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The relationship between CT value and clinical outcomes in renal patients with COVID-19

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Abstract

Purpose Concomitant kidney diseases raise the mortality rate due to the SARS-CoV-2 virus as an independent factor. Although a qualitative PCR test's result is sufficient for diagnosis, Cycle threshold value may present relevant information to the physicians in providing faster treatment in patients with chronic conditions, including kidney diseases, to prevent morbidity and subsequent mortality. Thus, the present study was conducted to determine the relationship between the Cycle threshold value and clinical outcomes in renal patients with the coronavirus 2019.

Methods This retrospective study was conducted on renal patients with the coronavirus 2019 infection admitted to Labbafinejad Hospital in Tehran, the capital of Iran, within a period of one year, from late February 2020 to February 2021. Data were collected per the prepared checklist. Cycle threshold values were measured by performing PCR on nasopharynx and oropharynx swab samples of patients.

Results According to the adjusted analysis, having high viral load increased the odds of in-hospital mortality (aOR = 11.65, 95% CI 3.93–34.54), ICU admission (aOR = 5.49, 95% CI 2.16–13.97), and invasive ventilation (aOR = 7.18, 95% CI 2.61–19.74). Having high viral load also increased the odds of O_2 therapy (aOR = 3.08, 95% CI 0.79–12.01), although the difference was not statistically significant ($P = 0.105$).

Conclusion Cycle threshold value was a significant predictor of mortality in renal patients. Nevertheless, further studies are required on how to render optimal use of the Cycle threshold value, given that the quality of the test sample and the different groups of patients under study affect the effectiveness of this marker in predicting disease severity.

Keywords Cycle threshold · Mortality · Clinical outcome · COVID-19 · Renal patients

Abbreviations

COVID-19	Coronavirus-2019
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
RT-PCR	Real-time reverse transcriptase-polymerase chain reaction
CKD	Chronic kidney disease
CT value	Cycle threshold value
SD	Standard deviation
OR	Odds ratio
CI	Confidence interval
eGFR	Estimated glomerular filtration rate

Introduction

The coronavirus 2019 (COVID-19) pandemic has imposed a heavy burden on healthcare systems worldwide. The adverse impacts of this disease can be easily observed within various aspects of the populations' health and socio-economic status worldwide [1, 2]. The disease is caused by an infection with SARS-CoV-2, which is an RNA virus that causes initial symptoms of pneumonia and acute respiratory syndrome [3]. Symptoms of the disease may range from an asymptomatic infection with loss of smell and taste to severe respiratory failure. Yet, the respiratory system is not the sole target of the virus [3, 4]. Extensive evidence indicates that COVID-19 with chronic conditions has a significant impact on mortality rates. Chronic lung, heart, liver, and kidney diseases, diabetes, and obesity have contributed to the mortality rates noted for COVID-19 [3, 5]. Accordingly, the role of chronic kidney disease (CKD) is particularly striking among other chronic

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conditions. Patients with CKD indicate a higher rate of all infections due to changes in their immune systems' function and the chronic and systemic inflammation that dominates their bodies. As a result, these individuals have higher odds of a more severe infection with the SARS-CoV-2 virus [3]. The incidence of COVID-19 infection is three times higher in CKD patients than in non-CKD patients.

Furthermore, CKD patients are 12 times more likely to be admitted to the ICU of a hospital following COVID-19 infection than patients without an underlying medical condition. This rate is higher than the rate for patients with diabetes and cardiovascular conditions. The mortality rate of COVID-19 in hemodialysis patients is 15–25%, even under no pulmonary involvement [3]. Ample evidence exists about the adverse impacts of coronavirus on patients' kidneys. SARS-CoV-2 is found in the urine samples of renal patients, and further pathological evidence confirms the impact of COVID-19 on the kidneys in the form of glandular and tubular damage. Indeed, the kidneys are one of the several organs that are highly attacked by this virus [4, 6]. Besides, concomitant kidney diseases raise the mortality rate due to the SARS-CoV-2 virus as an independent factor. This rate extends may be maximum in dialysis patients. Accordingly, dialysis patients are up to four times more prone to succumb to the coronavirus. Also, dialysis patients are more likely to experience complications of the disease and display the worst prognosis along with kidney transplant recipients. In addition, COVID-19 patients are more likely to face acute kidney damage as a complication of coronavirus infections if their condition worsens. Although the exact mechanism underlying these injuries is unknown, other factors affecting them require further examination [2, 4, 6–12].

An accurate and rapid diagnostic approach is necessary as the SARS-CoV-2 virus undermines the healthcare systems. In this regard, real-time reverse transcriptase-polymerase chain reaction (RT-PCR) is preferred, given its speed and accuracy. There are various semi-qualitative indexes associated with PCR (e.g., Cycle threshold). These indices appear to be able to assist us in predicting prognosis and infectivity in patients with COVID-19. In addition, the indices are associated with different aspects of disease severity. Some of these aspects include mortality, disease severity, disease progression, biochemical and hematological markers, and infectivity. Extensive studies have examined the link between Cycle threshold value (CT value) and each of these cases, leading to various outcomes. Although a qualitative PCR test's result is sufficient for diagnosis, CT value may present relevant information to the physicians in providing faster treatment in patients with chronic conditions, including kidney diseases, to prevent morbidity and subsequent mortality [13, 14]. Thus, the present study was conducted to determine the link between CT value and clinical outcomes in renal patients with COVID-19.

Methods

Study population and setting

This retrospective study was conducted to examine the relationship between Cycle threshold (CT) values and clinical outcomes in renal patients with COVID-19 infection admitted to Labbafinejad Hospital in Tehran, the capital of Iran. The data were taken from the Hospital Information System (HIS) unit of the Labbafinejad Hospital. Medical records of all renal patients with a positive COVID-19 PCR test were included in the study while patients with incomplete medical records were excluded.

