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The Predictive Value of Cystatin C for AKI in Patients with COVID-19

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Summary

Objective. To evaluate a potential of cystatin C blood concentration to predict acute kidney injury (AKI) in patients with severe and extremely severe pneumonia associated with COVID-19.

Materials and methods. An observational prospective study of 117 patients with severe and extremely severe pneumonia associated with a COVID-19 in an ICU setting was conducted in 2020–2022 (site: multifunctional Medical Center, 1586 Military Clinical Hospital of the Ministry of Defense of Russia, Moscow Region, Russia). Routine laboratory tests and instrumental examinations were performed according to generally accepted protocols. Cystatin C concentrations in blood (s-CysC) and urine (u-CysC) were measured by immunoturbidimetric method.

Results. AKI was diagnosed in 21 (17.9%) patients, kidney dysfunction without AKI was found in 22 (18.8%) patients with severe and extremely severe pneumonia associated with COVID-19. s-CysC and u-CysC levels in the group of patients with AKI were statistically significantly higher compared to the levels in the group of patients without AKI. The levels of s-CysC obtained within Day 1 — T (-1), and Day 2 — T (-2) prior to AKI onset turned out to be the independent factors for AKI development in patients with severe and extremely severe pneumonia associated with COVID-19: OR 5.37, Wald chi-square 5.534 (CI: 1.324; 21.788); P=0.019 and OR 3.225, Wald chi-square 4.121 (CI: 1.041; 9.989); P=0.042, respectively. s-CysC T (-2) value is informative, and s-CysC T (-1) is a highly informative predictor of AKI development in severe and extremely severe pneumonia associated with COVID-19: ROC AUC 0.853 (95% CI, 0.74–0.966), P<0.001) with 90% sensitivity and 73% specificity at a cut-off of 1.67 mg/L, and ROC AUC 0.905 (95% CI, 0.837–0.973), P<0.001) with 90% sensitivity and 73% specificity at a cut-off of 1.69 mg/l, respectively. Serum CysC levels started increasing 3 days prior to AKI onset, outpacing the increase of SCr levels. The u-CysC levels were not predictive of AKI development. Impaired renal function probability was increasing with patients' age (P<0.0001).

Conclusions. Serum CysC seems to be a statistically significant predictor of AKI. s-CysC levels started increasing 3 days prior to AKI onset, surpassing the increase of SCr levels in patients with severe and extremely severe pneumonia associated with COVID-19. Urine CysC did not achieve statistical significance as a predictor for AKI, although u-CysC concentrations were significantly higher on days 3, 2, 1 prior to AKI onset and on the day of AKI onset in the group of patients with AKI.

Keywords: acute kidney injury; AKI; cystatin C; s-CysC; u-CysC; COVID-19; pneumonia development

Conflict of Interest Disclosures. The authors declare no conflict of interest.

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Introduction

COVID-19 is an infectious disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [1]. The first outbreak of COVID-19 was reported in late 2019 in Wuhan City, Hubei Province, People's Republic of China [2]. According to the World Health Organization, as of June 10, 2022, there were more than 532,201,219 cases and 6,305,358 deaths from COVID-19 worldwide [3].

SARS-CoV-2 enters the human body through the epithelium of the upper respiratory tract [4], stomach and intestines [5]. Approximately 81% of people have a mild illness, while 14% have severe manifestations and 5% progress to an extremely severe illness [6].

Due to the severity of the disease, about 10.2% of patients with COVID-19 are treated in the intensive care unit (ICU) [7].

According to Li X. et al. (2020), 11% of patients treated in the ICU develop multiple organ failure [8], including acute kidney injury (AKI) with pulmonary-renal syndrome [9].

The combination of acute respiratory failure and renal injury may worsen the patient's condition, significantly reduce the efficacy of treatment, and complicate the outcome of the disease [10].

