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PREDICTIVE ADMISSION RISK FACTORS, CLINICAL FEATURES AND KIDNEY OUTCOMES IN COVID-19 HOSPITALISED PATIENTS WITH ACUTE KIDNEY INJURY

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ABSTRACT

Introduction: In COVID-19 patients, acute kidney injury (AKI) is recognized as a cause of high mortality. The aim of our study was to assess the rate and the predictors of AKI as well as survival among COVID-19 patients.

Methods: We analyzed clinical and laboratory admission data, predictors of AKI and outcomes including the need for renal replacement therapy (RRT) and mortality at 30 days.

Results: Out of 115 patients, 62 (53.9%) presented with AKI: 21 (33.9%) at stage 1, 7(11.3%) at stage 2, and 34 (54.8%) at stage 3. RRT was required in 22.6% of patients and was resolved in 76%. Pre-existing CKD was associated with a 13-fold risk of AKI (p=0.0001). Low albumin (p=0.017), thrombocytopenia (p=0.022) and increase of creatine kinase over 350UI (p=0.024) were independently associated with a higher risk for AKI. Mortality rates were significantly higher among patients who developed AKI compared to those without (59.6% vs 30.2%, p=0.003). Low oxygen blood saturation at admission and albumin were found as powerful independent predictors of mortality (OR 0.937; 95%CI: 0.917 – 0.958, p=0.000; OR 0.987; 95%CI: 0.885–0.991, p=0.024, respectively). Longer survival was observed in patients without AKI compared to patients with AKI (22.01± 1.703 vs 16.69 ± 1.54, log rank p= 0.009).

Conclusion: Renal impairment is significant in hospitalized COVID-19 patients. The severity of the disease itself is emphasized as main contributing mechanism in the occurrence of AKI, and lower blood saturation at admission is the strongest mortality predictor, surpassing the significance of the AKI itself.

Keywords: COVID-19, AKI, predictors, mortality, admission, outcomes

INTRODUCTION

Even though three years have passed since the first outbreak of the COVID-19 pandemic, many facts regarding its nature, mechanisms of short- and long-term consequences has remained unexplained. Besides causing substantial respiratory pathology, SARS-CoV-2 demonstrates high tropism towards many other human organic systems and tissues [1]. The literature has shown the kidney as being a highly vulnerable organ in COVID-19 patients. This can be manifested in many ways, emphasizing acute kidney injury (AKI) as the most frequently observed kidney complication [1, 2]. Unlike the reports from hospitals in China, which presented lower incidence of AKI in COVID-19 patients [3], multicenter studies from the USA and Europe reported much higher rates of AKI (exceeding over 50% in the ICU), especially in patients who presented with

more severe forms of the disease, thereby requiring hospitalization [4, 5]. What does not differ in any country, is that AKI was identified as an independent risk factor of mortality and an indicator of poor prognosis and outcome [2–5]. Therefore, a vast number of predictive analyses have been performed to identify the potential risk factors of AKI incidence and mortality. Also, a great effort has been invested in defining the exact pathophysiological mechanisms of AKI, in order to understand the unique pathways that play a key role in its occurrence. What is known at present is that age, chronic kidney disease (CKD), hypertension, diabetes (or 2 or more comorbidities, except chronic pulmonary and hepatic diseases) are associated with higher incidence of AKI. The published literature suggests that COVID-19 patients who developed AKI had a more severe form of pneumonia, lower blood oxygen saturation, higher levels of inflammatory markers (CRP, ESR, ferritin), cardiac injury (CK, CK-MB and troponin) and fibrinolysis markers (d-dimer), higher uric acid and serum creatinine levels at the admission, as well as a lower lymphocyte count, hemoglobin, and serum albumin levels [6]. The aim of our study was to estimate the rate and the predictions of AKI involvement among COVID-19 patients hospitalized at our department on the day of admission, and to see the impact of AKI on a patient's prognosis and life expectancy.

A retrospective cohort study was performed in our tertiary nephrology hospital to investigate AKI in patients admitted with COVID-19. The hospital serves approximately 2.1 million people.

DATA COLLECTION AND STUDY POPULATION

We analyzed all consecutively admitted patients with a positive nasopharyngeal swab test for SARS-CoV-2 from 11 November 2020 to 01 February 2021, including inter-hospital transfers. Those with a clinical presentation of COVID-19, and a first positive SARS-CoV-2 swab test on or until 7 days after admission, were included in the study. Patients with end-stage renal disease (ESRD) already requiring renal replacement therapy (RRT), and patients with kidney transplants, were excluded. Patients transferred between two hospital sites were treated as one admission. The study was retrospective and was performed according to the principles of the Declaration of Helsinki, in agreement with institutional policy for obtaining informed consent at hospital admission.

