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Prognostic Performance of Cystatin C in COVID-19: A Systematic Review and Meta-Analysis

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Abstract: Cystatin C is a specific biomarker of kidney function. We perform this meta-analysis to determine the association of Cystatin C with the COVID-19 severity. In this systematic review and meta-analysis, we searched PubMed, EMBASE, Cochrane library, and Web of Science for studies published until 2nd September 2022 that reported associations between Cystatin C levels and COVID-19 severity. The analysis was performed using a random-effects model to calculate pooled standard mean difference (SMD). Twenty-five studies were included in the meta-analysis. Pooled analysis showed statistically significant differences of Cystatin C levels among survive vs. decreased patients (0.998 ± 0.225 vs. 1.328 ± 0.475 mg/dL, respectively; SMD = −2.14; 95% CI: −3.28 to −1.01; p < 0.001). Cystatin C levels in COVID-19 severe vs. non-severe groups varied and amounted to 1.485 ± 1.191 vs. 1.014 ± 0.601 mg/dL, respectively (SMD = 1.81; 95% CI: 1.29 to 2.32; p < 0.001). Additionally, pooled analysis showed that Cystatin C levels in patients with acute kidney injury (AKI) was 1.562 ± 0.885 mg/dL, compared to 0.811 ± 0.108 mg/dL for patients without AKI (SMD = 4.56; 95% CI: 2.72 to 8.85; p = 0.04). Summing up, Cystatin C is a potentially very good marker to be used in the context of COVID-19 disease due to the prognosis of patients’ serious condition, risk of AKI and mortality. In addition, Cystatin C could be used as a marker of renal complications in COVID-19 other than AKI due to the need to monitor patients even longer after leaving the hospital.

Keywords: Cystatin C; cystatin 3; SARS-CoV-2; novel coronavirus; COVID-19; severity

1. Introduction

Global healthcare systems have been under intense pressure since the coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was announced in China in late 2019 and spread around the world [1]. Acute respiratory distress syndrome (ARDS) and mortality are the most severe signs of symptomatic COVID-19, but moderate fever (>37.5 °C) and cough are also common, and the disease has an erratic course. Due to this diversity, there is an urgent need for disease severity biomarkers so that patients may be managed effectively, and deadly consequences can be avoided. The use of biomarkers in diagnosis, risk assessment, and medical decision-making is common. Mortality has been linked to markers of organ failure, coagulation, and inflammation in COVID-19 hospitalized patients [2,3]. Identifying which patients are likely to pass away can help with early therapy intensification and closer
monitoring. Additionally, research into novel biomarkers may provide fresh insights into the pathogenesis of COVID-19 and its consequences.

All nucleated cells generate Cystatin C, a small molecule protein that is a member of the cysteine protease inhibitor superfamily. Cystatin C is a nonglycosylated basic protein that is continuously generated by nucleated cells and is easily filtrable from the glomerulus. The proximal tubular cells totally catabolize Cystatin C, preventing its return to the circulatory system [4]. Cystatin C levels can more accurately reflect changes in glomerular filtration rate (GFR) than serum creatinine does. Unlike the traditional detection indices, Cystatin C is unaffected by age, sex, race, infection, liver illness, or inflammation [5]. As a result, it is frequently utilized in the diagnosis and assessment of renal disorders [6]. It has been demonstrated that Cystatin C has higher sensitivity to changes in borderline renal function and rises earlier than creatinine in a variety of patient populations, including diabetic, surgical, and cardiovascular patients [7–9]. Moreover, a growing number of studies have shown conclusively that Cystatin C contributes to the pathophysiology of the immunomodulatory responses seen in inflammatory conditions and infections. Cystatin C can control the release of a variety of cytokines, including nitric oxide, interleukin-12, interleukin-10, and tumor necrosis factor [10]. The inducible isof orm of NO synthase (iNOS), in particular, is activated by Cystatin C and is principally in charge of the excessive NO synthesis seen in local and systemic proinflammatory conditions [11]. As a result, extremely reactive NO derivatives are produced, nitrosative stress is caused, and various intracellular components undergo irreversible changes with consequent cell apoptosis and organ failure occurring. While elevated blood levels of Cystatin C in individuals with COVID-19 are likely to indicate the existence of renal impairment, such as acute kidney injury (AKI), they may also be a sign of the excessive systemic inflammatory and pro-oxidant state that distinguishes patients with COVID-19 [12]. Cystatin C also may be employed as a trustworthy biological marker to predict AKI, particularly in assisting with early clinical identification of AKI, and AKI in hospitalized patients with COVID-19 is as high as 43% [13,14]. Renal biomarkers may help with early risk classification, monitoring, and therapy in patients with COVID-19 given the more common development of renal impairment in this population [14]. Nevertheless, the availability of biomarkers that might indicate not just the early presence of renal failure but also other aberrant processes, such as systemic inflammation, oxidative stress, and cytokine storm, may be particularly helpful in the COVID-19 pandemic. For these reasons, we decided to conduct a review and meta-analysis on the prognostic role of Cystatin C and its predictive role regarding the occurrence of AKI in patients with COVID-19.

