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# Prognostic Value of Cystatin C as a Predictor of Adverse Outcome in Severe Pneumonia Associated with COVID-19

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## Summary

**Objective.** To assess the cystatin C (CysC) prognostic value for probability of death in patients with severe and extremely severe pneumonia associated with COVID-19.

**Material and methods.** A single-center prospective study included 72 patients with severe and extremely severe pneumonia associated with COVID-19 undergoing treatment in the ICU of multifunctional medical center from September 2020 to October 2021. Recovered survivors (*N*=55) were analyzed as a Group 1, non-survivors (*N*=17) were considered as a Group 2.

**Results.** The serum (s-CysC) and urine (u-CysC) CysC concentrations were significantly lower in Group 1 patients vs Group 2, averaging 1.31 mg/l vs 1.695 mg/l (*P*=0.013550), and 0.25 mg/l vs 0.94 mg/l (*P*=0.026308), respectively. Significant differences were also revealed in the subgroups differed by age (*P*=0.0094), platelet count (*P*=0.001), serum fibrinogen concentration (*P*=0.016), as well as CURB (*P*=0.02334), CRB-65 (*P*=0.032564), and SOFA (*P*=0.042042) scores. Therefore, s-CysC and u-CysC were statistically significant predictors of death in patients with pneumonia associated with severe and extremely severe COVID-19: 16.273 (95% CI: 2.503–105,814), *P*=0.003 and 1.281 (95% CI: 1.011–1.622), *P*=0.040, respectively. Urine and serum CysC were established as predictors of death in pneumonia associated with severe and extremely severe COVID-19, where u-CysC was defined as highly informative (ROC AUC 0.938 (95% CI: 0.867–1.000; *P*=0.000), with 90% sensitivity and specificity), and s-CysC — as informative (ROC AUC 0.863 (95%CI: 0.738–0.988; *P*=0.000) with 80% sensitivity and 72% specificity) predictive markers.

**Conclusion.** Levels of S-CysC and u-CysC are of high prognostic significance and may contribute to identifying patients at a high risk of unfavorable outcome (death) due to pneumonia associated with severe and extremely severe COVID-19. Both S-CysC and u-CysC concentrations increasing up to ⩾1.44 mg/l and ⩾0.86 mg/l, respectively, were associated with high probability of death.

***Keywords: cystatin C, predictor; pneumonia; coronavirus infection; COVID-19; death; fatal outcome***

**Conflict of interest.** The authors declare no conflict of interest.

COVID-19 is an infectious disease caused by severe acute respiratory syndrome coronavirus (SARS-CoV-2). The first outbreak of COVID-19 occurred in late 2019, originating from Wuhan City, Hubei Province, People's Republic of China [1]. According to the World Health Organization (WHO), as of April 3, 2022, there have been more than 489 million cases and more than 6 million deaths from COVID-19 worldwide [2]. According to the Russian Federal State Agency for Health and Consumer Rights, as of April 8, 2022, there were 17,955,120 cases of COVID-19 in the Russian Federation [3].

SARS-CoV-2 virus enters the human body through the epithelium of the upper respiratory and gastrointestinal tracts, with the lungs being the target organ in most cases. Eighty-one percent of patients have mild COVID-19, 14% have severe COVID-19, and 5% have extremely severe (critical) COVID-19 [4].

Due to the severity of the disease, approximately 10.2% of those infected with SARS-CoV-2 coronavirus require intensive care unit (ICU) treatment [5]. Mortality in COVID-19 depends on disease severity, comorbidities, and treatment, and is approximately 49% in ICU patients [6].

The main reason for ICU admission is acute respiratory failure, which develops in 60–70% of ICU patients. The need for mechanical ventilation in different countries ranges from 29.3% (China) to 59% (UK) and up to 89.9% (USA) [4].

The systemic inflammatory response contributes significantly to the patient's deterioration. The SARS-CoV-2 enhanced immune response appears to play an important role in the pathogenesis and progression of COVID-19. The antiviral immune response is often exaggerated and characterized by massive release of pro- and anti-inflammatory cytokines [7], followed by lymphopenia and granulocyte and monocyte abnormalities [8]. Thus, the major pathogenetic events of the disease include infection, sepsis, and septic shock, leading to multiple organ failure.

The systemic inflammatory response is a universal component of critical illness, involving a cascade of interactions between pro- and anti-inflammatory cytokines and their imbalance [9]. As the disease progresses, hypercytokinemia eventually leads to multiple organ failure and can be fatal [10].

Currently, when assessing the severity of the patient's condition and immune status, including the decision on further treatment, both Russian and international protocols recommend measuring the traditional well-established markers of systemic inflammatory response, such as procalcitonin, C-reactive protein, fibrinogen, ferritin, leukocyte count, neutrophil percentage, appearance of immature leukocytes (left shift in the differential) and lymphocytes [11, 12].

Cystatin-C is a well-established marker of acute kidney injury (AKI) [13]. Meanwhile, AKI in COVID-19 is one of the earliest manifestations of multiple organ failure [4], which determined our interest in assessing cystatin as a criterion for multiple organ failure. We did not find any publications on u-CysC in COVID-19 in the available literature.

The intensity of the immune response is known to directly correlate with the severity of COVID-19 [11]. Therefore, it would be useful to have a readily available and reliable laboratory biomarker to objectively determine the prognosis of COVID-19 in a timely manner and to differentiate and/or predict clinical variants of the disease at an early stage, before the development of clinical manifestations and organ damage, thus enabling the administration of the optimal treatment regimen.

