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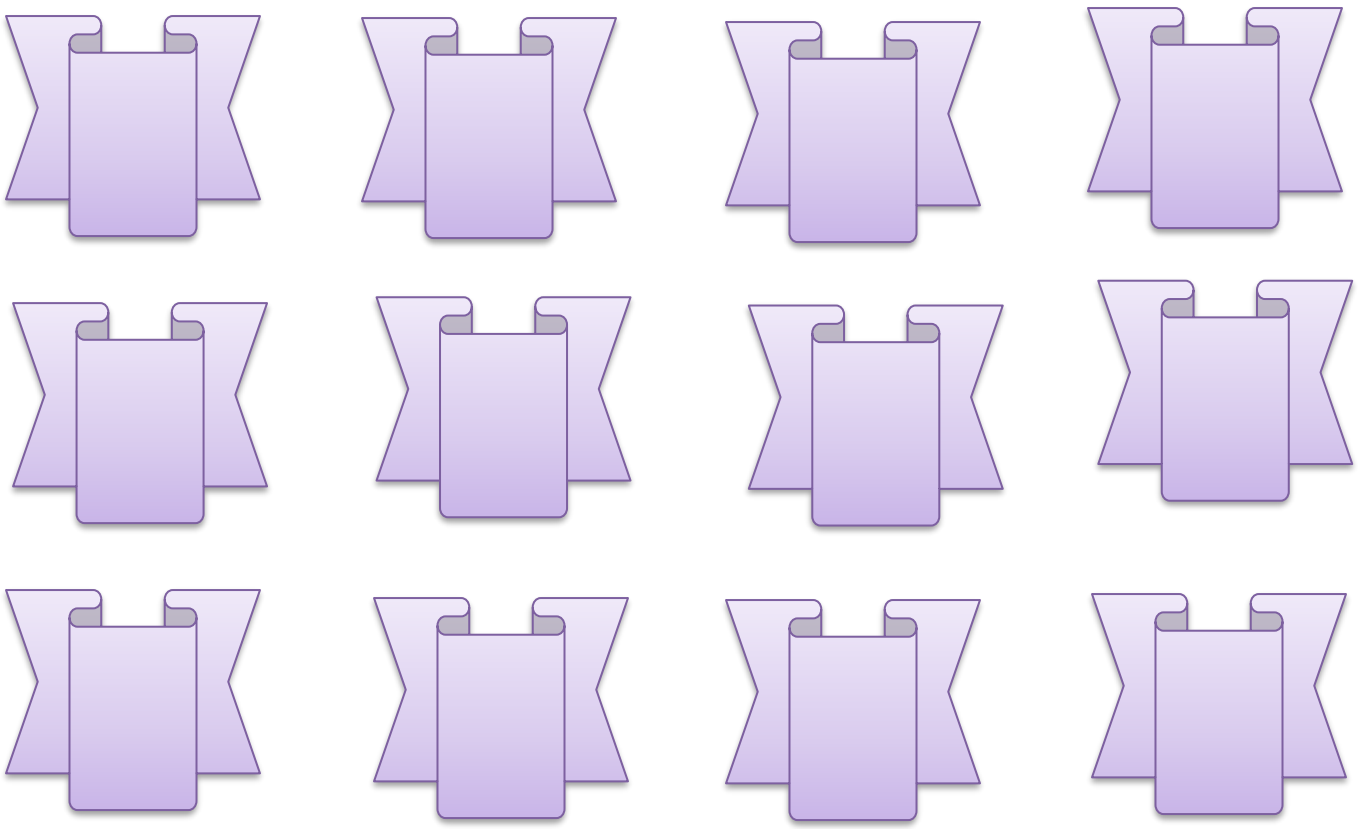

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Original Article

Diagnostic Significance of Serum Cystatin C as A Predictor of Severity in COVID-19 Infected Egyptian Patients

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ABSTRACT

Background: COVID-19 may produce a systemic inflammatory state and multiorgan dysfunction, including renal damage. Biochemical and radiological tests are important in assessing disease severity and selecting therapeutic options. Serum cystatin C [sCys C] is involved in immunomodulatory responses in inflammatory conditions and infections, and it reflects changes in borderline renal function.

The Aim of the work: Measurement of serum cystatin C levels in COVID-19 infected Egyptian participants as a predictor of the disease`s severity.

Patients and Methods: This was an observational case-control study carried out on 80 participants, including 60 Egyptian COVID-19 patients and 20 healthy individuals as controls. All participants were investigated for laboratory, medical, and radiological features of COVID-19 as well as serum cystatin C. Patients were distributed into three categories according to illness severity; each group involved 20 patients: mild cases [group I], moderate cases [group II], and severe cases [group III].