2. Materials and Methods

This systematic review and meta-analysis was performed in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [15]. Before commencing the study, all authors agreed on the analysis methods and the inclusion and exclusion criteria to be used.

2.1. Study Identification

We searched PubMed, EMBASE, Cochrane library, and Web of Science. An initial search was performed on 21 May 2020, including publications from 1st January 2020, followed by a final search on 2 September 2022 which incorporated all the manuscripts up to this date. The search was conducted using the terms: “Cystatin C” OR “cystatin 3” AND “SARS-CoV-2” OR “COVID-19” OR “novel coronavirus”. Additionally, references of relevant reviews, full-text articles, and the included literature were screened for additional studies that may have been missed. All references were saved in an EndNote (End Note, Inc., Philadelphia, PA, USA) library used to identify the duplicates.
2.2. Study Selection Criteria

Two reviewers independently screened articles according to pre-specified inclusion and exclusion criteria. The inclusion criteria were studies reporting Cystatin C levels among patients with COVID-19 who survive vs. dead or severe vs. non-severe COVID-19 status. Additionally, we also include trials reporting Cystatin C levels among patients with COVID-19 with and without acute kidney injury.

Furthermore, this review excluded the following types of studies: (1) papers not containing comparator group; (2) paper referring to pediatric population; (3) conference or poster papers; (4) reviews or meta-analyses; (5) case reports; (6) articles not containing original data; (7) articles published in other than English language.

2.3. Data Extraction

Two independent authors (M.M. and M.P.) extracted the data using predefined extraction form: first author surname, publication year, study designs, country of publication, study population characteristics, Cystatin C levels, and study quality. Disagreements were resolved by the third author (L.S.).

2.4. Quality Assessment

We referred to the Cochrane Handbook to guide the synthesis [16]. The methodological quality of the observational studies was assessed using the Newcastle Ottawa Scale [17]. NOS measures the quality of a study based on three aspects: selection, comparability, and exposure. The maximum scores of these three aspects were 4, 2 and 3 stars, respectively. Studies with NOS scores ≥ 7 were considered to be high-quality studies.

2.5. Statistical Analysis

Statistical analysis was performed using RevMan (ver. 5.4, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). The standard mean difference (SMD) was calculated with 95% confidence intervals (CIs). The SMD was calculated by using random-effects models. When the continuous outcome was reported in a study as median, range, and interquartile range, we estimated means and standard deviations using the Hozo et al. formula [18]. Heterogeneity was assessed using the tau coefficient and measured using the I2 index and we consider percentages of around I2 = 25%, I2 = 50%, and I2 = 75% as low, medium, and high heterogeneity, respectively [19]. The $p$-value ≤ 0.05 cut-point was used to declare statistical significance. Potential publication bias was assessed using funnel plots, and where possible, Egger’s regression test was performed. However, when a limited number of studies (<10) were included in the analysis, publication bias was not evaluated.

