Mass Screening Is Associated with Low Rates of Acute Kidney Injury among COVID-19 Patients in Hong Kong

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Existing Evidence

- Most jurisdictions adopted home isolation and admitted only severe COVID-19 patients during the 1st wave. Mass screening and contact isolation are increasingly called for globally. The Hong Kong cohort provided information on the burden of renal complications and associated hospitalization under a vigilant containment policy. Robust contact tracing also allowed characterization of asymptomatic patients and disease course since symptom onset.

Added Value of This Study

- The Hong Kong cohort was characterized by young age, short time from symptom onset to admission, low acute kidney injury (AKI) rate, low mortality, and long hospitalization.
- The incidence of in-hospital AKI and renal replacement therapy initiation was 3.72 and 0.68%, respectively. AKI increased the odds of prolonged hospitalization and disease course by 2.0- and 3.5-fold (defined as >90th percentile of hospitalization duration [35 days] and duration from symptom onset to discharge [43 days], respectively).
- Incidence of AKI was comparable between asymptomatic and symptomatic patients.
- There is a trend of persistent glomerular filtration rate (GFR) reduction (defined as post-discharge GFR lower than at admission) after 24 weeks of discharge among patients who developed in-hospital AKI.
- The median time from symptom onset to reaching peak serum Cr was 15 days among patients who developed in-hospital AKI.
- *Implications:* Among patients who developed in-hospital acute kidney injury (AKI), the duration of hospitalization is prolonged and kidney function impairment can persist for up to 6 months post-discharge. Mass surveillance for COVID-19 is warranted in identifying asymptomatic subjects for earlier AKI management.

Keywords

COVID-19 · Renal medicine · Acute kidney injury · Risk factors · Cohort

Abstract

Introduction: Renal involvement in COVID-19 is less well characterized in settings with vigilant public health surveillance, including mass screening and early hospitalization. We assessed kidney complications among COVID-19 patients in Hong Kong, including the association with risk factors, length of hospitalization, critical presentation, and mortality. **Methods:** Linked electronic records of all patients with confirmed COVID-19 from 5 major designated hospitals were extracted. Duplicated records due to interhospital transferal were removed. Primary outcome was the incidence of in-hospital acute kidney injury (AKI). Secondary outcomes were AKI-associated mortality, incident renal replacement therapy (RRT), intensive care admission, prolonged hospitalization and disease course (defined as >90th percentile of hospitalization duration [35 days] and duration from symptom onset to discharge [43 days], respectively), and change of estimated glomerular filtration rate (GFR). Patients were further stratified into being symptomatic or asymptomatic. **Results:** Patients were characterized by young age (median: 38.4, IQR: 28.4–55.8 years) and short time (median: 5, IQR: 2–9 days) from symptom onset to admission. Among the 591 patients, 22 (3.72%) developed AKI and 4 (0.68%) required RRT. The median time from symptom onset to in-hospital AKI was 15 days. AKI increased the odds of prolonged hospitalization and disease course by 2.0- and 3.5-folds, respectively. Estimated GFR 24 weeks post-discharge reduced by 7.51 and 1.06 mL/min/1.73 m² versus baseline (upon admission) in the AKI and non-AKI groups, respectively. The incidence of AKI was comparable between asymptomatic (4.8%, *n* = 3/62) and symptomatic (3.7%, *n* = 19/519) patients. **Conclusion:** The overall rate of AKI among COVID-19 patients in Hong Kong is low, which could be attributable to a vigilant screening program and early hospitalization. Among patients who developed in-hospital AKI, the duration of hospitalization is prolonged and kidney function impairment can persist for up to 6 months post-discharge. Mass surveillance for COVID-19 is warranted in identifying asymptomatic subjects for earlier AKI management.

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Introduction

Previous reports from Wuhan, China, showed that 75.4% of COVID-19 patients had abnormal urine dipstick tests or acute kidney injury (AKI), and AKI was associated with 10-fold increase in mortality [1]. However, increasing volume of epidemiological studies suggested that the demographics and clinical presentations varied geographically, partly related to the critical care capacity and the severity of patients being sampled [2–5].

In Hong Kong, the Centre for Health Protection was established after SARS in 2004 to strengthen the surveillance of infectious diseases. Since the outbreak of COVID-19 in December 2019, Hong Kong has maintained a low mortality rate by adopting mass surveillance screening (with compulsory border screening, volunteer community screening, and prehospital screening for all suspected cases), strict border control, and intensive social distancing during the first two waves of pandemics [6]. The contact source of majority of the COVID-19 cases could be traced, tested, identified, and hospitalized for isolation before symptoms develop. Therefore, Hong Kong provided a unique cohort to study the impact of COVID-19 under these public health measures, which are increasingly called for globally to mitigate the transmission [7–9]. The strict contact tracing also allows the characterization of asymptomatic patients.

AKI is common among hospitalized patients, especially for patients under intensive care [10]. Previous studies showed that in-hospital AKI is associated with increased use of renal replacement therapy (RRT) [11] and mortality [12, 13]. The disease burden of COVID-19 will soon switch from the acute outbreak phase to the end-organ sequela management in the coming months. Therefore, identifying the risk factors and determining the magnitude of AKI incidence in COVID-19 under different degrees of surveillance, public health interventions, and hospital admission policy would help forecasting the expected health services demand in the subsequent waves. We aimed to assess the renal involvement in COVID-19 in Hong Kong, including the association with risk factors, length of hospitalization, critical presentation, and mortality.

Methods

Study Design

This study is a retrospective cohort analysis of hospital registries with total sampling.

