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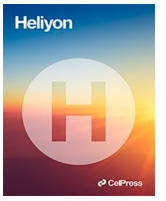

Research article

Relationship between creatinine–cystatin C ratio and all-cause mortality in hospitalized patients with COVID-19: A prospective study in China

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ABSTRACT

Background: This study was conducted to investigate whether baseline creatinine–cystatin C ratio is associated with all-cause mortality in adult Chinese patients hospitalized with coronavirus disease 2019.

Methods: This study included 933 patients with coronavirus disease 2019 who were admitted to The Affiliated Hospital of Guangdong Medical University between December 2022 and March 2023. All-cause mortality was determined by telephone follow-up after 28 days. Multivariate Cox proportional risk models were used to investigate the relationship between baseline creatinine–cystatin C ratio and all-cause mortality. Restricted cubic spline and two-piecewise Cox proportional hazards risk models were used to identify non-linear correlations.

Results: Of the 933 patients, 128 died during the 28 days follow-up. The restricted cubic spline analysis of hospitalized patients with coronavirus disease 2019 revealed an L-shaped association between baseline creatinine–cystatin C ratio and all-cause mortality, with a threshold creatinine–cystatin C ratio of $\leq$0.93 predicting all-cause mortality. Specifically, a baseline creatinine–cystatin C ratio below this threshold value was negatively correlated with mortality (hazard ratio 0.12, 95 % confidence interval 0.03–0.48), but a creatinine–cystatin C ratio $>$0.93 was not correlated with mortality (hazard ratio 1.29, 95 % confidence interval 0.65–2.55).

Conclusions: In Chinese adult patients hospitalized with coronavirus disease 2019, an L-shaped relationship was observed between the baseline creatinine–cystatin C ratio and all-cause mortality.

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1. Introduction

Coronavirus disease 2019 (COVID-19) poses a serious global public health threat due to its high infectivity [1]. As of March 2023, more than 680 million people had been diagnosed with COVID-19, and the death toll had reached 6.88 million, affecting more than 220 countries, regions, and territories [2]. Therefore, indicators to predict mortality risk in patients with COVID-19 have become a research hotspot.

Sarcopenia is a group of syndromes characterized by a gradual decrease in skeletal muscle quality, strength, and function [3]. Sarcopenia is related to age and is more common in older adults. In addition, diseases, poor nutrition, and lack of exercise can also lead to sarcopenia [4,5]. As one of the common complications of COVID-19, the prevalence of sarcopenia has been estimated at 48.0 % (95 % confidence interval [CI] 30.8%–65.1 %) [6]. Research has shown that sarcopenia can increase metabolic stress, reduce immune function, and result in dysfunction of the muscles related to swallowing and respiration. This may increase COVID-19 infectivity and lead to a poor prognosis in patients with COVID-19 [5,7]. Patients with COVID-19 also suffer from insufficient protein intake and reduced exercise due to social isolation, which leads to a decline in muscle quality and loss of muscle function [8,9]. All in all, this leads to a vicious circle that accelerates the deterioration of patients with COVID-19 [10]. Consequently, early identification of sarcopenia and its associated risk factors in patients with COVID-19 is of crucial importance in clinical practice.

At present, handgrip strength measurement, dual energy X-ray absorptiometry (DXA), and bioelectrical impedance analysis (BIA) are recommended for screening sarcopenia. However, due to their high cost, high radiation exposure, and the need for highly professional personnel for operation, their clinical application is limited [11,12]. The serum creatinine–cystatin C ratio (CCR) can be easily and quickly obtained by collecting serum from hospitalized patients for laboratory testing. Recently, the CCR has been recommended as a new screening tool for sarcopenia. As such, it has gradually become a new research hotspot [13,14]. Moreover, it has been confirmed that CCR is related to the prognosis of certain diseases. For example, an association between CCR and major cardiovascular adverse events has been observed in patients with obstructive coronary artery disease (COPD). Moreover, a relationship between CCR and mortality has also been found in patients with cancer, critically ill patients, and patients undergoing continuous renal replacement therapy [15–17]. Nonetheless, the value of CCR for predicting the prognosis of patients with COVID-19 has not yet been studied. The objective of this study was to assess whether CCR in hospitalized patients with COVID-19 is associated with all-cause mortality.