Clinical manifestations of renal dysfunction range from isolated proteinuria (43.9%) and hematuria (26.7%) [11] to AKI requiring renal replacement therapy (RRT). When renal dysfunction occurs, hospital mortality increases from 13.2% with normal blood creatinine levels to 33.7% with elevated blood creatinine levels [12]. According to American researchers (Richardson S. et al., 2020), among 5.700 patients hospitalized with COVID-19, AKI requiring RRT was diagnosed in 3.2% of cases, while in patients receiving ICU therapy it was found in 22% of cases [13]. AKI was more likely to develop in patients with elevated serum creatinine (SCr) at baseline compared with those in the reference range [11].

Chinese researchers (Cheng Y. et al., 2020) diagnosed AKI in 5.1% of 701 hospitalized patients with COVID-19 [11].

A similar incidence of AKI in COVID-19 was reported by other investigators (Yildirim C. et al., 2021), who identified AKI in 4.9% of patients with COVID-19 (17 cases out of 348) [14].

A significantly higher incidence of AKI was described in a retrospective study (Diao B. et al., 2021), where it was observed in 27.06% of cases (in 23 of 85 patients). Dependency analysis of factors in the groups of patients with AKI showed that the prevalence of AKI among patients was associated with age (65.22% if ⩾60 years vs. 24.19% if <60 years, $P<0.001$), comorbidities (69.57% if present, 11.29% if absent, $P<0.001$), hypertension (39.13% present, 2.90% absent, $P=0.0007$), and coronary artery disease (21.74% present, 4.84% absent, $P=0.018$) [15].

A meta-analysis by Chen Y.-T. et al. (2020), which included 20 studies (China, Italy, UK, USA), found that AKI occurred in 8.9% of 6,945 patients with COVID-19 (95% CI, 4.6–14.5) [16].

Currently, there is a need to identify a reliable, highly sensitive and specific biomarker for the prognosis and early diagnosis of AKI.

Literature review has shown that CysC is a reliable diagnostic and prognostic biomarker of AKI, and its concentration directly correlates with the severity of kidney damage [17]. The more renal function is impaired, the higher the concentration of cystatin-C in blood (s-CysC) and urine (u-CysC) is determined [18,19].

Literature data suggest both an anticipatory increase in s-CysC during AKI and an earlier decrease in its level compared to SCr when AKI resolves with treatment ($P<0.001$) [20].

CysC is a polypeptide that blocks the destruction of the extracellular protein matrix by inhibiting cysteine proteases. It is produced by nucleated cells, does not enter the systemic circulation, and is 99% metabolized in the kidneys [21], while the remaining insignificant amount is excreted unchanged in the urine [22].

The above kinetics and other characteristics provide a rationale for considering CysC as an almost ideal endogenous biomarker that allows an objective assessment of renal function [23].

Aim: To investigate the prognostic value of cystatin C levels in blood serum and urine for confirmation of acute kidney injury in patients with severe and extremely severe pneumonia associated with COVID-19.

Materials and Methods

An observational study with the participation of patients with severe and extremely severe (critical) COVID-19 treated in 2020–2022 in the ICU of the Multidisciplinary Medical Center, 1586 Military Clinical Hospital of the Ministry of Defense of Russia (1586 MCH) was conducted. The study included 117 patients with severe and critical COVID-19-associated pneumonia, of whom 75 were men and 42 were women.

Inclusion criteria:

— Age 18 to 80 years;

— COVID-19 confirmed by polymerase chain reaction (PCR) identification of viral genetic material in nasopharyngeal swabs; and/or antibodies detected by enzyme-linked immunoassay in blood; typical clinical and laboratory presentation, lung involvement documented by computed tomography;

— Signs of severe pneumonia, i.e, at least one of the following: dyspnea (respiratory rate >30/min), SpO_2⩽93%, oxygenation index ⩽300 mm Hg, agitation, impaired consciousness, hemodynamic instability (systolic blood pressure less than 90 mm Hg and/or diastolic blood pressure less than 60 mm Hg), oligo- or anuria, CT evidence of viral-induced lung injury (grade 3–4 on the semi-quantitative scale used in Russia), arterial blood lactate >2 mmol/L, two or more qSOFA scores, acute respiratory distress syndrome, respiratory failure requiring respiratory support, including high-flow oxygen therapy and noninvasive ventilation, septic shock, multiple organ failure.