The study population consists of renal patients with COVID-19 admitted to Labbafinejad Hospital within a period of 1 year, from late February 2020 to February 2021. Sampling was performed by the census method. 225 cases pertaining to renal patients with positive COVID-19 PCR tests were reviewed. Of these, 168 cases with all the information based on the checklist were included in the study. Data collection was conducted after the approval and receipt of a letter of introduction from the Ethics Committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.UNRC.REC.1400.019), which was presented to the concerned authorities.

Viral load assessment

In the present study, two nasopharynx and oropharynx swab samples of patients in a VTM (Viral transport medium) culture medium were collected by an experienced individual during the initial stage. The RNA was extracted by the GeneAll® RibospinTM vRD RNA extraction kit, following the kit's protocols. Next, PCR was performed using the Sansure® SARS-CoV-2 Multiplex Nucleic Acid Diagnostic Kit (PCR-Fluorescence Probing). By this kit, ORF 1ab, N and E genes were used to calculate and measure the CT value. If the disease was observed as positive in any gene, the gene's corresponding CT value was also reported. In case the disease was positive for more than one gene, the average CT value was reported.

Data collection

Data were collected per the prepared checklist. This tool includes demographic information (age, sex, and BMI), underlying conditions (hypertension, diabetes, chronic respiratory diseases, obesity, and cardiovascular disease), patient's condition in terms of renal diseases (CKD not on dialysis, CKD on dialysis, Kidney Transplant Recipients), physiological indices (PSO_2, DBP, SBP, mean arterial pressure, respiratory rate, heart rate), lung CT scan findings, and

CT value. Furthermore, based on their CT value, the patients were categorized into two classes: low viral load (CT > 20) and High viral load (CT ≤ 20). Estimated glomerular filtration rate (eGFR) was calculated by CKD-EPI equations. By eGFR, the patients were divided into six grade, based on the KDIGO CKD stages. All variables were collected at the time of admission. Clinical outcomes in the present study were as follows: ICU admission, O_2 Therapy, Invasive ventilation, and In-hospital mortality. All of the mentioned data were collected from the patient file in HIS (hospital information system).

Statistical analysis

Data analysis was carried out using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA) and graphs were depicted using GraphPad Prism, Version 8.0.1 (GraphPad Prism Software Inc., San Diego, CA, USA). Continuous variables are presented as median (interquartile range (IQR)) and compared using Mann–Whitney test. Categorical variables are presented as numbers (percentages) and compared using chi-square test.

Multiple logistic regression analysis was also applied to examine the relationships of clinical and demographic characteristics with outcome variables. The odds ratio (OR) and 95% confidence interval (CI) were calculated. All statistical tests were two-sided and level of significance was set at 0.05.

Results

The present study examined the potential relationship between the CT value and the occurrence of clinical outcomes (in-hospital mortality, invasive ventilation, O_2 Therapy, ICU admission) among renal patients infected by COVID-19 admitted to Labbafinejad Hospital in Tehran, the capital of Iran. Comparing the data in terms of mortality shows that of the 168 examined patients, 127 survived and 41 deceased. In these two groups (Deceased and Survived), the median CT value and its categories (CT ≤ 20 and CT > 20), median age ($P = 0.009$), diabetes ($P = 0.04$), number of comorbidities ($P = 0.004$), PSO_2 ($P = 0.005$), and CT chest ($P < 0.001$) showed a significant statistical relationship. Moreover, the eGFR ($P = 0.003$) and CKD stages ($P = 0.002$) were significantly different between these two groups. The eGFR was lower in deceased group and they also have higher CKD stages or worse kidney function (Table 1).

The results further show that 49 patients were admitted to the ICU. There was a significant statistical relationship between admittance to ICU and median CT value ($P = 0.001$) and its categories (CT ≤ 20 and CT > 20) ($P = 0.01$), number of comorbidities ($P = 0.006$), PSO_2 ($P = 0.02$), and CT chest ($P < 0.001$), the eGFR ($P = 0.014$) and CKD stages ($P = 0.016$) (Table 2).

Furthermore, the results show that invasive ventilation was used in 35 patients. A statistically significant relationship was observed between the use of invasive ventilation and CT value's mean ($P = 0.005$), its classification ((CT > 20) and (CT ≤ 20)), number of comorbidities ($P = 0.01$), PSO_2 ($P = 0.01$), and CT chest ($P < 0.001$), the eGFR ($P = 0.003$) and CKD stages ($P = 0.002$) (Table 3).

Moreover, the results show that among 133 patients using O_2 therapy, there is a statistically significant statistical relationship between O_2 therapy and median CT value ($P < 0.02$), the number of clinical symptoms ($P < 0.001$), number of comorbidities ($P = 0.04$), PSO_2 ($P = 0.005$), and CT chest ($P < 0.001$) (Table 4).

Figure 1 indicates the relationship between high viral load and increased clinical outcomes (in-hospital mortality, ICU admission, invasive ventilation, and O_2 therapy). Also, Fig. 2 (i.e., the impact of the type of renal disease on clinical outcomes) indicates that kidney transplant patients and similar dialysis patients recorded more mortality, ICU admission, invasive ventilation, and O2 therapy than the non-dialysis groups. As presented in Fig. 3, there was no significant correlation between eGFR and CT value ($r = 0.114$, $P = 0.142$).