2. Materials and methods

2.1. Patient selection

We obtained the information of patients with COVID-19 who were admitted to the Affiliated Hospital of Guangdong Medical University from December 2022 to March 2023 (N = 1026). The inclusion criteria were a diagnosis of COVID-19, hospitalization, and written informed consent. The diagnostic standard for COVID-19 is the 2019 Guidelines for the Diagnosis and Treatment of Coronavirus Disease issued by the National Health Commission of China (10th edition) [18]. Telephone follow-up was conducted 28 days later to record the mortality outcomes of the patients. After excluding patients who were aged <18 years (n = 7), were pregnant (n = 5), died upon admission or were transferred to another hospital during hospitalization (n = 10), had incomplete baseline data (n = 60), or were lost to follow-up (n = 11) (Fig. 1), 933 patients were included in the final analysis and provided written informed consent. All of the study procedures were conducted in accordance with the principles outlined in the Declaration of Helsinki. The study was approved by the Medical Ethics Committee of the Affiliated Hospital of Guangdong Medical University (ethics committee number

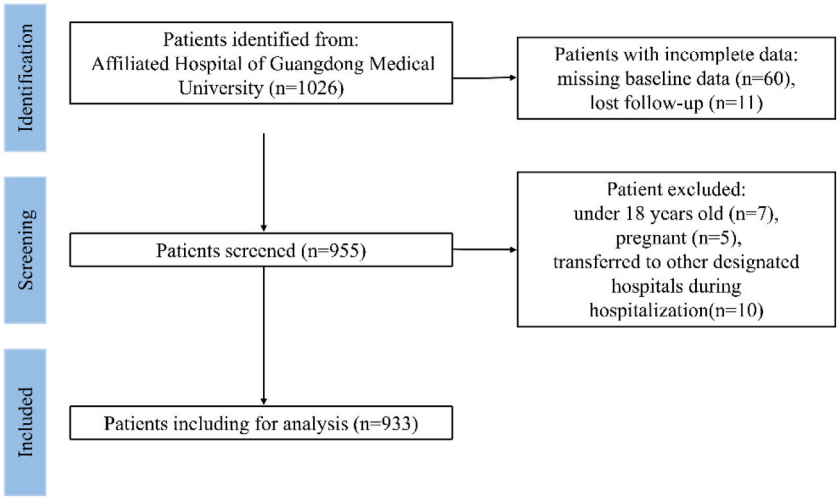

Fig. 1. Flow diagram of the study participants.

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2.2. Data source

2.2.1. Covariate assessment

We obtained the demographic information and clinical data of patients with COVID-19. The demographic data included age and sex, while the clinical data included disease severity (non-severe [mild or moderate cases] or severe [severe or extremely severe cases]), treatments (antiviral drugs, hormones, non-mechanical ventilation [NMV], invasive mechanical ventilation [IMV], or non-invasive mechanical ventilation [NIMV]), comorbidities (coronary atherosclerotic cardiopathy, COPD, carcinoma, diabetes mellitus, renal insufficiency, or cerebral infarction), imaging features (consolidation or ground-glass opacity), and laboratory parameters (white blood cell [WBC] count, hemoglobin, lymphocyte count, C-reactive protein [CRP], procalcitonin, estimated glomerular filtration rate [eGFR], blood urea nitrogen [BUN], serum creatinine [Scr], serum cystatin C [CysC], albumin, D-dimer, activated partial thromboplastin time [APTT], and prothrombin time [PT]).

2.2.2. CCR assessment

CCR was calculated according to the following formula: CCR = Scr (mg/dL) ÷ serum CysC (mg/dL) × 100 %. Scr was determined using the picric acid method, and serum CysC was measured by latex-enhanced immunoturbidimetry. The patients were divided into four groups (Q1–Q4) by CCR quartile, with group Q1 used as the control group.

2.2.3. Ascertainment of mortality

We conducted a 28-day telephone follow-up to assess the survival status of the enrolled patients with COVID-19 and recorded this for the mortality assessment.