3. Results

3.1. Study Selection and Characteristics

Overall, 422 studies were identified through database searches, and two additional articles were retrieved from the bibliographies of the included studies. Two hundred ninety-three duplicates were removed, and the remaining 131 articles were screened by title and abstract, which resulted in the exclusion of 92 irrelevant articles. Full-text screening was performed on 39 studies, and data for 25 studies were extracted for this meta-analysis [20–44]. Figure 1 depicts the various exclusions and selection procedures.

The systematic review included articles published between 2020 and 2022, comprising a total of 3916 COVID-19 participants (Table 1). The final set considered of 25 eligible studies [20–46], including 18 articles conducted in China [21–23,25–28,31,33,34,36–39,41–44], two articles in Turkey [32,40], and one article each from the following countries: Iraq [20], India [24], Mexico [29], USA [30] and Egypt [35].
Figure 1. The flow diagram for study search process.

Table 1. Baseline characteristics of the included studies.

| Study                  | Country | Study Group   | No. of Patients | Age            | Sex, Male | Cystatin C Level | NOS Scale |
|------------------------|---------|---------------|-----------------|----------------|------------|------------------|-----------|
| Abbas et al., 2022 [20]| Iraq    | Non-severe    | 35              | 56.82 ± 12.574 | 28 (80.0%) | 0.49 ± 0.104    | 8         |
|                        |         | Severe        | 36              | 63.04 ± 11.143 | 29 (80.6%) | 0.48 ± 0.103    |           |
| Cao et al., 2020 [21]  | China   | Survivors     | 85              | 54.75 ± 3.17   | 40 (47.1%) | 0.96 ± 0.23     | 9         |
|                        |         | Non-survivors | 17              | 72 ± 4.5       | 13 (76.5%) | 1.66 ± 0.97     |           |
| Deng et al., 2020 [22] | China   | Non-severe    | 53              | 34 ± 2         | 24 (45.3%) | 1.12 ± 0.224    | 8         |
|                        |         | Severe        | 12              | 33.25 ± 2      | 12 (100%)  | 0.788 ± 0.043   |           |
| He et al., 2022 [23]   | China   | Non-severe    | 54              | 49.7 ± 5.3     | 26 (48.1%) | 1.12 ± 0.224    | 8         |
|                        |         | Severe        | 23              | 63.25 ± 2.25   | 12 (52.2%) | 0.95 ± 0.1      |           |
| Kumar et al., 2022 [24]| India   | Non-severe    | 63              | 52.1 ± 11.1    | NS         | 0.82 ± 0.23     | 7         |
|                        |         | Severe        | 32              | 54.8           | NS         | 1.17 ± 0.55     |           |
| Li et al., 2020 [25]   | China   | Survivors     | 64              | 54.09 ± 14.95  | 30 (46.9%) | 0.8 ± 0.05      | 8         |
|                        |         | Non-survivors | 37              | 71.76 ± 10.012 | 23 (62.2%) | 1.05 ± 0.1      |           |
| Li et al., 2021 [26]   | China   | Survivors     | 230             | 56.25 ± 3.83   | 108 (47.0%)| 0.9 ± 0.067     | 8         |
|                        |         | Non-survivors | 96              | 70.75 ± 3      | 63 (65.6%) | 1.4 ± 0.167     |           |
| Lin et al., 2021 [27]  | China   | Non-severe    | 134             | 59.8 ± 13.0    | 64 (47.8%) | 1.36 ± 0.195    | 8         |
|                        |         | Severe        | 28              | 70.1 ± 12.7    | 20 (71.4%) | 1.07 ± 0.05     |           |
| Liu et al., 2021 [28]  | China   | Non-severe    | 76              | 62.9 ± 9.3     | 49 (64.5%) | 1.203 ± 0.113   | 9         |
|                        |         | Severe        | 76              | 64.5 ± 9.3     | 49 (64.5%) | 1.3 ± 0.22      |           |
Table 1. Cont.