Results: Serum cystatin C levels were found to be higher in group III patients, with a highly statistically significant difference between groups. Group III patients had higher levels of CRP, D-dimer, serum urea, and creatinine, with a highly statistically significant difference between groups. With a cutoff of >9.6, there was a significant link between serum systatin C and the severity of COVID-19 disease, with 96.8% sensitivity and 100% specificity.

Conclusion: The present study indicates that serum systatin C may serve as a tool for diagnosing potentially severe cases of COVID-19 infected Egyptian patients.

Keywords: COVID-19; Cystatin C; Acute phase response; Kidney injury.

INTRODUCTION

During the COVID-19 pandemic, Egypt experienced 515,970 confirmed cases by naso-pharyngeal swab and positive polymerase chain reaction [PCR] results between January 2020 and May 2023, with 24,826 fatalities.

COVID-19 produces renal dysfunction in 5–15% of patients [1]. Acute kidney injury [AKI] was reported to occur at a rate of 29% in severe cases and 69.6% within the 60-year-old group of people among hospitalized COVID-19 patients [2]. AKI is linked to an increased risk of mortality [AKI is 5.3 times more deadly than chronic illnesses] [3].

Several variables may be associated with the pathologic characteristics of the kidney following COVID-19. SARS-CoV2 infection infiltrates renal cells directly and has been found in renal tubules, podocytes and tubular epithelium [2].

In human physiology, the renin/Ang/aldosterone system is an essential vasoactive peptide-signaling pathway. SARS-CoV2 suppresses this pathway by interacting with the ACE2 receptor [4]. ACE2 is expressed in the epithelial cells of the proximal tubule, glomerular endothelial cells, renal vasculature, and podocytes [5].

Ang-receptor blockers and renin/Ang/aldosterone system inhibitors have been revealed to effect ACE2 expression and raise mortality during COVID-19 [6]. Additional indirect mechanisms that may lead to AKI include hemodynamic instability, hypoxia, sepsis, shock, and cytokine storms [7].

The immune response to SARS-COV2 may be detrimental to the kidney, leading to AKI pathogenesis. Complement activation, such as C5b-9, may be correlated to the development of AKI after COVID-19, causing damage to renal parenchymal tissue. Natural killer cells, macrophages, and T helper cells have been detected in renal parenchymal tissue 2. These immune responses can result in alterations to the microvascular system, fibrosis, and epithelial cell death. The high prevalence of AKI in COVID-19 individuals implies that kidney biomarkers might help in early risk categorization, evaluation, and treatment [8].

Serum cystatin C [sCys C] is a low-molecular-weight protein that relates to the cysteine protease inhibitor family. It is present in a variety of organs and tissues and eliminated by the kidney, so it is used to measure glomerular filtration rate [GFR], making it a good diagnostic of renal function. Unlike other renal markers, sCys C is less susceptible to biological effects and more sensitive to early declines in renal function [9]. In addition, sCys C has been linked to a variety of immunological reactions to different antigens, and its gene is controlled by a variety of cytokines during infection and inflammation [10].

sCys C can regulate the synthesis of cytokines such as interleukin-10, interleukin-12, tumor necrosis factor, and nitric oxide. sCys C activates the induced isoform of NO synthase [iNOS], which is primarily responsible for the increased NO production observed in local as well as systemic proinflammatory situations. As a result, highly reactive NO products are generated, nitrosative stress occurs, and numerous intra-cellular components experience irreversible alterations, resulting in cell death and organ failure. While increased blood levels of sCys C in COVID-19 patients are likely to suggest the presence of renal impairment, such as AKI, they may also be an indication of the patients' excessive systemic inflammatory and pro-oxidant condition [11]. In COVID-19 patients, sCys C levels may provide beneficial evidence about the presence of systemic inflammation and renal dysfunction and have a predictive value for AKI and death [12, 13].

The aim of this work is to measure sCys C levels in COVID-19-infected Egyptian participants as a predictor of the disease's severity

PATIENTS AND METHODS

This was an observational case-control study that included 80 participants categorized according to disease severity [14] into: Group I: mild COVID-19 cases; no pneumonia; no hypoxia [no = 20]; Group II: moderate COVID-19 cases; pneumonia without hypoxia [no = 20]; Group III: severe COVID-19 cases; pneumonia with hypoxia responding to oxygen therapy [no = 20]; Group IV: non-COVID-19 as a healthy control [no = 20].