2.3. Statistical analysis

R software version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria) was used for the statistical analysis. Categorical variables are expressed as number (percentage). Normally distributed continuous variables are presented as the mean ± standard deviation, while non-normally distributed continuous variables are presented as the median (interquartile range). When comparing the baseline characteristics and all-cause mortality of the CCR quartile groups, one-way analysis of variance and the chi-square test were used to compare continuous and categorical variables, respectively. Subsequently, to reduce the impact of confounding factors, we utilized multivariate Cox proportional hazards regression models to assess the association between baseline CCR and all-cause mortality. Model 1 was not adjusted for any covariates; Model 2 was adjusted for age and sex; and Model 3 was further adjusted for disease severity, treatment, comorbidities, and laboratory and clinical parameters on the basis of Model 2. Multiple imputation was performed on the covariates of the missing values. To assess the non-linear relationship between baseline CCR and mortality, we utilized Cox proportional hazards regression models with restricted cubic splines and smooth curve fitting. If the relationship was non-linear, we chose the most likely inflection point by testing all possible values. We then used a two-piecewise linear Cox proportional risk model. Finally, we performed subgroup analyses of all-cause mortality in patients with COVID-19 to determine the consistency in the correlation between CCR and mortality, considering age (≤65 vs. >65 years), sex (female vs. male), disease severity (non-severe vs. severe), antiviral drug use (yes vs. no), hormone use (yes vs. no), ventilation status (NMV vs. NIMV vs. IMV), renal insufficiency (yes vs. no), and consolidation or ground-glass opacity (yes vs. no). All P values were two-tailed, and $P < 0.05$ was considered statistically significant.

3. Results

3.1. Baseline characteristics

Overall, 933 patients with COVID-19 participated in the study. The baseline characteristics of the patients stratified by CCR quartile are shown in Table 1. Age, sex, clinical type, hormone use, ventilation, Charson comorbidities index (CCI), diabetes mellitus, renal insufficiency, BUN, Scr, CysC, eGFR, and albumin were significantly different among the CCR quartile groups. Compared with the other three groups, participants in the lowest quartile group (Q1) were older, had the highest CCI and eGFR values, had the lowest BUN and Scr values, were more frequently female and with severe disease, and more frequently had renal insufficiency.

3.2. Association between CCR and patient outcomes

The Kaplan–Meier plots revealed that the cumulative 28-day survival probability was significantly lower in the Q1 group than in the other quartile groups (log-rank $P < 0.001$). The cumulative 28-day survival probability sequentially improved with the increasing CCR quartiles (Fig. 2).

3.3. Relationship between CCR and all-cause mortality

Telephone follow-up was conducted after 28-day to record the mortality outcomes of the patients (Table 2). To reduce the impact of

Table 1
Baseline characteristics according to CCR quartiles.