Inclusion and Exclusion Criteria

All patients aged 18 or above with confirmed COVID-19 (by nasopharyngeal swab, throat swab, or posterior oropharyngeal saliva with RT-PCR testing), both symptomatic and asymptomatic, regardless of screening reason from 15 January to 31 May 2020 admitted to 5 major designated hospitals receiving COVID-19 patients in Hong Kong (Queen Mary Hospital, Princess Margaret Hospital, Queen Elizabeth Hospital, United Christian Hospital, and Pamela Youde Nethersole Eastern Hospital) were included.

Outcome Measures

The primary outcome was AKI during hospitalization (defined according to KDIGO 2012 guideline as $\geq 26.5 \mu\text{mol/L}$ [within 48 h] or 50% [within 7 days] increase in baseline serum Cr [SCr], or urine volume $< 0.5 \text{ mL/kg/h}$ for 6 h) [14]. Secondary outcomes included (1) mortality, (2) incident RRT (including any form of dialysis), (3) critical presentation (defined as intensive care admission) during hospitalization, (4) prolonged hospitalization ($\geq 90\text{th}$ percentile of duration from admission to discharge, 35 days), (5) prolonged disease course ($\geq 90\text{th}$ percentile of duration from symptom onset to discharge, 43 days), and (6) the change of SCr and estimated glomerular filtration rate (GFR) 4, 12, and 24 weeks after discharge. As the disease course and hospitalization period varied among different clinical settings, depending on the criteria of screening and discharge with no universal definition, we defined the prolonged strata according to the 90th percentile of the sample population to better stratify according to the clinical need. Estimated GFR was calculated by CKD-EPI equation [15].

Earliest tests taken within 24 h of admission were defined as baseline, as majority of our patients did not have prehospital SCr record. Discharge investigation was defined as the last test performed before discharge. Disease course was defined as the time from symptom onset to discharge. Patients were discharged after repeated negative RT-PCR.

Data Collection

Data were extracted through an electronic clinical management system with data linkage to all clinical, laboratory, imaging, and pharmacy records. Smoking history was ascertained by nursing record on admission. All data extraction was entered with a standardized data entry form, and verified by two researchers independently (K.Y.Y., P.Y., and K.W.C.) with at least one physician and clinical epidemiologist (K.W.C.). Duplicated records due to hospital transferal were identified and integrated by unique personal identifier. Outcomes were identified through consultation notes, laboratory investigations, and pharmacy record screening, and the records were last updated on 19 October 2020.

Data Analysis

Demographics were presented as mean $\pm$ standard deviation, median [interquartile range], or percentage. Differences in median, mean, and proportion between groups, including the difference in demographics and renal manifestations between (1) symptomatic versus asymptomatic patients and (2) patients admitted during the 1st versus 2nd waves of COVID-19, were tested by Wilcoxon rank sum test, *t* test, and χ^2 test.

AKI was further stratified into stage 1 (SCr ≥ 1.5 times baseline or increase of $\geq 0.3 \text{ mg/dL}$ within any 48-h period or urine volume $< 0.5 \text{ mL/kg}$ for 6–12 h), stage 2 (SCr ≥ 2.0 times baseline or urine volume $< 0.5 \text{ mL/kg}$ for $\geq 12 \text{ h}$), and stage 3 (SCr ≥ 3.0 times baseline

or increase to $\geq 4.0 \text{ mg/dL}$ or acute dialysis, or urine volume $< 0.3 \text{ mL/kg}$ for $\geq 24 \text{ h}$) [14]. AKI stages 2 and 3 were combined as secondary analysis when the strata were too small for odds ratio calculation. Diabetes history was stratified into nondiabetic (normal blood glucose at discharge without use of any antidiabetic agents) and diabetic (with the use of antidiabetic agent at baseline). Diabetes history was mainly determined by pharmacy record, as glycated hemoglobin was not routinely tested for COVID-19. Fasting blood glucose measures during hospitalization may represent transient change and are not an ideal diagnosis for diabetes. Hypertension history was stratified into non-hypertensive (without use of any antihypertensive agents) and hypertensive (with the use of hypertensive agent at baseline). Smoking history was stratified into nonsmoker, ex-smoker, and current smoker. Patients admitted on or before 22 February 2020 were classified as cases in the 1st wave and who admitted after 22 February 2020 were cases in the 2nd wave [16].

Univariable regression models were used to assess the odds ratios of different independent risk factors (demographics: age, gender, history and duration of smoking, and alcohol consumption; physical measurement: blood pressures and oxygen saturation; biochemical and hematological investigations: SCr, estimated GFR, C-reactive protein, creatine kinase, serum albumin, lactate dehydrogenase [LDH], alanine aminotransferase, alkaline phosphatase, hemoglobin, leukocyte, neutrophil, lymphocyte, and platelet; and intervention: use of ACE inhibitor/ARB, antivirals, antibiotics, and glucocorticoids) associated with dependent variable (AKI) individually. Multivariable regression models adjusting age and baseline GFR were used to assess the risk factors individually.

We also assessed the association between all AKI and mortality, critical presentation, length of hospitalization, and length disease course. The changes in SCr and estimated GFR from baseline to discharge, and from baseline to 4, 12, and 24 weeks after discharge were compared between the AKI and non-AKI groups by paired *t* test. Change score approach by paired *t* test was used instead of mixed model, and missing data were not imputed to provide a more illustrative presentation of the actual change in GFR and prevent over-fitting of data. All analyses were computed using STATA 15.1.

