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The association between baseline viral load and long-term risk in patients with COVID-19 in Hong Kong: a territory-wide study

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COVID-19 can increase the long-term risk of multiorgan dysfunction. Few studies investigated the long-term risk in Asian populations or investigated the association between viral load and long-term risk. We aimed to investigate the post-discharge rates of hospitalization and association with baseline viral load in all patients with COVID-19 in Hong Kong. This was a population-based cohort study included all patients with a positive RT-PCR test for SARS-CoV-2 in Hong Kong between January 1st 2020 and August 30th 2020, routinely admitted to public health care facilities for isolation and treatment. Viral Ct values were available in 3433 (85%) of patients. Outcomes of interest included death, cause-specific hospitalizations, and initiation of medication from the Hospital Authority's territory-wide electronic health records from the Clinical Data Analysis and Reporting System. In total, 4054 people in Hong Kong tested positive for COVID-19 and were admitted to a public health care facility, of whom 167 (4.1%) were admitted to ICU. During a median follow-up time of 251 (interquartile range 240–279) days, 408 (11.9%) were hospitalized for any reason and 16 (0.5%) patients died. After discharge, patients were most often readmitted for respiratory reasons, followed by gastro-intestinal reasons. A higher viral load (lower RT-PCR Ct values) was associated with a higher likelihood of death (Hazard ratio [HR] 5.86, 95% Confidence interval [CI] 2.57–13.33), hospitalization (HR 1.22, 95%CI 1.08–1.39) or hospitalization for cardiovascular disease (HR 12.78, 95%CI 3.67–44.48). Patients with higher viral loads more likely started ACE-inhibitors (HR 1.37, 95%CI 1.12–1.68) and non-opioid analgesics (HR 1.01, 95%CI 1.01–1.23). In a relatively mild COVID-19 population from Hong Kong, the post-acute risk of complications was substantial. Our results highlight that higher viral load predict post-acute complications in patients with relatively mild disease.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), responsible for causing coronavirus disease 2019 (COVID-19), has directly or indirectly affected the global population and caused a total of 2.9 million deaths to date. In the early stages of the pandemic, research and health services have predominantly focused on the immediate direct (through infection) and indirect (changes in behaviours and effect on health systems) effects of the virus¹.

While COVID-19 predominantly manifests as respiratory disease, there is increasing evidence of other organ involvement, including the heart². A prospective cohort study of 201 young low-risk individuals showed that

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almost 70% of participants had ongoing impairment of multiple organ systems³. In Wuhan, a sample of 1733 patients were followed up after discharge and reported mainly muscle fatigue and lethargy⁴.

Viral load measurements from nasopharyngeal swabs indicate active viral replication^{5,6}. Previous studies indicated that higher SARS-CoV-2 viral loads at presentation were independently associated with in-hospital mortality, or intubation^{5–9}. Furthermore, a higher viral load is associated with an increased risk of post-COVID-19 syndrome¹⁰. A previous systematic review found that respiratory virus real-time polymerase chain reaction cycle threshold (ct) values are associated with disease severity and outcomes¹¹. However, few studies investigated the association between SARS-CoV-2 viral loads at presentation and long-term outcomes or hospitalization in mild populations. Therefore, we studied the association of SARS-CoV-2 viral load with long-term outcomes in patients with COVID-19 in Hong Kong.

Methods

Data source

COVID-19 patients were identified using the Clinical Data Analysis and Reporting System (CDARS). CDARS is an electronic healthcare database developed by the Hospital Authority. The Hospital Authority is a statutory body that manages all public hospitals and public clinics in Hong Kong, covering over 80% of Hong Kong's population. In Hong Kong, all people testing positive for COVID-19 are admitted to hospital for isolation. Therefore, the included study population in CDARS represent all patients with proven COVID-19, regardless of disease severity. Electronic patient records include demographics, diagnoses date and disease coding, hospital admission and discharge dates, drug prescriptions and dispensing records, laboratory test results, and date of registered death for research and audit purposes. All patients were anonymised in this system, thus sensitive information such as name and ID were not accessible. The coding accuracy of CDARS has been well-validated and published previously^{12–17}.

The study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (reference number: UW 21-436) and the need for informed consent was waived by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster. This study was conducted under the principles of the Declaration of Helsinki.

