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# The Indirect Impact of COVID-19 Pandemic on Mortality, Complications, and Healthcare Utilization Among Patients With Chronic Respiratory Diseases in Hong Kong: An Interrupted Time Series Analysis

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## ABSTRACT

**Purpose:** This study aimed to investigate COVID-19's indirect influence on chronic respiratory disease (CRD) patients for two years since the COVID-19 pandemic began.

**Methods:** Using population-based data in Hong Kong, we included CRD patients diagnosed from January 2011 to December 2021. Interrupted Time Series Analysis were applied to assess mortality, complications, and healthcare utilization rates during the “pre-COVID-19 pandemic” (January 2012–January 2020), “initial COVID-19 pandemic” (February 2020–February 2021), and “post-initial COVID-19 pandemic” (March 2021–December 2021) periods.

**Results:** Among 587,049 patients with CRD, all-cause mortality had an increasing trend during the post-initial COVID-19 pandemic period (incidence rate ratio (95% CI): 1.019 (1.005, 1.034);  $p = 0.007$ ), compared with pre-COVID-19 pandemic period. Nonrespiratory mortality had an increasing trend in the initial COVID-19 pandemic period (1.020 (1.006, 1.033);  $p = 0.004$ ) and

**Abbreviations:** A&E, Accident and Emergency Department; AECOPD, Acute exacerbations of chronic obstructive pulmonary disease; ARF, Acute renal failure; CCI, Charlson Comorbidity Index; CI, Confidence interval; COVID-19, Coronavirus disease 2019; CRD, Chronic respiratory disease; HA CMS, Hospital Authority Clinical Management System; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICPC-2, International Classification of Primary Care, Second Edition; IRR, Incidence rate ratios; ITSA, Interrupted time series analyses; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; SOPC, Specialist outpatient clinics; WHO, World Health Organization.

Qi Kang and Yuk Kam Yau contributed equally.

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was higher than the pre-pandemic level in the post-initial COVID-19 pandemic. We observed abrupt declines in the incidence rates of asthma exacerbation, acute exacerbation of chronic obstructive pulmonary disease, pneumonia, and acute respiratory failure in the first month of initial COVID-19 pandemic period, remaining below pre-COVID-19 pandemic levels throughout the initial pandemic period.

**Conclusion:** The disruption of usual healthcare impacts mortality rates among patients with CRD without COVID-19, particularly nonrespiratory mortality. Contingency plans on continuing follow-up and monitoring of CRD patients are needed, for example, teleconsultations, shared primary care, and tele-reminders on red-flag symptoms for patients with CRD, when healthcare services may be disrupted during public health crises.

## 1 | Introduction

The coronavirus disease 2019 (COVID-19) pandemic has greatly impacted population health worldwide, not only via the direct effects of SARS-CoV-2 infection but also the indirect effects of disrupted use of health services. The unprecedented numbers of COVID-19 cases overwhelmed healthcare systems, resulting in the disruption of routine medical care among patients with chronic diseases but without COVID-19. The fear of contracting SARS-CoV-2 has also discouraged this patient population from seeking healthcare. Chronic respiratory disease (CRD) is a common noncommunicable disease, with a prevalence of 454.6 million people globally in 2019 [1]. Patients with CRD are more susceptible to pneumonia, which is a common cause of acute respiratory failure (ARF) [2, 3], a life-threatening condition. International guidelines recommend that patients with CRD have routine follow-ups to monitor symptoms and exacerbations, have regular check-ups, and adjust medication [4, 5]. There are concerns that disruptions to usual care may have led to suboptimal disease control and increased symptoms and exacerbations among patients with CRD. Consequently, this is likely to elevate their risk of pneumonia, ARF, and mortality. Therefore, it is vital to examine the changes in exacerbation, pneumonia, and ARF incidence and mortality rates before and after the first COVID-19 wave among CRD patients.