Results

Demographics

The flow of data extraction is summarized in Figure 1. 644 records were identified from total sampling of 5 (out of 7) major designated hospitals receiving COVID-19 cases. Seven duplicated (interhospital transferal), 10 non-retrievable (transit patients), and 36 pediatric patient records were removed. 591 consecutive adult patient records were available for analysis, representing 54.5% (591/1,085) of all Hong Kong cases by 31 May 2020 [16].

The median hospitalization duration was 18 [12–26] days (Table 1). The median age was 38.4 [28.4–55.8] years. In all, 5.9, 13.5, and 9.3% of patients had a his-

Color version available online

Fig. 1. Flow diagram of data extraction. A total sampling of 644 confirmed COVID-19 records were identified from 5 hospitals. Seven duplicated records of interhospital transferal, 10 non-retrievable records of transit patients, and 36 pediatric patient records were removed. 591 consecutive adult patient records were available from the electronic medical system, representing 54.5% (591/1,085) of all the Hong Kong cases by 31 May 2020 from the 5 (out of 7) major hospitals receiving COVID-19 cases.

tory of diabetes, hypertension, and CKD, respectively; 32.7% (166/507) patients were shown to have bilateral lung involvement by chest X-ray or computed tomography. The median time from symptom onset to admission and discharge was 5 [2–9] and 26 [19–34] days; 10.7% of patients were asymptomatic, and 20.8% of patients were diagnosed based on RT-PCR tests before onset of symptoms. The most frequent symptoms were cough (60.5%), fever (60.2%), fatigue (46.4%), sore throat (39.8%), and myalgia (38.4%). The median SCr and estimated GFR on admission were 72 [61–86] $\mu\text{mol/L}$ and 101.8 [88.6–115.1] mL/min/1.73 m^2 , respectively. The median peak SCr were 157 [106–254] and 80 [68–95] $\mu\text{mol/L}$ among the AKI and non-AKI patients, respectively ($p < 0.001$).

Renal and Other Key Clinical Outcomes

In all, 3.7 and 0.7% of the patients had AKI and RRT during hospitalization (Table 2); 4.6% of all patients were admitted to intensive care unit. The median time from symptom onset and admission to reaching peak SCr was 15 [10–18] and 5 [5–12] days, respectively, among patients who developed AKI. AKI developed 2 [1–7] days after admission. Thirteen, 3, and 6 patients had AKI of stages 1, 2, and 3, respectively.

Compared to non-AKI patient group, patients who developed in-hospital AKI were older; had higher baseline systolic blood pressure; had higher levels of C-reactive protein, LDH, and creatine kinase; had lower levels

of estimated GFR and serum albumin; and had diabetes, hypertension, CKD, cerebrovascular disease, and tumor history. The median time from symptom onset and admission to reaching peak LDH (285 [207–685] U/L) was 9 [8–15.5] and 4 [2–11] days among patients who developed AKI, respectively.

Four patients deceased. The 90th percentiles of disease course and hospital stay were 43 and 35 days, respectively. Patients who developed AKI were associated with 2 times (OR = 2.99, 95% CI: 1.19–7.49, $p = 0.02$) and 3.5 times (OR = 4.48, 95% CI: 1.64–12.29, $p = 0.004$) increased odds of prolonged hospitalization and disease course (Table 3), respectively.

Longitudinal Renal Function after Discharge

The mean absolute difference in GFR between admission and discharge was -9.11 and $1.18 \text{ mL/min/1.73 m}^2$ among the AKI and non-AKI groups ($p = 0.064$), respectively (Fig. 2). 242 patients attended 12-week post-discharge follow-up (median: 77.5 days, IQR: [70–86]). The mean absolute difference in GFR from admission was -3.03 and $-2.41 \text{ mL/min/1.73 m}^2$ among the AKI and non-AKI groups ($p = 0.919$), respectively. 100 patients attended 24-week post-discharge follow-up (median: 163 days, IQR: [146–181]). The mean absolute difference in GFR from admission was -7.51 and $-1.06 \text{ mL/min/1.73 m}^2$ among the AKI and non-AKI groups ($p = 0.301$), respectively.

Risk Factors for Developing AKI in the Hong Kong Cohort

Univariable regression analysis showed that older age; smoking; diabetes; hypertension, CKD; tumor history; use of ACE inhibitor/ARB; high baseline systolic blood pressure, C-reactive protein, LDH, and creatine kinase; low baseline serum albumin and estimated GFR; and bilateral lung infiltration were associated with in-hospital AKI in the Hong Kong cohort (Table 4). Patients with C-reactive protein $>20 \text{ mg/L}$ or LDH $>280 \text{ U/L}$ during hospital stay were associated with 2.49 times (OR = 3.492, 95% CI: 1.477–8.255, $p = 0.004$) and 4.18 times (OR = 5.182, 95% CI: 2.141–12.544, $p < 0.001$) increased odds of developing AKI. After adjusting for age and baseline GFR, smoking, diabetes, hypertension, use of ACE inhibitor/ARB, high baseline C-reactive protein, LDH, and creatine kinase, low baseline serum albumin, and bilateral lung infiltration remained as significant independent risk factors (online suppl. S2; for all online suppl. material, see www.karger.com/doi/10.1159/000514234).