The data that was obtained from the medical histories and National Electronic Health Records – Moj Termin (My Appointment) were: demographics as age and gender, comorbidities (hypertension, diabetes, cardiovascular disease including ischemic heart disease and heart failure, malignancy, neurological disease including dementia and lung disease), laboratory results (hemoglobin, neutrophil: lymphocyte ratio, platelet count, albumin, C-reactive protein,) serum creatinine, urea, potassium, sodium, calcium, uric acid, liver injury markers (aspartate aminotransferase-AST and alanine aminotransferase-ALT), and fasting admission glucose. Furthermore, the following data points were noted: admission and peak results of D-dimer, lactate dehydrogenase (LDH) and creatine kinase (CK) during hospitalization, also electrocardiogram abnormalities (including arrhythmia or ST segment changes) in patients without such previous medical history, admission blood saturation on ambulatory air, chest radiograph (defined as abnormal if the radiologist's report is consistent with features of COVID-19), and reports for thromboembolic events such as deep vein thrombosis (DVT) or pulmonary embolism (PE), shock (cardiogenic, hypovolemic, septic or hemorrhagic. Positive pharmacological history for ACE inhibitor (ACE) or angiotensin-receptor blocker (ARB) and immunosuppression use were also recorded. Based on the World Health Organization's (WHO) definition for disease severity according to the clinical presentation, patients were categorized as being with a moderate, severe, or critical form of the disease [9]. Creatinine measurements were obtained for up to the first 30 days of hospitalization and at the discharge. Validation of CKD was performed using previous electronic records and historical estimated glomerular filtration rate (eGFR) (explanation below). Outcomes that resulted in the need for RRT and inpatient mortality at 30 days were analyzed.

DEFINITIONS AND CALCULATIONS

Kidney Disease Improving Global Outcomes (KDIGO) criteria were used for diagnosis and CKD stage definition. (10) The diagnosis of

AKI was defined according to KDIGO criteria (11) and classified accordingly as stage 1 (increase in serum creatinine of ≥26.5micromol/l or 1.5–1.9 times baseline creatinine), stage 2 (increase to 2.0–2.9 times from baseline) or stage 3 (increase > 3 times baseline serum creatinine or a peak serum creatinine ≥353.6 μmol/l or initiation of RRT). Urine output was not included in the analysis, considering the lack of information. In order to acquire information on CKD, we recorded historical baseline creatinine as the most recent measurement within 8 to 365 days prior to hospital admission. If no information of CKD was found, the lowest creatinine during admission in the absence of RRT was recorded as a baseline, provided this was within the normal range. If the nadir creatinine was not within the normal range and there was no record of CKD, baseline creatinine was imputed based on the gender and race using the Modification of Diet in Renal Disease (MDRD) study equation, assuming that baseline eGFR is 75 ml/min per 1.73m2 [10]. Baseline eGFR was calculated using the MDRD formula and the recorded baseline creatinine value. Elevated AST and/or ALT exceeding 3 times the upper limit of the normal value indicated liver injury [7]. Fasting glucose above 7mmol/l was assumed significant for new-onset diabetes [8]. Severity of COVID-19 at admission was estimated according to WHO criteria, and patients were stratified into 3 categories (moderate, severe and critical), where patients with asymptomatic and mild forms of the disease did not require hospitalization [9]. Patients with signs of pneumonia and plus one of the following were defined as with severe form of COVID-19: respiratory rate >30, severe respiratory distress or sp02 < 90% on room air [9]. Recovery from AKI was defined as the absence of any stage AKI in the last recorded creatinine during hospitalization (i.e. serum creatinine < 1.5 times the baseline creatinine), in the absence of RRT [12, 13]. Follow-up creatinine data at 3 to 6 months were collected for patients with an AKI at stage 3.

STATISTICAL METHODS

Continuous variables are expressed as mean with standard deviation (SD) or median with interquartile range (IQR). Nominal data are presented as an absolute number with percentage. Chi-squared or Fisher exact test were used for comparison between groups for categorical variables, and Student's t-test or Wilcoxon rank test for numerical data. All tests were two-sided, and a p-value <0.05 was considered as significant. In order to identify factors associated with AKI we used binary logistic regression with odds ratios (ORs) where 95% confidence intervals presented (CIs). With Cox proportional hazards regression, we performed a time-to-event analysis for 30-day mortality. Hazard ratios (HRs), 95% CIs, and Kaplan-Meier survival curves were performed to show the impact of AKI on the outcome. Univariate analysis for both the logistic and Cox regression were used to determine factors associated with the outcomes, unadjusted for other variables. Where the association was significant at $p<0.10$, the variables were included in multivariable models to determine association with the outcome adjusting for potential confounders. This included age, gender, admission blood oxygen saturation, comorbidities (CKD, heart disease, diabetes, neurological and lung disease), AKI stages and laboratory results (albumin, CRP, neutrophil/lymphocyte ratio, D dimmers). SPSS statistical package version 21 was used for all statistical analysis.