| Study                        | Country | Study Group         | No. of Patients | Age        | Sex, Male | Cystatin C Level | NOS Scale |
|------------------------------|---------|---------------------|-----------------|------------|-----------|-----------------|-----------|
| Ramos-Santos et al., 2022    | Mexico  | Without AKI         | 11              | 60.2 ± 10.2| 7 (63.6%) | 0.73 ± 0.14     | 9         |
|                              |         | With AKI            | 27              | 52.5 ± 14.9| 21 (77.8%)| 1.39 ± 0.88     |           |
|                              |         | Survivors           | 15              | NS         | NS        | 1.01 ± 0.80     |           |
|                              |         | Non-survivors       | 23              | NS         | NS        | 1.32 ± 0.79     |           |
| Pode Shakked et al., 2022    | USA     | Without AKI         | 30              | 65.58 ± 2.93| 14 (63.6%)| 0.843 ± 0.063   | 8         |
|                              |         | With AKI            | 22              | 44.7 ± 3.7 | 17 (56.7%)| 2.098 ± 1.153   |           |
| Tang et al., 2020            | China   | Non-severe          | 60              | 54.25 ± 4.75| 26 (43.3%)| 1.305 ± 0.146   | 8         |
|                              |         | Severe              | 60              | 62.98 ± 6  | 40 (66.7%)| 0.93 ± 0.04     |           |
| Temiz et al., 2022           | Turkey  | Non-severe          | 24              | 38.5 ± 11.5| 17 (48.6%)| 2.33 ± 2.5      | 8         |
|                              |         | Severe              | 10              | 44 ± 9.8   | 6 (60.0%) | 0.81 ± 0.26     |           |
| Wang et al., 2020            | China   | Non-severe          | 509             | 47.5 ± 5.3 | 164 (32.2%)| 1.043 ± 0.138   | 8         |
|                              |         | Severe              | 53              | 57.75 ± 4.25| 7 (13.2%) | 0.945 ± 0.05    |           |
| Tang et al., 2020            | China   | Non-severe          | 60              | 54.25 ± 4.75| 26 (43.3%)| 1.305 ± 0.146   | 8         |
|                              |         | Severe              | 60              | 62.98 ± 6  | 40 (66.7%)| 0.93 ± 0.04     |           |
| Pode Shakked et al., 2022    | USA     | Without AKI         | 30              | 65.58 ± 2.93| 14 (63.6%)| 0.843 ± 0.063   | 8         |
|                              |         | With AKI            | 22              | 44.7 ± 3.7 | 17 (56.7%)| 2.098 ± 1.153   |           |
| Temiz et al., 2022           | Turkey  | Non-severe          | 24              | 53.96 ± 15.4| NS        | 0.86 ± 0.37     | 7         |
|                              |         | Severe              | 12              | 71.42 ± 14.62| NS       | 1.52 ± 0.66     |           |
| Wang et al., 2020            | China   | Non-severe          | 35              | 38.5 ± 11.5| 17 (48.6%)| 2.33 ± 2.5      | 8         |
|                              |         | Severe              | 10              | 44 ± 9.8   | 6 (60.0%) | 0.81 ± 0.26     |           |
| Wang et al., 2020 (B)        | China   | Non-severe          | 509             | 47.5 ± 5.3 | 164 (32.2%)| 1.043 ± 0.138   | 8         |
|                              |         | Severe              | 53              | 57.75 ± 4.25| 7 (13.2%) | 0.945 ± 0.05    |           |
