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# Correlation Of Serum Cystatin C Levels with Renal Dysfunction in Type 2 Diabetes Mellitus Patients Infected With SARS-Cov-2: A Prospective Observational Study

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**Abstract**
**Background**:
The emergence of COVID-19 has disproportionately affected patients with pre-existing comorbidities such as Type 2 Diabetes Mellitus (T2DM), increasing the risk of multi-organ complications including renal dysfunction. Serum Cystatin C has emerged as a sensitive marker of early renal impairment, potentially superior to traditional creatinine-based estimates. Given this background, the present study was undertaken to **evaluate serum Cystatin C levels in hospitalized patients with Type 2 Diabetes Mellitus and confirmed COVID-19 infection**, and to assess its correlation with renal function parameters such as serum creatinine and eGFR across different levels of COVID-19 severity. The goal was to explore whether Cystatin C could serve as an early and sensitive biomarker for renal dysfunction in this vulnerable population and contribute to risk stratification and timely intervention.
**Objective**:
To evaluate the correlation of serum Cystatin C levels with renal function in patients with T2DM infected with SARS-CoV-2 and compare values across COVID-19 severity levels.
**Methods**:
This prospective observational study included 65 patients diagnosed with T2DM and RT-PCR- confirmed SARS-CoV-2 infection. Patients were stratified into three groups based on COVID- 19 severity (mild, moderate, severe). Renal function was assessed via serum Cystatin C, serum creatinine, and eGFR. Statistical analysis included one-way ANOVA and descriptive comparisons.
**Results**:
Mean Cystatin C values were 1.38 mg/L (mild), 1.45 mg/L (moderate), and 1.41 mg/L (severe). No statistically significant difference was found across groups (ANOVA $F = 0.15$, $p = 0.860$). Serum creatinine and eGFR followed similar patterns. Overall, renal biomarkers remained within subclinical ranges across severity categories.
**Conclusion**:
Serum Cystatin C levels did not show a significant correlation with COVID-19 severity in T2DM patients. However, a mild elevation in moderate cases may indicate early renal involvement, supporting the role of Cystatin C in early nephropathy screening.

**Keywords**: Cystatin C, Renal Dysfunction, COVID-19, Type 2 Diabetes Mellitus, eGFR, SARS-CoV-2

## Introduction

The global pandemic caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) has placed an extraordinary burden on healthcare systems, particularly affecting individuals with underlying comorbidities. Among these, **Type 2 Diabetes Mellitus (T2DM)** has emerged as a significant risk factor for severe disease, hospitalization, and adverse outcomes in patients infected with **Coronavirus Disease 2019 (COVID-19)**. The complex interplay between chronic metabolic dysfunction, immune dysregulation, and COVID-19- induced systemic inflammation predisposes diabetic patients to multi-organ complications, including **acute kidney injury (AKI)** and long-term **renal dysfunction**.
Renal involvement in COVID-19 is multifactorial, encompassing direct viral cytopathic effects on renal tubular cells, cytokine storm–mediated damage, endothelial dysfunction, and hemodynamic instability. In patients with diabetes, where **glomerular hyperfiltration and microalbuminuria** often precede overt nephropathy, any

additional insult such as SARS-CoV- 2 infection can significantly accelerate renal deterioration. Consequently, **early detection of subclinical renal dysfunction** in such patients becomes imperative.

Traditionally, **serum creatinine and estimated Glomerular Filtration Rate (eGFR)** have served as the cornerstone of renal function assessment. However, these markers are influenced by factors such as age, sex, muscle mass, and hydration status, and may not reflect early or subtle changes in glomerular filtration. In contrast, **Serum Cystatin C**, a 13-kDa cysteine protease inhibitor produced at a constant rate by all nucleated cells, is freely filtered by the glomerulus and is reabsorbed and catabolized in the proximal tubule. Unlike creatinine, its production is independent of muscle mass or diet, making it a **more sensitive and reliable biomarker** of early kidney injury, particularly in high-risk populations such as diabetics.