Exclusion criteria were chronic kidney disease or suspected chronic kidney disease; proteinuria and hematuria in the previous 3 months; history of renal transplantation; iatrogenic complications (pneumothorax, hemothorax, chylothorax, aspiration pneumonia, allergic reactions to medications).

Patients received intensive multimodal intensive therapy according to the current provisional guidelines for prevention, diagnosis and treatment of novel coronavirus infection (COVID-19).

According to the results of the studies performed, patients were divided into two groups: group 1 ($N=96$) including patients without AKI and group 2 ($N=21$) of patients with AKI.

The clinical, laboratory and instrumental characteristics of the groups are shown in Table 1.

Table 1. Clinical and laboratory characteristics of patients.

Parameters	Values of parameters in groups				
	Patients, total, *n*=117	Without AKI, n=96	With AKI, n=21	Mann–Whitney *U*-test	*P*-value
Age, years	49 (43; 62)	47,5 (41; 55)	65 (58; 71)	*U*=157.5; *Z*=3.755	0.0002
Male/female, *n*/*n*	75/42	66/30	9/12	—	—
Mortality, *n* (%)	26 (22.2)	15 (15.62)	11 (52,4)	—	—
Severity of disease according to the NEWS scale, points, max	10 (8; 11)	9 (8; 11)	12.5 (10; 13)	*U*=202.5; *Z*=–3.219	0.001
Urea, mmol/L, max	8.55 (6.7; 12.1)	7.7 (6.6; 10.4)	17.25 (11,6; 20.2)	*U*=103; *Z*=–4.486	0.00001
Creatinine, μmol/L, max	104 (94; 129)	99.5 (94; 104)	174.5 (156; 309)	*U*=15; *Z*=–5.632	<0.001
C-reactive protein, mg/L, max	134.25 (62; 1759)	118.1 (58.65; 166.1)	173.8 (63.1; 203.5)	*U*=303; *Z*=–1.881	0.0599
Ferritin, μg/L, max	560.9 (102; 708.3)	596.35 (102; 711)	102 (102; 579.5)	*U*=298; *Z*=1.971	0.0486
Leukocyte count, 1,000 cells/μL, min	7.05 (5.76; 8.92)	6.65 (5.38; 8.41)	8.45 (6.95; 10.7)	*U*=285.5; *Z*=–1.983	0.0473
Lymphocytes, %, min	3.5 (2; 7)	4 (2; 8)	2.5 (1; 4)	*U*=344.5; *Z*=1.352	0.1763
Platelets, 1,000 cells/μL, min	165 (120; 220)	178 (147; 224)	99 (51; 123)	*U*=168.5; *Z*=3.231	0.0012
D-dimer, mg/L, max	2.19 (0.66;7. 67)	1.55 (0.61; 4.53)	9.995 (2.78; 10)	*U*=229.5; *Z*=–2.841	0.0045

Note. For rows 1, 4–12, results given as *Me* (*Q1*; *Q3*). Max represents the maximum value for all days of stay in the ICU, min represents the minimum value for all days of stay in the ICU.

The study was approved by the local ethics committee of the Moscow Haass Medical and Social Institute and was conducted in accordance with the principles of good clinical practice (GCP) and national standards of medical care to ensure the safety and well-being of study participants.

Laboratory Methods. All instrumental and laboratory tests were performed at 1586 MCH according to existing standards and protocols, and the results were documented prospectively from the time of patient admission to the ICU until discharge from the hospital. Venous blood and urine samples were collected simultaneously during the first 24 hours of ICU admission and then once daily from 6:00 am to 7:00 am, and delivered to the laboratory within 10–20 minutes. In some cases, samples were frozen at –20°C and brought to the laboratory as they accumulated, followed by a single thaw.