RESULTS

Out of 146 consecutively admitted patients, 8 kidneys were transplanted and 23 ESRD patients on RRT were excluded from the study. A total of 115 were included into the final analysis. Most of the patients presented with saturation below 85% at admission and more than a half had severe pneumonia on X-ray. The median Ne/Ly ratio of 9 indicated a severe form of COVID 19 in most of patients, and respiratory failure was evident at 60%, and other organs were also affected. Nearly one third of patients had liver affection or muscle injury (possible rhabdomyolysis), 12% were in shock, 20 % had ECG de novo or worsening signs of arrhythmia and 54% had AKI. According to the severity index, there were no patients in the asymptomatic and mild group. Most of the patients (90%) fulfilled the criteria for severe and critical illness, and only 10 % were in the moderate group (Table 1).

Table 1. *Admission patient clinical characteristics*

	All N=115 (%)
SpO2 (%), Median (IQR)	83 (70.91%)
Infiltrations X-ray/CT scan >50% infiltrates, n (%)	58 (53.7%)
Liver lesion (3-fold elevated ALT), n (%)	32 (28%)
De novo DM, n (%)	4 (3.5%)
High temperature, n (%)	92 (80%)
Thrombotic event, n (%)	6 (5.2%)
Arrhythmia (de novo/worsening) n (%)	23 (20%)
Shock, n (%) (hemorrhagic, septic, cardiac)	14 (12.2%)
CRP (mg/L)	98 (35, 135%)
Muscle injury CPK > 350 U/L, n (%)	34 (29.6%)
Ne/Ly Ratio Median (IQR)	9.8 (5.6, 17.9%)
AKI	62 (53.9%)
Admission disease severity category	
Moderate, n (%)	11 (9.6%)
Critical and severe n (%)	104 (90,4%)

Abbreviations: SpO2 blood oxygen level, *IQR* interquartile range, *ALT* alanine aminotransferase, *DM* diabetes mellitus, *CRP* C-reactive protein, *CPK creatine* phosphokinase, *Ne/Ly* neutrophil lymphocyte ratio, *AKI* acute kidney injury.

AKI INCIDENCE AND PATIENT CHARACTERISTICS

Demographics and baseline clinical characteristics are described in Table 2. Patients who had developed AKI were significantly older, and no differences were found among gender, presence of diabetes, lung, and neurological diseases. A diagnosis of pre-existing CKD (baseline eGFR< 60 ml/min/1.73m2), heart disease and hypertension were more frequent in AKI patients, (56.7%; 51.6%; and 21%, respectively). The median serum levels of albumin, hemoglobin, thrombocytes, and calcium were significantly lower in AKI patients, while the median levels of neutrophil/lymphocyte ratio, CK and D-dimer were found to be much higher in AKI patients (13.1 vs 8.7; 238.5 vs 120.0; 3011 vs 1368, respectively). No difference was found between patients in respect of AKI and levels of CRP, ACE/ARB medications use and occurrence of deep vein thrombosis (DVT) or PE at the admission.

BINARY LOGISTIC REGRESSION FOR AKI

The univariate logistic regression analysis revealed that older patients, those with pre-existing CKD, hypertension, heart disease, anemia, hypoalbuminemia, and thrombocytopenia were more prone to AKI. Also, a higher neutrophil/lymphocyte ratio, CK and D-dimer levels were associated with AKI. In the multivariate analysis, pre-existing CKD was associated with a 13-fold risk of AKI (OR 13.04; 95%CI 3.85–44.06, $p < 0.0001$) adjusted for demographics and comorbidities (Table 3). Other variables independently associated with increased AKI risk were low albumin, thrombocytopenia, and muscle injury (possible rhabdomyolysis). The neutrophil/lymphocyte ratio remained borderline significant ($p = 0.053$)

RENAL FUNCTION AND OUTCOMES

Renal outcomes are presented in Table 4. Out of 62 cases of AKI, 21 (33.9%) met KDIGO criteria for stage 1, 7 (11.3%) for stage 2 and 34 (54.8%) for stage 3. A total of 26 patients (22.6% of total, 41.9% of all AKI) required RRT and the relevant modalities including CVVHDF, HD, PD or any modality combination thereof (different modalities for a single patient were used at different times and according to clinical indication and resource availability). Of those discharged alive, AKI had been resolved in 76 %, and 24% still needed RRT following hospital discharge.

Table 2. *Baseline and admission characteristics and comparison between AKI and non AKI patients.*