Real clinical practice shows that the organization of medical care in COVID-19 pandemic, with the shortage of medical staff and beds, especially in the ICU, requires objective markers [1] that allow timely prediction of the need for ICU admission for intensive care and monitoring of vital functions.

In this context, the level of CysC deserves attention as a potential predictor of COVID-19 severity and as an indicator of the intensity of the immune response to coronavirus.

The current literature shows that CysC is a reliable diagnostic and prognostic biomarker for acute kidney injury (AKI), and its level directly correlates with the severity of renal damage. The more severe the kidney damage and the worse the nephron function, the higher the concentration of cystatin-C in blood (s-CysC) and urine (u-CysC) [14]. Currently, there is considerable evidence that s-CysC levels are elevated in kidney disease and that s-CysC not only increases earlier than serum creatinine (SCr) in AKI, but also decreases earlier than SCr ($P<0.001$) [15]. An international expert group (International Survey on the Management of Acute Kidney Injury and Continuous Renal Replacement Therapies) concluded in 2018 that novel biomarkers should be used to detect AKI in routine clinical practice. The most common new-generation routine diagnostic laboratory marker for AKI (19% of cases) was CysC [16].

The CysC polypeptide is produced at the same rate by all nucleated cells and 99% of it is metabolized by the kidneys, while the remaining CysC is excreted unchanged in the urine. Due to its low molecular weight, CysC is freely filtered through the renal glomerular filter with subsequent reabsorption and catabolism in the proximal convoluted tubule of the nephron without entering the systemic bloodstream. Such kinetics allow CysC to be considered an almost ideal noninvasive biomarker for the assessment of renal function [17].

Although the exact mechanisms are still unknown, a considerable body of clinical and experimental evidence has accumulated indicating the direct involvement of CysC in many immunological processes, including COVID-19. An increase in serum and urine CysC levels in the midst of complete renal «normality» has been observed [18, 19].

The production of CysC is regulated by different inflammatory processes in response to various endogenous and exogenous antigens, while CysC affects the systemic inflammatory process by inducing immune response [20].

We suggest that CysC is not only a reliable diagnostic and prognostic biomarker of AKI, but may also serve as a marker of the intensity of the immune response in COVID-19 and predict severe disease, allowing early adjustments in therapy, including early initiation of biologic therapy and steroid pulse treatment.

In 1991, Collins A. R. et al. evaluated the inhibitory effect of recombinant human CysC on human OC43 and 229e coronaviruses in a laboratory experiment [21]. Both viruses were found to be 99% inhibited at a CysC concentration of 0.1 mM. The beneficial effects of CysC were attributed to its ability to inhibit papain-like proteases, which are part of the coronavirus polymerase complex. Human coronaviruses OC43 and 229e were also inhibited at moderate CysC concentrations of 1–2 μM (physiological CysC levels in biological media are much lower, e.g. 0.5 μM in cerebrospinal fluid and 0.1 μM in blood serum).

Similar results were shown by Collins A.R. et al. (1998), who investigated the effect of cystatin D (a salivary cysteine protease inhibitor) on the replication of human OC43 and 229e coronaviruses. After incubation of human OC43 and 229e coronaviruses and subsequent addition of recombinant cystatin D, a significant reduction in virus replication to IC50 of 0.8 pM (its reference range in human saliva is 0.12–1.9 pM) was observed for both virus strains. The authors concluded that cystatin D is a potent inhibitor of coronavirus replication [22].

There are also published studies showing antiviral activity of CysC against other viruses [23], such as herpes simplex virus type 1 [24], human immunodeficiency virus [25], rotavirus [26].

CysC has also been investigated as a promising antiviral drug to inhibit picornavirus replication [27].

Thus, CysC is a proven biochemical marker of AKI, but given the pathophysiological mechanisms of its elevation, it can be considered as a broader diagnostic and prognostic marker, especially in critical illness.

Aim: To study the prognostic value of cystatin-C in assessing the probability of death in patients with severe and extremely severe pneumonia associated with novel coronavirus infection (COVID-19).

## Materials and Methods

Patients with severe and extremely severe pneumonia associated with COVID-19, treated in the ICU of the Multidisciplinary Medical Center of the 1586 Military Clinical Hospital of the Ministry of Defense of Russia from September 2020 to October 2021, were included in this single-center prospective study.

Inclusion criteria:

— age 18 to 80 years;

— diagnosis of COVID-19 confirmed by detection of specific nucleic acids in nasopharyngeal swabs by polymerase chain reaction and/or antibodies in blood by enzyme-linked immunosorbent assay; as well as typical clinical and laboratory manifestations, lung damage confirmed by computed tomography;

— severe pneumonia evidenced by at least one of the following: dyspnea (respiratory rate >30/min), $SpO_2 \leqslant 93\%$, oxygenation index ⩽300 mm Hg, agitation, decreased consciousness, hemodynamic instability (systolic blood pressure less than 90 mm Hg and/or diastolic blood pressure less than 60 mm Hg), oligo- or anuria, computed tomography pattern typical of severe lung injury (CT grade 3–4, i.e, >50% lung volume involvement according to the semiquantitative scale used in Russia), arterial lactate >2 mmol/l, 2 or more points on the qSOFA scale, acute respiratory distress syndrome, respiratory failure requiring respiratory support, including high-flow oxygen therapy and noninvasive ventilation, septic shock, multiple organ failure.

Exclusion criteria:

— underlying renal and urinary tract diseases, other acute infectious and internal diseases, malignant neoplasms, including multiple myeloma, hyper- or hypothyroidism;

— history of cardiac, aortic, or great vessel surgery.