Variables	Total (n = 933)	Q1 (n = 233)	Q2 (n = 234)	Q3 (n = 233)	Q4 (n = 233)	*P* value
CCR	0.93 (0.04–7.62)	0.69 (0.04–0.78)	0.86 (0.78–0.93)	1.02 (0.93–1.14)	1.41 (1.14–7.62)	<0.001
Age (years), mean ± SD	70.46± 14.02	75.88 ± 12.84	73.01± 12.09	69.88 ± 12.86	63.09 ± 14.90	<0.001
Sex, n (%)						<0.001
Male	639 (68.5)	128 (54.9)	155 (66.2)	173 (74.2)	183 (78.5)	
Female	294 (31.5)	105 (45.1)	79 (33.8)	60 (25.8)	50 (21.5)	
Clinical types, n (%)						<0.001
Non-severe case	586 (62.8)	120 (51.5)	145 (62.0)	157 (67.4)	164 (70.4)	
Severe case	347 (37.2)	113 (48.5)	89 (38.0)	76 (32.6)	69 (29.6)	
Using antiviral drug, n (%)						0.855
No	673 (72.1)	168 (72.1)	166 (70.9)	166 (71.2)	173 (74.2)	
Yes	260 (27.9)	65 (27.9)	68 (29.1)	67 (28.8)	60 (25.8)	
Using hormone, n (%)						0.001
No	479 (51.3)	110 (47.2)	110 (47.0)	113 (48.5)	146 (62.7)	
Yes	454 (48.7)	123 (52.8)	124 (53.0)	120 (51.5)	87 (37.3)	
Ventilation, n (%)						0.002
NMV	789 (84.6)	187 (80.3)	201 (85.9)	210 (90.1)	191 (82.0)	
NIMV	52 (5.6)	14 (6.0)	17 (7.3)	12 (5.2)	9 (3.9)	
IMV	92 (9.9)	32 (13.7)	16 (6.8)	11 (4.7)	33 (14.2)	
CCI, mean ± SD	4.99 ± 2.20	5.36 ± 2.22	5.02 ± 2.05	4.78 ± 2.20	4.80 ± 2.28	0.014
Coronary atherosclerotic cardiopathy, n (%)						0.849
No	755 (80.9)	187 (80.3)	189 (80.8)	186 (79.8)	193 (82.8)	
Yes	178 (19.1)	46 (19.7)	45 (19.2)	47 (20.2)	40 (17.2)	
Chronic obstructive pulmonary disease, n (%)						0.051
No	826 (88.5)	202 (86.7)	203 (86.8)	203 (87.1)	218 (93.6)	
Yes	107 (11.5)	31 (13.3)	31 (13.2)	30 (12.9)	15 (6.4)	
Diabetes mellitus, n (%)						0.028
No	697 (74.7)	182 (78.1)	178 (76.1)	180 (77.3)	157 (67.4)	
Yes	236 (25.3)	51 (21.9)	56 (23.9)	53 (22.7)	76 (32.6)	
Cerebral infarction, n (%)						0.062
No	750 (80.4)	175 (75.1)	190 (81.2)	198 (85.0)	187 (80.3)	
Yes	183 (19.6)	58 (24.9)	44 (18.8)	35 (15.0)	46 (19.7)	
Carcinoma, n (%)						0.255
No	887 (95.1)	225 (96.6)	217 (92.7)	222 (95.3)	223 (95.7)	
Yes	46 (4.9)	8 (3.4)	17 (7.3)	11 (4.7)	10 (4.3)	
Renal insufficiency, n (%)						<0.001
No	744 (79.7)	203 (87.1)	201 (85.9)	198 (85.0)	142 (60.9)	
Yes	189 (20.3)	30 (12.9)	33 (14.1)	35 (15.0)	91 (39.1)	
WBC (× 10^9/L), mean ± SD	8.41 ± 15.20	9.74 ± 29.30	7.94 ± 4.80	7.81 ± 4.91	8.16 ± 4.44	0.486
LY (× 10^9/L), mean ± SD	1.56 ± 12.56	2.69 ± 25.03	1.35 ± 2.22	1.12 ± 0.68	1.09 ± 0.70	0.467
CRP (mg/L), mean ± SD	57.48 ± 58.77	54.83 ± 55.23	57.34 ± 63.48	59.42 ± 58.88	58.34 ± 57.44	0.855
PCT (mg/L), mean ± SD	3.26 ± 10.60	2.66 ± 9.45	2.37 ± 7.94	3.13± 8.65	4.90 ± 14.83	0.046
BUN (mg/dL), mean ± SD	8.74 ± 8.29	6.56 ± 3.62	6.79 ± 4.31	7.40 ± 5.54	14.21 ± 13.17	<0.001
Scr (mg/dL), mean ± SD	151.37 ± 218.95	72.93 ± 33.93	91.53 ± 51.42	107.99 ± 76.71	333.30 ± 371.44	<0.001
CysC (mg/dL), mean ± SD	1.43 ± 1.13	1.29 ± 0.57	1.21 ± 0.67	1.19 ± 0.84	2.02 ± 1.79	<0.001
eGFR (mL/min/1.73m^2), mean ± SD	67.65 ± 30.90	81.94 ± 29.60	72.81 ± 22.88	69.01 ± 23.74	46.81 ± 34.67	<0.001
ALB (g/dL), mean ± SD	34.96 ± 5.75	32.85 ± 5.77	35.43 ± 5.15	36.17 ± 5.39	35.39 ± 6.14	<0.001
D-dimer (g/dL), mean ± SD	3.14 ± 5.82	3.62 ± 7.39	3.19 ± 5.44	2.77 ± 5.38	2.98 ± 4.74	0.434
PT (g/dL), mean ± SD	13.95 ± 2.49	14.09 ± 2.36	13.89 ± 2.31	13.75 ± 1.94	14.08 ± 3.19	0.396
APTT (g/dL), mean ± SD	37.74 ± 8.27	38.87 ± 11.22	37.24 ± 6.59	36.90 ± 6.57	37.94 ± 7.75	0.051
Consolidation or ground-glass opacity, n (%)						0.074
No	381 (40.8)	86 (36.9)	86 (36.8)	109 (46.8)	100 (42.9)	
Yes	552 (59.2)	147 (63.1)	148 (63.2)	124 (53.2)	133 (57.1)	