The studied patients were selected from Al-Zahraa University Hospital from February 2022 to the end of April 2022**.** Only the moderate and severe groups were hospitalized, and the treatment was prescribed according to Egyptian guidelines [15]. Informed permission was taken from all participants included in the research.

Inclusion and exclusion criteria

Patients aged more than 18 years old with typical clinical findings and laboratory and imaging features of SARS-CoV2 were included in this study.

Participants with any of the following illnesses were omitted from the study: chronic kidney disease, liver disease, thyroid diseases, systemic lupus erythematous, obstructive sleep apnea, parkinson's disease, malignancies, chemotherapy, and HIV.

All participants were subjected to the following:

1. Taking a complete medical history, which includes a person's past and present as well as their occupation and family history.

2. General and local chest examinations.

3. SARS-CoV2 RTPCR test.

4. Laboratory investigations

Blood sample: 7 milliliters of fasting venous blood were drawn and divided into two portions: 2 milliliters went into an EDTA-containing tube for CBC analysis [as determined by Sysmex XB and Celdyne Ruby, Automated Hematology Analyzer]; 5 milliliters were left to clot; and 5 milliliters were centrifuged to separate the serum and divide it into two portions. Urea, creatinine, and liver function tests were determined using the 1st aliquot [measured by the Cobas C311 auto analyzer utilizing Roch]. The 2nd aliquot was frozen at –20 °C to assess human cystatin later on.

Bioassay Technology Laboratory Company's ELISA kit with Cod E1104Hu intra-assay precision 4.3 was used to measure human cystatin. This kit performs an enzyme-linked immunosorbent assay [ELISA]. The human cystatin antibody has been pre-coated on the plate. The addition of cystatin to the sample causes it to attach to antibodies coated on the wells. A biotinylated human cystatin antibody was added, and it binds to cystatin in the sample. The biotinylated cystatin antibody is then bound by the addition of streptavidin-HRP. Unbound Streptavidin-HRP was removed during a washing step after incubation. Substrate solution was then added, and the color increased in direct proportion to the amount of human cystatin present. By adding an acidic stop solution, the process was stopped, and absorbance at 450 nm was measured. The range of detection was 0.5–1.5 mg/dl.

5. Imaging: Chest CT scan for groups I, II, and III.

Ethics approval: This study was carried out in accordance with the principles of the Helsinki Declaration. The Ethics Committee of Damietta Faculty of Medicine, Al-Azhar University approved the application [Date 12-6-2023/No; DFM-IRB 00012367-23-06-010]."

Statistical analysis: The data was analyzed using the Statistical Package for Social Science [SPSS] application [version 23]. The non-parametric factors were reported as median and interquartile range, whereas parametric factors were presented as mean $\pm$ SD. For quantitative factors, the interquartile range [IQR] was employed, whereas percentages and frequency values were used for qualitative variables. The p-value was determined to be significant as follows: Non-significant [$P > 0.05$]. $P \leq 0.05$ indicates that the difference is significant.

RESULTS

There was a statistically significant difference among the studied groups as regards age, and oxygen saturation in the severe group in comparison to other groups [Table 1].

There was a statistically significant increase in the severity of COVID-19 disease in patients with hypertension and diabetes compared to other groups [Table 2].

The main symptoms in patients with mild and moderate disease were fever and cough 100%. For patients with severe disease, the main symptoms were fever [95%], cough [93%], dyspnea, and generalized body pain [90%] [Figure 1].

There was neutropenia in all patient groups, which was marked in patients with severe disease. There was a statistically significant difference in neutrophil and platelet counts among the studied groups. Patients with severe COVID-19 disease had higher neutrophil/ lymphocyte ratio [NLR] values compared to other patients and the control [table 3].

There was statistically significant increase of serum blood urea, fasting blood sugars, CRP, D-

dimer, SGPT, serum creatinine, and SCys C in COVID-19 patients in comparison to control group [Table 4].

Table [5] shows statistically significant higher mean value of serum sCys C in severe group [III], followed by moderate group [II] and mild group [I], and the lowest value in control group, with p-value [p<0.001], while there is no statistically significant difference between mild [I], moderate [II] and severe group [III], with p-value [p>0.05].

There was no statistically significant correlation between [mg/L] and the studied lab parameters [Table 6].