All patients received standard comprehensive intensive care according to the current provisional guidelines for the prevention, diagnosis and treatment of novel coronavirus infections (COVID-19).

Patients were divided into two groups based on clinical outcome:

— group 1 (survivors), 55 patients;

— group 2 (non-survivors), 17 patients.

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

The study was approved by the local ethics committee of the Haas Moscow Medical and Social Institute and was conducted in accordance with the current legislation of the Russian Federation and the ethical principles adopted by the World Medical Association (Declaration of Helsinki).

**Laboratory tests.** All instrumental and laboratory tests were performed at the 1586 Military Hospital according to existing standards and protocols, and the results were documented and evaluated retrospectively from the time of patient admission to the ICU until transfer to the infectious disease unit. Venous blood and urine samples were collected simultaneously on the first day of ICU admission and sent to the laboratory within 10–20 minutes.

The concentration of s-CysC and u-CysC was determined by the immunoturbidimetric method on an automated biochemical analyzer AU 480 from Beckman Coulter, Inc., USA, using reagents from DiaSys Diagnostic Systems GmbH, Germany.

In planning the study, a sample size corresponding to a power of 90% with an error of less than 0.05 was considered optimal [28]. The minimum power for a significance level of <0.05 was 44 subjects [29]. The calculation was performed to one of the endpoints, death/recovery. The sample size was 72 patients (17 died, 55 recovered), which, according to the results of the analysis using XLSTAT software, was characterized by a multivariate Cox regression power of 1.0 with an acceptable first-level error of less than 0.05. The size of the effect was calculated using Cohen's formula $d=(X1-X2)/\sqrt{(SD1^2-SD2^2)/2}$ [30]. The magnitude of effect for s-CysC was 0.589 (mean effect size) and for u-CysC was 0.761 (mean effect size).

Statistical analysis of the material was performed using Excel 2013 of Microsoft Office 2013 (Microsoft, USA) and SPSS Statistics (IBM, USA) package. Statistical significance of differences between groups was determined using the nonparametric Mann–Whitney *U* test. Multivariate Cox regression was used to determine the association between s-CysC, u-CysC and adverse outcome (death). The optimal threshold for predicting death with sensitivity and specificity was determined using the ROC curve. Quantitative data were presented as median (*Me*) and interquartile range (25%; 75%). Differences were considered significant at $P<0.05$.

## Results

SARS-CoV-2 virus was identified by polymerase chain reaction in 47 patients. The pattern of antibodies to SARS-CoV-2 virus in blood serum was as follows: IgM positive in 34 patients, negative in 11 patients; IgG positive in 23 patients, negative in 19 patients. The mean time of admission after the onset of illness was 7.6±4.45 days, and the ICU stay was 9.46±4.2 days. Mortality was 23.6% (*N*=17), the main causes of death were acute respiratory failure (10), multiple organ failure (3), heart failure (1).

A significant difference in CysC concentrations was observed between survivors and non-survivors.

The s-CysC level was 1.31 (1.04;1.61) mg/mL in group 1 and 1.695 (1.3;2.02) mg/mL in group 2 (*P*=0.013550). The u-CysC level was 0.25 (0.17; 0.46) mg/L in group 1 and 0.94 (0.35; 7.21) mg/L in group 2 (*P*=0.026308).

The mean age of the surviving patients was lower than that of the non-surviving patients (*P*=0.0094). Platelet count (*P*=0.001) and fibrinogen level (*P*=0.016) were also significantly different.

There were intergroup differences in CURB (*P*=0.02334), CRB-65 (*P*=0.032564), and SOFA (*P*=0.042042) scores.

According to the results of multivariate Cox regression analysis (Table 2), s-CysC 16.273 (95% CI, 2.503–105.814, *P*=0.003) and u-CysC 1.281 (95% CI, 1.011–1.622, *P*=0.040) were significant predictors of fatal outcome.