	All (N=115)	No AKI (N=53)	AKI (N=62)	p
Demographics				
Age (years) mean (SD)	63.74 (13.6)	58.74 (14.6)	68.02 (11.2)	0.0001
Male n (%)	76 (66.1)	38 (71.7)	38 (61.3)	0.323
Comorbidities				
CKD[a] ,n (%)	41 (35.7)	6 (11.3)	35 (56.7)	0.000
Malignancy, n (%)	17 (4.8)	4 (7.5)	13 (21)	0.064
Hypertension, n (%)	88 (76.5)	34 (64.2)	54 (87.1)	0.004
IHD/HF, n (%)	46 (40%)	14 (26.4)	32 (51.6)	0.008
DM, n (%)	35 (30.4)	14 (26.4)	21 (33.9)	0.422
Neurological history, (dementia, other), n (%)	15 (13)	4 (17.7)	11 (7.5)	0.164
Lung disease (COPD, Asthma, other), n (%)	10 (8.7)	5 (9.4)	5 (8.1)	1.0
Medications				
ACE/ARB use, n (%)	70 (60.9)	29 (54.7)	49 (66.1)	0.252
Laboratory results				
Neutrophil/Lymphocyte ratio, Median (IQR)	9.8(5.6, 17.9)	8.7 (5.25, 13.40)	13.1 (6.65, 25.35)	0.007
CRP (mg/l), Median (IQR)	98 (35, 176)	83(27.95, 173.5)	106(44.25,178.15)	0.521
Albumin (g/l), Median (IQR)	36 (33, 40)	38 (34.5, 41.0)	34.5 (30, 37)	0.001
Hemoglobin (g/dl), Median (IQR)	120.64 (27.8)	127.60 (24.04)	114.68 (29.67)	0.006
Platelet count ($\times 10^9$ /l), Median (IQR)	201.5 (130.5, 288.0)	230.5(121.9,319.5)	165.50 (115, 253.5)	0.002
CPK (U/L**)** Median (IQR)	209 (76, 454)	120 (52, 307,75)	238.5 (110.25, 694.25)	0.006
Calcium (mmol/L) Median (IQR)	1.9 (1.8, 2.0)	1.98 (1.88, 2.10)	1.88 (1.69, 1.98)	0.000
D-dimer (ng/ml) Median (IQR)	1916 (1026, 8228)	1368 (999, 7664)	3011(1185, 8411)	0.052
Clinical characteristics				
Inpatient PE or DVT, n (%)	6	3	3	1.0

Abbreviations: AKI acute kidney injury, *CKD* chronic kidney disease, *IHD* ischemic heart disease, *HF* heart failure, *DM* diabetes mellitus, *COPD* chronic obstructive pulmonary disease, *ACE-I* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *CRP*C reactive protein, *CPK* creatine phosphokinase, *PE* pulmonary embolism, *DVT* deep vein thrombosis, defined as eGFR< 60 ml/min/1.73m^2

Table 3. *Univariate and multivariate logistic regression analyses of risk factors associated with the development of AKI*

Univariate regression Binary logistic analysis	Unadjusted OR	95%CI	P	Adjusted OR	95%CI	p
Male	0.625	0.285 – 1.372	0.241	N/A		
Age	1.059	1.025 - 1.094	0.001	1.034	0.991 – 1.078	0.121
Malignancy	3.250	0.990 – 10.668	0.052	1.009	0.174 – 5.845	0.992
Neurologic disease	2.642	0.788 – 8.858	0.115	N/A		
Diabetes mellitus	1.430	0.636 – 3.194	0.387	N/A		
Hypertension	3.772	1.487 – 9.568	0.005	0.808	0.186 – 3.509	0.776
ACE/ARB use	1.616	0.760 – 3.436	0.213	N/A		
Lung disease (COPD, Asthma, other)	0.842	0.230 – 3.083	0.795	N/A		
IHD/HF	2.971	1.351 – 6.534	0.007	1.218	0.361 – 4.107	0.781
e GFR<60	10.154	3.785 – 27.274	0.000	13.037	3.857 – 44.068	0.0001
Hemoglobin	0.982	0.967 – 0.997	0.000	0.998	0.978 – 1.084	0.810
Albumin	0.895	0.831 – 0.964	0.003	0.895	0.797 – 0.970	0.017
CRP	1.000	0.997 – 1.004	0.859	N/A		
Thrombocytes	0.995	0.992 – 0.993	0.014	0.994	0.988– 0.999	0.022
Neutrophil/lymphocyte Ratio	1.068	1.023 – 1.115	0.003	1.059	0.999 – 1.123	0.053
CPK>350U/L	2.800	1.183 – 6.628	0.019	3.600	1.184 – 10.950	0.024
D dimer>1000ng/ml	2.590	0.944 – 7.104	0.064	0.781	0.210 – 0.289	0.711

Abbreviations: ACE-I angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *COPD* chronic obstructive pulmonary disease, *IHD* ischemic heart disease, *HF* heart failure, *eGFR* estimated glomerular filtration rate*, CRP* C-reactive protein, *CPK* creatine phosphokinase.