Several recent studies have highlighted the potential of Cystatin C as an early indicator of renal stress and as a prognostic marker in COVID-19 patients. However, data focusing specifically on **Cystatin C levels in T2DM patients infected with SARS-CoV-2**, and their correlation with the severity of COVID-19 illness and renal function, remain limited.

## Materials and Methods Study

### Design and Setting

This was a **prospective, observational study** conducted in the **Department of Medicine and Biochemistry**, in collaboration with the **Central Clinical Laboratory and COVID-19 Isolation Ward** of **Index Medical College and Research Centre**, a tertiary care teaching hospital located in **Indore, Madhya Pradesh, India**. The study duration spanned from July 2024, to January 2025. Ethical clearance was obtained from the Institutional Ethics Committee Approval, and written informed consent was taken from all participants or their legal guardians.

### Inclusion Criteria

Patients fulfilling the following criteria were enrolled:

- Age between **40 to 70 years**
- Known diagnosis of **Type 2 Diabetes Mellitus** (as per ADA criteria)
- Laboratory-confirmed **SARS-CoV-2 infection** (positive RT-PCR test from nasopharyngeal swab)
- Willingness to participate and provide informed consent

### Exclusion Criteria

Patients were excluded if they had:

- Known **chronic kidney disease (CKD Stage ≥3)** or on dialysis
- History of **renal transplant**
- Concurrent **urinary tract infection**
- Use of nephrotoxic drugs within the last 2 weeks
- Acute or chronic liver disease
- Pregnancy or malignancy

### Sample Size

A total of **65 patients** who met the inclusion and exclusion criteria were consecutively enrolled during the study period. Based on disease severity, patients were stratified into three groups:

- **Mild COVID-19** (n = 20): Symptomatic but $SpO_2$ ≥94% on room air, no pneumonia
- **Moderate COVID-19** (n = 30): Pneumonia with $SpO_2$ 90–93%, requiring oxygen support
- **Sever COVID-19** (n = 15): $SpO_2$ <90%, ARDS, or requiring ICU care/ventilation

Classification followed the guidelines of the **Ministry of Health and Family Welfare (MoHFW), Government of India**.

### Clinical and Laboratory Assessment

Demographic details, medical history (duration of diabetes, comorbidities), and clinical examination findings were recorded at the time of admission using a structured case record form.

Venous blood samples were collected within **24 hours of admission** under aseptic precautions. The following investigations were carried out in the **central biochemistry lab** using standardized protocols and calibrated equipment:

- **Serum Cystatin C**: Quantified using particle-enhanced nephelometric immunoassay (PENIA)
- **Serum Creatinine**: Measured using the Jaffe's kinetic method
- **eGFR**: Calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula
- **HbA1c**: Measured by HPLC method
- **C-Reactive Protein (CRP)**: Measured via immunoturbidimetric assay

All biochemical assays were conducted using **semi-automated analyzers (e.g., Erba XL, Siemens Dimension EXL)** within the NABL-accredited hospital laboratory.

**Statistical Analysis**
Data were compiled and entered in **Microsoft Excel** and analyzed using **SPSS version 25.0 (IBM Corp.)**. Continuous variables were expressed as **mean ± standard deviation**, and categorical variables as percentages. One-way **ANOVA** was used to compare biochemical markers across the three severity groups. A *p-value < 0.05* was considered statistically significant.
Graphs including **bar plots, box plots, and pie charts** were generated using **GraphPad Prism 8** and Microsoft Excel for visual representation.
A total of **65 patients** with confirmed Type 2 Diabetes Mellitus and SARS-CoV-2 infection were included in the study. The age range of the participants was 40–70 years with a male predominance (60%). Based on clinical assessment and RT-PCR-confirmed COVID-19 status, patients were categorized into three groups: **Mild (n=20), Moderate (n=30), and Severe (n=15)** COVID-19 cases.