Table 1. Characteristics of the Hong Kong cohort

Characteristic	All cases (<i>n</i> = 591)	AKI during hospitalization (<i>n</i> = 22)	No AKI during hospitalization (<i>n</i> = 569)	<i>p</i> value (AKI vs. non-AKI)
Age, median [IQR], years	38.4 [28.4–55.8]	61.4 [42.4–69.3]	38.1 [27.9–54.6]	<0.001
Female, <i>n</i> (%)	275 (46.5)	9 (40.9)	266 (46.8)	0.590
Current smoking, <i>n</i> (%)	38 (6.4)	0 (0)	38 (6.7)	0.007
Known comorbidities, <i>n</i> (%)				
Diabetes	35 (5.9)	7 (31.8)	28 (4.9)	<0.001
Hypertension	80 (13.5)	12 (54.6)	68 (12.0)	<0.001
Chronic lung disease	39 (6.6)	2 (9.1)	37 (6.5)	0.631
CKD	55 (9.3)	6 (27.3)	49 (8.6)	0.003
Coronary artery disease	14 (2.4)	1 (4.6)	13 (2.3)	0.494
Cerebrovascular disease	1 (0.2)	1 (4.6)	0 (0)	<0.001
Tumor	14 (2.4)	2 (9.1)	12 (2.1)	0.035
Days from symptom onset to admission, median [IQR]	5 [2–9]	7 [4–9]	5 [2–9]	0.325
Signs and symptoms on admission, <i>n/N</i> (%)				
Fever	313/520 (60.2)	11 (50)	302 (60.6)	0.318
Cough	291/481 (60.5)	16 (80)	275 (59.7)	0.068
Fatigue/malaise	83/179 (46.4)	6 (60)	77 (45.6)	0.374
Shortness of breath	56/291 (19.2)	5 (33.3)	51 (18.5)	0.155
Chills	60/178 (33.7)	3 (50)	57 (33.1)	0.390
Sore throat	130/327 (39.8)	4 (33.3)	126 (40)	0.643
Sputum	127/337 (37.7)	4 (26.7)	123 (38.2)	0.368
Myalgia	79/206 (38.4)	3 (37.5)	76 (38.4)	0.960
Nausea	14/172 (8.1)	1 (16.7)	13 (7.8)	0.437
Vomiting	15/273 (5.5)	0 (0)	15 (5.7)	0.437
Diarrhea	117/399 (29.3)	6 (40)	111 (28.9)	0.355
Rhinorrhea	101/285 (35.4)	3 (30)	98 (35.6)	0.714
Asymptomatic	62/581 (10.7)	3 (13.6)	59 (10.6)	0.646
Vital signs on admission, mean (SD)				
Systolic blood pressure, mm Hg	137.9 (19.2)	148.4 (20.9)	137.4 (19.0)	0.031
Diastolic blood pressure, mm Hg	84.8 (12.0)	87.9 (9.5)	84.7 (12.1)	0.155
Heart rate, bpm	85.8 (15.0)	87.6 (16.6)	85.7 (15.0)	0.606
Respiratory rate, breaths/min	16.5 (7.8)	16.9 (4.3)	16.5 (8.0)	0.783
Oxygen saturation, <i>n</i> (%)	98.1 (2.0)	97.7 (1.6)	98.1 (2.0)	0.247
Laboratory findings on admission, median [IQR]				
Hemoglobin, g/dL	13.9 [12.9–15]	13.3 [12.4–14.4]	13.9 [12.9–15]	0.118
Leukocyte, $\times 10^9$ /L	5.4 [4.3–6.8]	4.8 [4.1–7.2]	5.4 [4.3–6.8]	0.597
Neutrophils, $\times 10^9$ /L	3.3 [2.4–4.5]	3.4 [2.4–5.2]	3.3 [2.4–4.5]	0.911
Lymphocytes, $\times 10^9$ /L	1.4 [1–1.9]	1.1 [0.9–1.6]	1.4 [1.0–1.9]	0.076
Platelets, $\times 10^9$ /L	219 [178–271]	187 [158–236]	221 [179–271]	0.063
Alanine aminotransferase, U/L	23 [16–34]	33.5 [17–42]	23 [16–34]	0.110
Alkaline phosphatase, U/L	60 [50–74]	67.5 [51–76]	60 [50–74]	0.468
C-reactive protein, mg/L	2 [0–9]	10.8 [1.3–56.2]	2 [0–8.2]	0.002
Lactate dehydrogenase, U/L	179 [155–217]	241 [177–306]	178 [155–215]	<0.001
Bilirubin, μ mol/L	7 [5–10]	8 [6–10]	7 [5–10]	0.117
Cr, μ mol/L	72 [61–86]	77.5 [57–92]	72 [61–86]	0.494
GFR (CKD-EPI), mL/min/1.73 m ²	101.8 [88.6–115.1]	86.4 [72.9–104.5]	101.8 [89.1–115.7]	0.008
Serum albumin, g/L	42 [38–45]	37.5 [35–42]	42 [38–45]	0.001
Creatine kinase, U/L	82 [58–122]	122.5 [58–324]	82 [58–120]	0.037
Radiological findings, <i>n/N</i> (%)				
Bilateral infiltrate	166/507 (32.7)	14 (73.7)	152 (31.2)	<0.001
Right lobes infiltrate	230/507 (45.4)	16 (84.2)	214 (43.9)	0.001
Left lobes infiltrate	196/507 (38.7)	15 (78.9)	181 (37.1)	<0.001
Any abnormalities	260/507 (51.3)	17 (89.5)	243 (49.8)	0.001

Table 1 (continued)