Levels of s-CysC and u-CysC were determined by immunoturbidimetric method on an automated biochemical analyzer AU 480 (Beckman Coulter, Inc., Brea, CA, USA), using reagents from DiaSys Diagnostic Systems GmbH, Holzheim, Germany.

The following abbreviations were used to indicate the stages of the study: T (-3) — 3 days before development of AKI; T (-2) — 2 days before development of AKI; T (-1) — 1 day before development of AKI; T (0) — day of development of AKI; T — first day of ICU admission.

Statistical Analysis. After the initial assessment of clinical and laboratory data, differences between the groups were determined. Statistical analysis was performed with Excel 2013 (Microsoft Office 2013, Microsoft, USA) and SPSS Statistics (IBM, USA) software packages. Significance of intergroup differences was determined by the nonparametric Mann–Whitney *U* test. Logistic regression was used to predict the likelihood of AKI using multiple s-CysC and u-CysC values. The optimal threshold for predicting AKI with relevant sensitivity and specificity was determined using the ROC curve. Data were presented as median (*Me*) and interquartile range (*Q1* and *Q3*).

The estimated power of the sample was determined according to the method (formula) of Peduzzi P. et al. (1996), developed to determine the minimum sample size in logistic regressions [24], and was 55 patients. Considering that the estimated sample size was less than 100 patients, the power was increased using the method of J. Scott Long [25].

Differences at $P<0.05$ were considered significant.

Results

Of the 117 patients enrolled in the study, 17.9% (*N*=21) were diagnosed with AKI according to KDIGO (Kidney Disease: Improving Global Outcomes) criteria, including 10 patients with stage 1, 4 patients with stage 2 and 7 patients with stage 3.

Increased SCr was observed in all cases, while urine volume decreased in only three patients. Renal dysfunction (increased SCr above the reference range but not meeting KDIGO diagnostic criteria) was observed in 18.8% (*N*=22) of cases, suggesting that renal function was impaired in at least 36.8% (*N*=43) of patients overall. RRT (sessions of prolonged veno-venous hemodiafiltration) was performed in four patients.

22.2% of patients (*N*=26) died, including 52.4% (*N*=11) in the group with AKI and 15.62% (*N*=15) in the group without AKI (χ^2 test 13.468, $P<0.001$).

The immediate cause of death was acute respiratory failure in 19 patients, sepsis in 2, and heart failure in 5.

CysC concentrations in the groups are shown in Table 2. The analysis showed significant intergroup differences in s-CysC at different time points: T (*P*=0.0270), T (0) (*P*<0.001), T (-1) (*P*<0.001), T (-2) (*P*=0.0002), T (-3) (*P*=0.0218).

We also observed significant intergroup differences in u-CysC levels, except for the first day of hospitalization in ICU: T (*P*=0.1299), T (0) (*P*=0.0396),

Table 2. Intergroup differences in the levels of CysC, *Me* (*Q1*; *Q3*).