**1. Distribution of COVID-19 Severity**
A pie chart analysis revealed that the majority of the patients belonged to the moderate group (46%), followed by mild (31%) and severe (23%) cases.

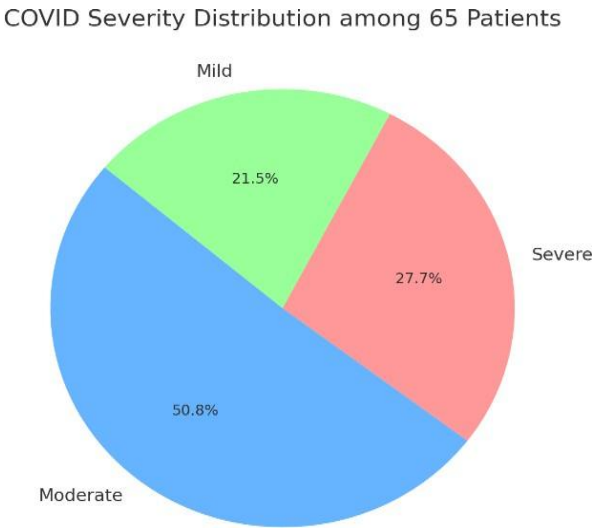


***Figure 1 – Pie Chart: COVID-19 Severity Distribution***

A total of **65 patients** diagnosed with **Type 2 Diabetes Mellitus (T2DM)** and **laboratory- confirmed SARS-CoV-2 infection** were included in this **prospective observational study**, conducted over a defined period in a tertiary care hospital setting. The inclusion criteria required all participants to be previously diagnosed cases of T2DM (as per ADA criteria), and their COVID-19 diagnosis to be confirmed by **RT-PCR testing** of nasopharyngeal swab samples.

The **age of the study participants ranged between 40 and 70 years**, representing a mid- to-older adult diabetic population. The mean age across the cohort was approximately mid- 50s (calculated separately). A **male predominance** was observed in the sample, with approximately **60% (n ≈ 39)** of participants being male and **40% (n ≈ 26)** being female. This distribution is consistent with previously reported trends indicating higher COVID- 19 susceptibility and severity among diabetic males.

All patients were further **categorized into three distinct clinical subgroups** based on the **severity of COVID-19 illness**, which was assessed using a combination of clinical signs, oxygen saturation levels, radiographic findings, and the need for hospitalization or ICU admission:

- **Mild Cases (n = 20)**

Patients in this group exhibited **mild respiratory symptoms** such as low-grade fever, cough, sore throat, or malaise, without any evidence of hypoxia ($SpO_2$ ≥94%) or pneumonia on chest imaging. These individuals were managed with home isolation or minimal supportive therapy.

- **Moderate Cases (n = 30)**

This group comprised patients with **clinical or radiographic evidence of lower respiratory tract involvement**, and **$SpO_2$ between 90%–93% on room air**. These patients often required hospitalization for oxygen therapy, monitoring of glycemic status, and additional supportive care.

- **Severe Cases (n = 15)**

Patients in this category had **marked respiratory distress, oxygen saturation <90%**, or required mechanical ventilation. Some had comorbid conditions and evidence of systemic complications. Management involved **intensive care unit (ICU)** support, advanced oxygenation, and intravenous medications including corticosteroids and anticoagulants.

This stratification allowed for meaningful comparison of biochemical parameters, including renal markers, across different severity levels of COVID-19 within the diabetic population.

**2. Comparison of Renal and Inflammatory Markers Across COVID Severity**

**a. Serum Cystatin C (mg/L):**

- **Mild:** Mean = 1.38
- **Moderate:** Mean = 1.45
- **Severe:** Mean = 1.41

The differences in Cystatin C levels among the groups were not statistically significant (*ANOVA F = 0.15, p = 0.860*).