Study design and patients selection

This is a population-based retrospective cohort study. COVID patients were identified based on a positive SARS-CoV-2 RT-PCR test or disease classification (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code: 079.89, 480.8, 519.8) between January 1, 2020, and August 31, 2020. Patients who tested positive on ART, but negative on RT-PCR were excluded. Demographic information, date of the first positive lab result, baseline medication, baseline comorbidities, baseline laboratory result, admission date and principal diagnosis during follow up, and other clinical information were extracted from CDARS.

The index date was defined as the first date of positive PCR test. Follow-up started from the date of discharge until the occurrence of outcome, death, or study end (2021-04-13). Patients aged < 18 years at the index date or who died during hospitalisation were excluded.

Outcome

The main outcome of this study were all-cause mortality and all-cause re-hospitalisation after COVID discharge. Secondary outcomes included cause specific hospitalizations and new-onset medication use. Cause specific hospitalizations included hospitalization for respiratory reasons, gastro-intestinal reasons, mental/psychiatric reasons and cardiovascular reasons. Supplementary Table 1 shows details on the ICD codes used for each outcome. New onset medication use included angiotensin receptor blocker (ARB), beta-blockers (BBs), calcium channel blockers (CCBs), statins, anti-depressants, aspirin and non-steroidal anti-inflammatory drugs (NSAIDs). Supplementary Table 2 provides a detailed overview of the coding used to identify medications.

Statistical analysis

Baseline characteristics of all included patients were presented. Mean and standard deviation (SD) were used to present continuous variables, frequencies and percentages were used to present categorical variables. Normality of continuous variables was evaluated by visualizing histograms and inspecting the distribution. The incidence was presented as the rate per 100 person-year with the 95% confidence interval. We modelled the association of baseline viral load (CT values) as continuous variables with the risk of death, total- and cause-specific hospitalizations using restricted cubic splines and Cox regression analyses. We fitted models with 2–5 knots and chose the optimal number of knots for each spline using the Akaike Information Criterion. (AIC). Because we found a non-linear increase in risk with lower CT values for most outcomes, we dichotomized the CT values based on a cut-off point identified from the restricted cubic splines. To account for factors associated with higher viral loads, we weighed the hazards by balancing weights calculated from the propensity scores using the CBPS package^{18,19}. We dichotomized the CT values according to the median and calculated propensity scores using the dichotomized CT values as the dependent variable. Supplementary Table 3 provides a full list of variables used for weighting, including age, sex, medical history, baseline medication and intensive care unit (ICU) stay. Variables for the multivariable models were included based on clinical relevance and data availability. All analyses were performed using R, version 4.0.5 (2021-03-31) and a two-sided *P* value of < 0.05 was considered statistically significant.

Results

Baseline characteristics

Figure 1 depicts the consort diagram on patient inclusion. A total of 4,602 patients with COVID-19 were identified in CDARS between 1 Jan 2020 to 31 Aug 2020. Patients aged < 18 years ($n = 440$) and who died before discharge ($n = 108$) were excluded. Out of the remaining 4054 patients, 3433 (85%) patients had CT values.

Table 1 shows the baseline characteristics of the 4054 patients with COVID-19 discharged alive. The median age was 47 (interquartile range [IQR] 32–60) years and 49.2% ($n = 1995$) were men. Most patients had a low prevalence of comorbidities. Diabetes was the most common comorbidity, followed by a history of ischemic heart disease. Calcium channel blockers (CCBs) and statins were the most common medication at baseline. 4.1% of patients were admitted to ICU. The median ICU stay was 9 (IQR 5–15) days.

Outcomes and association with viral load

Table 2 shows the event rates of patients discharged alive. During a median follow up of 251 (IQR 240–279) days, 16 patients died, and 408 patients were rehospitalized. The incidence rate of death was 0.47 (95% confidence interval [CI] 0.27–0.764) per 100 patient years (py) and 11.88 (95% CI 10.76–13.1) per 100 py for hospitalization for any reason. The most common reason for rehospitalization was respiratory, followed by gastro-intestinal, mental and cardiovascular reasons.

Figure 2 depicts the restricted cubic splines for the association of CT values at presentation with death, total- and cause-specific hospitalization. We found a non-linear association of higher of lower CT values with a higher relative risk of death, total hospitalization and cardiovascular hospitalization ($P < 0.001$ for all), but not for mental, respiratory and GI hospitalizations. The risk for death, total and CV and respiratory hospitalizations decreased linearly until 20 repeats, after which the relative risk fell to 1.