Characteristic	All cases (<i>n</i> = 591)	AKI during hospitalization (<i>n</i> = 22)	No AKI during hospitalization (<i>n</i> = 569)	<i>p</i> value (AKI vs. non-AKI)
Concurrent treatment, <i>n/N</i> (%)				
ACE inhibitor/ARB	41/591 (6.9)	6 (27.3)	35 (6.2)	<0.001
Antivirals	399/591 (67.5)	22 (100)	377 (66.3)	0.001
Lopinavir/ritonavir	365/591 (61.8)	22 (100)	343 (60.3)	<0.001
Ribavirin	328/591 (55.5)	17 (77.3)	311 (54.7)	0.036
Interferon	195/591 (33.0)	8 (36.4)	187 (32.9)	0.732
Antibiotics	170/591 (28.8)	10 (45.5)	160 (28.1)	0.078
Glucocorticoids	47/591 (8.0)	1 (4.6)	46 (8.1)	0.547

AKI, acute kidney injury; GFR, glomerular filtration rate. ¹ Within 48 h of admission. Among patients with AKI, 13, 3, and 6 had AKI stages 1, 2, and 3, respectively.

Table 2. Clinical outcomes and association between peak serum Cr and key biomarkers

Characteristic	All cases (<i>n</i> = 591)	AKI during hospitalization (<i>n</i> = 22)	No AKI during hospitalization (<i>n</i> = 569)	<i>p</i> value (AKI vs. non-AKI)
Mortality, <i>n</i> (%)	4 (0.7)	3 (13.6)	1 (0.2)	<0.001
Intensive care admission, <i>n</i> (%)	27 (4.6)	5 (22.7)	22 (3.9)	<0.001
AKI, <i>n</i> (%)	22 (3.7)			<i>n/a</i>
Renal replacement therapy, <i>n</i> (%)	4 (0.7)	4 (18.2)	0 (0)	<0.001
Days from symptom onset to discharge, median [IQR]	26 [19–34]	29 [19–69]	26 [19–33]	0.162
Length of intensive care, median [IQR], days	12 [7–22]	26 [16–50]	10.5 [7–16]	0.010
Length of hospitalization, median [IQR], days	18 [12–26]	22 [14–59]	18 [12–26]	0.080
Peak sCr, median [IQR], $\mu\text{mol/L}$	81 [68–96]	157 [106–254]	80 [68–95]	<0.001
Peak increase in sCr, median [IQR], %	9.7 [0–21.1]	71.1 [53.7–233.3]	9.1 [0–20]	<0.001
Days to reach peak sCr from symptom onset, median [IQR]	9 [5–15]	15 [10–18]	9 [5–14]	0.003
Days to reach peak sCr from admission, median [IQR]	4 [1–6]	5 [5–12]	3 [1–6]	<0.001
Peak C-reactive protein, median [IQR], mg/L	3.1 [0.6–17.4]	22.4 [3–248]	3 [0.5–15]	<0.001
Days to reach peak C-reactive protein from symptom onset, median [IQR]	8 [5–13]	12 [9–15]	8 [5–13]	0.038
Days to reach peak C-reactive protein from admission, median [IQR]	4 [1–6]	5 [5–12]	3 [1–6]	<0.001
Peak LDH, median [IQR], U/L	202 [171–255]	285 [207–685]	202 [171–249]	<0.001
Days to reach peak LDH from symptom onset, median [IQR]	10 [6–15]	9 [8–15.5]	10 [6–15]	0.606
Days to reach peak LDH from admission, median [IQR]	3 [1–7]	4 [2–11]	3 [1–7]	0.080

Among patients with AKI, 13, 3, and 6 had AKI stages 1, 2, and 3, respectively. AKI, acute kidney injury; sCr, serum Cr; LDH, lactate dehydrogenase.

Differences in Renal Manifestations between Asymptomatic and Symptomatic Patients

Sixty-two patients were asymptomatic before admission. Asymptomatic patients were characterized by less bilateral lung infiltration (asymptomatic: 11.5% vs. symptomatic: 35.2%, $p = 0.001$) and lower C-reactive protein level (asymptomatic: 0.3 vs. symptomatic: 2.3 mg/L, $p < 0.001$) (online suppl. S3, S4). The incidence of AKI was comparable between asymptomatic (4.8%) and symp-

tomatic (3.7%) patients. Asymptomatic patients had a shorter hospitalization period (13 vs. 19 days, $p < 0.001$) (Table 5).

Differences in Renal Manifestations between Two Waves

The 2nd wave ($n = 539$) was characterized by a younger average age (1st: 59.0 vs. 2nd: 37.4 years, $p < 0.001$) and with less comorbidities (online suppl. S5, S6). There is a

Table 3. Prognosis associated with different stages of AKI (Hong Kong cohort)