Despite these concerns, several nationwide studies found significant declines in CRD exacerbations, with a reduction of up to 48% in 2020 reported in Scotland and a sustained decrease over the entire pandemic period reported in France [6–11]. One study in Denmark with a cohort of 14,007 individuals with CRD and without COVID-19 reported a significant reduction of 17% in all-cause mortality during the social distancing period in 2020 [8], but changes in all-cause mortality after the first months of the COVID-19 pandemic remain unknown. Another national study showed that the annual non-COVID mortality rates decreased by 15% among patients with CRD in 2020 [9]. Prior studies on the indirect effect of COVID-19 on non-COVID-19 mortality have focused on the first year of the pandemic, when there were multiple COVID-19 waves and stringent infection control measures, such as social distancing and lockdowns. However, there is a lack of literature on the impact in the year immediately following the initial COVID-19 pandemic and in the years between COVID-19 waves. There is a need for further studies to assess more precisely the temporal effects

of COVID-19 on the incidence of diagnosed complications and mortality among CRD patients without COVID-19 to inform how healthcare services can be better prepared for future public health crises.

Hong Kong adopted the “zero-COVID policy” from the beginning of the pandemic until 2022, with strict containment measures including social distancing, universal masking, contact tracing, and quarantines [12]. Consequently, it has successfully controlled four local waves in 2020 [13]. Hong Kong implemented the vaccination program at the end of February 2021 and recorded almost zero COVID-19 cases until the Omicron wave in January 2022, which was the most significant wave in Hong Kong.

To address these gaps, we aimed to investigate the effect of the COVID-19 pandemic on mortality, complications, and healthcare utilization among patients with CRD without prior COVID-19 in Hong Kong in the first two-year period of the pandemic, using an interrupted time series analysis (ITSA) with a population-based study.

## 2 | Methods

### 2.1 | Data Source

The data in this study was retrieved from the Hospital Authority Clinical Management System (HA CMS), a comprehensive electronic medical record system used by all public healthcare sectors in Hong Kong. The HA CMS covers nearly 90% of hospitalizations, 50% of specialist outpatient clinics (SOPCs), and 30% of first-contact outpatient services in public healthcare in Hong Kong [14]. Clinical information, including demographics, diagnoses, drug prescriptions, laboratory tests, and healthcare attendance, was recorded in HA CMS.

### 2.2 | Study Design and Population

We utilized an open cohort design to examine the effect of COVID-19 on patients with CRD in Hong Kong from January 2011 to December 2021. We included individuals aged 20 years or older with a confirmed CRD diagnosis, identified using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and International Classification of

**TABLE 1** | Baseline demographics of patients with CRD.

	<b>N = 587,049</b>
<b>Follow-up time, years</b>	6.87 ± 3.32
<b>Age, years</b>	59.71 ± 16.82
<b>Age group, N (%)</b>	
20–44	112,655 (19.19)
45–64	232,728 (39.64)
≥65	241,666 (41.17)
<b>Female, N (%)</b>	321,303 (54.73)
<b>CCI</b>	1.30 ± 0.94
<b>CCI group, N (%)</b>	
0	500,611 (85.28)
1	43,234 (7.36)
2	24,610 (4.19)
≥3	18,594 (3.17)
<b>COVID-19 infection, N (%)</b>	1648 (0.28)
<b>Death, N (%)</b>	88,107 (15.01)
<b>Comorbidity</b>	
Heart failure	40,277 (6.86)
Peripheral vascular disease	8941 (1.52)
Cerebrovascular disease	60,467 (10.30)
Dementia	29,103 (4.96)
Diabetes mellitus	17,880 (3.05)
Cancer	55,216 (9.41)

Abbreviation: CCI: Charlson Comorbidity Index.

Note: Continuous variables (follow-up time, age, and CCI) are presented as mean ± standard deviation (SD).

Primary Care, Second Edition (ICPC-2). Additionally, the records of death were classified using the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) (Table S1). Individuals who have been diagnosed with COVID-19 were removed from the study from the month of their diagnosis. The index date of patients was defined as the earliest date of medical records of CRD. To minimize the influence of unknown confounders, a one-year washout period was used to exclude patients who died within one year after the index date of CRD. The participants were followed up from the index date until one of the following: (1) confirmed SARS-CoV-2 infection, (2) death, or (3) last follow-up censored until December 2021, whichever came first. COVID-19 cases were defined based on a documented diagnosis of COVID-19 (ICPC-2, code A77) (Table S1), positive results from polymerase chain reaction (PCR) testing, or administration of antiviral treatments of Paxlovid or Molnupiravir.