Table 3 shows results of the association between dichotomized CT values (< 20 repeats versus ≥ 20 repeats) and the different outcomes, weighed for probability weights using propensity scores. We observed that patients with high viral loads (< 20 CT repeats) were at a higher risk for death, total hospitalization, and CV hospitalization than those with lower viral loads (≥ 20 CT repeats). Patients with high viral loads more likely started ACE-inhibitors than patients with lower viral loads (≥ 20 repeats).

Discussion

In our study, we found that post-discharge rehospitalization for patients with COVID-19 in Hong Kong were common. Higher SARS-CoV-2 viral loads at admission were associated with an increased likelihood of post-discharge death or rehospitalization, particularly for myocardial infarction or stroke, independent of initial ICU stay. Early risk stratification for long-term dismal outcomes after COVID-19 infection remains a challenge. Our results suggest that patients with higher viral loads at admission might benefit from close follow-up, early initiation of treatment and a holistic and multidisciplinary long-term care plan.

In Hong Kong, one in ten patients with COVID-19 were rehospitalized during a median follow-up of 251 days. In the United Kingdom, over a third of patients admitted for COVID-19 were readmitted and more than 1 in 10 died after discharge²⁰. Strict lockdown measures and quarantine orders in Hong Kong have kept COVID-19 numbers lower in Hong Kong than most other countries²¹. Therefore, all COVID-19 patients in Hong Kong who

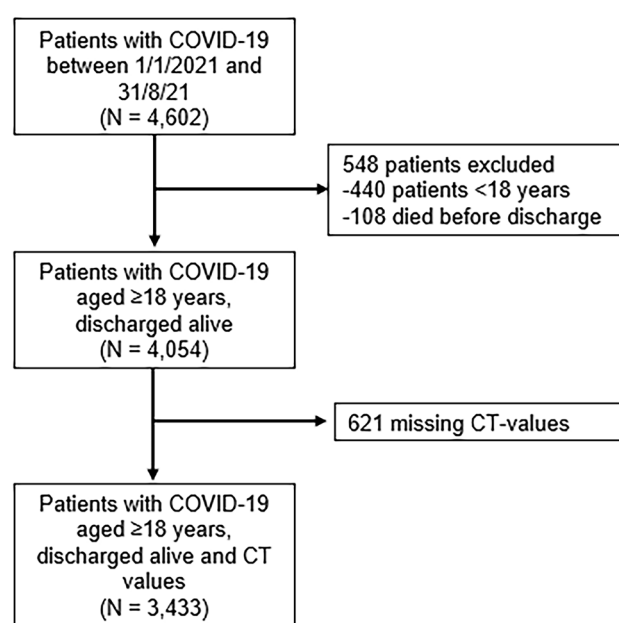


Figure 1. CONSORT diagram.

N	4054
Age, median (IQR)	47 (32,60)
Men, n (%)	1995 (49.2%)
AF (n, %)	25 (<1%)
Cancer (n, %)	51 (1.3%)
Dementia (n, %)	7 (<1%)
Diabetes mellitus (n, %)	258 (6.4%)
Hypertension (n, %)	492 (12.1%)
Ischemic heart disease (n, %)	70 (1.7%)
Kidney disease (n, %)	19 (<1%)
Hyperlipidaemia (n, %)	259 (6.4%)
Liver disease (n, %)	39 (<1%)
Mental disease (n, %)	117 (2.9%)
Obesity (n, %)	106 (2.6%)
Smoking-related disease (n, %)	10 (<1%)
Vascular disease (n, %)	61 (1.5%)
ACEI (n, %)	194 (4.8%)
Antibiotic (n, %)	396 (9.8%)
Antiplatelet (n, %)	30 (<1%)
ARB (n, %)	177 (4.4%)
Aspirin (n, %)	188 (4.6%)
BB (n, %)	242 (6.0%)
CCB (n, %)	507 (12.5%)
Statin (n, %)	451 (13.1%)
Diuretics (n, %)	93 (2.7%)
Analgesic (n, %)	17.42 (21.4%)
Antianxiety (n, %)	1321 (32.6%)
Antidepressant (n, %)	95 (2.3%)
Antiemetic (n, %)	115 (2.8%)
Anti-epileptic drug (n, %)	280 (6.9%)
Dementia drug (n, %)	57 (1.4%)
Others CNS drugs (n, %)	8 (<1%)
CNS stimulant (n, %)	2 (<1%)
Parkinson disease drugs (n, %)	2 (<1%)
Psychosis drug (n, %)	36 (<1%)
Substance abuse drugs (n, %)	133 (3.3%)
Beta agonist (n, %)	3 (<1%)
Inhaled steroid (n, %)	87 (2.2%)
Anti-muscarinic (n, %)	30 (<1%)
Theophylline (n, %)	12 (<1%)
Other beta agonist (n, %)	12 (<1%)
ICU (n, %)	167 (4.1%)
ICU Days, median (IQR)	9 (5,15)