**Table 1. Clinical, laboratory and instrumental characteristics of patients.**

| № | Parameter | Values of parameters in groups (*Me* (*Q1*; *Q3*)) | | | Mann–Whitney | *P* |
|---|---|---|---|---|---|---|
| | | Total, *N*=72 | Group 1, *N*=55 | Group 2, *N*=17 | *U*-test | |
| 1 | Age, years | 48 (43; 55) | 47.5 (42; 51) | 55 (52; 80) | *U*=90; *Z*=–2.59232595 | **0.009466** |
| 2 | Men/women, *N* | 72 | 46/14 | 6/6 | — | — |
| 3 | Time of admission to the hospital from the onset of the disease, days | 7 (5; 10) | 7 (5; 11) | 7 (5; 8) | *U*=130; *Z*=1.60968 | 0.107470 |
| 4 | Time of admission to the ICU from the onset of the disease, days | 10 (7; 12) | 9 (7; 11) | 10 (8; 12) | *U*=192; *Z*=–0.06242 | 0.95022 |
| 5 | Duration of treatment in the ICU, days | 6 (4; 10) | 6 (4; 10) | 8 (6; 13) | *U*=159; *Z*=–0.88422 | 0.37658 |
| **6–14** | **Severity of disease according to scales, points** | | | | | |
| 6 | NEWS | 7 (7; 8) | 7 (7; 8) | 7 (7; 8) | *U*=165; *Z*=–0.77392 | 0.43898 |
| 7 | CRB-65 | 1 (0; 1) | 0 (0; 1) | 1 (1; 1) | *U*=116; *Z*=–2.13742 | **0.032564** |
| 8 | CURB | 1 (0; 1) | 1 (0; 1) | 1 (1; 2) | *U*=110.5; *Z*=–2.26781 | **0.023340** |
| 9 | SMRT-CO | 4 (3; 4) | 4 (3; 4) | 4 (4; 4) | *U*=155; *Z*=–1.18055 | 0.23778 |
| 10 | SMSRT-COP | 4 (3; 4) | 4 (3; 4) | 4 (4; 4) | *U*=151; *Z*=–1.27735 | 0.20147 |
| 11 | PORT(PSI) | 15 (0; 30) | 15 (0; 30) | 0 (0; 40) | *U*=89.5; *Z*=–0.35807 | 0.720280 |
| 12 | SOFA | 2 (2; 3) | 2 (1.5; 3) | 3 (2; 3) | *U*=117; *Z*=–2.03311 | **0.042042** |
| 13 | qSOFA | 1 (1; 1) | 1 (1; 1) | 1 (1; 1) | *U*=171.5; *Z*=1.20176 | 0.22946 |
| 14 | APACHE II | 5 (4; 7) | 5 (4; 7) | 5 (4; 6) | *U*=194.5; *Z*=0.012567 | 0.98997 |
| 15 | CT score of lung involvement (semi-quantitative assessment) on admission to the ICU | 4 (3; 4) | 4 (3; 4) | 4 (3; 4) | *U*=142.5; *Z*=0.625257 | 0.531803 |
| 16 | Hemoglobin, g/l | 140 (133; 149) | 140 (133; 149) | 140 (128; 154) | *U*=162.5; *Z*=–0.794389 | 0.426969 |
| 17 | Red blood cells, $10^{12}$/L | 4.81 (4.54; 5.05) | 4.81 (4.50; 5.05) | 4.6 (4.56; 5.05) | *U*=184; *Z*=–0.26050 | 0.794473 |
| 18 | White blood cells, $10^9$/L | 9.1 (7.4; 13.6) | 9.2 (7.8; 13.8) | 8 (6; 10.15) | *U*=129.5; *Z*=1.61261 | 0.10683 |
| 19 | Lymphocytes, % | 9 (5; 15) | 11 (4; 16) | 6 (5; 9) | *U*=145; *Z*=1.23033 | 0.21857 |
| 20 | Platelets, $10^9$/L | 226 (196; 296) | 268 (207.8; 303) | 181 (138; 202) | *U*=65.5; *Z*=3.20042 | **0.00137** |
| 21 | Total protein, g/L | 65 (62; 71) | 66 (62; 72) | 64 (62; 66) | *U*=152; *Z*=1.05607483 | 0.29093 |
| 22 | Urea, mmol/L | 6.3 (5; 7.5) | 5.8 (4.8; 7.5) | 6.7 (6.4; 7.9) | *U*=147; *Z*=–1.17902195 | 0.23839 |
| 23 | Creatinine, μmol/L | 89 (79; 97) | 88 (77; 96) | 94 (83; 99) | *U*=137.5; *Z*=–1.414835 | 0.157120 |
| 24 | Cystatin C in blood, mg/L | 1.32 (1.08; 1.63) | 1.31 (1.04; 1.61) | 1.695 (1.3; 2.02) | *U*=95; *Z*=–2.46879 | **0.013550** |
| 25 | Cystatin C in urine, mg/L | 0.28 (0.17; 0.51) | 0.25 (0.17; 0.46) | 0.94 (0.35; 7.21) | *U*=105; *Z*=–2.22164 | **0.026308** |
| 26 | CRP, mg/L | 96.9 (30.8; 145.2) | 101.6 (41.3; 146.6) | 89.4 (13.3; 126.7) | *U*=156; *Z*=–0.95507 | 0.339544 |
| 27 | Fibrinogen, g/L | 4.3 (3.4; 6.84) | 4.76 (3.5; 8) | 3.79 (3.3; 4.08) | *U*=98.5; *Z*=2.39513 | **0.016615** |
| 28 | Ferritin, μg/L | 684.5 (529.7; 712.7) | 671 (422.5; 720.7) | 681.7 (579.5; 689.2) | *U*=94; *Z*=0.387332 | 0.698510 |
| 29 | Procalcitonin, ng/mL | 0.5 (0.5; 0.5) | 0.5 (0.5; 0.5) | 0.5 (0.5; 0.5) | *U*=162; *Z*=0.00 | 1.000000 |
| 30 | D-dimer, mg/L | 0.46 (0.28; 0.83) | 0.46 (0.28; 0.83) | 0.43 (0.19; 0.95) | *U*=189; *Z*=0.13664 | 0.89130 |

**Note.** Q — quartile; CRP — C-reactive protein.

**Table 2. Multivariate regression analysis (Cox) of predictors of death.**

| Selected parameters | B | SE | p-value | Exp (B) | 95% CI | |
|---|---|---|---|---|---|---|
| | | | | | Lower limit | Upper limit |
| s-CysC, mg/l | 2.789 | 0.955 | 0.003 | 16.273 | 2.503 | 105.814 |
| u-CysC, mg/l | 0.247 | 0.121 | 0.040 | 1.281 | 1.011 | 1.622 |

**Note.** Values measured during the first 24 hours after ICU admission. B — coefficient; SE — standard error; Exp (B) — odds ratio (the predicted change in odds for a unit increase in the predictor).