### 2.3 | Outcomes

The primary outcomes were the monthly incidence rates (per 100,000 individuals) of mortality (all-cause mortality, respiratory-related mortality, and nonrespiratory-related mortality) and

complications (asthma exacerbations, acute exacerbations of chronic obstructive pulmonary disease (AECOPD), pneumonia, and ARF). Respiratory-related mortality was defined as the deaths due to chronic respiratory diseases (such as COPD and asthma) and respiratory infections. Nonrespiratory mortality is the all-cause mortality excluding the above respiratory deaths and injury deaths. Detailed definitions of respiratory-related mortality, nonrespiratory-related mortality, and complications are shown in Table S1. The secondary outcomes were the monthly healthcare utilization rates for patients with CRDs, including primary care clinic visits, SOPCs, hospital admissions, and Accident & Emergency (A&E) departments. The monthly healthcare utilization rate (per 1000 persons) was calculated by the total number of visits divided by the number of the population with CRD in a given month. Rates were sex- and age-standardized to the CRD cohort in 2019 adjusted for age and sex in different years [15].

### 2.4 | Statistical Analysis

ITSA was computed to estimate the effect of the COVID-19 pandemic on mortality, complications, and healthcare utilization among CRD patients in Hong Kong from January 2011 to December 2021 in Hong Kong [16]. We applied quasi-Poisson regression models with Newey-West standard errors to adjust for autocorrelation. Quasi-Poisson regression is a statistical modeling used to analyze count data or adapted to rates that exhibit overdispersion, a common situation in real-world scenarios [17]. We divided the time series into three periods, including one pre-pandemic phase and two pandemic phases. We set two breaking time points based on specific COVID-19 waves and governmental policy implementation. The first break point was set as February 2020 since the first local COVID-19 case was confirmed on February 4, 2020 [18]. This date was chosen to mark the onset of confirmed local transmission. The second breakpoint was set in March 2021. The Hong Kong government announced that the COVID-19 vaccination program would officially launch in February 2021. By March 2021, Hong Kong had experienced four initial waves of COVID-19 and maintained a low incidence rate, entering a relatively stable period. Therefore, the three periods were (1) the pre-COVID-19 pandemic period (January 2012–January 2020), (2) the “initial COVID-19 pandemic” period (February 2020–February 2021), and (3) the post-initial COVID-19 pandemic period (March 2021–December 2021). The models incorporated step and slope variables as regressors to capture both immediate changes (change in level) and progressive changes (change in trend). The model adjusts seasonal fluctuations by using harmonic terms, including sines and cosines with 3-, 6-, and 12-month periods in those rates, using a 1-month time unit. Then, we calculated expected incidences in initial and post-initial COVID-19 pandemic periods [19] based on the model developed using pre-COVID-19 pandemic period data, assuming the pandemic had not occurred. The effect of COVID-19 on outcomes was assessed by comparing actual rates to the counterfactual estimation, as detailed in the [Supplementary Methods](#).

Subgroup analyses were conducted based on sex (female and male), age (<45, 45–64, ≥65 years), and Charlson Comorbidity Index (CCI) groups each year (CCI: 1, 2, 3, ≥4)[20] (Table S2).

We conducted multiple sensitivity analyses. First, we adjusted for seasonality over 6- and 12-month periods using a quasi-Poisson regression model. Second, we used generalized linear models with log-transformed rates and adjusted 3-, 6- and 12-month period seasonality. Third, we substituted the 12-month washout period with a 6-month washout period to eliminate the washout period. Fourth, as recent literature showed that ICD-9-CM codes 480–488 for pneumonia were associated with COVID-19 cases during the pandemic [21, 22], we excluded all individuals diagnosed with pneumonia in the assessment of the changes in mortality rates. Lastly, since it remains uncertain whether the disease was already circulating in the population before 2020, we redefined the COVID-19 pandemic to started in December 2019.