Table [1]: Demographic data among studied groups

		Mild [I] [No.=20]	Moderate [II] [No.=20]	Severe [III] [No.=20]	Control [IV] [No.=20]	Total [No.=80]	Test	p- value
Age		40.55±12.29	63.75±11.41	68.95±8.69	52.8±11.05	56.5±14.35	**F= 26.46**	**<0.001***
Sex	Female	7 [35%]	12 [60%]	5 [25%]	8 [40%]	32 [40%]	**X^2 =5.41**	**0.13**
	Male	13 [65%]	8 [40%]	15 [75%]	12 [60%]	48 [60%]		
Hypoxia [<92%]		0	0	20	0	20	**X^2 =75.09**	**<0.001***

*: Significant

Table [2]: Risk factors among the studied groups

	Mild [I] No [%]	Moderate [II] No [%]	Severe [III] No [%]	X^2	p-value
Hypertension	8 [40%]	3 [15%]	15 [75%]	17.43	0.001*
Diabetes	8 [40%]	2 [10%]	9 [45%]	9.27	0.026 *
Ischemic heart disease	3 [15%]	0	2 [10%]	3.6	0.30
Asthma	2 [10%]	2 [10%]	2 [10%]	0.47	0.92
COPD	0	1 [5%]	0	-	-
Hypercholesterolemia	0	1 [5%]	0	-	-

COPD: Chronic obstructive pulmonary disease; *: significant.

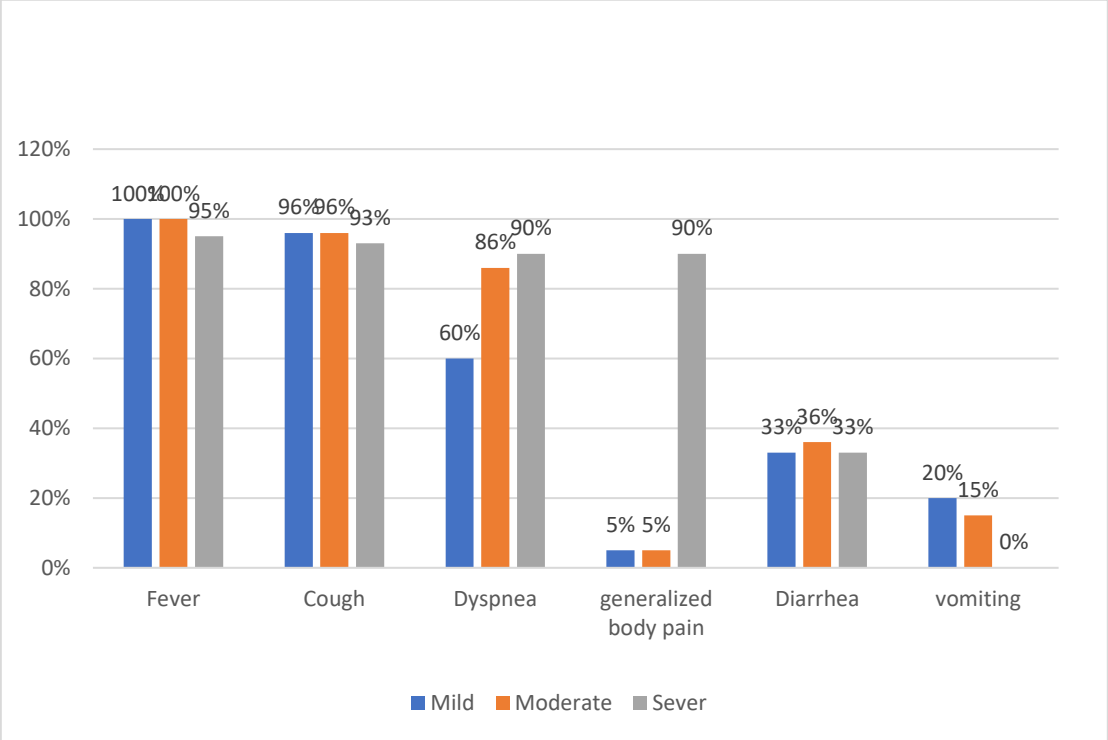

Figure [1]: The main symptoms among COVID-19 groups

Table [3]: Comparison of CBC among the studied groups

	Mild [I] No [25]	Moderate [II] No [25]	Severe [III] No [25]	Control No [25]	F	p-value
HGB [gm/dl]	11.58±1.41	11.34±1.75	11.82±1.70	11.85±1.63	0.42	0.733
WBCs count [$\times10^3$/microl]	7.20±3.67	9.67±5.38	6.88±4.23	7.67±2.64	1.86	0.14
LYM Count [$\times10^9$/L]	15.95±6.65	12.07±4.42	11.32±3.86	26.85±4.57	40.84	<0.001*
PLT [$\times10^3$/microl]	246.65±60.44	297.15±76.015	227.60±68.20	243.10±65.27	3.96	0.011*
Neutrophil count [$\times10^9$/L]	51.85±17.14	67.0±18.85	74.3±14.96	58.8±19.62	5.907	0.001*
NLR	3.4	5.5	6.7	2.1	-	-