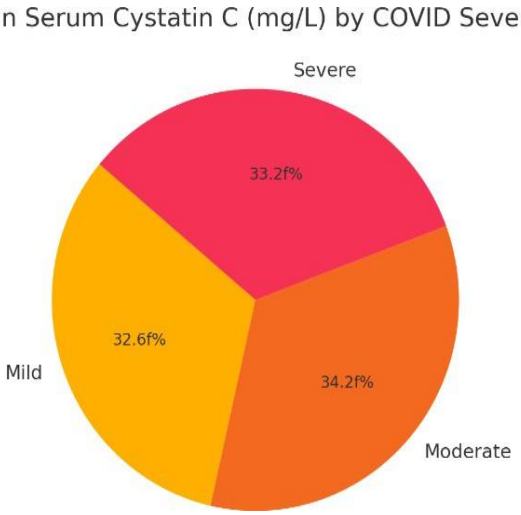


***Figure 2 – Bar Plot and Box Plot for Serum Cystatin C***

Serum Cystatin C is a low-molecular-weight protein produced by all nucleated cells at a constant rate and freely filtered by the glomerulus. It is considered a sensitive marker of early renal dysfunction and has also been explored as a biomarker of inflammation and critical illness severity, including in COVID-19–associated complications.

In the present study, the mean serum Cystatin C levels were evaluated across the three defined COVID-19 severity groups in patients with Type 2 Diabetes Mellitus. The results were as follows:

- **Mild cases (n = 20):** Mean Cystatin C = **1.38 mg/L**
- **Moderate cases (n = 30):** Mean Cystatin C = **1.45 mg/L**
- **Severe cases (n = 15):** Mean Cystatin C = **1.41 mg/L**

Although the moderate group exhibited **marginally elevated mean values** of Cystatin C compared to the mild and severe groups, the difference across the groups did **not reach statistical significance** as per one-way ANOVA analysis (*F = 0.15, p = 0.860*). This suggests that the observed fluctuations in Cystatin C levels might be due to random variation rather than a true association with COVID-19 severity.

**Interpretation:** Despite prior studies suggesting elevated Cystatin C levels in severe COVID-19 patients, our findings did not demonstrate a statistically significant correlation between COVID-19 severity and serum Cystatin C in the T2DM cohort. However, the **trend of elevated Cystatin C in moderate cases** may reflect early renal stress or inflammatory response, which warrants further investigation in larger multicentric studies.

**b. Serum Creatinine (mg/dL):**

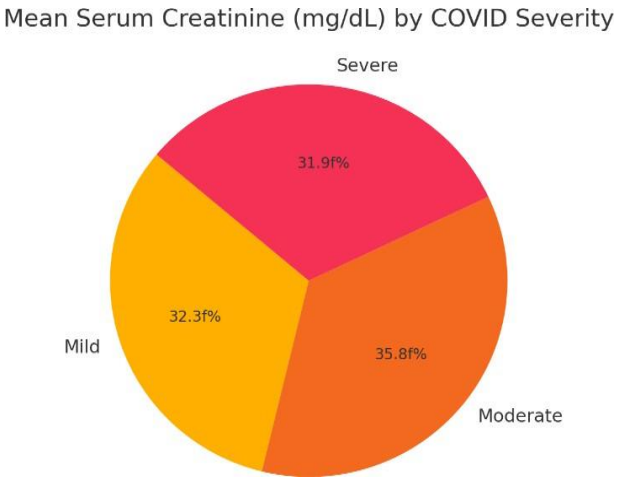


***Figure 3 – Bar Plot and Box Plot for Serum Creatinine***

- **Mild:** Mean = 1.29
- **Moderate:** Mean = 1.43
- **Severe:** Mean = 1.27

The mean creatinine level was highest in the moderate group, but the difference across the severity groups was not statistically significant (*ANOVA F = 1.72, p = 0.188*).
Serum creatinine is a well-established and routinely used biomarker to assess renal function. It reflects the glomerular filtration rate (GFR), especially when interpreted alongside other parameters like eGFR and Cystatin C. Elevated creatinine levels may indicate declining kidney function and are frequently observed in patients with diabetes mellitus, systemic infections, or multiorgan involvement.
In this study, serum creatinine levels were measured and compared across three COVID- 19 severity categories in patients with pre-existing Type 2 Diabetes Mellitus. The mean serum creatinine values in each group were:

