23.7)	> 0.05
Others, n (%)†	23 (19.2)	5 (13.2)	> 0.05
Hb, g/dl, median (IQR)	12.85 (11.45-14.15)	12.05 (10.2-12.9)	< 0.001
NLR, median (IQR)	3.16 (1.82-5.88)	4.73 (3.09-9.1)	< 0.01
PLR, median (IQR)	176.05 (113.93-267.13)	233.31 (169.5-298.8)	< 0.05
Creatinine, mg/dl, median (IQR)	0.79 (0.67-0.92)	1.25 (1.04-1.73)	< 0.001
eGFR, ml/min/1.73 m², median (IQR)	87.55 (77.58-99.82)	45.22 (31.97-54.43)	< 0.001
C-reactive protein, mg/l, median (IQR)	12,000 (4,300-39,200)	30,200 (8,200-62,450)	< 0.05
D dimer, ng/mL, median (IQR)	815 (482-1305)	1,026 (589-2,216)	> 0.05
Therapies			
O2 therapy, n (%)	78 (65)	29 (76.3)	> 0.05
Corticosteroids, n (%)	98 (81.7)	24 (63.2)	< 0.01
Antiviral, n (%)	37 (30.8)	8 (21.1)	> 0.05
Antibiotic, n (%)	57 (47.5)	18 (47.4)	> 0.05
Heparin, n (%)	100 (83.3)	33 (86.8)	> 0.05
Death or transfer in ICU, n (%)	12 (10)	15 (39.5)	< 0.001

†Others: 19 patients with Hashimoto's disease, 7 patients with autoimmune diseases and 2 patients with hepatic diseases. †The analysis was performed in 158 patients due to missing data. HRCT: high resolution computed tomography; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; eGFR: estimated glomerular filtration rate; CKD: chronic kidney disease; ICU: intensive care unit.

the incidence increases with age and with risk of cardiovascular diseases as the major cause of the early morbidity and mortality[10]. Of the CKD-related deaths, up to 50% were attributed to cardiovascular complications, while acute infections (bacterial, viral, and fungal), contribute substantially to the high rates of hospitalization and cause of non-cardiovascular morbidity and mortality in patients with advanced CKD[11]. Kidney disfunction has been independently related to progressive increase in both susceptibility to SARS-CoV-2/COVID-19 and subsequent risk of adverse outcomes[5,6]. Few recently published studies[12,13] reported that R2CHA2DS2-VASc score, that including renal function in the score, was associated both with 30-day mortality rates among COVID-19 hospitalized patients[12], and R2CHA2DS2-VASc was better than CHA2DS2-VASc and CHA2DS2-VASc-HS score to predict mortality in hospitalized COVID-19 patients[13]. The significance of CKD as an underlying condition for severe COVID-19 remains less well understood, but kidney impairment is associated with an increased risk of infection due to advanced comorbidity, uremia-associated immune dysfunction with disruptions of the natural skin barrier[14]. Disturbances of the immune system in end stage renal disease (ESRD) are represented by pro-inflammatory cytokines, activation of complement and abnormalities of monocytes,