*: significant; NLR: neutrophil lymphocyte ratio

Table [4]: Laboratory data among the studied groups

	Mild [I] No [25]	Moderate [II] No [25]	Severe [III] No [25]	Control No [25]	F	P-value
SGPT [mg/dL]	32.20±15.70	21.45±7.28	29.43±12.18	28.0±10.07	3.026	0.035*
SGOT [mg/dL]	36.5±11.48	29.12±13.29	36.42±9.74	30.65±15.10	1.874	0.141
Blood urea [mg/dL]	25.87±9.13	53.66±27.86	74.17±47.27	23.32±7.31	14.906	0.000*
s.creatinine [mg/dL]	0.98±0.31	1.29±0.52	1.28±0.52	0.87±0.51	3.907	0.012*
FBS [mg/dL]	200	183.125	210	100	-	0.0001 *
CRP [mg/dL]	42.15±20.82	47.8±19.6	48.20±20.01	5.35±6.81	9.612	0.000*
D-dimer [ng/mL]	250	629.50±643.01	2057.50±315.49	250	5.71	0.001*
SCys C [mg/dL]	17.44±2.45	18.36±6.87	38.38±46.88	4.38±3.37	3.459	0.0262*

*: Significant

Table [5]: Comparison of SCys C [mg/L] among the studied groups as regard the disease severity

Serum SCys C	Mild [I] No [25]	Moderate [II] No [25]	Severe [III] No [25]	Control No [25]	F-test	p-value
Mean±SD	17.97±2.76	18.14±6.48	35.28±8.94	4.60±3.31	6.468	<0.001*
Range	12.9-22.3	2.94-30.3	14.2-166.2	1.14-9.6		
Multiple comparison: Post Hoc test: Tukey's test						
I vs. II	I vs.III	I vs.IV	II vs.III	II vs.IV	III vs.IV	
0.915	0.084	<0.001*	0.089	<0.001*	0.003*	

One-way Analysis of Variance test was utilized using Mean ± SD & Multiple comparison across groups using Post Hoc test: Tukey's test *: significant.