Material	CysC concentration. mg/L			Mann-Whitney *U*-test	*P-value*
	Patients, total, *n*=117	Without AKI, *n*=96	With AKI, *n*=21		
		Blood			
During all days in the ICU, max	1.64 (1.54; 1.98)	1.52 (1.22; 1.69) max	2.3 (1.86; 3.25)	*U*=61; *Z*=5.033	<0.001
T	1.37 (1.09; 1.69)	1.325 (1.055; 1.625)	1.67 (1.37; 1.79)	*U*=268.5; *Z*=–2.211	0.0270
T (0)	1.59 (1.31; 1.83)	1.52 (1.22; 1.69) max	2.155 (1.9; 2.6)	*U*=57; *Z*=–5.085	<0.001
T (-1)	1.56 (1.285; 1.82), *n*=76		1.98 (1.82; 2.3)	*U*=78; *Z*=–4.566	<0.001
T (-2)	1.555 (1.26; 1.79), *n*=74		1.9 (1.79; 2.1), *n*=16	*U*=102; *Z*=–3.708	0.0002
T (-3)	1.55 (1.26; 1.7), *n*=73		1.705 (1.58; 1.91), *n*=15	*U*=171.5; *Z*=–2.294	0.0218
		Urine			
During all days in the ICU, max	0.465 (0.19; 1.87)	0.36 (0.17; 1.55)	1.835 (0.9; 5.53)	*U*=219; *Z*=–2.969	0.0030
T	0.35 (0.15; 0.685)	0.25 (0.15; 0.51)	0.57 (0.32; 1.42)	*U*=320.5; *Z*=–1.514	0.1299
T (0)	0.42 (0.19; 1.7)	0.36 (0.17; 1.55) max	1.055 (0.41; 4.59)	*U*=289.5; *Z*=2.057	0.0396
T (-1)	0.45 (0.19; 1.75)		1.2 (0.6; 3.27)	*U*=175.5; *Z*=2.636	0.0084
T (-2)	0.42 (0.18; 1.73)		1.315 (0.63; 2.7)	*U*=214; *Z*=1.668	0.0452
T (-3)	0.42 (0.19; 1.54)		1.2 (0.57; 1.5)	*U*=159; *Z*=2.156	0.0311

Note. For tables 2–4: T — first day of the hospitalization in the ICU; T (0) — the day of AKI development; T (-1) — 1 day prior to AKI development; T (-2) — 2 days prior to AKI development; T (-3) — 3 days prior to AKI development. max — the maximum value for all days of ICU stay.

T (-1) (*P*=0.0084), T (-2) (*P*=0.0452), T (-3) (*P*=0.0311).

In the control patients (without AKI), cystatin-C was not measured daily but every 48–72 hours, so the maximum cystatin-C concentrations during all days in the ICU were used to calculate intergroup differences, logistic regression and ROC analyses.

Regression analysis (Table 3) showed a significant relationship between s-CysC level on the day of AKI development (s-CysC, T (0) mg/L: B=2.175; Wald χ^2=8.184; exponent=8.805 [95% CI, 1.984; 39.081]; *P*=0.004), 1 day earlier (s-CysC, T (-1) mg/L: B=1. 681; Wald χ^2=5.534; OR 5.37; [95% CI, 1.324; 21.788]; *P*=0.019) and 2 days earlier (s-CysC, T (-2) mg/L: B=1.171; Wald χ^2=4.121; OR 3.225 [95% CI, 1.041; 9.989]; *P*=0.042), and no significant association between u-CysC and development of AKI.

The s-CysC, T (0), s-CysC, T (-1), and s-CysC, T (-2) were the prognostically significant models, and ROC analysis was performed to evaluate their quality and determine the area under the ROC curve and the optimal CysC threshold for predicting the development of AKI (Table 4): (s-CysC, mg/L, T (0) ROC AUC 0.936 (95% CI, 0.883-0.99; *P*<0.001), sensitivity 92%, specificity 84%; s-CysC, threshold value 1.79 mg/L, T (-1) ROC AUC 0.905 (95% CI, 0.837–0.973; *P*<0.001), sensitivity 92%, specificity 78%; s-CysC, 1.69 mg/L, T (-2) ROC AUC 0.853 (95% CI, 0.74–0.966; *P*<0.001), sensitivity 90%, specificity 73%; CysC, mg/L, threshold value 1.79 mg/L (Fig.).

Discussion

The search for promising laboratory markers to assess the COVID-19 patients and predict potential complications, including AKI, continues.

Studies have been published showing an increase in s-CysC concentration prior to the development of AKI and progression of lung infiltration in COVID-19. It has also been reported that s-CysC levels are higher in patients who later died.

In the present study, 36.8% (*N*=43) of the patients had impaired renal function. AKI developed in 17.9% (*N*=21) and renal dysfunction without progression to AKI was revealed in 18.3% patients (*N*=22), indicating a significant prevalence of renal impairment.