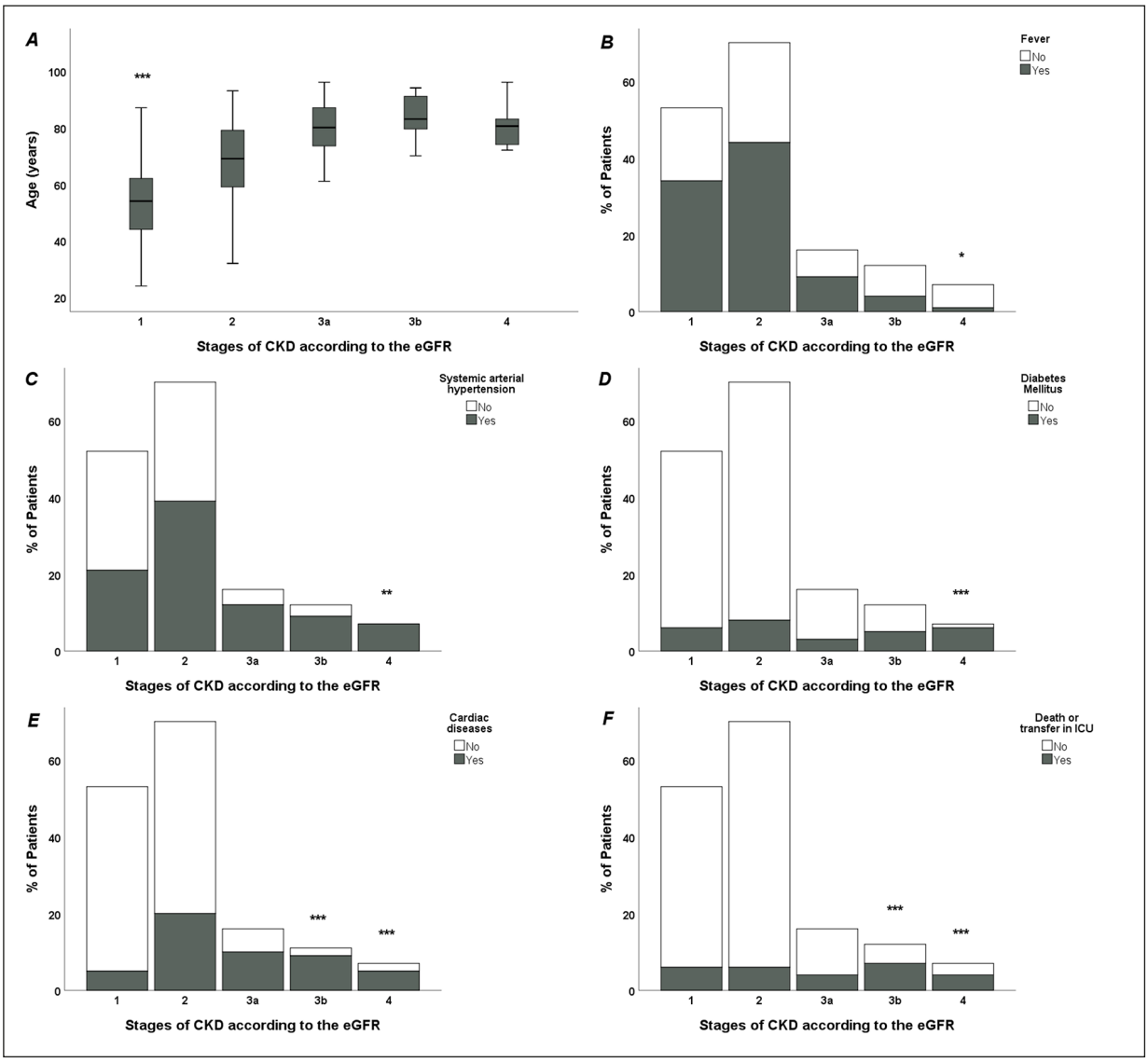

Figure 1. Differences in clinical characteristics according to renal function stages. **A,** Median age; **B,** Frequency of fever; **C,** Frequency of systemic arterial hypertension; **D,** Frequency of diabetes mellitus; **E,** Frequency of cardiac diseases; F, hospitalization outcome. CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate. Asterisks denote statistical significance *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

neutrophils, and dendritic cells that are associated with infection risk in this patient population[14]. The pro-inflammatory role of neutrophils and lymphocytes in immune system regulation is well proven. Elevated NLR and PLR are inflammatory biomarkers in course of several diseases, such as cancer and cardiovascular morbidities, including CKD[15] in which high values have been associated with the progression of CKD towards ESRD with a high mortality rate[16,17]. In the present study among different factors, NLR and PLR showed significant predictive value for death or transfer to ICU. In multivariate analysis, only eGFR < 60 ml/min/1.73m^2 and PLR showed a significant predictive value for death or transfer to ICU. Neutrophil to lymphocyte ratio values is characterized by increased neutrophil counts and decreased lymphocyte counts demonstrating the balance between systemic inflammation and immune response. Also, platelets play an essential role in the inflammatory process and immunological responses[15] and PLR, obtained by dividing the absolute platelet count by the absolute lymphocyte count, is also associated

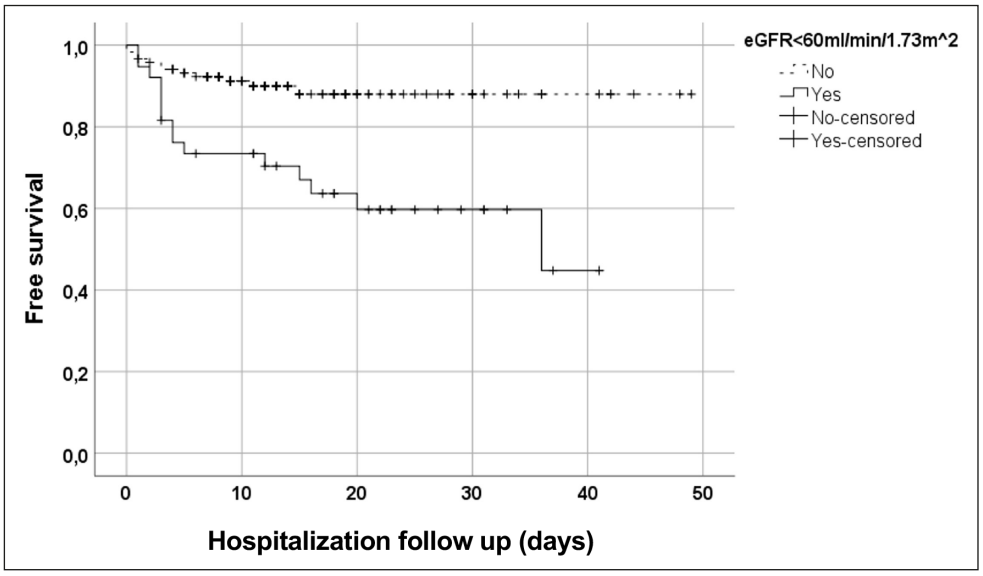

Figure 2. Kaplan-Meier curves for poor outcome (death or transfer to ICU) in patients with chronic kidney disease (CKD) and patients without CKD (Log Rank < 0.001).