**Table 3. ROC analysis of the significance of predictors of death.**

| Selected parameters | AUC of the ROC-curve | *P*-value | 95% CI | | Cut-off value | Sensitivity, % | Specificity, % |
|---|---|---|---|---|---|---|---|
| | | | Lower limit | Upper limit | | | |
| s-CysC, mg/l | 0.863 | 0.000 | 0.738 | 0.988 | 1.44 | 80 | 72 |
| u-CysC, mg/l | 0.938 | 0.000 | 0.867 | 1.000 | 0.86 | 90 | 90 |

**Note.** Values measured during the first 24 h of admission to the ICU.

Using ROC analysis, we identified u-CysC as the most significant predictor of death with 90% sensitivity and 90% specificity (*P*=0.000) (Table 3, Fig.), indicating excellent model quality. For s-CysC, the sensitivity was 80% and the specificity was 72% (*P*=0.000) (Table 3, Figure), corresponding to a good predictive ability for adverse outcomes.

## Discussion

The search for promising and advanced laboratory markers that can objectively assess the severity of COVID-19 patients and predict possible poor (fatal) outcomes is ongoing. In our opinion, both s-CysC and u-CysC deserve attention as indicators of systemic inflammation and COVID severity, in addition to their well-established role as reliable biomarkers of renal injury.

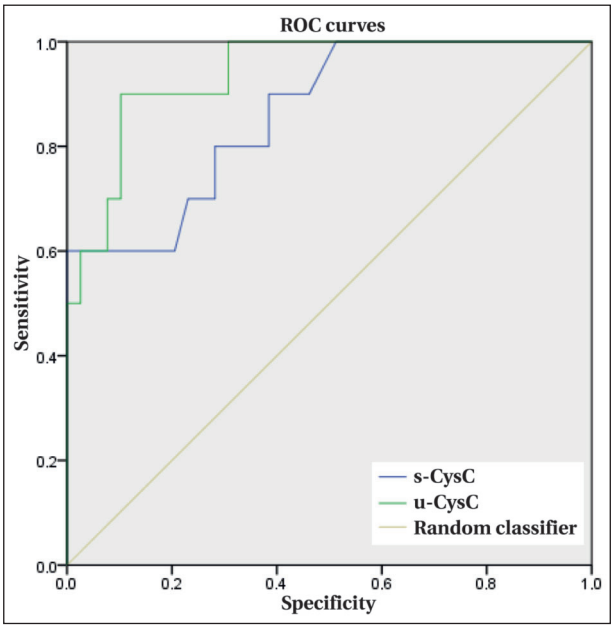
The significant increase in s-CysC and u-CysC levels in the group of non-survivors is probably associated with a more severe systemic inflammation and an increase in their production by nucleated cells.

However, a partial or, in some cases, complete dysfunction of the tubular system that interferes with the tubular reabsorption of CysC in the kidneys cannot yet be excluded.

The lack of intergroup differences in the levels of such a common marker of systemic inflammation as C-reactive protein (CRP) may be partially explained by the use of biological and steroid therapy prior to ICU admission in 57.14% (*N*=28) of cases.

Similar results were reported by authors from China (Li Y. et al., Wuhan, China, 2020), citing data from a single-center retrospective study of the prognostic value of s-CysC in patients with severe COVID-19 [31]. Adult patients without renal comorbidities (*N*=101) were evaluated and divided into two groups, including survivors (*N*=64) and non-survivors (*N*=37). The s-CysC was found to be an independent risk factor for death in severe COVID-19 patients (odds ratio=1.812, 95% CI: 1.300–2.527; *P*<0.001). s-CysC had an area under the AUC curve of 0.755 for predicting death (sensitivity 86.5%, specificity 56.2%). The authors concluded that patients with s-CysC of 0.80 mg/L or higher had a greater risk of death.

This is consistent with data from a meta-analysis by Zinellu A. et al. (2021) that included 13 studies (*N*=2.510) comparing s-CysC concentrations in patients with COVID-19. The authors concluded that the severity of COVID-19 and mortality increased with increasing s-CysC [32].




**AUC ROC value of s-CysC and u-CysC to predict poor outcome (death).**

A retrospective cohort study by Chen D. et al. (2020) evaluated the relationship between s-CysC levels and the severity of COVID-19 in 481 patients [33]. The highest s-CysC level was independently associated with the most severe manifestations of systemic inflammation, multiple organ failure and adverse outcome (*P*<0.05). Similarly, APACHE II and SOFA scores increased with increasing s-CysC (*P*<0.05). Notably, high s-CysC levels correlated significantly with increased lactate, CRP, procalcitonin, high neutrophil/lymphocyte ratio, and leukocytosis (*P*<0.05) and decreased oxygenation index (*P*<0.05). In conclusion, the investigators recommended regular monitoring of s-CysC in patients with COVID-19 to predict the severity of COVID-19.

The results of the study by Ouyang S.-M. et al. (2020) support the idea that increased s-CysC is associated with the risk of death and COVID-19 progression (*P*<0.05) [34].

Similarly, Wang J. et al. (2020) showed that severe COVID-19 is associated with increased s-CysC and hemoglobin and decreased blood oxygen saturation [35].

Similar results were reported by Chen S. et al. (2021), who showed that s-CysC increases earlier

than SCr in patients with impaired renal function in COVID-19 and is also more valuable in predicting disease severity [36].

Another recent study by Yang Z. et al. (2021) demonstrated that an increase in s-CysC may be associated with an increase in infiltration area on lung computed tomography within 6±1 to 24 hours [37].

Thus, the above studies suggest that an increase in s-CysC precedes the progression of pulmonary infiltration and the development of AKI. The level of s-CysC was also found to be significantly higher in the non-survivors than in the survivors.