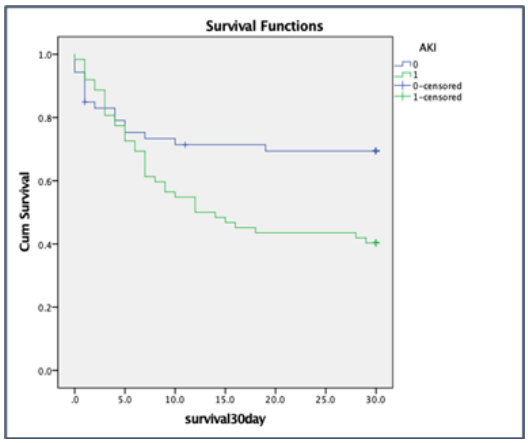
Table 4. *Renal characteristics and outcomes*

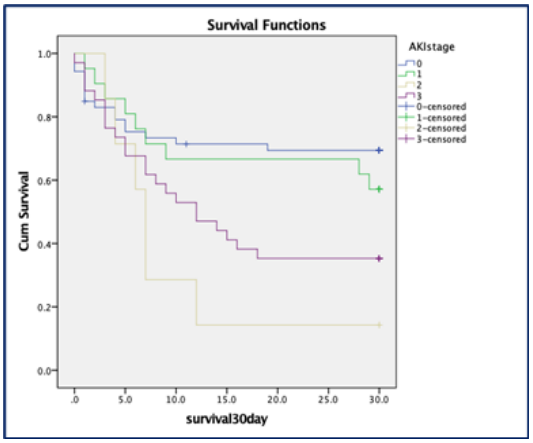
	All (N=115)	No AKI (N=53)	AKI (N=62)	p
Baseline Cr (μmol/l)**,** Median (IQR)	85 (70, 130)	75 (67, 86.5)	111.5 (77.5, 242.50)	0.0001
Baseline eGFR (ml/min/1.73m^2)**,** Median (IQR)	79.27 (43.11, 96.12)	91.5 (78.28, 100.82)	49.84 (20.49, 82.80)	0.0001
Admission Cr (μmol/l), Median (IQR)	136 (70.00, 500)	70 (62, 87.5)	462 (170.75, 723.00)	0.000
RRT, n (%)	26 (22.6)	N/A	26 (41.9)	
RRT modality, n (%)				
HD	26 (22.6)		26 (41.9)	
None	89 (77.4)		36 (58.1)	
RRT after discharge, n (%)	6 (9.6)	N/A	6 /24 (24)	
Discharge Cr (μmol/l)**,** Mean (SD)	70 (58.5, 122.5)	64.5 (55.75, 72)	442 (170, 723)	0.000
Cr recovered to baseline, n (%) (alive patients only *n* = 62)	19/62 (30.6)	N/A	19/25 (76%)	
Admission outcome, n (%)				
Death in hospital	53 (46.1)	16 (30.2)	37 (59.6)	0.003
Discharged alive	62 (53.9)	37 (59.7)	25 (40.3)	0.006

Abbreviations: AKI acute kidney injury, *Cr* creatinine, *IQR* interquartile range, *eGFR* estimated glomerular filtration rate, *RRT* renal replacement therapy; *HD* hemodialysis, *SD* standard deviation

COX REGRESSION ANALYSIS

The total mortality rate was 46.1%. Patients without AKI survived longer than patients with AKI (22.01±1.703 vs 16.69 ± 1.54, log rank p= 0.009), as illustrated in the Kaplan-Meier curve (Fig. 1-A). Also, patients in all stages of AKI survived less than patients without AKI (21.42 ± 2.60; 9.857 ± 3.26; 15.76 ± 2.017; vs 22.01 ± 1.703, log rank p= 0.006), as shown in the Kaplan-Meier curve (Fig.1-B).





(Figure 1. A.) Kaplan–Meier survival curves illustrating longer survival for patients without AKI compared to those with AKI (Figure 1B). Kaplan–Meier survival curves demonstrating worse prognosis in patients with all stages of AKI compared to those without.

Table 5. *Cox Regression Analyses*

Univariate / Multivariate Cox regression analysis	Unadjusted OR	95%CI	p	Adjusted OR	95%CI	p
$Sp0_2$	0.963	0.950 – 0.980	0.000	0.937	0.917 – 0.958	0.000
Male	2.247	1.307 – 3.861	0.003	2.213	1.207 – 4.056	0.01
Age	1.555	1.028 – 1.062	0.000	1.059	1.025 – 1.053	0.001
Neurology	2.480	1.297 – 4.741	0.006			ns
AKI stages (0-3)	2.128	1.182 – 3.813	0.012			ns
DM	1.633	0.9111 – 2.833	0.081			ns
IHD/HF	2.258	1.310 – 3.892	0.003			ns
e.GFR <60	0.989	0.981 – 0.996	0.003	1.879	0.976 – 3.716	0.059
Albumen	0.924	0.885 – 0.965	0.000	0.987	0.885 – 0.991	0.024
CRP	1.002	1.0 – 1.005	0.078			ns
Ne/Ly Ratio	1.022	1.005 – 1.059	0.011			ns
D dimer>1000	2.077	0.824 – 5.235	0.121			

Abbreviations: SpO2 blood oxygen saturation, *AKI* acute kidney injury, *DM* diabetes mellitus, *IHD* ischemic heart disease, *HR* heart failure, *e GFR* estimated glomerular filtration rate, *CRP* C reactive protein, *Ne/Ly* neutrophil lymphocyte ratio

Mortality rates were significantly higher among patients who developed AKI compared to those who did not (59.6% vs 30.2%, p<0.003). In the univariate model (Table 5), increased mortality was associated with age, gender, AKI, heart and neurological diseases, lower blood oxygen saturation, eGFR, albumen serum levels, and a higher neutrophil/lymphocyte ratio. The multiple Cox regression analysis for the 30-day mortality rate demonstrated that older age and male gender were independently associated with the risk of death at 30 days (Table 5). Low blood saturation at admission and albumin were also powerful predictors of mortality (OR 0.937; 95%CI 0.917 – 0.958, p=0.000; OR 0.987; 95%CI 0.885–0.991, p<0.024, respectively). In the final statistical model, the CKD marker showed borderline significance (p=0.059) and AKI lost its significance.