The incidence of renal impairment in COVID-19 varies widely from 0.5 to 36.6% [26] and may depend on the clinical manifestations of COVID-19, direct toxic effects of the virus, hypoxia and development of shock [27]. Proteinuria has been reported in

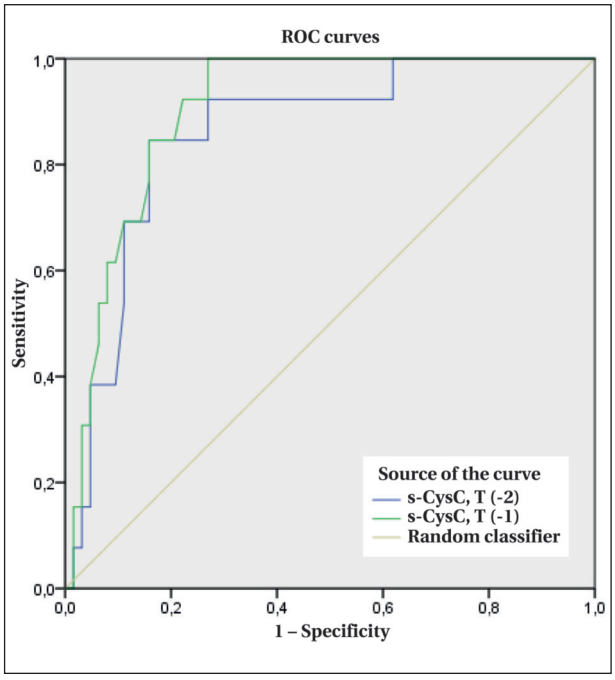

Fig. AUC ROC value of s-CysC T (-2), s-CysC T (-1) for the prediction of AKI development.

Table 3. Logistic regression for predicting AKI development in patients with severe and extremely severe pneumonia associated with COVID-19.

Time of CysC measurement	B	SE	Wald χ^2	*P*-value	OR	95% CI	
						Lower limit	Upper limit
Blood							
T	1.238	0.852	2.109	0.146	3.448	0.649	18.327
T (0)	2.175	0.76	8.184	0.004	8.805	1.984	39.081
T (-1)	1.681	0.715	5.534	0.019	5.37	1.324	21.788
T (-2)	1.171	0.577	4.121	0.042	3.225	1.041	9.989
T (-3)	0.585	0.495	1.398	0.237	1.794	0.681	4.73
Urine							
T	0.072	0.136	0.279	0.597	1.074	0.823	1.402
T (0)	0.119	0.97	1.513	0.219	1.127	0.932	1.363
T (-1)	0.089	0.113	0.618	0.432	1.093	0.876	1.363
T (-2)	0.057	0.123	0.212	0.645	1.058	0.832	1.346
T (-3)	0.061	0.126	0.235	0.628	1.063	0.831	1.359

Note. B — coefficient; SE — standard error; OR — odds ratio.

Table 4. ROC analysis for predicting the development of AKI in patients with severe and extremely severe pneumonia associated with COVID-19.

Time of measurement of CysC	AUC of the ROC-curve	*P*-value	SE	95% CI		Cut-off value of CysC, mg/L	Sensitivity, %	Specificity, %
				Lower limit	Upper limit			
T (0)	0.936	<0.001	0.027	0.883	0.99	1.79	92	84
T (-1)	0.905	<0.001	0.035	0.837	0.973	1.69	92	78
T (-2)	0.853	<0.001	0.058	0.74	0.966	1.67	90	73

43.9% and hematuria in 26.7% of COVID-19 patients [11].

A group of researchers (Richardson S. et al., 2020) analyzed the outcomes of 5.700 patients admitted for COVID-19 and reported that RRT was performed in 3.2% (*N*=81) of general ward patients and in 22% of ICU patients [13].