with poor prognosis in several diseases[15]. The predictive role of NLR and PLR on mortality of ESRD patients on dialysis has been studied and compared. Several studied[18,19] have demonstrated the superiority of NLR in predicting all causes of mortality and poor renal outcome especially in the advanced stages of renal disease than PLR. In contrast, high PLR values seem to be a predictive factor for cardiovascular mortality. In addition, Yaprak et al[20] demonstrated the superiority of PLR to predict mortality compared to NLR in the adjusted model. Moreover, Brito et al[21] showed that the PLR, but not the NLR, was associated with C reactive protein in non-dialysis CKD patients. In our study none of the patients was on renal replacement therapy. Comparative analysis between patients with poor outcome (death or transfer to ICU) and patients with good outcome (home isolation or negativization with discharge) showed that in the first group age, fever, symptoms onset, diabetes, cardiac disease, hemoglobin level, were

Table IV. Univariable and multivariable analysis with hazard ratio (HR) and 95% confidence interval (CI) for poor outcome (death or transfer in ICU).

	Univariable		Multivariable	
	HR (CI)	p	HR (CI)	p
Age	1.031 (1.004-1.058)	0.026	0.993 (0.965-1.022)	0.642
Gender	0.524 (0.240-1.145)	0.105	-	-
Fever	0.369 (0.166-0.823)	0.015	0.569 (0.242-1.339)	0.197
Systemic arterial hypertension	0.705 (0.329-1.512)	0.369	-	-
Diabetes mellitus	3.474 (1.622-7.438)	0.001	2.158 (0.942-4.945)	0.069
Dyslipidemia	1.346 (0.587-3.086)	0.483	-	-
Cardiac diseases	2.126 (0.998-4.528)	0.05	1.310 (0.528-3.247)	0.561
Chronic obstructive pulmonary disease	1.002 (0.301-3.331)	0.998	-	-
Cancer	1.410 (0.565-3.516)	0.462	-	-
eGFR<60 ml/min/1.73 m^2	3.728 (1.783-7.993)	0.001	2.915 (1.11-7.659)	0.03
NLR	1.040 (1.009-1.073)	0.011	0.992 (0.951-1.034)	0.701
PLR	1.004 (1.002-1.006)	0.001	1.004 (1.002-1.007)	0.002

NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; eGFR: estimated glomerular filtration rate; ICU: intensive unit care.

significantly different. Most patients with worse outcome had an eGFR <60 mL/min, therefore CKD appears to be a relevant prognostic factor in this population. Furthermore, patients with worse outcomes were older, with comorbidities (such as diabetes mellitus, dyslipidemia, heart disease, chronic obstructive pulmonary disease and oncological diseases) and elevated inflammatory indices (NLR, PLR, CRP, D-dimer) and low fever, as well as patients with CKD, were older, more frequently female, with a much less present and defined onset symptomatology, very high inflammation indices and low fever, as reported by Gholami et al[22], which has shown that patients with CKD have a more serious pathology and with high inflammatory indices. Also, Portolés et al[23] showed that CKD in 1,603 COVID-19 patients increased in-hospital mortality. A systematic review by Izcovich et al[24], including 207 studies aimed at identifying prognostic factors that may help in the management choices of patients with SARS-CoV-2 infection, showed the unfavorable role of CKD in course of infection and mortality, also in association with parameters such as leukocyte, platelet, and neutrophil counts, also used in our study. Moreover, we found low fever in patients with poor outcome and CKD patients, also in other study the fever was not associated with disease severity[25], however there are currently no studies that can justify the reduced manifestation of fever in patients with CKD and with poor outcome, even if we could hypothesize alterations in the immune system in CKD, with a state of immune dysfunction characterized by immunodepression that could predispose more to infections but with a leukocytopenia and a reduced presence of fever[14].

Limitations

Our study has several limitations. First, this was a retrospective study based on a single-center database, and selection bias was inevitable. Second, specific data on nutritional assessment and urinalysis were missing. Data analysis was limited by the availability of information during hospitalization.

Conclusions

In conclusion, impaired renal function on admission during the first wave was an independent predictor for death or transfer to ICU among hospitalized COVID-19 patients. Early assessment and monitoring of renal function, across all stages of CKD, is mandatory, in order to prevent the progression towards poor outcome in hospitalized COVID-19 patients. The presence of CKD could be regarded as a relevant factor in risk stratification for COVID-19.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Authors' Contribution

All authors contributed to the study conception and design. The first draft of the manuscript was written by Silvia Lai and Antonietta Gigante and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Availability of Data and Materials

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

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Ethics Approval

The Ethics Committee of Policlinico Umberto I approved the study with number 109/2020.

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