Patients with clinical presentation of severe and critical form of the disease (Fig.2), experienced higher mortality compared to those with moderate form of the disease (0% vs 51%, respectively).

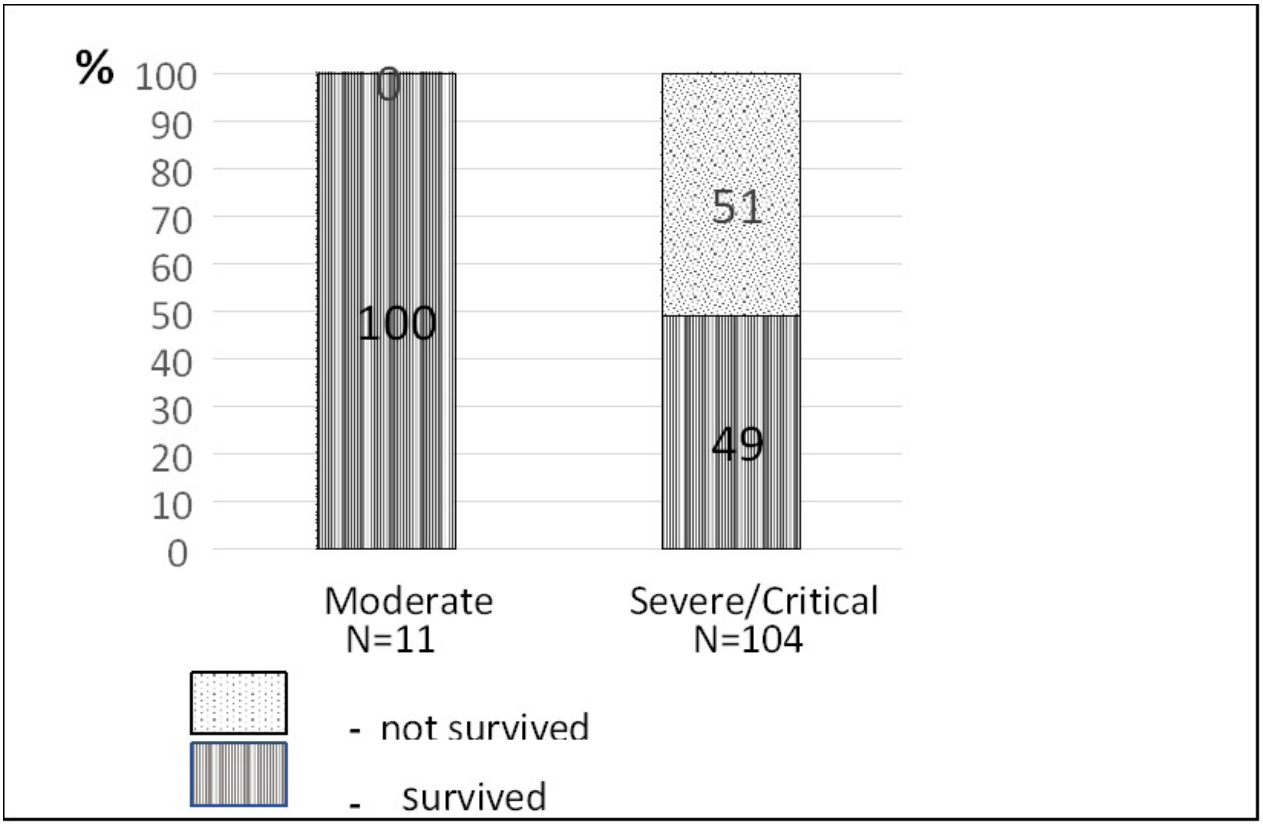


Figure 2. *Mortality in respect of clinical presentation at admission*

DISCUSSION

We analyzed data from 115 patients, consistent with clinical features for COVID-19, admitted in our nephrology department during the first pandemic wave. On the day of admission, more than half of the patients from our group (excluding those with kidney transplants and on a chronic dialysis regime) presented with acute kidney injury or acute worsening of the pre-existing CKD. This is consistent with numbers in the ICU units [4, 5]. This might be explained with the triage process in the COVID-19 emergency centers, from whence patients with AKI were intentionally redirected to our unit for further treatment. According to the current evidence, the first pandemic wave revealed the highest incidence of AKI. This has been thus subsequently reduced [5,14]. In our study group, patients with AKI were significantly older, with known comorbidities for hypertension, heart disease and CKD. This is consistent with the current published literature [5, 15]. Patients with pre-existing CKD had a 13-fold greater risk of developing AKI, compared to those without. This could be related to the increased chances of forming microvascular thrombi in COVID-19 patients with CKD, as some studies report [15]. Our findings about

the use of ARE/ARB in COVID-19 patients and the risk of AKI, confirm there is no association between them, since these drugs do not increase the susceptibility to the virus, nor promotes endothelial injury [15]. However, we could not find any association with gender and diabetes in the prediction of AKI [5, 15]