Statistical significance was defined as a *p*-value less than 0.05. All analyses were conducted using R version 4.2.1.

### 3 | Result

This study included 587,049 individuals with CRD from January 2011 to December 2021. Among those CRD patients, 88,107 (15.01%) deaths were recorded, and 1648 (0.28%) individuals who have documented COVID-19 were excluded from the analysis. Patient baseline characteristics are presented in Table 1. The median follow-up was  $6.87 \pm 3.32$  years (mean  $\pm$  standard deviation). Overall, the mean age was  $59.71 \pm 16.82$  years, with a mean CCI of  $1.30 \pm 0.94$ . Additionally, 321,303 (54.73%) individuals were female.

#### 3.1 | Health Outcomes

The relative changes in all mortality rates, respiratory-related mortality, and nonrespiratory mortality are shown in Table 2 and Figure 1. During the initial COVID-19 pandemic period, there was an increasing trend in nonrespiratory-related mortality (incidence rate ratio (IRR):1.020, 95% confidence interval (CI): (1.006, 1.033); *p* = 0.004), followed by a level increase (1.137 (1.058, 1.223); *p* = 0.001) at the beginning of the post-initial COVID-19 pandemic period. During the post-initial COVID-19 pandemic period, we found an increasing trend in all-cause mortality (1.019 (1.005, 1.034); *p* = 0.007). The trend was similar in respiratory-related mortality (1.032 (1.018, 1.045); *p* < 0.001) and nonrespiratory mortality (1.009 (1.000, 1.018); *p* = 0.046) during the post-initial COVID-19 pandemic period.

Table 2 and Figure 1 illustrate the changes in the incidence rate of asthma exacerbation, AECOPD, pneumonia, and ARF. At the beginning of initial COVID-19 pandemic period, an immediate decrease was observed in asthma exacerbation (0.594 (0.498, 0.708); *p* < 0.001), AECOPD (0.607 (0.506, 0.728); *p* < 0.001), pneumonia (0.645 (0.546, 0.762); *p* < 0.001), and ARF (0.634 (0.553, 0.726); *p* < 0.001). During the initial and post-initial COVID-19 pandemic periods, there were progressive increases in asthma exacerbation, pneumonia, and ARF, with rebounds to pre-pandemic levels.

#### 3.2 | Healthcare Utilization

Table 3 and Figure 2 show changes in healthcare utilization rates over time. When the initial pandemic COVID-19 period began, we observed immediate decreases in all healthcare services, including primary care clinics (0.832 (0.775, 0.892); *p* < 0.001), SOPCs (0.901 (0.848, 0.957); *p* = 0.001), hospital admission (0.739 (0.651, 0.839); *p* < 0.001), and A&E departments (0.727 (0.621, 0.850); *p* < 0.001). During the initial and post-initial COVID-19 pandemic periods, there were gradual rebounds across all service use, including primary care clinics, SOPCs, hospital admission, and A&E departments.

Similar results in health outcomes and healthcare utilization were observed in subgroup analyses for sex, age, and CCI groups (Tables S10–S15) and sensitivity analyses (Tables S3–S9).