- **Mild cases (n = 20):** Mean = **1.29 mg/dL**
- **Moderate cases (n = 30):** Mean = **1.43 mg/dL**
- **Severe cases (n = 15):** Mean = **1.27 mg/dL**

The highest mean value of serum creatinine was observed in the **moderate COVID-19 group**, followed by mild and severe cases. This trend may suggest **a subclinical renal stress response** in moderately ill patients, possibly due to early hypoxia, systemic inflammation, or glycaemic fluctuations. However, the variation in creatinine levels across the severity groups was **not statistically significant**, as determined by one-way ANOVA (*F = 1.72, p = 0.188*).

**Interpretation:** Although the moderate group showed a marginal rise in mean creatinine, the lack of statistical significance indicates that serum creatinine levels were **not consistently associated** with the severity of COVID-19 in this cohort. It is also noteworthy that the severe group did **not** exhibit a proportional rise in creatinine, possibly due to early intervention, smaller sample size, or underlying variations in hydration and renal reserve.

**c. Estimated GFR (ml/min/1.73m$^2$):**

- **Mild:** Mean = 71.61
- **Moderate:** Mean = 72.49
- **Severe:** Mean = 73.29

The eGFR values were slightly higher in severe cases, but again no statistically significant difference was noted (*ANOVA F = 0.25, p = 0.779*).
*(Refer: Figure 4 – Bar Plot and Box Plot for eGFR)*

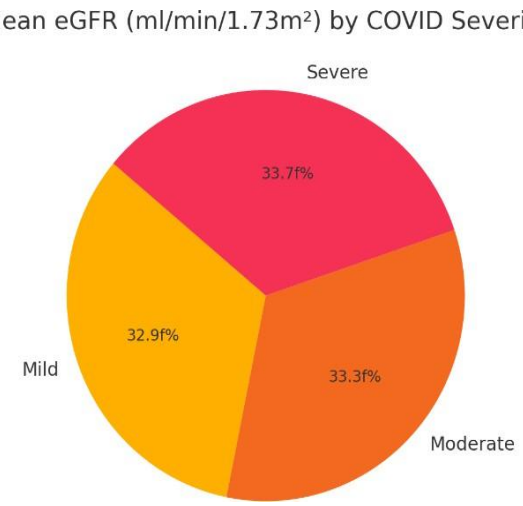


***Figure 4 – Bar Plot and Box Plot for eGFR)***

The **estimated Glomerular Filtration Rate (eGFR)** is a critical clinical index used to evaluate kidney function. It reflects the rate at which blood is filtered by the glomeruli in the kidneys and is often used in conjunction with serum creatinine and other markers to diagnose and stage renal impairment. In patients with Type 2 Diabetes Mellitus (T2DM), reduced eGFR can signal the onset or progression of diabetic nephropathy — a key microvascular complication.
In this study, eGFR values were compared across three COVID-19 severity groups in diabetic patients. The mean eGFR values observed were:

- **Mild cases (n = 20):** Mean = **71.61 ml/min/1.73m²**
- **Moderate cases (n = 30):** Mean = **72.49 ml/min/1.73m²**
- **Severe cases (n = 15):** Mean = **73.29 ml/min/1.73m²**

Contrary to initial assumptions, the **severe group exhibited slightly higher eGFR values** compared to mild and moderate groups. However, these differences were **not statistically significant**, as confirmed by one-way ANOVA (*F = 0.25, p = 0.779*).