Table 1. Baseline characteristics. *ACEI* ACE-inhibitor, *AF* atrial fibrillation, *ARB* angiotensin receptor II blocker, *BB* beta-blocker, *CCB* calcium channel blocker, *CNS* central nervous system, *ICU* intensive care unit.

test positive on RT-PCR, are isolated in hospitals or community facilities. The CDARS data represents all patients with COVID-19 in Hong Kong registered with the Hospital Authority, which includes a substantial number of asymptomatic individuals. This explains the lower numbers of post-discharge death and rehospitalization in Hong Kong than the UK. However, in a large study from the Veterans Health Administration among 73,435 uses with COVID-19 who were not hospitalized and survived the first 30 days after diagnosis, the risk of long-term rehospitalization and death was still higher than matched negative-controls, particularly for respiratory signs and symptoms and incident hypertension²².

Various studies indicated that higher SARS-CoV-2 viral loads at presentation was independently associated with in-hospital mortality, or intubation^{5–9}. Respiratory and plasma viral loads of SARS-CoV-2 predicted the risk of in-hospital death, predominantly due to pneumonia⁵. This was confirmed in a 3,014 patients hospitalized in 3 large New York City hospitals⁶. All of these previous studies^{5–9} were performed in countries with a more significant burden of the epidemic and consequently higher admission threshold than Hong Kong and did not

	Incidence rate per 100 py (95%CI)	N (%)
Death	0.47 (0.27, 0.76)	16 (<1%)
Hospitalization	11.88 (10.76, 13.1)	408 (11.9%)
Respiratory	4.46 (3.78, 5.22)	153 (4.5%)
GI	1.46 (1.08, 1.92)	50 (1.5%)
Mental hospitalization	0.06 (0.01, 0.21)	2 (<1%)
CV hospitalization	0.32 (0.16–0.57)	11 (<1%)
Medication		
Non-opioid analgesic	19.63 (18.18, 21.17)	674 (19.6%)
NSAID	7.78 (6.87, 8.77)	267 (7.8%)
Antiplatelet	0.06 (0.01, 0.21)	2 (<1%)
ACEi	4.98 (4.26, 5.79)	171 (5.0%)
ARB	5.56 (4.8, 6.41)	191 (5.6%)
Aspirin	5.48 (4.72, 6.32)	188 (5.5%)
BB	6.32 (5.51, 7.22)	217 (6.3%)
CCB	15.38 (14.1, 16.75)	528 (15.4%)
Thiazide diuretics	0.58 (0.36, 0.9)	20 (<1%)
Other diuretics	1.81 (1.38, 2.32)	62 (1.8%)
Statin	13.11 (11.92, 14.38)	450 (13.1%)
Anti-depressants	3.47 (2.87, 4.15)	119 (3.5%)

Table 2. Event rates. *ACEi* ACE-inhibitor, *AF* atrial fibrillation, *ARB* angiotensin receptor II blocker, *BB* beta-blocker, *CCB* calcium channel blocker, *CV* cardiovascular, *GI* gastro-intestinal.

include long-term outcome. The current study is unique, due to its large representative sample size, inclusion of long-term outcomes and many asymptomatic patients. To our knowledge, we are the first to report on the association of viral load and long-term outcomes in patients with COVID-19.

We found that higher viral loads (lower CT-values) independently predicted death, total rehospitalization and rehospitalization for stroke or myocardial infarction, independent of ICU stay. In a previous study from the United States²², patients discharged after hospitalization for COVID-19 had an increased risk of CV conditions after discharge²². Similar results were observed in the United Kingdom in patients after discharge for hospitalization with more severe COVID-19²⁰. A recent study in Sweden confirmed the increased risk of incident stroke and myocardial infarction in patients who recovered from COVID-19²³. In our study, a higher viral load was associated with an increased risk of hospitalization for myocardial infarction, chest pain, and stroke. We also found that higher viral loads were associated with an increased risk of incident ACEi use. However, these associations were non-linear, such that the risk for death, hospitalization and medication use decreased linearly until 20 repeats, after which the relative risk remained stable at 1. Literature on cut-off values for CT repeats is not conclusive⁹, but many studies considered a viral load < 25 CT values as high⁹. Patients with a high viral load commonly also have more severe disease^{5–9}. However, we did not find a significant interaction between viral load and ICU stay for any of the outcomes.