Based on adjusted analysis, the odds of death increased with rising age. As compared to patients aged ≤ 60 years, those aged > 60 years were 2.91 (95% CI 1.08–7.83) times more likely to die from COVID-19. Compared with CKD not on dialysis group, patients with kidney transplant were at significantly increased risk of death (OR = 2.99, 95% CI 1.05–8.49). Patients with 1 and ≥ 2 comorbidities had significantly increased odds of death (OR = 6.39, 95% CI 1.21–33.73 and OR = 6.06, 95% CI 1.22–30.16, respectively) as compared with patients with no comorbidities. Other variables were not significantly associated with death (Table 5).

Regarding ICU admission, patients with CKD on dialysis and patients with kidney transplant were at increased risk of ICU admission (OR = 1.75, 95% CI 0.62–4.92, OR = 2.11, 95% CI 0.83–5.34) as compared with CKD not on dialysis group, although these increases were not statistically significant ($P = 0.290$ and $P = 0.115$, respectively). Patients with 1 and ≥ 2 comorbidities had significantly increased odds of ICU admission (OR = 8.36, 95% CI 1.71–40.82 and OR = 7.51, 95% CI 1.58–35.73, respectively) as compared with patients with no comorbidities. For every one-unit increase in GFR, the odds of mortality and invasive ventilation decreased by 3% (OR = 0.97, 95% CI 0.95–0.99 and OR = 0.97, 95% CI 0.94–0.99, respectively) (Table 5).

As presented in Table 6, patients with high viral load significantly had higher in-hospital mortality, ICU admission and invasive ventilation as compared with patients with low viral load. O2 therapy in patients with high viral load was higher than patients with low viral load, although this

Table 1 Characteristics of patients with pre-existing chronic kidney disease and COVID-19 by in-hospital mortality

	In-hospital mortality		*P*
	Survived ($n=127$)	Deceased ($n=41$)	
Demographics			
Age (years)	57.0 (42.0–66.0)	64.0 (53.5–72.5)	0.009
Age group (years)			0.019
≤60	67 (52.8)	13 (31.7)	
>60	60 (47.2)	28 (68.3)	
Male sex	86 (67.7)	30 (73.2)	0.511
Active smoking	7 (5.5)	4 (9.8)	0.339
No. of symptoms	3.0 (2.0–5.0)	4.0 (2.5–5.0)	0.208
Chronic kidney disease			0.393
CKD not on dialysis	49 (38.6)	11 (26.8)	
CKD on dialysis	23 (18.1)	9 (22.0)	
Kidney transplant recipients	55 (43.3)	21 (51.2)	
eGFR	34.0 (14.0–58.0)	18.0 (8.5–34.5)	0.003
CKD-EPI stage			0.002
Stage 1	5 (3.9)	2 (4.9)	
Stage 2	23 (18.1)	0 (0)	
Stage 3a	24 (18.9)	3 (7.3)	
Stage 3b	14 (11.0)	7 (17.1)	
Stage 4	26 (20.5)	10 (24.4)	
Stage 5	35 (27.6)	19 (46.3)	
Comorbidities			
Hypertension	79 (62.2)	30 (73.2)	0.201
Diabetes	54 (42.5)	25 (61.0)	0.040
Chronic respiratory diseases	6 (4.7)	6 (14.6)	0.032
Cardiovascular disease	31 (24.4)	16 (39.0)	0.070
Obesity	24 (18.9)	11 (26.8)	0.277
No. of comorbidities	1.0 (0–2.0)	2.0 (1.0–3.0)	0.004
Physiological parameters			
SBP	123.0 (113.0–140.0)	130.0 (113.0–152.5)	0.361
DBP	79.0 (70.0–80.0)	76.0 (71.0–85.0)	0.809
Mean arterial pressure	93.3 (86.0–101.0)	95.3 (88.2–103.0)	0.289
Respiratory rate	18.0 (18.0–20.0)	18.0 (17.0–21.0)	0.858
Heart rate	85.0 (79.0–95.0)	88.0 (80.0–94.0)	0.387
PSo2	93.0 (89.0–95.0)	90.0 (80.0–94.5)	0.005
CT Chest			<0.001
Normal	33 (26.0)	5 (12.2)	
Mild	53 (41.7)	1 (2.4)	
Moderate	34 (26.8)	10 (24.4)	
Severe	7 (5.5)	25 (61.0)	
Ct value	28.0 (24.0–31.0)	23.0 (18.0–29.0)	0.001
Ct value category			<0.001
Low viral load (Ct>20)	114 (89.8)	23 (56.1)	
High viral load (Ct≤20)	13 (10.2)	18 (43.9)	

Values are given as number (percentage) for categorical variables and as median (interquartile range) for continuous variables

CKD chronic kidney disease; *eGFR* estimated glomerular filtration rate

Table 2 Characteristics of patients with pre-existing chronic kidney disease and COVID-19 by ICU admission