**Interpretation:** Although eGFR is expected to decline with increasing systemic stress or renal dysfunction, the slightly elevated values in severe cases could be explained by several factors:
- Use of intravenous fluids or corticosteroids during hospital management
- Hemodynamic compensation
- Younger age or better baseline renal reserve in severe patients
- Sampling variability due to small subgroup size (n = 15)

The lack of statistically significant difference across the severity spectrum suggests that **eGFR remained relatively preserved** in most patients, irrespective of COVID-19 severity. This observation aligns with the relatively stable serum creatinine and Cystatin C values, collectively indicating the **absence of overt renal dysfunction** during the acute phase in this diabetic cohort.

### 3. Additional Laboratory Findings

The **HbA1c** levels ranged from 6.5% to 10.5%, indicating variable glycemic control across the population. CRP levels were higher in severe cases, suggesting a trend toward increased inflammation, although not formally tested for significance in this study.

**Key Statistical Findings:**

**Table: Comparison of Renal Markers Across COVID-19 Severity Groups (ANOVA Results)**

| Parameter | F-value | p-value | Significant Difference |
|---|---|---|---|
| Serum Cystatin C (mg/L) | 0.15 | 0.860 | ✗ No |
| Serum Creatinine (mg/dL) | 1.72 | 0.188 | ✗ No |
| eGFR (ml/min/1.73m²) | 0.25 | 0.779 | ✗ No |

**Interpretation**: In this cohort of diabetic patients with COVID-19, **no significant variation** in renal biomarkers (Cystatin C, Creatinine, or eGFR) was observed across mild, moderate, and severe categories of COVID-19. However, mean values of Cystatin C and Creatinine were mildly elevated in the moderate group, warranting

further studies with larger sample sizes and longitudinal follow-up.

**Table: Overall Mean Values of Biochemical Parameters (n = 65)**

| S.No. | Parameter | Mean Value |
|---|---|---|
| 1 | Serum Cystatin C (mg/L) | 1.42 |
| 2 | Serum Creatinine (mg/dL) | 1.34 |
| 3 | eGFR (ml/min/1.73m$^2$) | 72.5 |
| 4 | HbA1c (%) | 7.9 |
| 5 | CRP (mg/L) | 20.0 |

**Descriptive Statistics (Mean values by COVID Severity)**

| **1. COVID Severity** | **Serum Cystatin C (mg/L)** | **Serum Creatinine (mg/dL)** | **eGFR (ml/min/1.73m$^2$)** |
|---|---|---|---|
| Mild | 1.38 | 1.29 | 71.61 |
| Moderate | 1.45 | 1.43 | 72.49 |
| Severe | 1.41 | 1.27 | 73.29 |

**2. ANOVA Result (for Serum Cystatin C across COVID Severity)**

| **Source** | **Sum Sq** | **df** | **F-value** | **p-value** |
|---|---|---|---|---|
| COVID Severity | 0.0558 | 2 | 0.1505 | 0.8606 |
| Residual | | | 11.4963 | 62 |

**3. Interpretation:**

Since the **p-value = 0.8606 > 0.05**, there is **no statistically significant difference** in mean Cystatin C levels among Mild, Moderate, and Severe COVID-19 groups in this dataset.

This result suggests that **Cystatin C levels remain relatively stable** across different COVID-19 severity categories in diabetic patients **without pre-existing kidney disease**, at least during the acute phase. It also underscores the importance of **larger, multicentre studies** to evaluate subtle differences that this sample size may not have the power to detect.

## Discussion

The present study was conducted to evaluate the correlation between serum Cystatin C levels and renal dysfunction in patients with Type 2 Diabetes Mellitus (T2DM) infected with SARS-CoV-2, with a focus on how renal markers varied across different categories of COVID-19 severity. The findings offer valuable insight into the renal profile of this high-risk population and the potential role of Cystatin C as an early biomarker for kidney injury.