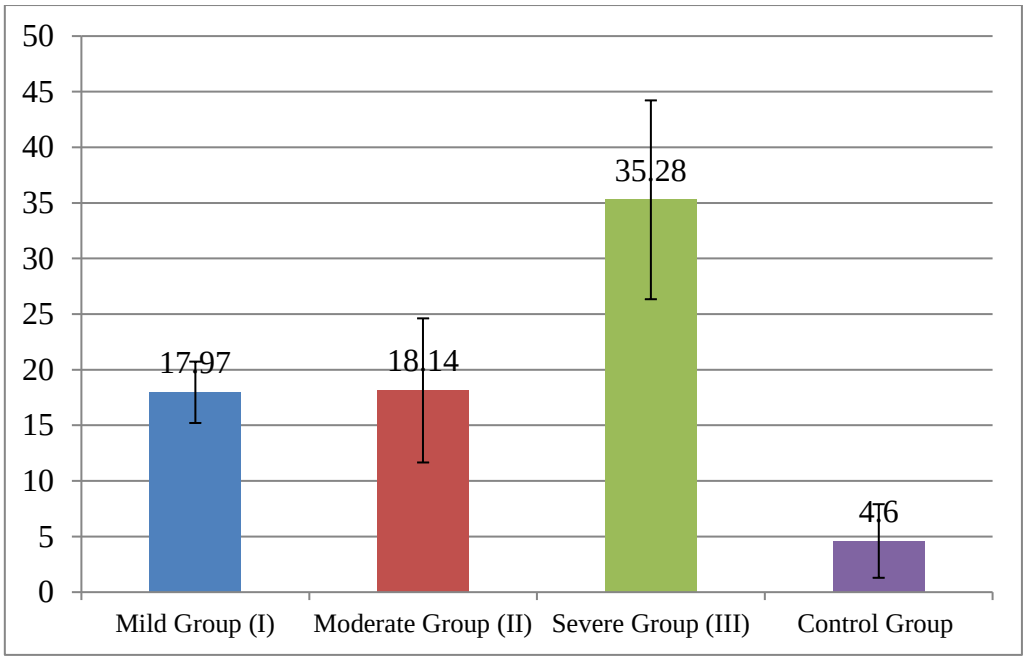

Figure [2]: SCys C in COVID-19 patients in comparison to the control group

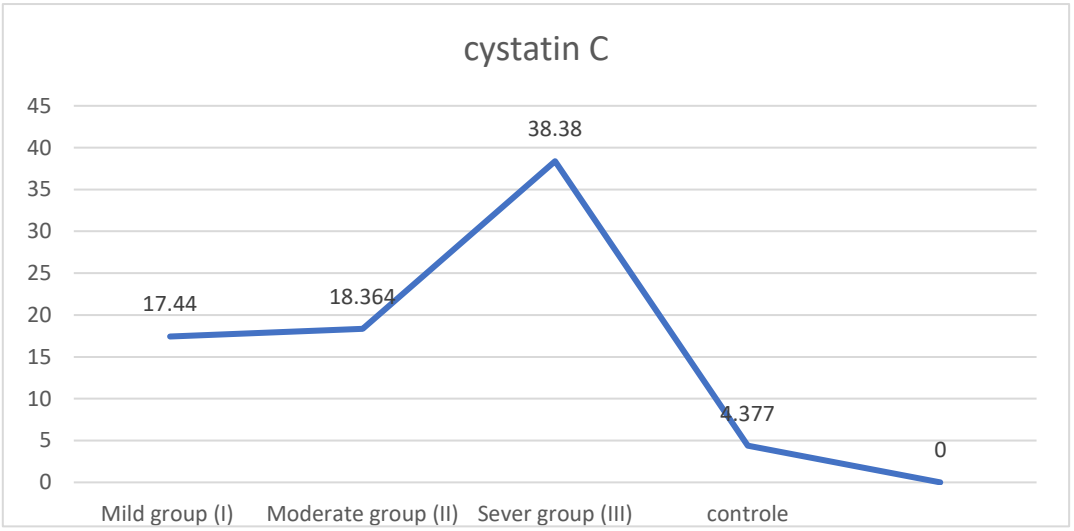

Figure [3]: Correlation between sCys C and disease severity

Table [6]: Correlation between sCys C "mg/L" and all different parameters in all studied patient groups, using Spearman's rank correlation coefficient [rs]

Parameters	SCys C [mg/L]	
	R-value	p-value
Age [Years]	0.108	0.410
S Creatinine [mg/dL]	0.050	0.721
HGB [gm/dl]	-0.059	0.601
Blood urea [mg/dL]	0.0151	0.248
WBC [$\times 10^3$ /microl]	0.135	0.233
LYM [$\times 10^9$ /L]	-0.159	0.160
PLT [$\times 10^3$ /microl]	-0.197	0.080
CRP [mg/dL]	0.171	0.130
D-dimer [ng/mL]	0.034	0.765
SGPT [mg/dL]	0.00863	0.939
SGOT [mg/dL]	0.095	0.403

Table [7]: Diagnostic performance of SCys C in discrimination of severity of COVID-19 and control

Grade	Cut-off	Sensitivity	Specificity	PPV	NPV	AUC	p-value
Control vs. Patients	**> 9.6**	96.8%	100%	100%	91.3%	0.983	<0.001*
Control vs. Mild	**> 9.6**	100%	100%	100%	100%	1.000	<0.001*
Control vs. Moderate	**> 9.6**	90.5%	100%	100%	91.3%	0.950	<0.001*
Control vs. Severe	**> 9.6**	100%	100%	100%	100%	1.000	<0.001*
Mild vs. Moderate	**> 18.6**	52.4%	52.4%	52.4%	52.4%	0.519	0.834
Mild vs. Severe	**> 19.7**	52.4%	81.0%	73.3%	63.0%	0.615	0.215
Moderate vs. Severe	**> 21.6**	42.9%	79.5%	69.2%	58.6%	0.574	0.427

PPV: Positive predictive value; NPV: Negative predictive value; AUD: Area Under the Curve; *: significant