CCR: creatinine-cystatin C ratio; Q1: quartile 1; Q2: quartile 2; Q3: quartile 3; Q4: quartile 4; SD: standard deviation; NMV: non-mechanical ventilation; NIMV: noninvasive mechanical ventilation; IMV: invasive mechanical ventilation; CCI: Charlson Comorbidity Index; WBC: white blood cell; LY: lymphocyte absolute value.
CRP: C-reactive protein; PCT: procalcitonin; BUN: blood urea nitrogen; Scr: serum.

creatinine; CysC: cystatin C; eGFR: estimated glomerular filtration rate; ALB: albumin; PT: prothrombin time; APTT: activated partial thromboplastin time.

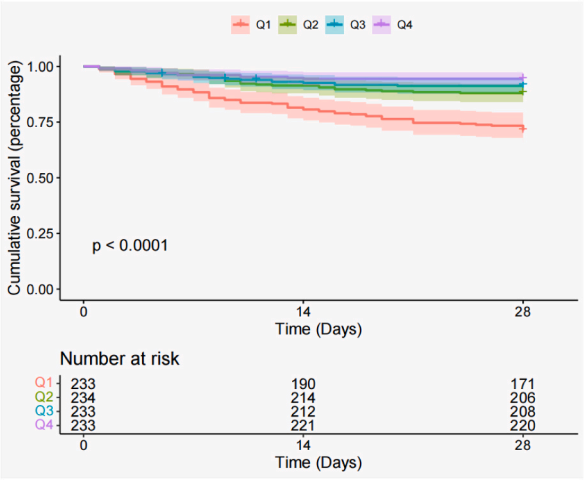

Fig. 2. Kaplan–Meier curves of 28 days survival stratified to CCR quartiles.

Table 2
Risk association between CCR and all-cause mortality.

	Quartiles of CCR				
	Q1 (0.04–0.78)	Q2 (0.78–0.93)	Q3 (0.93–1.14)	Q4 (1.14–7.62)	*P* trend
All-cause mortality Number of deaths	67 (28.8)	28 (12.0)	20 (8.6)	13 (5.6)	
Model 1					
HR (95 % CI),	1	0.38 (0.25, 0.59)	0.27 (0.17, 0.45)	0.17 (0.10, 0.32)	<0.001
P		<0.001	<0.001	<0.001	
Model 2					
HR (95 % CI),	1	0.40 (0.26, 0.63)	0.31 (0.19, 0.52)	0.23 (0.12, 0.44)	<0.001
P		<0.001	<0.001	<0.001	
Model 3					
HR (95 % CI),	1	0.53 (0.33, 0.86)	0.42 (0.24, 0.73)	0.15 (0.07, 0.33)	<0.001
P		0.009	0.002	<0.001	

Model 1: unadjusted.
Model 2: age, sex.
Model 3: age, sex, clinical types, using antiviral drug, using hormone, ventilation, CCI, renal insufficiency, consolidation or ground-glass opacity, WBC, CRP, PCT, ALB, BUN, D-dimer, PT, APTT.
CCR: creatinine-cystatin C ratio; HR: hazard ratio; CI: confidence interval; Q: quartile; Q1: quartile 1; Q2: quartile 2; Q3: quartile 3; Q4: quartile 4.