| Wasyf et al., 2022           | Egypt   | Without AKI         | 64              | 60 ± 2     | 37 (57.8%)| 0.93 ± 0.23     | 9         |
|                              |         | With AKI            | 25              | 65.5 ± 2.5 | 14 (56.0%)| 1.06 ± 0.25     |           |
| Wasfy et al., 2022           | Egypt   | Survivors           | 63              | NS         | NS        | 0.93 ± 0.24     |           |
|                              |         | Non-survivors       | 26              | NS         | NS        | 1.07 ± 0.23     |           |
| Wu et al., 2020              | China   | Survivors           | 40              | 49.28 ± 4.1| 31 (77.5%)| 0.934 ± 0.088   | 9         |
|                              |         | Non-survivors       | 44              | 67.8 ± 3.9 | 29 (65.9%)| 1.105 ± 0.145   |           |
| Xiang et al., 2021           | China   | Non-severe          | 125             | NS         | NS        | 0.855 ± 0.055   | 7         |
|                              |         | Severe              | 29              | NS         | NS        | 0.81 ± 0.037    |           |
| Yang et al., 2020            | China   | Non-severe          | 202             | 47.6 ± 1.1 | 101 (50.0%)| 1.01 ± 0.04     | 7         |
|                              |         | Severe              | 71              | 53.5 ± 1.9 | 33 (46.5%)| 0.8 ± 0.1       |           |
| Yao et al., 2020             | China   | Non-severe          | 83              | 47.5 ± 3.67| 30 (36.1%)| 1.896 ± 0.829   | 9         |
|                              |         | Severe              | 25              | 59.9 ± 6.28| 13 (52.0%)| 1.415 ± 0.087   |           |
|                              |         | Survivors           | 96              | 48.72 ± 4.79| 7 (58.3%) | 1.428 ± 0.129   |           |
|                              |         | Non-survivors       | 12              | 63.6 ± 6.5 | 3 (25.0%) | 2.318 ± 1.025   |           |
| Yildirim et al., 2021        | Turkey  | Without AKI         | 331             | 37 ± 2.67  | 146 (44.1%)| 0.788 ± 0.025   | 8         |
|                              |         | With AKI            | 17              | 71.6 ± 2.6 | 12 (70.6%)| 1.63 ± 0.225    |           |
| Zhang et al., 2020           | China   | Non-severe          | 47              | 60.8 ± 3.3 | 18 (39.3%)| 1.183 ± 0.103   | 8         |
|                              |         | Severe              | 27              | 70.8 ± 5.8 | 18 (66.7%)| 0.91 ± 0.09     |           |
| Zhang et al., 2021           | China   | Survivors           | 410             | 52.5 ± 4.7 | 219 (53.4%)| 1.043 ± 0.058   | 9         |
|                              |         | Non-survivors       | 22              | 64 ± 4     | 11 (50.0%)| 1.488 ± 0.308   |           |
| Zhao et al., 2021            | China   | Non-severe          | 112             | 44.95 ± 4  | 40 (31.7%)| 0.808 ± 0.038   | 8         |
|                              |         | Severe              | 52              | 54.8 ± 4.2 | 32 (61.5%)| 0.773 ± 0.032   |           |
| Zhou et al., 2022            | China   | Non-severe          | 126             | 44.95 ± 4  | 40 (31.7%)| 0.808 ± 0.038   | 8         |
|                              |         | Severe              | 52              | 54.8 ± 4.2 | 32 (61.5%)| 0.773 ± 0.032   |           |