A discussion on the potential mechanisms of the association between higher viral loads and increased myocardial infarction and stroke risk is warranted. COVID-19 infection creates a pro-thrombotic state²⁴. Several previous publications suggested that this prothrombotic phenotype might be mediated by ACE2^{25,26}. SARS-CoV2 enters the host cell by binding to ACE2, similar to other Corona viruses²⁵, leading to enhanced shedding of ACE2 and release of soluble protein. Decreased ACE2 activity is potentially thrombogenic through angiotensin-2 activity and plasminogen activator inhibitor-1 expression²⁷. Increased ACE2 plasma levels, potentially reflecting excess shedding, were associated with an increased risk of myocardial infarction and stroke in the PURE study²⁸. Our study suggests that increased viral loads in patients with COVID-19 are associated with an increased risk of myocardial infarction and stroke, potentially mediated through reduced ACE2 activity. The results of our study might have several important clinical implications. First, our results suggest that viral load should not only be used for increased risk stratification but might also be a good indicator for the risk of long-term outcomes. Second, in the post-vaccination era, more patients will have milder disease. Therefore, future studies should investigate whether COVID-19. While our results indicate the association between COVID-19 viral load and long-term clinical outcomes, future prospective studies, including those accounting for vaccination, should confirm our findings-19 that viral loads are related to long-term risk in those with milder disease post-vaccination.

Limitations

The strength of our study was the inclusion of all patients with COVID-19 in Hong Kong, from a real-world cohort with a wide spectrum of disease severity. A limitation of the current analyses is that viral load measurements were missing in 16% of patients. Ascertainment bias might have affected the reliability of the study due to inaccurate entry of certain diagnosis codes for comorbidities, namely DM, and hypertension. Socioeconomic status was not available for many of the patients. However, because all patients with COVID-19 were mandated