confounding factors, we conducted multivariate Cox proportional hazards regression models. Three models were used to assess the independent association between baseline CCR and all-cause mortality (Table 2). In Model 3, after adjustment for age, sex, clinical type, antiviral drug use, hormone use, ventilation, CCI, renal insufficiency, consolidation or ground-glass opacity, WBC count, CRP, procalcitonin, serum CysC, albumin, BUN, D-dimer, PT, and APTT, the multivariate-adjusted hazard ratios (HRs) for all-cause mortality and their 95 % CIs from the lowest to the highest CCR quartile (0.04–0.78, 0.78–0.93, 0.93–1.14, and 1.14–7.62) were 1.00 (control group), 0.55 (0.33, 0.86), 0.42 (0.24, 0.73), and 0.15 (0.07, 0.33), respectively.

3.4. Detection of non-linear relationships

Interestingly, when using the Cox proportional hazards regression models with restricted cubic splines and smooth curve fitting to investigate whether there was a non-linear relationship between CCR and all-cause mortality, we identified an approximate L-shaped relationship between them (Fig. 3). We then used two-piecewise Cox proportional hazards regression models and subsequently identified that the CCR inflection point for all-cause mortality was 0.93 (Table 3). Specifically, after adjusting for age, sex, clinical type, antiviral drug use, hormone use, ventilation, CCI, renal insufficiency, consolidation or ground-glass opacity, WBC count, CRP, procalcitonin, serum CysC, albumin, BUN, D-dimer, PT, and APTT, mortality was negatively correlated with CCR when CCR was ≤0.93. The all-cause mortality risk decreased by around 60 % (HR 0.40, 95 % CI 0.22–0.71) with each unit increase in CCR on the left side of

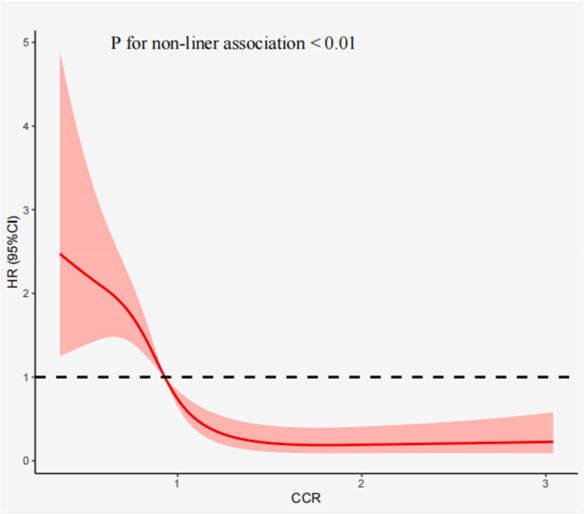

Fig. 3. Association between CCR and all-cause mortality in hospitalized patients with COVID-19.

Table 3
Threshold effect analysis of CCR on all-cause mortality in hospitalized 40 COVID-19 patients.

All-cause mortality	Adjusted HR (95 % CI)	P value
Total	0.40 (0.22, 0.71)	
Fitting by two-piecewise Cox proportional risk		
ModelInflection point	0.93	
≤0.93	0.12 (0.03, 0.48)	<0.003
>0.93	1.29 (0.65, 2.55)	0.467

Adjusted: age, sex, clinical types, antiviral drug, hormone, ventilation, CCI, renal insufficiency, ground glass nodule, WBC, CRP, PCT, ALB, BUN, D-dimer, PT, APTT.
CCR: creatinine-cystatin C ratio; COVID-19: coronavirus disease 2019; HR: hazard.
ratio; CI: confidence interval.

this threshold. Furthermore, the baseline CCR threshold represented the lowest risk of all-cause mortality (Table 3, Fig. 3). However, baseline CCR was not related to all-cause mortality when >0.93 (HR 1.29, 95 % CI 0.65–2.55, $P = 0.467$).