In a meta-analysis (Silver S. A. et al., 2021) based on MEDLINE, Embase, and Cochrane databases, 54 research papers with 30,639 patients were reviewed, of which 2,525 patients receiving inpatient therapy for COVID-19 in 48 studies were analyzed for the need for RRT. The overall prevalence of AKI was 28% (95% CI, 22–34%; I^2=99%), with 9% of patients receiving RRT (95% CI, 7–11%; I^2=97). Among patients treated in the ICU, AKI occurred in 46% (95% CI, 35–57%; I^2=99%) of cases and RRT was initiated in 19% (95% CI, 15–22%; I^2=88%) of patients [28].

In a retrospective study (Kanbay M. et al., 2022) (*N*=770), AKI was detected in 11.9% (*N*=92) of patients hospitalized with COVID-19. We also found that the duration of treatment in the ICU (16 days vs. 9.9 days, *P*<0.001), the rate of ICU admission (63% vs. 20.7%, *P*<0.001), the development of cytokine storm (25.9% vs. 14%, *P*=0.009) and mortality (47.2% vs. 4.7%, *P*<0.001) were significantly higher in the AKI group.

In the same study, data on the management of adult patients (*N*=100) with severe COVID-19 treated in the ICU were summarized. AKI (according to KDIGO criteria) was diagnosed in 81% of patients (*N*=81), including 44, 10, and 27 patients with stage 1, 2, and 3 AKI, respectively [29].

Chan L. et al. (2021) found that of 3,993 patients hospitalized for COVID-19, AKI occurred in 46% of patients (*N*=1835), with 19% (*N*=347) receiving RRT. Stage 1 AKI occurred in 39%, stage 2 in 19% and stage 3 in 42% of patients. 24% of patients (*N*=976) were admitted to the ICU, and AKI was diagnosed in 76% of cases (*N*=754). Proteinuria was detected in 84% of the 435 patients with AKI, hematuria in 81%, and leukocyturia in 60%. The mortality rate was 50% in the group with AKI and 8% in the group without AKI (OR 9.2; 95% CI, 7.5–11.3). At hospital discharge, 35% of patients in the AKI group had not recovered renal function [30].

Fisher M. et al (2022) investigated the prevalence of AKI in patients with COVID-19 in a retrospective observational study. Of 3,345 patients, 56.9% (*N*=1,903) developed AKI. Male sex, black race, and age over 50 years were found to be independent risk factors for the development of AKI [31].

The relatively lower incidence of AKI in COVID-19 (18.3%) in the patients we observed may be explained by the fact that the infectious hospital with ICU was located in a recently built building, which largely determined the low frequency of hospital-acquired infections.

The overall mortality of patients was 22.2% (*N*=26), and it was significantly higher in the group with AKI (52.4%, *N*=11) compared with the group

without AKI (15.62%, *N*=15) (χ^2 test=13.468, $P \leqslant 0.001$), suggesting an adverse effect of AKI on mortality.

Pei G. et al. (Wuhan, China, 2020) showed in a retrospective single-center study that the incidence of AKI (according to KDIGO criteria) in the cohort of hospitalized patients was 4.7% (22 of 467 patients). At the same time, proteinuria was observed in 65.8% and hematuria in 41.7%, indicating a high incidence of renal injury in patients with COVID-19. The latter patients had a higher mortality compared to patients without renal impairment: 11.2% (28 of 251) vs. 1.2% (1 of 82) [32].

Intergroup differences in s-CysC levels at time points T (*P*=0.0270), T (0) (*P*<0.001), T (-1) (*P*<0.001), T (-2) (*P*=0.0002), T (-3) (*P*=0.0218) and in u-CysC at time points T (*P*=0.1299), T (0) u-max (*P*=0. 0396), T (-1) u-max (*P*=0.0083), u-max (*P*=0.0452), T (-3) u-max (*P*=0.0310), which cannot be explained by impaired urinary filtration and reabsorption or CysC metabolism alone. Hyperproduction of CysC with the underlying severe systemic inflammation may play a role in the increase of CysC concentration in severe and critical pneumonia associated with COVID-19.