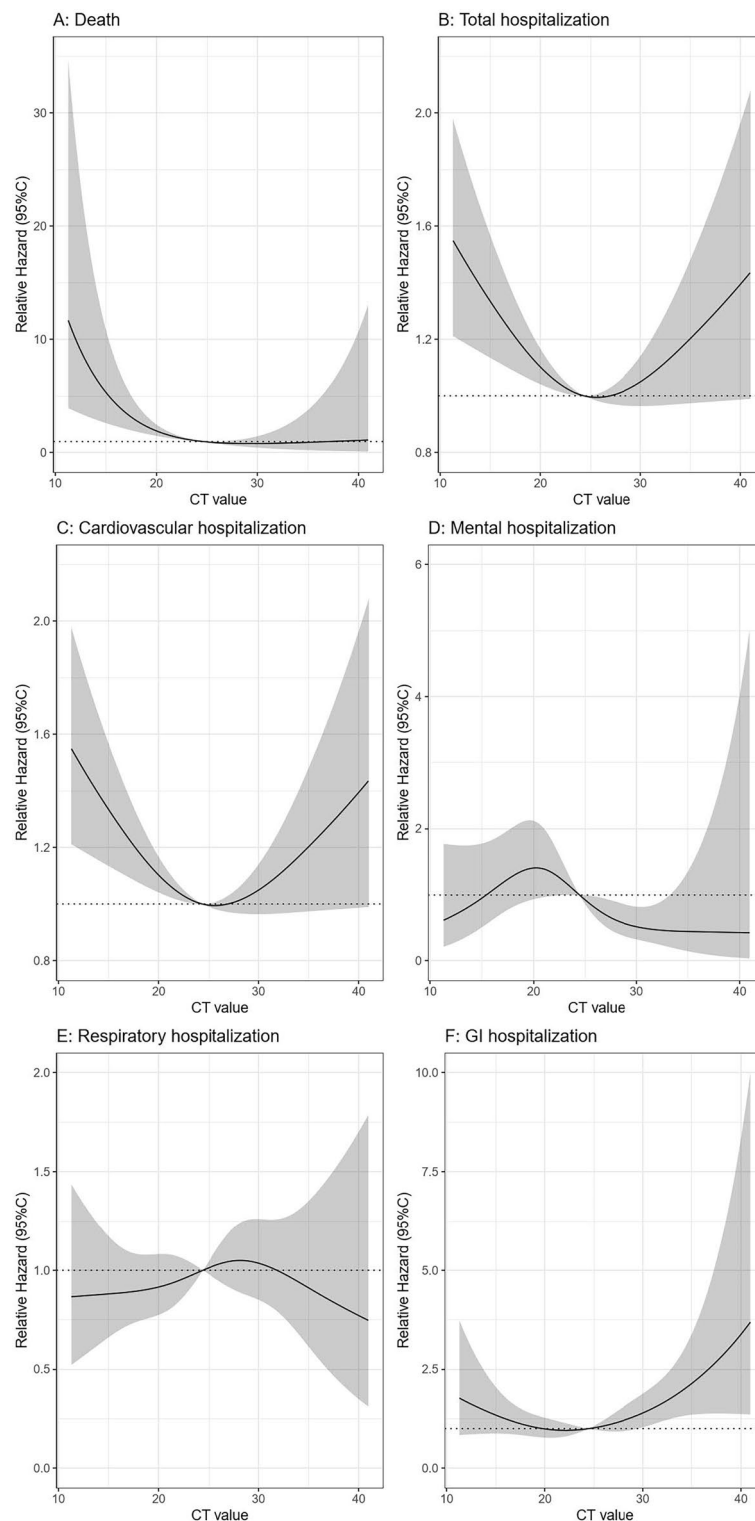


Figure 2. Splines showing the association between CT values (viral load) and the relative risk of death (A), any hospitalization (B), cardiovascular hospitalization (C), hospitalization for mental reasons (D), respiratory hospitalization (E) or hospitalization for gastro-intestinal reasons (F).

to be hospitalized, this will likely not have influenced our results. Finally, some patients might have had laboratory tests performed outside of the public hospitals. Patient-reported outcome measurements (PROMs) and cognitive status measurements were not available for this study, which can provide valuable insights into patient

	HR (95%CI)	P value
Death	5.86 (2.57–13.33)	<0.001***
Hospitalization	1.22 (1.08–1.39)	<0.01**
Respiratory	0.99 (0.80–1.24)	0.95
GI	0.87 (0.62–1.22)	0.41
Mental hospitalization	1.50 (0.95–2.39)	0.09
CV hospitalization	12.78 (3.67–44.48)	<0.001***
Medication		
Non-opioid analgesic	1.11 (1.01–1.23)	<0.05*
NSAID	1.17 (0.99–1.37)	0.07
Antiplatelet	1.43 (0.92–2.21)	0.11
ACEi	1.37 (1.12–1.68)	<0.01**
ARB	0.97 (0.81–1.16)	0.72
Aspirin	1.05 (0.88–1.25)	0.61
BB	1.03 (0.87–1.23)	0.71
CCB	1.11 (0.99–1.24)	0.07
Thiazide diuretics	1.17 (0.65–2.11)	0.61
Other diuretics	1.33 (0.98–1.80)	0.07
Statin	1.08 (0.96–1.22)	0.20
Anti-depressants	1.11 (0.86–1.42)	0.44

Table 3. Cox regression analyses for outcomes in patients with higher (<20 CT values) compared to lower (≥ 20 CT values) viral loads. ACEi ACE-inhibitor, AF atrial fibrillation, ARB angiotensin receptor II blocker, BB beta-blocker, CCB calcium channel blocker, CV cardiovascular, GI gastro-intestinal.

outcomes²⁹. It is unclear how results from Hong Kong validate in other geographic regions. Unfortunately, costing variables were not available for this paper and not included in the analyses.

Conclusion

In Hong Kong, rehospitalization after discharge for COVID-19 infection was common, especially for respiratory and gastro-intestinal reasons. A higher viral load at diagnosis is an independent risk factor for death, all-cause rehospitalization and CV rehospitalization, particularly in patients with CT values < 20. Our results can inform global discussion on the post-acute manifestations of COVID-19 and risk stratification of patients based on their viral load.

Data availability

The datasets used in the main manuscript or additional supporting files during the current study are available from the corresponding author at reasonable request.

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Author contributions

J.T., M.W., W.O., C.S.P., K.H.Y. conceived the study and wrote the main manuscript. J.T., M.W. performed analyses. All authors reviewed the manuscript and made critical revisions.

Competing interests

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Additional information

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