	ICU admission		*P*
	Ward ($n=119$)	ICU ($n=49$)	
Demographics			
Age (years)	61.0 (46.0–67.0)	63.0 (49.5–70.0)	0.184
Age group (years)			0.428
≤60	59 (49.6)	21 (42.9)	
>60	60 (50.4)	28 (57.1)	
Male sex	78 (65.5)	38 (77.6)	0.126
Active smoking	9 (7.6)	2 (4.1)	0.512
No. of symptoms	3.0 (2.0–5.0)	4.0 (2.0–5.0)	0.680
Chronic kidney disease			0.156
CKD not on dialysis	47 (39.5)	13 (26.5)	
CKD on dialysis	19 (16.0)	13 (26.5)	
Kidney transplant recipients	53 (44.5)	23 (46.9)	
eGFR	33.0 (14.0–56.0)	18.0 (8.0–38.5)	0.014
CKD-EPI stage			0.016
Stage 1	6 (5.0)	1 (2.0)	
Stage 2	18 (15.1)	5 (10.2)	
Stage 3a	22 (18.5)	5 (10.2)	
Stage 3b	16 (13.4)	5 (10.2)	
Stage 4	25 (21.0)	11 (22.4)	
Stage 5	32 (26.9)	22 (44.9)	
Comorbidities			
Hypertension	73 (61.3)	36 (73.5)	0.135
Diabetes	51 (42.9)	28 (57.1)	0.092
Chronic respiratory diseases	6 (5.0)	6 (12.2)	0.110
Cardiovascular disease	29 (24.4)	18 (36.7)	0.105
Obesity	21 (17.6)	14 (28.6)	0.113
No. of comorbidities	1.0 (0–2.0)	2.0 (1.0–3.0)	0.006
Physiological parameters			
SBP	123.0 (115.0–140.0)	128.0 (112.0–150.0)	0.199
DBP	80.0 (70.0–81.0)	76.0 (70.5–85.0)	0.729
Mean arterial pressure	93.3 (85.0–101.0)	95.33 (88.2–103.2)	0.189
Respiratory rate	18.0 (18.0–20.0)	18.0 (17.0–21.5)	0.644
Heart rate	83.0 (79.0–95.0)	88.0 (80.0–93.0)	0.203
PSo2	93.0 (89.0–96.0)	91.0 (87.5–94.0)	0.022
CT chest			<0.001
Normal	34 (28.6)	4 (8.2)	
Mild	51 (42.9)	3 (6.1)	
Moderate	27 (22.7)	17 (34.7)	
Severe	7 (5.9)	25 (51.0)	
Ct value	27.0 (23.0–31.0)	26.0 (18.0–29.0)	0.011
Ct value category			<0.001
Low viral load (Ct>20)	106 (89.1)	31 (63.3)	
High viral load (Ct≤20)	13 (10.9)	18 (36.7)	

Values are given as number (percentage) for categorical variables and as median (interquartile range) for continuous variables

CKD chronic kidney disease, *ICU* intensive care unit; *eGFR* estimated glomerular filtration rate

Table 3 Characteristics of patients with pre-existing chronic kidney disease and COVID-19 by invasive ventilation

	Invasive ventilation		*P*
	No ($n=133$)	Yes ($n=35$)	
Demographics			
Age (years)	61.0 (45.5–67.0)	63.0 (49.0–72.0)	0.156
Age group (years)			0.310
≤60	66 (49.6)	14 (40.0)	
>60	67 (50.4)	21 (60.0)	
Male sex	92 (69.2)	24 (68.6)	0.945
Active smoking	10 (7.5)	1 (2.9)	0.462
No. of symptoms	3.0 (2.0–5.0)	4.0 (2.0–5.0)	0.238
Chronic kidney disease			0.584
CKD not on dialysis	50 (37.6)	10 (28.6)	
CKD on dialysis	24 (18.0)	8 (22.9)	
Kidney transplant recipients	59 (44.4)	17 (48.6)	
eGFR	34.0 (14.0–56.0)	14.0 (8.0–33.0)	0.003
CKD-EPI stage			0.002
Stage 1	5 (3.8)	2 (5.7)	
Stage 2	23 (17.3)	0 (0)	
Stage 3a	24 (18.0)	3 (8.6)	
Stage 3b	17 (12.8)	4 (11.4)	
Stage 4	29 (21.8)	7 (20.0)	
Stage 5	35 (26.3)	19 (54.3)	
Comorbidities			
Hypertension	85 (63.9)	24 (68.6)	0.693
Diabetes	58 (43.6)	21 (60.0)	0.084
Chronic respiratory diseases	6 (4.5)	6 (17.1)	0.019
Cardiovascular disease	34 (25.6)	13 (37.1)	0.175
Obesity	25 (18.8)	10 (28.6)	0.205
No. of comorbidities	2.0 (1.0–3.0)	2.0 (1.0–3.0)	0.018
Physiological parameters			
SBP	124.0 (114.0–140.0)	130.0 (113.0–156.0)	0.350
DBP	79.0 (70.0–80.0)	76.0 (70.0–85.0)	0.668
Mean arterial pressure	93.3 (86.2–101.2)	96.7 (88.3–104.0)	0.251
Respiratory rate	18.0 (18.0–20.0)	18.0 (17.0–21.0)	0.395
Heart rate	84.0 (79.0–91.0)	88.0 (80.0–98.0)	0.126
PSo2	93.0 (89.0–95.0)	90.0 (85.0–94.0)	0.014
CT chest			<0.001
Normal	36 (27.1)	2 (5.7)	
Mild	52 (39.1)	2 (5.7)	
Moderate	36 (27.1)	8 (22.9)	
Severe	9 (6.8)	23 (65.7)	
Ct value	27.0 (23.5–0.0)	23.0 (18.0–30.0)	0.005
Ct value category			<0.001
Low viral load (Ct>20)	117 (88.0)	20 (57.1)	
High viral load (Ct≤20)	16 (12.0)	15 (42.9)	

Values are given as number (percentage) for categorical variables and as median (interquartile range) for continuous variables

CKD chronic kidney disease; *eGFR* estimated glomerular filtration rate

Table 4 Characteristics of patients with pre-existing chronic kidney disease and COVID-19 by O_2 therapy