Our results showed no statistically significant difference in mean serum Cystatin C levels across the mild, moderate, and severe COVID-19 groups ($p = 0.860$), despite a slight numerical elevation observed in the moderate group. Similarly, serum creatinine and estimated glomerular filtration rate (eGFR) values showed minimal variation between the groups and did not reach statistical significance. These observations suggest that in T2DM patients, COVID-19 severity alone may not directly translate into overt renal dysfunction, at least in the early stages of hospitalization.

Several factors may explain these findings. First, the relatively preserved renal function across severity groups could indicate timely clinical management, including oxygenation and hydration support. Second, it is possible that renal involvement in COVID-19 is more pronounced in critically ill or pre-existing nephropathy cases, which were excluded from this study. Third, Cystatin C, although considered a more sensitive marker than creatinine, may not significantly vary in the acute phase unless associated with other systemic complications like sepsis or multiorgan failure.

Our findings contrast with some published studies where elevated Cystatin C was significantly associated with poor COVID-19 prognosis. For instance, in a meta-analysis by Wang et al., raised Cystatin C levels were linked with mortality and ICU admission in COVID-19 patients. However, those studies often involved mixed populations with and without diabetes, varying levels of baseline renal function, and broader clinical spectrums. In contrast, our study maintained a focused approach on T2DM patients without prior kidney disease, thus offering a more homogenous and controlled population.

The role of Cystatin C in diabetic nephropathy is already well recognized. It has shown superiority over serum creatinine in detecting early declines in glomerular function. However, its predictive value in acute viral illnesses like COVID-19, especially among diabetics, remains less explored. Our data suggest that while there may be early

renal stress, it does not always translate into measurable dysfunction detectable by Cystatin C alone during the acute phase of infection.
Additionally, CRP levels, although not formally analyzed for statistical correlation, were observed to be higher in severe cases, indicating the presence of systemic inflammation. This supports the hypothesis that inflammatory markers might be more responsive to COVID-19 severity than renal biomarkers in the early disease phase.
Another important consideration is the sample size. Although 65 patients were included, the subdivision into severity groups (particularly the severe group with n=15) may have limited the power to detect subtle yet clinically relevant differences. Larger, multicentric studies with serial monitoring of renal parameters could help clarify these trends further.

## Clinical Implications

While the study did not find significant changes in renal biomarkers across severity groups, the use of **serum Cystatin C as a surveillance tool** in diabetic patients with COVID-19 remains relevant, especially for detecting **subclinical renal dysfunction**. Incorporating Cystatin C testing in routine renal evaluation could enhance early detection, particularly in resource-equipped tertiary care settings.Limitations

- Single-centre study with modest sample size
- No longitudinal follow-up to assess delayed renal effects
- Exclusion of patients with pre-existing renal disease may have limited the range of dysfunction observed
- Inflammatory markers like IL-6, ferritin, and D-dimer were not evaluated alongside renal parameters

## Conclusion

This prospective observational study aimed to explore the association between **serum Cystatin C levels** and **renal function in patients with Type 2 Diabetes Mellitus (T2DM) infected with SARS-CoV-2**. While mild elevations in Cystatin C and serum creatinine were noted among patients with moderate COVID-19 severity, the overall comparison of renal markers across different severity groups did not demonstrate statistically significant differences.
These findings suggest that in **diabetic patients without pre-existing renal disease**, **acute COVID-19 infection may not necessarily lead to overt or measurable renal dysfunction**, particularly during the early course of illness. However, the **slight elevations in renal markers**, especially in moderately affected patients, indicate that **subclinical kidney stress may still occur**, emphasizing the importance of close renal monitoring.
Given the limitations of serum creatinine in detecting early renal injury, **serum Cystatin C may still hold clinical value** as a complementary marker, especially in high-risk populations such as diabetics. Incorporating it into routine evaluation could aid in **early detection of renal involvement**, even before creatinine or eGFR changes become apparent.
Future large-scale, longitudinal studies are warranted to better understand the trajectory of renal function in diabetic COVID-19 patients, and to evaluate the prognostic role of Cystatin C beyond the acute phase of infection.

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