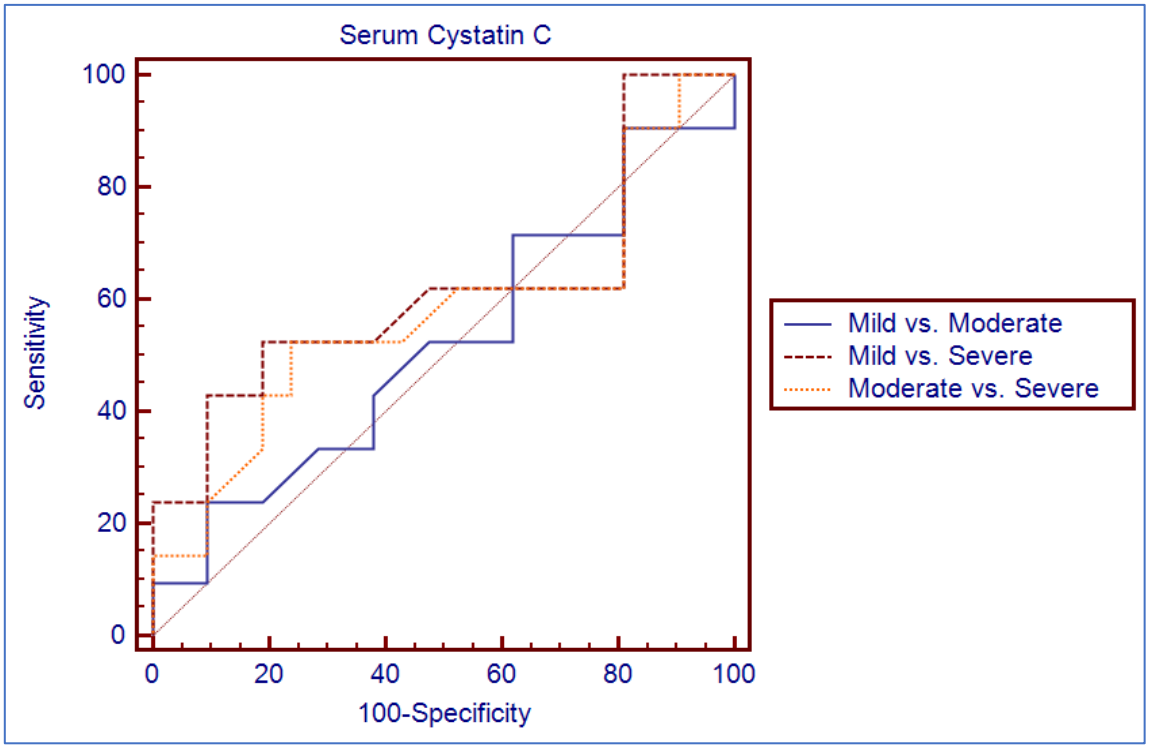

Figure [4]: Receiver-operating characteristic [ROC] curve to discrimination of SCys C between severities of COVID-19

DISCUSSION

With the uncontrollable worldwide spread of COVID-19 that caused high morbidity and mortality in Egypt and around the world, finding an easily available, accurate biomarker to predict COVID-19 severity was critical [16].

SCys C is produced by almost all body cells at a constant rate and is excreted by the kidneys. It is a more accurate indicator of kidney function than creatinine, the most commonly used marker. In COVID-19 patients, elevated levels of sCys C have been observed, which may indicate kidney damage or dysfunction. This study was done to evaluate sCys C level as a predictor of disease severity in Egyptian patients with COVID-19 infection [13].

The present study investigated serum cystatin C levels in 60 Egyptian COVID-19 patients with different degrees of disease severity, together with 20 selected normal controls.

In the present study, severe illness was associated with low O_2 saturation, older age, hypertension, and diabetes. The main symptoms were fever, cough, dyspnea, and fatigue. Patients with severe illness also had neutropenia, a high NLR, elevated serum blood urea nitrogen [BUN], creatinine, CRP, and D-dimer levels.

The present study outcomes were consistent with **Omran *et al.*** [17] who investigated predictors of critical illness severity and development in Egyptian COVID-19 patients and demonstrated that older individuals, exhaustion, high temperature, elevated pulse, lower oxygen levels, the presence of diabetes, tumors, heart disease, kidney

disorders, and lung disease were all associated with a critical illness.

Another study by **Sun *et al.*** [18] concluded that COVID-19 severity increased with advancing age. $CD8^+$ T cells, CRP, and D-dimer were independent indicators of COVID-19.

In the current study, serum BUN and creatinine were also higher in severe COVID-19 patients, indicating renal dysfunction. Renal dysfunction in COVID-19 patients could be due to the direct effect of viral infection or cytokine storm syndrome, depletion of volume, or failure of multiple organs [19]. The frequency of renal impairment in COVID-19 patients suggests that renal biomarkers may help in early monitoring and management of these patients [20].

In the present study, patients with severe COVID-19 disease had higher mean levels of sCys C [35.28±8.94] than patients with mild, moderate cases, and control groups, respectively [17.97±2.76, 18.14±6.48, 4.60±3.31]. SCys C was found to have a positive correlation with illness severity. The present findings agreed with those of **Chen *et al.*** [21], who discovered that the higher baseline sCys C levels were related to the severity of the inflammatory state and poor outcomes in COVID-19 patients. **Lin *et al.*** [16] also stated that COVID-19 patients with increased sCys C levels are at higher risk and require early management. **Murty *et al.*** [22] reported similar findings and stated that increased sCys C levels indicate impaired renal function.