	O_2 therapy		*P*
	No ($n=35$)	Yes ($n=133$)	
Demographics			
Age (years)	55.0 (40.0–71.0)	61.0 (47.0–67.0)	0.614
Age group (years)			0.612
≤60	18 (51.4)	62 (46.6)	
>60	17 (48.6)	71 (53.4)	
Male sex	21 (60.0)	95 (71.4)	0.193
Active smoking	1 (2.9)	10 (7.5)	0.321
No. of symptoms	2.0 (2.0–3.0)	4.0 (3.0–4.0)	<0.001
Chronic kidney disease			0.545
CKD not on dialysis	15 (42.9)	45 (33.8)	
CKD on dialysis	5 (14.3)	27 (20.3)	
Kidney transplant recipients	15 (42.9)	61 (45.9)	
eGFR	26.0 (16.0–58.0)	25.0 (11.0–52.0)	0.442
CKD-EPI stage			0.516
Stage 1	4 (11.4)	3 (2.3)	
Stage 2	4 (11.4)	19 (14.3)	
Stage 3a	2 (5.7)	25 (18.8)	
Stage 3b	5 (14.3)	16 (12.0)	
Stage 4	13 (37.1)	23 (17.3)	
Stage 5	7 (20.0)	47 (35.3)	
Comorbidities			
Hypertension	20 (57.1)	89 (66.9)	0.281
Diabetes	13 (37.1)	66 (49.6)	0.188
Chronic respiratory diseases	0 (0)	12 (9.0)	0.074
Cardiovascular disease	6 (17.1)	41 (30.8)	0.109
Obesity	7 (20.0)	28 (21.1)	0.891
No. of comorbidities	1.0 (0–3.0)	2.0 (1.0–3.0)	0.042
Physiological parameters			
SBP	127.0 (115.0–150.0)	125.0 (113.0–140.0)	0.388
DBP	78.0 (70.0–90.0)	79.0 (70.0–83.0)	0.926
Mean arterial pressure	93.3 (84.0–106.7)	93.3 (86.7–101.2)	0.879
Respiratory rate	18.0 (18.0–20.0)	18.0 (18.0–20.0)	0.283
Heart rate	84.0 (80.0–95.0)	85.0 (79.5–94.5)	0.697
PSo2	95.0 (92.0–96.0)	92.0 (88.0–95.0)	0.005
CT chest			<0.001
Normal	13 (37.1)	25 (18.8)	
Mild	19 (54.3)	35 (26.3)	
Moderate	2 (5.7)	42 (31.6)	
Severe	1 (2.9)	31 (23.3)	
Ct value	30.0 (22.0–35.0)	27.0 (22.0–30.0)	0.022
Ct value category			0.090
Low viral load (Ct>20)	32 (91.4)	105 (78.9)	
High viral load (Ct≤20)	3 (8.6)	28 (21.1)	

Values are given as number (percentage) for categorical variables and as median (interquartile range) for continuous variables