## Conclusion

The study of s-CysC and u-CysC level changes during COVID-19 is a promising trend that will allow to optimize the therapy of pneumonia associated with severe and extremely severe COVID-19, while high levels of s-CysC (more than 1.44 mg/L) and u-CysC (more than 0.86 mg/L) are reliable predictors of death.

An increase in s-CysC concentration to 1.44 mg/L and more and u-CysC concentration to 0.86 mg/L and more is associated with a high risk of death, therefore their increase in pneumonia associated with severe and extremely severe COVID-19 should be considered life-threatening and requires early use of life-saving medicinal and other critical care options.

## References


1. *Хаджиева М.Б., Грачева А.С., Ершов А.В., Чурсинова Ю.В., Степанов В.А., Авдейкина Л.С., Гребенчиков О.А., с соавт.* Биомаркеры повреждения структур аэрогематического барьера при COVID-19. *Общая реаниматология*. 2021; 17 (3): 16–31. [*Khadzhieva M.B., Gracheva A.S., Ershov A.V., Chursinova Yu.V., Stepanov V.A., Avdeikina L.S., Grebenchikov O.A. et al.* Biomarkers of Air-Blood Barrier Damage In COVID-19. *General Reanimatology*. 2021; 17 (3): 16–31. (in Russ.)]. DOI: 10.15360/1813-9779-2021-3-2-0.
2. World Health Organization. Weekly epidemiological update on COVID-19 [Электронный ресурс/ Electronic resource]. URL: https://www.who.int/publications/m/item/weekly-epidemiological-update-on-COVID-19---5-april-2022 (дата обращения: 26.05.2022/ Accessed May 26, 2022).
3. Федеральная служба по надзору в сфере защиты прав потребителей [Электронный ресурс]. URL: https://rospotrebnadzor.ru/ about/info/news_time/ news_details.php?ELEMENT_ID=13566 (дата обращения: 08.04.2022). [Federal Service for Supervision of Consumer Rights Protection and Human Well-Being/Federalnaya sluzhba po nadzoru v sfere zashchity prav potrebiteley I blagopoluchiya cheloveka Electronic resource] (in Russ.)]. (Accessed April 8, 2022). https://rospotrebnadzor.ru/about/info/ news_time/ news_details.php?ELEMENT_ID=13566.
4. *Магомедалиев М.О., Корабельников Д.И., Хорошилов С.Е.* Острое повреждение почек при тяжелом течении пневмоний, ассоциированных с новой коронавирусной инфекцией (COVID-19). *Вестник Российской Военно-Медицинской Академии*. 2022; 24 (3): 511–520. [*Magomedaliev M.O., Korabelnikov D.I., Khoroshilov S.E.* Acute kidney injury in severe pneumonia associated with COVID-19. *Bull Russ Mil Med Acad./ Vestnik Rossiyskoy Voenno- Meditsinskoy Akademii*. 2022; 24 (3): 511–520. (in Russ.)]. DOI: 10.17816/brmma109938.
5. *Oliveira E., Parikh A., Lopez-Ruiz A., Goldberg J., Cearras M., Fernainy K., Andersen S.* et al. ICU outcomes and survival in patients with severe COVID-19 in the largest health care system in central Florida. *PLoS One*. 2021; 16 (3): e0249038. DOI: 10.1371/journal.pone.0249038. PMID: 33765049
6. *Wu Z., McGoogan J.M.* Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *JAMA*. 2020; 323 (13): 1239–1242. DOI: 10.1001/jama.2020.2648. PMID: 32091533
7. *Ершов А.В., Сурова В.Д., Долгих В.Т., Долгих Т.И.* Цитокиновый шторм при новой коронавирусной инфекции и способы его коррекции. *Антибиотики и Химиотерапия*. 2020; 65 (11–12): 27–37. [*Ershov A.V., Surova V.D., Dolgikh V.T., Dolgikh T.I.* Cytokine storm in the novel coronavirus infection and methods of its correction. *Antibiotics and Chemotherapy/Antibiotiki i Khimioterapiya* 2021; 65 (11–12): 27–37. (In Russ.)]. DOI: 10.37489/0235-2990-2020-65-11-12-27-37.