According to research conducted by **Matuszewski *et al.*** [11], high sCys C levels in severe COVID-19 may be produced by one or more concurrent events such as compromised renal function, elevated proinflammatory cytokine production, antiviral consequences, hypoxia, and a cytokine storm. He also stated that SCys C has been shown to be a very strong diagnostic marker for patients with COVID-19 as well as for the early detection of AKI and other later renal problems.

In the present study, a value > 9.6 at the time of admission was the best cut-off value. ROC curve analysis proved the good discriminating power of the sCys C in COVID-19 vs. the control with a sensitivity of 96.8%, a specificity of 100%, a p-value < 0.001, and the area below the curve was variable according to the severity of COVID-19.

Individuals with sCys C levels greater than 0.84 ng/mL had a 23-fold higher chance of getting AKI [OR, 23.7, 95% CI, 2.59- 217.00, p = 0.005], according to **Ramos-Santos *et al.*** [23], Increased sCys C, on the other hand, was not linked with mortality in the Mexican population [OR, 1.01, 95% CI, 0.66-1.56, p = 0.959]. **Lin *et al.*** [16] determined that 1.245 mg/L was the best cut-off value for determining severe COVID-19 disease, with sensitivity and specificity of 79.1% and 60.7%, respectively. A greater sCys C level was related to an increased risk of severe COVID-19 in invariable analysis [unadjusted OR 4.95, 95% CI 2.31- 10.57]. After controlling for age and gender, higher sCys C levels were still linked with severe COVID-19 [adjusted OR 3.04, 95% CI 1.30- 7.13]. The typical sCys C range is 0.62- 1.15 mg/L. Values may differ across labs. Higher sCys C levels, in general, indicate impaired kidney function.

According to research, variables such as aging, kidney function, inflammation, impairment of thyroid function, glucocorticoid usage, tumors, and chemotherapy can all impact sCys C levels. Higher sCys C values in individuals in general are linked to an elevated risk of cardiovascular disease and preeclampsia in pregnant women [24, 25].

The present findings revealed that sCys C levels were not linked to serum BUN or creatinine levels. This might be explained by changes in sCys C occurring earlier than changes in creatinine in acute renal damage. According to **Murty *et al.*** [22], serum creatinine values do not rise until there is a moderate to severe decrease in GFR, and using them to estimate GFR in early AKI delays the identification of kidney injury.

SCys C levels can better indicate variations in GFR than serum creatinine. SCys C has been shown to be more sensitive to alterations in borderline kidney function than creatinine in a wide range of patient groups, including diabetics, surgical patients, and cardiac patients [11].

However, investigations by **Liu *et al.*** [26] and **Chen *et al.*** [27] found a significant difference in estimated GFR based on serum creatinine and sCys C in critically sick COVID-19 patients. The severity of the disease and the inflammatory state may influence the difference.

In line with the present findings, **Chen *et al.*** [27] and **Ramos-Santos *et al.*** [23] concluded that high sCys C, which appears sooner than serum

creatinine, is beneficial for the early detection of abnormalities in renal function and may have a better indicator for COVID-19 severity, whereas elevated creatinine levels may have a better indicator value for the risk of death.

Serum creatinine concentrations, on the other hand, are controlled by nutrition and muscle bulk, and serum creatinine can be released by renal tubular cells and cells of the gastrointestinal tract. Furthermore, there is a time lag between serum creatinine rise and renal cell destruction. As a result, serum creatinine is less responsive to renal injury than sCys C [28].

sCys C was higher in severe COVID-19 patients in the current investigation, but it was not connected with other parameters in the examined patients, which was consistent with **Zinellu and Mangoni** [12].

Dexamethasone medication was associated with lower eGFR in ICU patients with COVID-19, according to **Larsson *et al.*** [29]. Corticosteroid-induced increases in sCys C might explain this observation.

The limitations of the study include: having a relatively small number of patient groups; the timing of the blood sampling being random, with some samples taken at the onset of diagnosis while others were taken after admission; this being a single-center study; an inability to estimate the patient outcomes and their relation to serum cystatin; diabetes mellitus not being excluded; and there being no information on urine output or other signs of severe renal failure.

In conclusion, sCys C is a more sensitive indicator of renal function than creatinine. There is a significant link between sCys C and the severity of COVID-19 disease, so sCys C may serve as a tool for diagnosing potentially severe cases of COVID-19 in adult Egyptians.

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