CKD chronic kidney disease; *eGFR* estimated glomerular filtration Rate

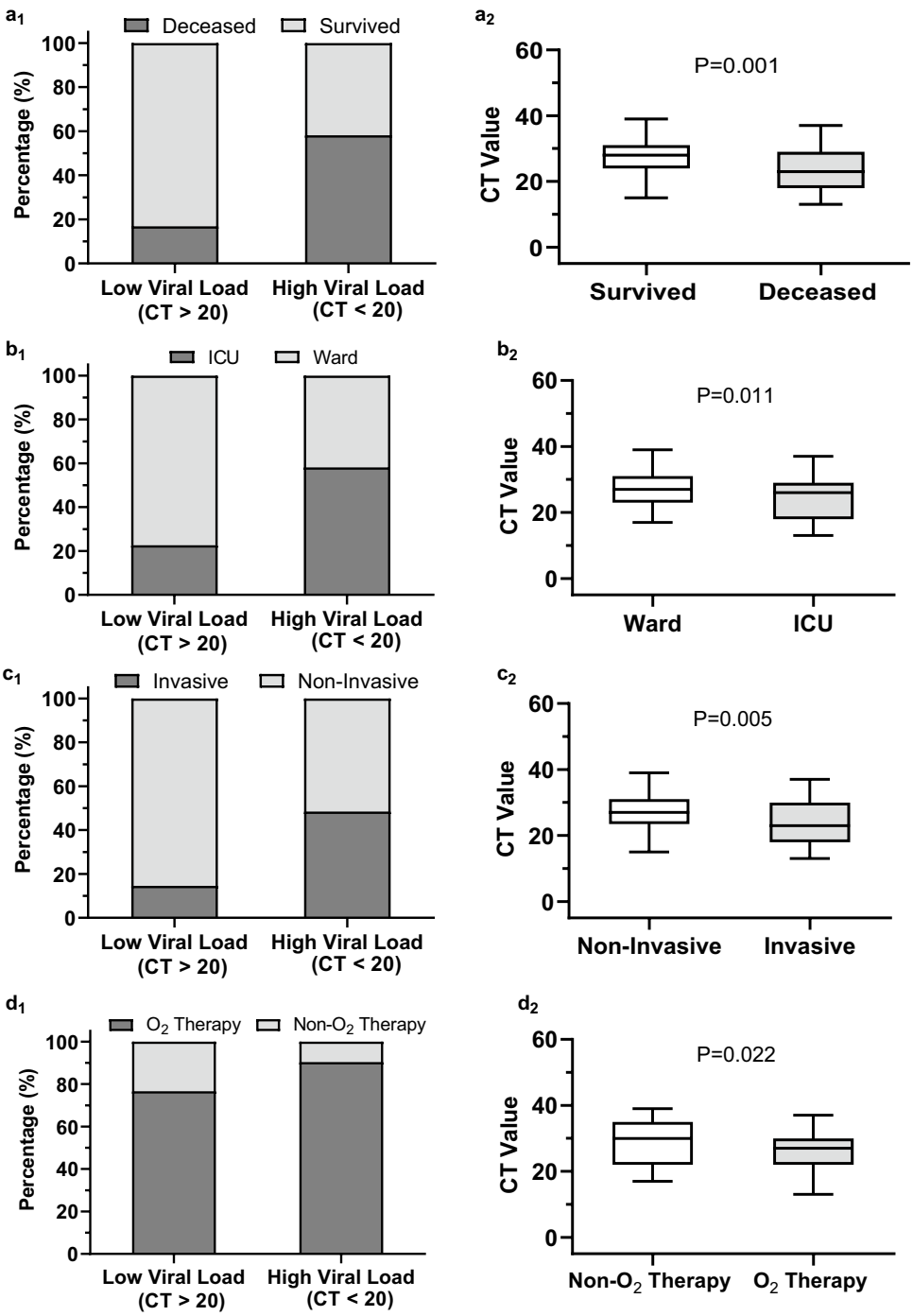

Fig. 1 Relationship between Ct value and clinical outcomes, **a** in-hospital mortality, **b** ICU admission, **c** invasive ventilation, and **d** O2 therapy

difference was not statistically significant (90.3% vs 76.6%, $P=0.105$). After adjusting for the variables, having high viral load increased the odds of in-hospital mortality (aOR = 11.65, 95% CI 3.93–34.54), ICU admission (aOR = 5.49, 95% CI 2.16–13.97), and invasive ventilation (aOR = 7.18, 95% CI 2.61–19.74). Having high viral load also increased the odds of O2 therapy (aOR = 3.08, 95% CI 0.79–12.01), although the difference was not statistically significant ($P=0.105$) (Table 6).

Discussion

Severe acute respiratory syndrome (SARS-CoV-2), known as COVID-19, has been the most formidable healthcare issue for physicians worldwide to date. In the coronavirus pandemic, managing the conditions of patients with either chronic kidney diseases or acute kidney injuries and kidney transplant patients undergoing immunosuppressive therapy proves a clinical challenge for nephrologists,

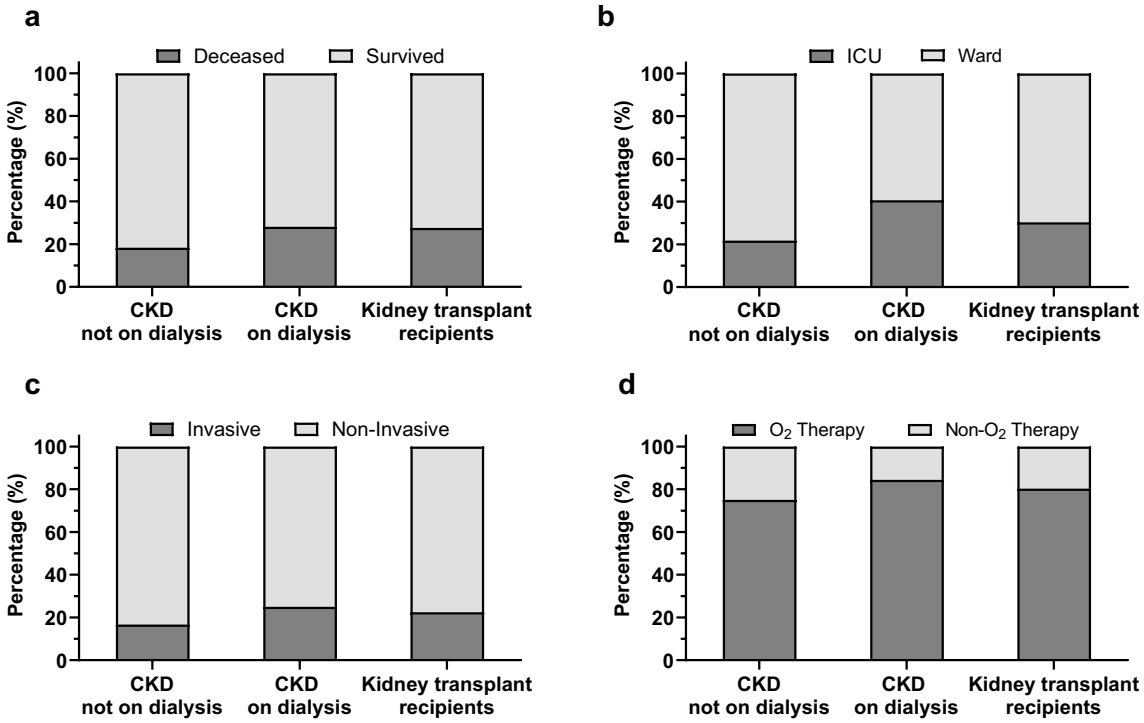

Fig. 2 Relationship between type of chronic kidney disease and clinical outcomes, **a** in-hospital mortality, **b** ICU admission, **c** invasive ventilation, and **d** O2 therapy

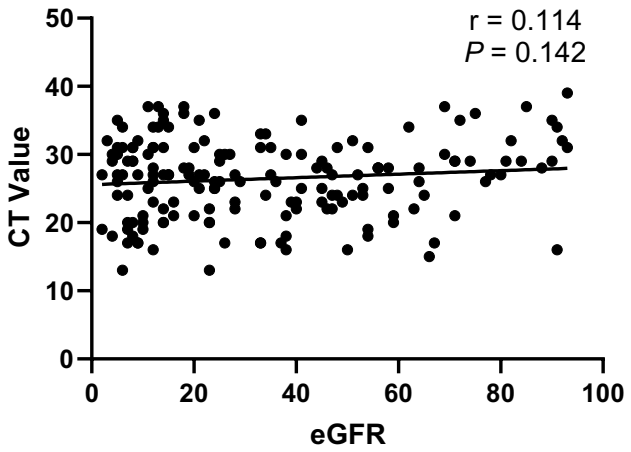

Fig. 3 Relationship between eGFsR and CT Value among patients with CKD

particularly in patients with severe COVID-19. Under such circumstances, efficient management is necessary to mitigate side effects and drug interactions due to renal failure [15, 16], given the absence of specific anti-COVID-19 treatment programs. Efficient management of these patients demands markers that are both effortlessly measurable and can help predict the condition of these patients. In this respect, CT value has been proposed as an approximate measure of the initial viral load in SARS-CoV-2 [17].