8. *Rello J., Belliato M., Dimopoulos M.-A., Giamarellos-Bourboulis E.J., Jaksic V., Martin-Loeches I., Mporas I.* et al. Update in COVID-19 in the intensive care unit from the 2020 HELLENIC Athens International symposium. *Anaesth Crit Care Pain Med*. 2020; 39 (6): 723–730. DOI: 10.1016/j.accpm.2020.10.008. PMID: 33172592
9. *Bone R.C., Balk R.A., Cerra F.B., Dellinger R.P., Fein A.M., Knaus W.A., Schein R.M.* et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of chest physicians/ Society of critical care medicine. *Chest*. 1992; 101 (6): 1644–1655. DOI: 10.1378/chest.101.6.1644. PMID: 1303622
10. *Хорошилов С.Е., Никулин А.В.* Эфферентное лечение критических состояний. *Общая реаниматология*. 2012; 8 (4): 30. [*Khoroshilov S.E., Nikulin A.V.* Efferent treatment for critical conditions. *Gen Reanimatol./ Obshchaya Reanimatologya*. 2012; 8 (4): 30. (in Russ.)]. DOI: 10.15360/1813-9779-2012-4-30
11. Временные методические рекомендации «Профилактика, диагностика и лечение новой коронавирусной инфекции (COVID-19)». Версия 13.1 от 17.11.2021. [Temporary Guidelines «Prevention, diagnosis treatment of new coronavirus Infect (COVID-19)» Version 13.1 (11.17. 2021)/ Vremennye metodicheskie rekomendatsyi «Profilaktika, diagnostika i lecheniye novoy koronavirusnoy infektsii (COVID-19)». Versiya 13.1 (17.11.2021). (In Russ.)]. https://www.garant.ru/products/ ipo/prime/doc/ 402985106/. Accessed April 28, 2023.
12. *Зайцев А.А., Чернов С.А., Стец В.В., Паценко М.Б., Кудряшов О.И., Чернецов В.А., Крюков Е.В.* Алгоритмы ведения пациентов с новой коронавирусной инфекцией COVID-19 в стационаре. Методические рекомендации. *Consilium Medicum*. 2020; 22 (11): 91–97. [*Zaitsev A.A., Chernov S.A., Stets V.V., Patsenko M.B., Kudriashov O.I., Chernetsov V.A., Kriukov E.V.* Algorithms for the management of patients with a new coronavirus COVID-19 infection in a hospital. Guidelines. *Consilium Medicum*. 2020; 22 (11): 91–97. (In Russ.)]. DOI: 10.26442/20751753. 2020.11.200520
13. *Магомедалиев М.О., Корабельников Д.И., Хорошилов С.Е.* Прогностическое значение цистатина-С как предиктора развития острого повреждения почек при COVID-19. *Общая реаниматология*. 2023; 19 (2): 14–22. [*Magomedaliev M.O., Korabelnikov D.I., Khoroshilov S.E.* The predictive value of cystatin C for AKI in patients with COVID-19. *General Reanimatology/Obshchaya Reanimatologya*. 2023; 19 (2): 14–22. (In Russ.)]. DOI: 10.15360/1813-9779-2023-2-224
14. *Корабельников Д.И., Магомедалиев М.О.* Современные биомаркеры острого повреждения почек. *ФАРМАКОЭКОНОМИКА. Современная фармакоэкономика и фармакоэпидемиология*. 2023; 16 (1): 87–104. [*Korabelnikov D.I., Magomedaliev M.O.* Modern biomarkers of acute kidney injury. *PHARMACOECONOMICS. Modern Pharmacoeconomics and Pharmacoepidemiology / FARMAKOEKONOMIKA. Sovremennaya Farmakoekonomika I Farmakoekoepidemiologiya* 2023; 16 (1): 87–104. (In Russ.)]. DOI: 10.17749/2070-4909/ farmakoekonomika. 2023.171.
15. *Gharaibeh K.A., Hamadah A.M., El-Zoghby Z.M., Lieske J.C., Larson T.S., Leung N.* Cystatin C predicts renal recovery earlier than creatinine among patients with acute kidney injury. *Kidney Int Rep*. 2018; 3 (2): 337–342. DOI: 10.1016/j.ekir.2017.10.012. PMID: 29725637