	Mortality, odds ratio (95% CI) (n = 4/591)	Critical presentation ¹ , odds ratio (95% CI) (n = 27/591)	Prolonged disease course ² , odds ratio (95% CI) (n = 164/587)*	Prolonged hospitalization ³ , odds ratio (95% CI) (n = 59/587)*
AKI	89.7 (8.91–902.50) <i>p</i> < 0.001, <i>n</i> = 3/22	7.31 (2.47–21.63) <i>p</i> < 0.001, <i>n</i> = 5/22	2.99 (1.19–7.49) <i>p</i> = 0.02, <i>n</i> = 10/19	4.48 (1.64–12.29) <i>p</i> = 0.004, <i>n</i> = 6/19
Stage 1	47.33 (2.79–802.21) <i>p</i> = 0.008, <i>n</i> = 1/13	2.07 (0.26–16.65) <i>p</i> = 0.493, <i>n</i> = 1/13	1.34 (0.40–4.53) <i>p</i> = 0.63, <i>n</i> = 4/12	0.88 (0.11–6.98) <i>p</i> = 0.906, <i>n</i> = 1/12
Stage 2	n/a	12.43 (1.09–142.34) <i>p</i> = 0.043, <i>n</i> = 1/3	5.38 (0.48–59.72) <i>p</i> = 0.171, <i>n</i> = 2/3	4.86 (0.43–54.48) <i>p</i> = 0.200, <i>n</i> = 1/3
Stage 3	284 (21.22–3,801.18) <i>p</i> < 0.001, <i>n</i> = 2/6	24.86 (4.75–130.25) <i>p</i> < 0.001, <i>n</i> = 3/6	n/a	n/a
Stage 1 [#]	47.33 (2.79–802.21) <i>p</i> = 0.008, <i>n</i> = 1/13	2.07 (0.26–16.65) <i>p</i> = 0.493, <i>n</i> = 1/13	1.34 (0.40–4.53) <i>p</i> = 0.63, <i>n</i> = 4/12	0.88 (0.11–6.98) <i>p</i> = 0.906, <i>n</i> = 1/12
Stages 2 and 3 [#]	162.29 (13.14–2,003.94) <i>p</i> < 0.001, <i>n</i> = 2/9	19.89 (4.99–79.23) <i>p</i> < 0.001, <i>n</i> = 4/9	16.13 (1.93–135.06) <i>p</i> = 0.01, <i>n</i> = 6/7	24.29 (4.60–128.28) <i>p</i> < 0.001, <i>n</i> = 5/7

AKI, acute kidney injury. ¹ Defined as intensive care admission. ² Defined as interval between symptom onset and discharge more than or equal to 43 days. ³ Defined as duration of hospitalization more than or equal to 35 days, both equivalent to the 90th percentile in the Hong Kong cohort. [#] Regrouped due to small strata of stage 2 and 3 AKI patients. AKI stage defined according to KDIGO 2012. * Excluded 4 patients deceased at the time of censor.

Table 4. Factors associated with in-hospital AKI in the Hong Kong cohort

Independent factors	Odds ratio (OR)/regression coefficient (RC) (95% CI)
Age	RC: 0.050 (0.028–0.072), <i>p</i> < 0.001
Ex-smoker	OR: 5.432 (1.449–20.362), <i>p</i> = 0.012
Diabetes history	OR: 9.017 (3.404–23.887), <i>p</i> < 0.001
Hypertension history	OR: 8.841 (3.680–21.243), <i>p</i> < 0.001
CKD history	OR: 3.980 (1.489–10.634), <i>p</i> = 0.006
Tumor history	OR: 4.642 (0.973–22.133), <i>p</i> = 0.054
Concurrent use of ACE inhibitor/ARB	OR: 5.721 (2.108–15.531), <i>p</i> = 0.001
Baseline systolic blood pressure (mm Hg)	RC: 0.287 (0.007–0.050), <i>p</i> = 0.010
Baseline C-reactive protein (mg/L)	RC: 0.009 (0.004–0.013), <i>p</i> < 0.001
Baseline LDH (U/L)	RC: 0.008 (0.004–0.011), <i>p</i> < 0.001
Baseline GFR (mL/min/1.73 m ²)	RC: –0.033 (–0.051 to –0.014), <i>p</i> = 0.001
Baseline serum albumin (g/L)	RC: –0.145 (–0.222 to –0.069), <i>p</i> < 0.001
Baseline creatine kinase (U/L)	RC: 0.005 (0.002–0.007), <i>p</i> < 0.001
Bilateral lung infiltration	OR: 6.189 (2.190–17.493), <i>p</i> = 0.001
C-reactive protein surpassed 20 mg/L during hospitalization	OR: 3.492 (1.477–8.255), <i>p</i> = 0.004
LDH surpassed 280 U/L during hospitalization	OR: 5.182 (2.141–12.544), <i>p</i> < 0.001

AKI, acute kidney injury; LDH, lactate dehydrogenase; GFR, glomerular filtration rate. Assessed by univariable logistic regression model with in-hospital AKI as dependent variable.

Fig. 2. Mean percentage change of estimated GFR from baseline (* $p < 0.05$, ** $p < 0.01$). Estimated GFR change from baseline. 95% confidence intervals are shown. GFR was estimated by CKD-EPI equation. Patients who developed AKI during hospitalization had a trend of greater reduction in GFR but not to a statistically significant level. GFR, glomerular filtration rate; AKI, acute kidney injury.

Table 5. Renal manifestation difference between symptomatic and asymptomatic patients

	Asymptomatic	Symptomatic	<i>p</i> value (asymptomatic vs. symptomatic)
Mortality, <i>n/N</i> (%)	1/62 (1.6)	3/519 (0.6)	0.352
Intensive care admission, <i>n/N</i> (%)	0/62 (0)	27/519 (5.2)	0.066
AKI, <i>n/N</i> (%)	3/62 (4.8)	19/519 (3.7)	0.646
Renal replacement therapy, <i>n/N</i> (%)	0/62 (0)	4/519 (0.8)	0.488
Length of hospitalization, median [IQR], days	13 [7–19]	19 [12–27]	<0.001

Incidence of AKI was comparable between asymptomatic and symptomatic patients. AKI, acute kidney injury.

lower rate of mortality (0.4 vs. 3.9%, $p = 0.004$), intensive care admission (3.9 vs. 11.5%, $p = 0.012$), AKI (2.4 vs. 17.3%, $p < 0.001$), and median length of hospitalization (18 vs. 22.5 days, $p = 0.001$) than in the 1st wave (Table 6).