3.5. Subgroup analysis

We performed subgroup analyses of all-cause mortality in patients with COVID-19 to determine the consistency in the correlation between CCR and mortality while accounting for age (≤65 vs. >65 years), sex (female vs. male), disease severity (non-severe vs. severe), antiviral drug use (yes vs. no), hormone use (yes vs. no), ventilation status (NMV vs. NIMV vs. IMV), renal insufficiency (yes vs. no), and consolidation or ground-glass opacity (yes vs. no) (Table 4). The results showed no significant interaction between baseline CCR and other stratified variables except for ventilation status (NMV vs. NIMV vs. IMV) ($P > 0.05$).

4. Discussion

In this study, we investigated a sample of 933 hospitalized patients with COVID-19 between the ages of 19 and 101 years to evaluate the association between baseline CCR and all-cause mortality. To our knowledge, this is the first study to investigate the relationship between CCR and all-cause mortality in patients with COVID-19. Our results demonstrated an approximate L-shaped relationship between baseline CCR and all-cause mortality in hospitalized patients with COVID-19 in the Chinese population, with a threshold of 0.93 for predicting all-cause mortality. Specifically, baseline CCR below this threshold was negatively correlated with mortality, but when CCR exceeded 0.93, it was not correlated with mortality. These findings suggest that baseline CCR has the potential to predict mortality risk among hospitalized patients with COVID-19.

Previous studies have reported that CCR is an important independent predictor that can be used to assess hospitalization risk in patients with COPD and predict the long-term prognosis of critically ill neurological patients [19,20]. In addition, CCR is associated with the risk of death in patients with cancer, COPD with acute exacerbation and hospitalization, and chronic kidney disease with and without dialysis, as well as in patients in the intensive care unit [16,21]. In the present study, CCR could also predict the risk of all-cause mortality in hospitalized patients with COVID-19.

Table 4
Stratified analyses of the associations between CCR and all-cause mortality.

Characteristic	HR (95%CI)	*P* interaction
Age		0.367
≤65	0.40 (0.08, 1.98)	
>65	0.36 (0.21, 0.61)	
Gender		0.520
Male	0.13 (0.03, 0.51)	
Female	0.51 (0.30, 0.88)	
Clinical types		0.561
Non-severe case		
Severe case	0.59 (0.36, 0.96)	
Using antiviral drug		0.096
No	0.56 (0.30, 1.03)	
Yes	0.21 (0.08, 0.54)	
Using hormone		0.912
No	0.30 (0.12, 0.71)	
Yes	0.40 (0.22, 0.75)	
Ventilation		<0.001
NMV	0.35 (0.19, 0.67)	
NIMV	0.69 (0.09, 5.51)	
IMV	0.37 (0.12, 1.13)	
Renal insufficiency		0.328
No	0.38 (0.20, 0.71)	
Yes	0.74 (0.32, 1.70)	
Consolidation or ground-glass opacity		0.136
No	0.20 (0.07, 0.57)	0.393
Yes	0.48 (0.27, 0.85)	

Above subgroups were adjusted for age, sex, clinical types, antiviral drug, hormone. ventilation, CCI, renal insufficiency, consolidation or ground-glass opacity, WBC, CRP. PCT, ALB, BUN, D-dimer, PT, APTT, except for its stratified variables. CCR. creatinine-cystatin C ratio; HR: hazard ratio; CI: confidence interval; NMV: non-. mechanical ventilation; NIMV: noninvasive mechanical ventilation; IMV: invasive. mechanical ventilation.