A previous report pointed out that the severity of the inflammation, the occurrence of AKI and the percentage requiring dialysis are much greater in COVID, compared to non-COVID hospitalized patients. In addition, the recovery rate is much lower [16, 17]. Hence, there might be a knowledge gap regarding the occurrence of AKI which cannot be explained by the traditional risk factors and pathways. Therefore, our patients were analyzed regarding their severity status (based on the clinical manifestations and known biochemical markers), AKI prediction and mortality. Almost 90% of the hospitalized patients, upon admission, were categorized as with severe or critical forms of the disease, with impaired blood oxygen saturation and other organ concomitant affection. Besides kidney and lung issues a great percentage of the patients presented with liver lesion (threefold increase in ALT) and muscle damage (CPK above 350UI). 14 patients were admitted in a state of shock, 20% had worsening or new onset of arrhythmia, 4 patients were diagnosed with de novo DM, and 6 cases of new thrombotic events were reported. This finding is in line with previous reports, which show an association of COVID-19 with multi-organ affection of the virus [18]. Although the exact pathophysiological mechanisms of AKI development, based on the severity of the disease are not completely explained, the aberrant immunological response (cytokine storm), the hypoperfusion of the kidneys and subsequent ischemia, the lung-kidney crosstalk, rhabdomyolysis and the hypercoagulable/prothrombotic state remain as the main contributing mechanisms [19, 20]. Trying to understand and identify some of the mechanisms, besides monitoring the biochemical markers of different organ damage and impaired function, we also analyzed the biochemical, inflammatory, and hematological biomarkers that have been linked with the severe form of the disease [21]. We confirmed the significance in the binary logistic regression analysis for AKI for the increased NLR, D dimmers and CPK, also lower platelets, hemoglobin, calcium, and albumin, emphasizing the hypoalbuminemia, thrombocytopenia, CPK and NLR as undependable risk factors. These are almost all recognized as severity biomarkers [21]. Hence, increased CPK may also indicate viral muscle damage and rhabdomyolysis that is linked with higher incidence of renal impairment in COVID-19 patients [22]. Insufficient data for the myoglobin, troponin levels and urine-analysis, prevented us in clarification of the diagnosis rhabdomyolysis for all the patients. The small number of participants in the study was also factor of limitation. Low platelets and high D dimmers (which may be partially explained throw several mechanisms like decreased production because of the cytokine storm), increased destruction (elevating autoantibodies and immune complexes), might also be results of an increased consumption because of the increased aggregation and formation of the microthrombi [23]. The viral binding to ACE 2 receptors may neutralize their function and increase activation of the complement induced angiotensin II and promote endothelial dysfunction, platelets activation, hypercoagulability and microangiopathy with a consequent hypoxia and hypotension leading to AKI [23, 24]. Hence, the association of AKI with lower platelet values can be a result of both the severity of the disease from one side and the coagulation disorders from the others [24]. Increased NLR has been identified as an independent risk factor of severe forms of the disease and of in-hospital mortality in COVID-19 patients [25]. Also, there are studies that demonstrate that patients with sepsis and increased NLR are at greater risk of developing AKI, compared to those without high NLR [26].

Lower values of serum calcium were noted as more frequent in patients with AKI, but because of the great percent of patients with pre-existing CKD, potential overlapping between these two conditions was possible, and more detailed investigations are needed to consider calcium as relevant factor of prediction.

The percentage of the patients with AKI from our study that needed any modality of RRT was estimated to be around 41%. From the patients with AKI that were discharged alive, 76% restored their renal function, and 24% remained with further need of RRT. This is well correlated with the published literature [4, 16, 17, 27]. Further follow up analyses are required to estimate the long-term impact of the corona virus on CKD.

In the other part from our research, we dedicated ourselves to identifying the predictors of

mortality and 30-day survival in COVID-19 hospitalized patients, based on the admission demographics, clinical and laboratory findings. Although we had an incidence of AKI in more than half of the study population, the percent of survival and recovery from AKI did not differ from the statistics in Europe and the USA [2, 4, 5] A Kaplan Mayer curve confirmed that for patients with AKI, regardless the stadium of AKI they were in, the 30-day survival was worse compared to those without AKI [4, 5]