Discussion

Incident in-hospital AKI was associated with increased odds of prolonged disease course, prolonged hospitaliza-

Table 6. Renal manifestations difference between the 1st and 2nd waves

	1st wave	2nd wave	<i>p</i> value (1st vs. 2nd wave)
Mortality, <i>n/N</i> (%)	2/52 (3.9)	2/539 (0.4)	0.004
Intensive care admission, <i>n/N</i> (%)	6/52 (11.5)	21/539 (3.9)	0.012
Acute kidney injury, <i>n/N</i> (%)	9/52 (17.3)	13/539 (2.4)	<0.001
Renal replacement therapy, <i>n/N</i> (%)	1/52 (1.9)	3/539 (0.6)	0.251
Days from symptom onset to admission, median [IQR]	5.5 [3–9]	5 [2–9]	0.594
Days from symptom onset to discharge, median [IQR]	29 [23–35]	25 [19–33]	0.024
Length of intensive care, median [IQR], days	9 [4–16]	13 [9–22]	0.255
Length of hospitalization, median [IQR], days	22.5 [17–31]	18 [11–26]	0.001

The disease course and length of hospitalization were shorter during the 2nd wave.

tion, intensive care admission, and mortality among individual patients. The incidence of AKI was comparable between asymptomatic and symptomatic patients. COVID-19 patients' GFR showed a trend of persistent reduction after 24 weeks of discharge.

Unique Characteristics of the Hong Kong Cohort

The incidence of in-hospital AKI and mortality in the Hong Kong cohort were among the lowest from reported studies from Wuhan and the USA [17, 18]. However, there were 18.9% of the AKI patients required RRT, which is comparable to the Wuhan cohort (15%) reported earlier [17]. From the demographics, our 2nd wave cohort was younger, with less comorbidities, had a shorter time from symptom onset to admission, less symptomatic, and with shorter hospitalization and disease course. Hong Kong had a relatively mild cohort partly due to the effective border and community surveillance that led to early detection and hospital isolation of RT-PCR confirmed cases. These factors contributed to the observation of overall lower severity of patients in our cohort and provided a unique source of information to assess the health services need under strong surveillance when compared to other cohorts globally, which is of high demand lately. Noteworthy, the Hong Kong cohort also had a longer hospitalization period, partly due to the reduced latent period between symptom onset to admission and the repeated negative RT-PCR results before discharge.

Clinical Implication – Prolonged Hospitalization and Disease Course

Since the outbreak of COVID-19, the overloading of intensive care service, hospital beds, ventilators, and dialysis machines has been widely reported worldwide [19, 20], which was postulated to cause delay in treatment ac-

cess, prolong viral shedding, and increase mortality [21, 22]. The data from the Hong Kong cohort showed that AKI and RRT were associated with 3.5 times increased odds of prolonged hospitalization (over 35 days) and longer intensive care stay (AKI: 26 days vs. non-AKI: 10.5 days), as AKI involves pathophysiology of multiple organs, which leads to more complicated management [10, 23]. The prevention of AKI would be important to reduce the overall health service burden, as the incidence of AKI could reach 30–50% in some settings.

The presentation of AKI in COVID-19 and SARS was different in Hong Kong. The incidence of AKI was lower and earlier in COVID-19 (3.7%) than in SARS (6.4%) [24, 25]. For COVID-19, the median time to develop AKI after admission was 2 [1–7] days, and the median time from symptom onset and admission to reaching peak SCr were 15 [10–18] and 5 [5–12] days, whereas the median time from the onset of viral infection to AKI was 20 [5–48] days in SARS [24]. In our cohort, SCr reached the peak (median: 15 days) following LDH (median: 9 days) among patients who developed AKI. The increase in serum LDH indicates organ injury including AKI. The chronological sequence suggested that the increase in LDH could partially come from AKI, and LDH has been proposed as a predictor of AKI previously [26]. The median day to reach peak LDH was comparable between the AKI and non-AKI groups, and the median days to reach peak C-reactive protein and SCr were longer in the AKI group, indicating that the progression of AKI could be associated with sustained systemic inflammation [27].

We also identified a series of risk factors associated with the onset of AKI from our cohort (Table 4). Of these factors, lower baseline serum albumin was observed among COVID-19 patients who subsequently developed

AKI, which was a common risk factor shared with SARS [24]. Strategies to prevent or correct hypoalbuminemia including dietary intervention or albumin administration could be potential trial interventions. Evidence on more amenable factors that associated with faster and better AKI recovery is limited, requiring urgent clarification. A recent review showed that the mortality of COVID-19 AKI patients reached 76.5% and was comparable to that of SARS (86.6%) and MERS (68.5%) [28]. The 1-year mortality hazard ratio among AKI survivors in previous studies varied from 1.63 to 2.48, positively correlated to the preceding CKD stage [12].

The use of ACE inhibitors/ARB was found associated with increased odds of developing AKI in our cohort, which reconciled with other studies [29]. However, the magnitude of association between diabetes, hypertension, and AKI was greater, and the use of ACE inhibitors/ARB was more likely in the causal pathway instead of being the root cause of AKI. Previous retrospective studies showed that discontinuing ACE inhibitors/ARB was associated with increased risk of AKI among COVID-19 patients [30]. Preliminary data of the BRACE CORONA trial also showed similar results [31]. Nevertheless, evidence on the mortality and AKI incidence associated with different add-on medications for hypertension management in COVID-19 is lacking.