Despite limited studies on using the CT value as a predictor of disease severity in renal patients, the result of the present study indicated that kidney patients with high viral loads displayed higher in-hospital mortality (10.14 times) than patients with low viral loads.

Rajyalakshmi et al. concluded that low CT value is associated with increased ICU hospitalization, mortality, and length of stay in the ICU. Elsewhere, Rajyalakshmi et al. maintained that the CT value could be regarded as one of the prognostic variables beside some other biomarkers [18]. Similarly, Magleby et al. demonstrated that the SARS-CoV-2 viral load in hospitalized patients was associated with the risk of intubation and in-hospital mortality as an independent variable [19]. The link between CT levels and duration of symptoms with mortality in COVID-19 patients was further confirmed in another study by Miller et al. [20]. Regarding the cause of higher mortality in renal patients with low CT values (i.e., high viral loads) observed in the above studies and the present one, it is noteworthy that the immune system's function is reduced due to uremia in these patients. In addition, the mortality rate and critical conditions are higher in patients with kidney transplantations due to using immunosuppressive agents to prevent transplant rejection [21].

In contrast, researchers such as Karahasan Yagci et al. concluded that viral load was not a significant factor in hospitalization and mortality [22]. The difference in these results may be attributed to the differences in study

Table 5 Multivariate logistic regression models of factors associated with clinical outcomes

	In-hospital mortality		ICU admission		Invasive ventilation		O_2 Therapy	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Age (years)								
≤60	1		1		1		1	
>60	2.91 (1.08–7.83)	0.034	1.25 (0.53–2.94)	0.602	1.45 (0.54–3.85)	0.459	0.86 (0.30–2.43)	0.774
Sex								
Male	1.11 (0.46–2.65)	0.823	1.91 (0.84–4.34)	0.124	0.90 (0.38–2.17)	0.820	1.92 (0.81–4.58)	0.141
Female	1		1		1		1	
Smoking								
No	1		1		1		1	
Yes	1.26 (0.26–6.03)	0.776	0.34 (0.06–1.89)	0.219	0.24 (0.03–2.22)	0.207	1.68 (0.17–16.67)	0.657
CKD								
CKD not on dialysis	1		1		1		1	
CKD on dialysis	0.94 (0.30–2.95)	0.911	1.75 (0.62–4.92)	0.290	0.91 (0.28–2.92)	0.873	1.31 (0.37–4.64)	0.676
Kidney transplant	2.99 (1.05–8.49)	0.040	2.11 (0.83–5.34)	0.115	1.92 (0.67–5.50)	0.223	1.08 (0.39–2.99)	0.876
eGFR	0.97 (0.95–0.99)	0.003	0.98 (0.97–1.00)	0.068	0.97 (0.94–0.99)	0.004	0.99 (0.97–1.01)	0.263
No. of Comorbidity								
0 (none)	1		1		1		1	
1	6.39 (1.21–33.73)	0.029	8.36 (1.71–40.82)	0.009	4.47 (0.84–23.95)	0.080	1.83 (0.62–5.41)	0.273
≥2	6.06 (1.22–30.16)	0.028	7.51 (1.58–35.73)	0.011	5.56 (1.10–29.07)	0.038	3.34 (1.10–10.10)	0.033
No. of symptoms	1.23 (0.96–1.58)	0.095	1.05 (0.84–1.31)	0.652	1.27 (0.98–1.64)	0.067	1.61 (1.23–2.10)	<0.001

OR odds ratio; *CI* confidence interval; *CKD* chronic kidney disease; *ICU* intensive care unit; *eGFR* estimated glomerular filtration rate

Table 6 Model-adjusted and unadjusted analysis risk of clinical outcomes

Outcome	Prevalence, *n* (%)	Unadjusted analysis		Adjusted analysis	
		OR (95% CI)	*P*	OR (95% CI)	*P*
In-hospital mortality					
Ct value		0.89 (0.84–0.95)	<0.001	0.88 (0.82–0.95)	0.002
CT value category					
Low viral load (Ct > 20)	23 (16.8%)	1		1	
High viral load (Ct ≤ 20)	18 (58.1%)	6.86 (2.96–15.94)	<0.001	11.65 (3.93–34.54)	<0.001
ICU admission					
Ct value		0.92 (0.86–0.98)	0.006	0.92 (0.86–0.98)	0.012
CT value category					
Low viral load (Ct > 20)	31 (22.6%)	1		1	
High viral load (Ct ≤ 20)	18 (58.1%)	4.73 (2.09–10.73)	<0.001	5.49 (2.16–13.97)	<0.001
Invasive ventilation					
Ct value		0.90 (0.84–0.97)	0.003	0.90 (0.83–0.97)	0.006
CT value category					
Low viral load (Ct > 20)	20 (14.6%)	1		1	
High viral load (Ct ≤ 20)	15 (48.4%)	5.48 (2.35–12.82)	<0.001	7.18 (2.61–19.74)	<0.001
O_2 therapy					
Ct value		0.92 (0.85–0.98)	0.014	0.94 (0.87–1.01)	0.087
CT value category					
Low viral load (Ct > 20)	105 (76.6%)	1		1	
High viral load (Ct ≤ 20)	28 (90.3%)	2.84 (0.81–9.97)	0.102	3.08 (0.79–12.01)	0.105

OR odds ratio; *CI* confidence interval; *ICU* intensive care unit

populations. In Karahasan Yagci et al.'s study, both hospitalized patients and outpatients were examined, but the present study merely examined hospitalized patients.