For the prediction of mortality, we analyzed each patient's premorbid characteristics (age, gender, and medical history) as well as the laboratorial and clinical findings on admission day. In the univariate analysis, our patients' data already confirmed published findings. Meaning that older age, male gender, presence of AKI, preexisting CKD, neurological and cardiovascular comorbidities, lower oxygen saturation and albumin on admission, or increased NLR were associated with increased risk of mortality and a worse outcome [28, 31]. In the multiple cox regression, analysis for the 30-day mortality, the strongest independent predictor of mortality was the blood saturation upon admission. Patients with more a severe form of pneumonia and lower blood oxygen saturation on admission had the highest risk of death, even greater than those with AKI. Male gender and older age kept their significance. A vast number of studies were conducted to develop sophisticated prediction algorithms for mortality and deterioration in COVID-19 patients, including the 4C Mortality and 4C Deterioration prediction model, in which these three predictive factors (older age, male sex, and low admission blood saturation) play key roles [29–31]. The lower serum albumin, as a marker of severe inflammation and malnutrition, kept its significance as a predictor of mortality in our study, as mentioned in many studies so far, in which a six-fold increase in poor outcome is registered in those with hypoalbuminemia compared with those without [28, 32]. Published literature has recognized both AKI and previously diagnosed CKD as factors of possible disease progression to severe condition, but AKI demonstrated statistically higher risk for ICU hospitalizations and mortality than CKD [33]. Nevertheless, we observed a difference in our mortality prediction analyzes, in which CKD exceeded the significance of AKI itself [33]. This might have been explained by the high prevalence of the CKD patients (41%) in our study group and the potential overlap and inter-dependence between AKI and CKD.

CONCLUSION

Renal impairment in COVID-19 patients occurs in significant percentage and is a factor of poor prognosis. The severity of the disease itself, explained by the clinical, biochemical, and hematological features, is emphasized as the main contributing mechanism in the occurrence of AKI. Also, lower blood oxygen saturation upon admission is also associated with the severe or critical forms of the disease. This is the strongest mortality predictor, outperforming the significance of AKI itself. Developing a prediction tool is important, so that risk stratification can be conducted in all patients in the initial stages of the disease (prior or on the day of the admission). This could optimize individual care and prevent unfavorable outcomes.

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Резиме

ПРЕДИКТИВНИ РИЗИК-ФАКТОРИ, КЛИНИЧКИ ОСОБЕНОСТИ И РЕНАЛЕН ИСХОД КАЈ ХОСПИТАЛНО ЛЕКУВАНИ ПАЦИЕНТИ СО КОВИД-19 И АКУТНО БУБРЕЖНО ОШТЕТУВАЊЕ

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Вовед: Акутнотото бубрежно оштетување (АБО) кај пациентите со КОВИД-19 е докажан фактор за висока смртност. Целта на нашата студија беше да се утврдат инциденцијата и предиктивните фактори на акутното бубрежно оштетување кај пациентите со КОВИД-19, како и да се одреди стапката на преживување.

Методи: Анализирани беа клиничките и лабораториските параметри на пациентите на денот на прием во болница, предикторите на акутно бубрежно оштетување, како и крајниот исход од него, вклучувајќи ја потребата од ренална заместителна терапија и триесетдневна смртност.

Резултати: Од вкупно 115 лекувани пациенти, 62 (53,9 %) се презентираа со клиничка манифестација на акутно бубрежно оштетување, и тоа: 21 (33,9 %) прв стадиум, 7 (11,3 %) втор стадиум и 34 (54,8 %) трет стадиум на АБО. Кај 22,6 % од испитаниците со АБО имаше потреба од лекување со ренална заместителна терапија, а 76 % од нив ја опоравија бубрежната функција. Преегзистирачката хронична бубрежна болест беше асоцирана со 13-кратен ризик за развој на АБО (p = 0,0001). Ниските вредности на серумскиот албумин (p = 0,017), тромбоцитопенијата (p = 0,022) и високите вредности на креатинин киназата над 350UI (p = 0,024) се издвоија како независни предиктивни фактори асоцирани со висок ризик за развој на АБО. Стапката на смртност кај пациентите со АБО беше значително повисока, споредена со онаа на пациентите без (59,6 % vs 30,2 %, p = 0,003). Најсилна статистичка значајност во предикцијата на смртноста презентираа: ниската кислородна сатурација во крвта на денот на приемот и вредноста на серумскиот албумин (OR 0;937; 95 % CI: 0,917–0,958, p = 0,000; OR 0,987; 95 % CI: 0,885–0,991, p = 0,024, последователно). Подолго преживување беше забележано кај пациентите без, споредено со оние што манифестираа кој било стадиум на АБО (22,01 ± 1,703 vs 16,69 ± 1,54, log rank p = 0,009).

Заклучок: Пациентите со КОВИД-19 и потреба од болничко лекување демонстрираат висок процент на бубрежно засегање. Тешката клиничката слика на болеста се издвојува како клучен фактор во настанувањето на акутното бубрежно оштетување. Ниската кислородна сатурација во крвта на денот на приемот е најсилниот предиктор за смртност, кој ја надминува значајноста на акутното бубрежно оштетување.

Клучни зборови: КОВИД-19, АБО, предиктори, смртност, прием, исход