Urgency of Strategies to Speed Up AKI Recovery before Strong Surveillance

Early detection could lead to earlier treatment and therefore lower the severity of COVID-19 patients [32]. Nevertheless, early detection would lead to an exponential increase in positive mild cases and increased hospital service load. Therefore, strategies to shorten hospital stay, mitigate transmission, and control the overall incidence of COVID-19 are crucial, should mass surveillance be adopted. To this end, efficient AKI management is critical. Our cohort showed that although increased surveillance did not increase the average hospitalization period, AKI was associated with substantial increased risk of prolonged hospitalization among individuals. Evidence on strategies to fasten the recovery of AKI is lacking, yet of paramount importance. Targeted protection and screening on vulnerable patient groups, for example, the elderly, diabetic, hypertensive, and patients with chronic diseases, are needed, as these factors are also significantly associated with AKI. To shorten hospital stay, previous studies demonstrated the early use of interferon may shorten the disease course [32].

Current Prevention and Management of AKI in COVID-19

Management of AKI in COVID-19 should be individualized depending on the overall hemodynamic and respiratory status. In the absence of high-quality evidence, it is reasonable to take into consideration a recently proposed lung-kidney interaction model that advocates mitigating volutrauma and barotrauma through adopting lung-protective ventilation approaches [33]. This is believed to lower the risk of incident or worsening AKI by limiting ventilation-induced hemodynamic disturbance and a putative cytokine burden on the kidney.

For the prevention of AKI, an important aspect is early recognition of abnormal fluid balance [34]. In the Hong Kong cohort, the rate of in-hospital AKI was comparable between symptomatic and asymptomatic patients, suggesting AKI may not be timely recognized if asymptomatic patients were not admitted. Prompt volume correction may avert AKI, as volume depletion on admission might be common in patients with COVID-19, given that they typically present with fever and prehospital fluid resuscitation is rarely performed [35]. Stringent infection control and early treatment for high-risk individuals are other important measures, as patients had the highest viral load near presentation [36], and early triple antiviral therapy shortens the duration of viral shedding and hospital stay [32], potentially reducing the chance of renal endothelial cell damage by viremia, progression to overwhelming sepsis and a multi-organ dysfunction syndrome [35].

Long-Term Renal Involvement after COVID-19

AKI and the need of RRT also have significant implication to the health service provision post-outbreak. AKI is associated with 1.7 and 3.81 times increased hazard for developing CKD and end-stage kidney disease [37], and 79% of RRT patients did not recover 6 months after discharge, as reported in previous studies [38]. In our cohort, patients who developed in-hospital AKI had a trend of persistent GFR reduction after 24 weeks of discharge when compared to patients who did not have AKI, which is consistent with the Wuhan cohort (32% non-recoverable at discharge) [17, 39]. As 1-year interval was previously shown to divide the hazard of mortality [12], adequate provision of renal follow-up service within the first 12 months would be critical to reduce the intermediate-term increase in mortality. The residual renal impairment at population level, especially incident end-stage kidney disease, is expected to substantially increase the demand for long-term renal care including dialysis, for which the access could be limited and costly [40].

Limitations

In the retrospective cohort, we only analyzed key manifestations including AKI and RRT, as the records on these 2 outcomes were more complete among patients. We did not analyze the incidence and effect of proteinuria and hematuria and other biomarkers (e.g., glycated hemoglobin, lipids, and troponins), as they were not routinely tested for all COVID-19 patients in our setting and could lead to substantial selection bias. Also, information on the comparison between AKI developed based on urine output changes versus Cr and both is limited and underpowered. Besides, the quantitative viral load was not routinely available in the electronic medical record. The association between viral load on admission and key clinical outcomes requires further research. Since our cohort captured a unique pool of younger patients with less comorbidity, majority did not have prehospital SCr records. Prehospital AKI could not be assessed, and the incidence of AKI may be underestimated. The number of patients with in-hospital AKI was small, and therefore, multivariable regression analysis on risk factors was conducted as a supplementary analysis, and the confidence intervals of the odds ratios are large. Last, only a portion of patients attended follow-up and the analysis is underpowered. However, the incompleteness of follow-up was due to standard protocol of follow-up cessation and the relocation of overseas patients, and therefore, selection bias is minimal.

Conclusion

The overall rate of AKI among COVID-19 patients in Hong Kong is low, which could be attributable to a vigilant screening program and early hospitalization. Among patients who developed in-hospital AKI, the duration of hospitalization is prolonged and kidney function impairment can persist for up to 6 months post-discharge. Mass surveillance for COVID-19 is warranted in identifying asymptomatic subjects for earlier AKI management.

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Statement of Ethics

This study was approved by the Institutional Review Boards of the 5 corresponding hospital clusters of the Hospital Authority Hong Kong via Central Coordination Office (Ref.: CCO-2020-0011). This study is reported according to STROBE.

Conflict of Interest Statement

None declared. Part of the results in the article has been accepted as poster presentation at the American Society of Nephrology Kidney Week 2020.

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Author Contributions

S.C.-W.T. and K.W.C. conceived the study. I.F.-N.H., O.T.-Y.T., T.C.W., E.Y.-K.T., K.C.L., G.C.W.-C., S.S.-H.W., and J.W.-M.C. recruited the patients and provided clinical service. K.Y.Y. and K.W.C. retrieved the cohort data. K.W.C. performed the statistical analyses. K.W.C. and S.C.-W.T. drafted the manuscript. All authors proofread the manuscript.

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