Because of its simple operation and low cost, CCR has the potential to become a new screening indicator for sarcopenia [12,22]. Research has shown that sarcopenia development is accompanied by a decline in muscle mass and strength, and systemic inflammatory storms, reduced physical exercise, and malnutrition are important factors affecting muscle function [23,24]. COVID-19 affects multiple physiological processes, including increased muscle consumption caused by systemic inflammatory storms, reduced physical exercise leading to social isolation, and insufficient nutrition intake due to anorexia and loss of smell [6,25]. These are some of the reasons for the high incidence of sarcopenia in patients with COVID-19 [6]. On the contrary, sarcopenia can weaken respiratory muscle strength, thereby affecting respiratory function, which worsens severe pneumonia and exacerbates acute respiratory distress syndrome [26]. In addition, sarcopenia affects the muscles used to swallow, which increases the risk of aspiration pneumonia in patients with COVID-19 who are bedridden [27,28]. As a result, the increase in disease severity in patients with COVID-19 may lead to an increase in mortality. Moreover, in the chronic inflammatory state, the WBC count and the serum CysC concentration increase, while the Scr concentration decreases. Therefore, CCR, as the ratio of Scr to CysC, reflects the inflammatory state of the body [29]. The cytokine storm driven by coronavirus generates a large number of inflammatory cytokines, which severely damage the organs, including the lungs, heart, and kidneys, thus resulting in a high mortality rate in patients with COVID-19 [30]. Therefore, the inflammatory storm is accompanied by a high mortality rate and a low CCR. Overall, CCR may be associated with changes in Scr and serum CysC concentrations mediated by sarcopenia and the inflammatory storm. Thus, CCR may serve as a predictor of mortality in patients with COVID-19. Hence, routine assessment of CCR in the management of hospitalized patients with COVID-19 may be helpful to achieve early sarcopenia intervention, thus reducing mortality.

Our findings have relevant clinical implications and strengths. As CCR can be quickly calculated from laboratory test results on admission, clinicians may be able to identify high-risk patients with COVID-19 at an early stage. Thus, treatment strategies can be modified accordingly to reduce the mortality of hospitalized patients with COVID-19. As this is an observational study and is susceptible to various confounders, we adopted strict methods of statistical adjustment to minimize potential confounding. In addition, we tested the robustness of the results by repeating the analyses by CCR quartiles and in different subgroups stratified by age, sex, disease severity, antiviral drug and hormone use, ventilation status, history of renal insufficiency, and imaging features with and without consolidation or ground-glass opacity.

This study also has some limitations that should be considered. First, although we adjusted for the impact of confounding factors in the multivariate analysis, there were still residual confounding factors that may have affected the prognosis of patients with COVID-19. Second, this study lacked data on traditional tools for evaluating sarcopenia, including CT, DXA, and BIA, which limits the interpretation of the relationship between CCR and sarcopenia. Third, this study only evaluated the relationship between baseline CCR and mortality, without assessing the prognostic value of changes in CCR during follow-up. Therefore, the dynamic changes in CCR deserve

further analysis. Four, there was an interaction between baseline CCR and ventilation status in subgroup analyses. Given these limitations, we need well-designed multi-center prospective trials with larger sample sizes to validate our findings. Finally, further studies are needed to determine whether the conclusions of this study are also applicable to populations outside of Guangdong Medical University Affiliated Hospital.

5. Conclusions

In conclusion, CCR on admission to the hospital was closely related to all-cause mortality in hospitalized patients with COVID-19, showing an approximate L-shaped relationship. When the CCR was $\leq$0.93, mortality was negatively correlated with CCR. CCR may be considered a potentially useful predictive indicator of all-cause mortality in hospitalized patients with COVID-19. However, further validation of the relationship between CCR and all-cause mortality is needed for its generalized application.

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Ethics approval and consent to participate

The research was approved by the Ethics Committee of the Affiliated Hospital of Guangdong Medical University (PJ2020-026). All participants provided written informed consent for participation. No image of any patient was used in this study. Permission for the retrieval of patient data from the Hospital Information System was granted by the ethics committee. Patients' identifiable information, such as names, telephone numbers, and addresses, was not extracted from the Hospital Information System because of privacy concerns.

Data availability statement

The original data of this study have not been deposited into a publicly available repository, but the data are available from the corresponding author upon reasonable request.

CRediT authorship contribution statement

Dong Wu: Writing – original draft. **Jiahao Cao:** Writing – original draft. **Yiyan Lin:** Methodology. **Xiaoer Chen:** Investigation. **Bingyu Long:** Validation, Formal analysis. **Bangxiao Huang:** Data curation. **Gege Liu:** Formal analysis. **Xiaofang Fu:** Project administration. **Bin Wu:** Supervision. **Dan Huang:** Writing – review & editing. **Yuanli Zhang:** Supervision. **Duolao Wang:** Writing – review & editing, Supervision. **Xuanna Zhao:** Writing – review & editing, Supervision, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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