Legend: AKI: acute kidney injury; NS: not specified.

3.2. Meta-Analysis

Ten studies reported Cystatin C levels among patients who survived to hospital discharge vs. patients who decreased. Pooled analysis showed statistically significantly differences between those groups (0.998 ± 0.225 vs. 1.328 ± 0.475 mg/dL, respectively; SMD = −2.14; 95%CI: −3.28 to −1.01; p < 0.001; Figure 2).
Figure 2. Forest plot of Cystatin C levels among COVID-19 survive vs. decrease patients. The center of each square represents the standard mean differences for individual trials, and the corresponding horizontal line stands for a 95% confidence interval. The diamonds represent pooled results. Legend: CI: confidence interval; SD: standard deviation [21,24–26,28,29,35,36,39,42].

Pooled analysis of Cystatin C levels in COVID-19 severe vs. non-severe groups varied and amounted to 1.485 ± 1.191 vs. 1.014 ± 0.601 mg/dL, respectively (SMD = 1.81; 95%CI: 1.29 to 2.32; p < 0.001; Figure 3).

Figure 3. Forest plot of Cystatin C levels among severe vs. non-severe patients with COVID-19. The center of each square represents the standard mean differences for individual trials, and the corresponding horizontal line stands for a 95% confidence interval. The diamonds represent pooled results. Legend: CI: confidence interval; SD: standard deviation [20,22–24,27,28,31–34,36–39,41–44].

Additionally, three studies reported Cystatin C levels among patients with COVID-19 with and without AKI. Pooled analysis showed that Cystatin C levels in patients with AKI was 1.562 ± 0.885 mg/dL, compared to 0.811 ± 0.108 mg/dL for patients without AKI (SMD = 4.56; 95%CI: 0.27 to 8.85; p = 0.04; Figure 4).
which makes it the broadest and most comprehensive meta-analysis available in this area.

The elevated amounts of Cystatin C may be explained by a reduction in the functional pores' pore widths, according to previous research [49]. The term “Shrunken pore syndrome” was recently developed to indicate a smaller pore size of the glomerular membranes, which may explain why Cystatin C is a better predictor of death [50]. According to our research, severe SARS-CoV-2 infection may cause kidney injury since Cystatin C levels were considerably higher in patients with severe COVID-19 illness than in patients with non-severe COVID-19.

Our study also shows the important role of Cystatin C in the prediction of AKI among patients with COVID-19—AKI vs. non-AKI (SMD = 6.28; 95%CI: 1.11 to 11.44; p = 0.02). Moreover, COVID-19 increases CKD risk in addition to AKI related to it, according to American research that used electronic health data from the Veterans Health Administration to carry out a thorough evaluation long-COVID-19. Among those who experienced a major illness, this risk was the highest. Even after the initial 30 days following COVID-19 diagnosis, urinary tract infections, AKI, and CKD have been associated with poor renal symptoms in patients who needed to be hospitalized [51]. Patients with COVID-19 in China showed that 35% of patients had renal impairment (estimated glomerular filtration rate [eGFR] 90 mL/min/1.73 m²) 6 months following hospitalization for COVID-19. Surprisingly, 13% of patients who did not experience AKI while hospitalized exhibited a decline in eGFR.
during the follow-up [52]. A 30% loss in renal function was seen in around 5% of the study’s more than 1.7 million participants, 90,000 of whom are COVID-19 survivors with symptoms lasting at least 30 days (eGFR). This eGFR decreased by 30% more frequently in long-COVID-19 infected individuals than in healthy controls, or 25% more frequently in those who survived more severe illness. However, many people who were not hospitalized were nonetheless impacted by the disease [53]. When we are dealing with a significant number of patients with renal diseases and some studies indicate that 5% of vaccinated individuals require a long time to acquire COVID-19 while 11% of the unvaccinated group may face substantial nephrological challenges both during and after the pandemic occurs [54]. Cystatin C and its predictive function in terms of kidneys could also be used to predict other kidney diseases related to COVID-19 apart from AKI, although AKI as the most serious and fastest progressing one seems to be the most important– nevertheless, the ability to quickly test for levels Cystatin C among patients who have already left the hospital additionally emphasizes the role of this marker in terms of delayed complications of the disease [55].

These findings collectively lend credence to the idea that elevated serum Cystatin C levels in severe COVID-19 may be caused by one or more coexisting processes, such as impaired renal function, excessive proinflammatory cytokine release, antiviral effects, iNOS-mediated stimulation of NO synthesis, and cytokine storm. This meta-analysis also shows the potential use of Cystatin C as a prognostic marker of patients with COVID-19 and the early diagnosis of AKI and other subsequent renal disorders.

5. Conclusions

Cystatin C is a potentially very good marker to be used in the context of COVID-19 disease due to the prognosis of patients’ serious condition, risk of AKI and mortality. In addition, Cystatin C could be used as a marker of renal complications in COVID-19 other than AKI, due to the need to monitor patients even longer after leaving the hospital.

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