16. *Digvijay K., Neri M., Fan W., Ricci Z., Ronco C.* International survey on the management of acute kidney injury and continuous renal replacement therapies: year 2018. *Blood Purif.* 2019; 47 (1–3): 113–119. DOI: 10.1159/000493724. PMID: 30269144
17. *Каюков И.Г., Смирнов А.В., Эмануэль В.Л.* Цистатин С в современной медицине. *Нефрология.* 2012; 16 (1): 22–39. [*Kayukov I.G., Smirnov A.V., Emanuel V.L.* Cystatin C in current medicine. *Nephrology/ Nefrologiya* (Saint-Petersburg). 2012; 16 (1): 22–39. (In Russ.)]. DOI: 10.24884/1561-6274-2012-16-1-22-39.
18. *Магомедалиев М.О., Корабельников Д.И., Хорошилов С.Е.* Способ оценки неблагоприятного исхода пневмонии тяжелого течения, ассоциированной с COVID-19, по уровню s-CysC. Российский патент RU 2779581C2 2022 г. по МПК G01N33/68 G01N33/49 G01N33/53. *Бюллетень.* 2022; 25: 3. [*Magomedaliev M.O., Korabelnikov D.I., Khoroshilov S.E.* A method for assessing the adverse outcome of severe pneumonia associated with COVID-19 by the level of s-CysC. Russian patent RU 2 779581 C2, IPC G01N 33/68, G01N 33/49, G01N 33/53. *Bulletin.* 2022; 25: 3. (in Russ.)]. https://patenton.ru/patent/RU2779581C2
19. *Магомедалиев М.О. Корабельников Д.И. Хорошилов С.Е.* Способ оценки неблагоприятного исхода пневмонии тяжелого течения, ассоциированной с COVID-19, по уровню u-CysC. Российский патент RU 2779579C2 2022 г. по МПК G01N 33/68, G01N 33/493, G01N 33/53. *Бюллетень.* 2022; 25: 3. [*Magomedaliev M.O, Korabelnikov D.I., Khoroshilov S.E.* A method for assessing the adverse outcome of severe pneumonia associated with COVID-19 by the level of u-CysC. Russian patent RU2779579 C2, IPC G01N 33/68, G01N 33/493, G01N 33/53. *Bulletin.* 2022; 25: 3. (in Russ.)]. https://patenton.ru/patent/RU2779579C2
20. *Zi M., Xu Y.* Involvement of cystatin C in immunity and apoptosis. *Immunol Lett.* 2018; 196: 80–90. DOI: 10.1016/j.imlet.2018.01.006. PMID: 29355583
21. *Collins A.R., Grubb A.* Inhibitory effects of recombinant human cystatin C on human coronaviruses. *Antimicrob Agents Chemother.* 1991; 35 (11): 2444–2446. DOI: 10.1128/AAC.35.11.2444. PMID: 1804023
22. *Collins A.R., Grubb A.* Cystatin D, a natural salivary cysteine protease inhibitor, inhibits coronavirus replication at its physiologic concentration. *Oral Microbiol Immunol.* 1998; 13 (1): 59–61. DOI: 10.1111/j.1399-302X.1998.tb00753.x. PMID: 9573825
23. *Clemente V., D'Arcy P., Bazzaro M.* Deubiquitinating enzymes in coronaviruses and possible therapeutic opportunities for COVID-19. *Int J Mol Sci.* 2020; 21 (10): 3492. DOI: 10.3390/ijms21103492. PMID: 32429099
24. *Björck L., Grubb A., Kjellén L.* Cystatin C, a human proteinase inhibitor, blocks replication of herpes simplex virus. *J Virol.* 1990; 64 (2): 941–943. DOI: 10.1128/JVI.64.2.941-943.1990. PMID: 2153254
25. *Vernekar V., Velhal S., Bandivdekar A.* Evaluation of cystatin C activities against HIV. *Indian J Med Res.* 2015; 141 (4): 423–430. DOI: 10.4103/0971-5916.159282. PMID: 26112843
26. *Nakamura S., Hata J., Kawamukai M., Matsuda H., Ogawa M., Nakamura K., Jing H.* et al. Enhanced anti-rotavirus action of human cystatin C by site-specific glycosylation in yeast. *Bioconjug Chem.* 2004; 15 (6): 1289–1296. DOI: 10.1021/bc049838s. PMID: 15546195
27. *Carrasco L.* Picornavirus inhibitors. *Pharmacol. Ther.* 1994; 64 (2): 215–290. DOI: 10.1016/0163-7258(94)90040-X. PMID: 7533301.
28. *Murray P.T., Le Gall J.-R., Miranda D.D.R., Pinsky M.R., Tetta C.* Physiologic endpoints (efficacy) for acute renal failure studies. *Curr Opin Crit Care.* 2002; 8 (6): 519–525. DOI: 10.1097/00075198-200212000-00007. PMID: 12454536
29. *Наркевич А.Н., Виноградов К.А.* Методы определения минимально необходимого объема выборки в медицинских исследованниях. *Социальные аспекты здоровья населения. Электронный научный журнал.* 2019; 65 (6): 2–19. [*Narkevich A.N., Vinogradov K.A.* Methods for determining the minimum required sample size in medical research. *Social Aspects of Public Health. Electronic Scientific Journal/ Socialniye Aspecty Zdorovya Naseleniya. Electronny Nauchny Zhurnal.* 2019; 65 (6): 2–19. (In Russ.)]. DOI: 10.21045/2071-5021-2019-65-6-10
30. *Larner A.J.* Effect size (Cohen's d) of cognitive screening instruments examined in pragmatic diagnostic accuracy studies. *Dement Geriatr Cogn Dis Extra.* 2014; 4 (2): 236–241. DOI: 10.1159/000363735. PMID: 25177332
31. *Li Y., Yang S., Peng D., Zhu H.-M., Li B.-Y., Yang X., Sun X.-L.* et al. Predictive value of serum cystatin C for risk of mortality in severe and critically ill patients with COVID-19. *World J Clin Cases.* 2020; 8 (20): 4726–4734. DOI: 10.12998/wjcc.v8.i20.4726. PMID: 33195640
32. *Zinellu A., Mangoni A.A.* Cystatin C, COVID-19 severity and mortality: a systematic review and meta-analysis. *J Nephrol.* 2022; 35 (1): 59–68. DOI: 10.1007/s40620-021-01139-2. PMID: 34390479
33. *Chen D., Sun W., Li J., Wei B., Liu W., Wang X., Song F.* et al. Serum cystatin C and coronavirus disease 2019: a potential inflammatory biomarker in predicting critical illness and mortality for adult patients. *Mediators Inflamm.* 2020: 3764515. DOI: 10.1155/2020/ 3764515. PMID: 33061826
34. *Ouyang S.-M., Zhu H.-Q., Xie Y-N, Zou Z.-S., Zuo H.-M., Rao Y.-W., Liu X.-Y.* et al. Temporal changes in laboratory markers of survivors and non-survivors of adult inpatients with COVID-19. *BMC Infect Dis.* 2020; 20 (1): 952. DOI: 10.1186/s12879-020-05678-0. PMID: 33308159
35. *Wang J., Guo S., Zhang Y., Gao K., Zuo J., Tan N., Du K. et al.* Clinical features and risk factors for severe inpatients with COVID-19: a retrospective study in China. *PLoS One.* 2020; 15 (12): e0244125. DOI: 10.1371/journal.pone.0244125 PMID: 33332437
36. *Chen S., Li J., Liu Z., Chen D., Zhou L., Hu D., Li M. et al.* Comparing the value of cystatin C and serum creatinine for evaluating the renal function and predicting the prognosis of COVID-19 patients. *Front Pharmacol.* 2021; 12: 587816. DOI: 10.3389/fphar.2021.587816. PMID: 33828483
37. *Yang Z., Shi J., He Z., Lü Y., Xu Q., Ye C., Chen S. et al.* Predictors for imaging progression on chest CT from coronavirus disease 2019 (COVID-19) patients. *Aging (Albany NY).* 2020; 12 (7): 6037–6048. DOI: 10.18632/aging.102999. PMID: 32275643

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