Findings signify that the ICU hospitalization of the high viral load renal patients (CT ≤ 20) was higher (5.7 times) than the ICU hospitalization of the low viral load renal patients (CT > 20). Additionally, invasive ventilation in patients with high viral load was 6.69 times higher than in the other group. According to Rajyalakshmi et al. a low CT was associated with increased ICU hospitalization and prolonged the patient's stay. Rajyalakshmi et al. also reported a negative link between the length of stay in ICU and the CT value [18]. In another study, Wenyuchen concluded that increasing the viral load is a key factor leading to higher immune response and disease progression. Lung damage and respiratory dysfunctions, which develop after the disease, need invasive ventilation [23]. In contrast, Atique et al. did not observe statistically significant differences in disease severity between different CT value groups [24]. The difference in the results might be attributed to the way the CT value is divided. In the above study, CT value is divided into three categories, while the present study opts for two categories.

O_2 treatment was higher in patients with high viral loads than in patients with low viral loads, and this difference was not deemed statistically significant (90.3% versus 76.6%). Abdulrahman et al. concluded that viral load had no significant association with oxygen demand during hospitalization [25]. Accordingly, the discrepancy between viral load and oxygen demand is because most hospitalized patients undergo intermittent or permanent oxygen therapy following COVID-19 infection.

The CKD Stages and eGFR was significantly different between survived and deceased groups. The eGFR was higher in the survived group. Moreover, more patients in the deceased group had CKD stages four and five. Generally, the survived group had better kidney function. The COVID-19 was also more severe in the patients with lower kidney function. Therefore, the eGFR was lower in the patients needed invasive oxygen therapy or admission to ICU and they had more sever CKD stages. In a study conducted by Gibertoni et al., the incidence and mortality of COVID-19 was higher in non-dialysis chronic kidney disease than patients without comorbid diseases. Furthermore, the mortality rate was higher in CKD-EPI stage 4[26]. Ozturk et al. achieved the same result in a retrospective study on CKD patients. They concluded that CKD stage 3–5 patients had highest mortality rate after COVID-19 infection among the CKD patients[27].

Examining the impact of other variables on clinical outcomes revealed that the probability of death increases with age. Renal patients over 60 years were 2.93 times more likely to succumb to COVID-19 than those below 60 years. Oto et al. observed that factors such as ischemic heart diseases and inadequate transplant function were among the leading causes of higher mortality following COVID-19 in individuals over the age of 60 [28]. In another study, on a predominantly African-American population, increasing age was linked to worsening prognosis in chronic renal patients with COVID-19 infection [29].

In the present study, kidney transplant patients were significantly (2.74 times) more likely to succumb to COVID-19 than chronic kidney patients who were not on dialysis. In a systematic review by Alfishawy, COVID-19 was linked to higher mortality in transplant recipients, including kidney transplant recipients. Accordingly, this high mortality rate is attributed to immunosuppressive drug intakes [30]. In another study concerning kidney transplant patients with COVID-19, the mortality rate in these patients was higher than in hemodialysis patients [31].

The present study revealed that the presence of comorbid disease(s) in kidney patients significantly increases the probability of death (by 6.34 times) compared to patients without any comorbid disease. Symptoms of COVID-19 range from asymptomatic infection to severe pneumonia with respiratory failure and even death. More severe cases with higher mortality have been reported in elderly patients and individuals with chronic conditions such as hypertension, diabetes, or cardiovascular diseases. Hence, patients with chronic kidney diseases (CKD) are more likely to suffer from various infections and cardiovascular diseases than the general population. The significantly altered and suppressed immune system in CKD patients may predispose these individuals to infectious complications. In addition, it is of note that CKD patients have a chronic systemic inflammation that may also increase morbidity and mortality [3].

Patients on dialysis and kidney transplant were more likely to be admitted to the ICU than non-dialysis patients, although with a non-significant difference. In dialysis patients, symptoms develop more severely than in non-dialysis patients, and laboratory parameters indicators of inflammation such as lymphocyte and neutrophil count, and creatine kinase are observed higher. Hence, the severity of COVID-19 diseases and the need for ICU hospitalization will be higher in patients under dialysis [4].

Accordingly, the probability of admission to the ICU, the use of invasive ventilation, and oxygen therapy had significantly increased in patients with one, two, or more comorbid conditions than in those without any comorbidity. The presence of any of the comorbidities alone can be associated with increased mortality and morbidity following COVID-19 infection. Therefore, this issue is exacerbated in the presence of multiple comorbidities [32, 33].

Conclusion

Kidney transplant patients and similarly dialysis patients had higher mortality, ICU admission, invasive ventilation, and oxygen therapy following COVID-19 than the non-dialysis group. As a result, early prediction of the severity of COVID-19 in renal patients via laboratory markers may help manage treatment to prevent mortality and morbidity. In the present study, CT value was a significant predictor of mortality in renal patients. Nevertheless, further studies are required on how to render optimal use of the CT value, given that the quality of the test sample and the different groups of patients under study affect the effectiveness of this marker in predicting disease severity.

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Declarations

Conflict of interest The authors declared that they have no conflict of interests.

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