Analysis of the association of s-CysC with the development of AKI showed that s-CysC concentration 2 days (OR 3.225, Wald χ^2=4.121 (CI, 1.041; 9.989); *P*=0.042) and 1 day (OR 5.37, Wald χ^2=5.534 (CI, 1.324; 21.788); *P*=0.019) before the development of AKI was a significant predictor of AKI. The level of s-CysC started to increase three days before the development of AKI (intergroup difference, *P*=0.021753) before the increase in SCr levels, demonstrating the validity of these models for predicting AKI.

Analysis of u-CysC changes showed that it was not a significant predictor of AKI development.

We could not find any published studies addressing u-CysC evolution during COVID-19.

ROC analysis (Table 4) of significant predictors of AKI showed excellent performance of the s-CysC T(-1) model (ROC AUC 0.905 (95% CI, 0.837–0.973), *P*<0.001) and good performance of the s-CysC T(-2) model (ROC AUC 0.853 (95% CI, 0.74–0.966), *P*<0.001) in predicting AKI development at thresholds of 1.69 mg/L and 1.67 mg/L, respectively.

A single-center observational retrospective study by Yildirim C. et al (2021) evaluated the diagnostic and prognostic value of s-Cys C for the control of COVID-19-induced AKI. Among 348 patients with COVID-19, 17 (4.9%) cases developed AKI (including stage 1 in 1.3% (*N*=4), stage 2 in 9.0% (*N*=3), and stage 3 in 76.9% (*N*=10)). ROC analysis demonstrated the feasibility of using s-Cys C to predict COVID-19-induced AKI (AUC 0.96 (0.90–1.0) with sensitivity 90.0 (55.5–99.75), specificity 88.5 (84.6–91.7) [14].

Pode Shakked N. et al. (2022) also published a paper showing that s-CysC is an excellent predictor of COVID-19-associated AKI (ROC AUC 0.87) and the need for RRT (ROC AUC 0.95). Fifty-two patients with COVID-19 treated in the emergency department of the University of Cincinnati Medical Center (USA) were followed up. Of these, 42.3% (*N*=22) developed AKI and 36.4% (8 of 22) required RRT [33].

This is consistent with data from another study (Chen S. et al. 2021) showing that s-Cys C level increased earlier than that of SCr in patients with COVID-19 with renal impairment and was also more valuable in predicting disease severity [34].

The direct correlation between s-Cys C level and COVID-19 severity was also confirmed in our study: s-CysC and u-CysC had high prognostic significance for poor outcome (death) in pneumonia associated with severe and critical COVID-19. Elevated levels of s-CysC (1.44 mg/L and above) and u-CysC (0.86 mg/L and above) were associated with a fatal outcome [35, 36].

Ramos-Santos K. et al. (2022) confirmed the association between an increase in s-CysC and the development of AKI. In the group with AKI, the level of s-CysC was higher than in the group without AKI (*P*=0.001), and it increased earlier than SCr. An increase in s-CysC above 0.84 ng/mL increased the risk of developing AKI by a factor of 23 (OR, 23.7, 95% CI, 2.59–217.00, *P*=0.005) [37].

Conclusion

s-CysC is a significant predictor of AKI: its level starts to increase 3 days before the development of AKI and outpaces the increase in SCr concentration in patients with COVID-19-associated severe and critical pneumonia. u-CysC has only moderate relative value in predicting the development of AKI.

The use of s-CysC as a novel AKI biomarker in the management of patients with COVID-19 may contribute to the early detection of renal dysfunction enabling the prevention of AKI through initiation of preventive renal protection.

Authors' contribution.

Magomedali O. Magomedaliev: idea of the study, study design; review of publications on the subject of the paper; statistical processing of the material; obtaining data; database storage and processing; data analysis; discussion of the results; discussion of the paper format; drafting the manuscript, design of illustrations.

Daniil I. Korabelnikov: idea of the study, study design; review of publications on the subject of the paper; data analysis; discussion of the results; discussion of the paper format; drafting the manuscript; editing the manuscript; translation into English.

Sergey E. Khoroshilov: idea of the study; discussion of the results.

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