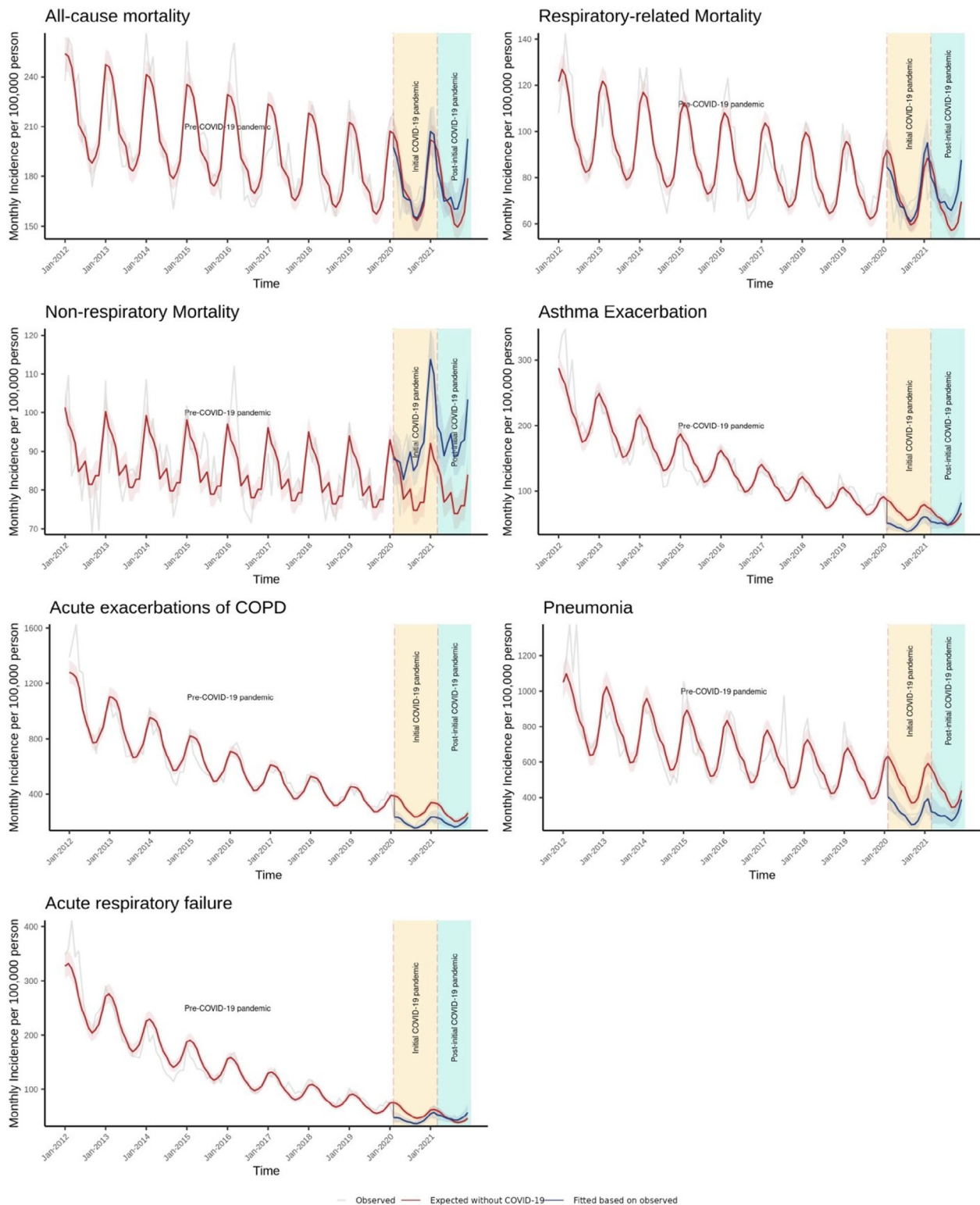
### 4 | Discussion

To the best of our knowledge, this was the first study to report mortality changes over a year from the onset of the COVID-19 pandemic among patients with CRD who had no documented COVID-19. We found an increasing trend in all-cause mortality during the initial COVID-19 pandemic period. Nonrespiratory mortality had a rising trend in the initial COVID-19 pandemic period and was higher than the pre-pandemic level during the initial COVID-19 pandemic and post-initial COVID-19 pandemic periods. We observed that the respiratory mortality rate increased during the post-initial COVID-19 pandemic period when the incidence rate of respiratory complications rebounded. Healthcare utilization rates decreased across all services during the initial period. These findings suggest that the COVID-19 pandemic had a potential indirect adverse effect on mortality among patients with CRD. A possible cause was the healthcare disruption and delayed access to care among these high-risk patients, but further studies are required to explore the true mechanism.

During the initial COVID-19 pandemic period, there were no significant changes in all-cause mortality among people with CRD without prior confirmed COVID-19. This contrasts with findings reported in Denmark, where a significant 17% reduction in all-cause mortality was observed during the first 25 weeks of 2020 compared to the same period of 2019. The differences in the findings between this study and the Danish study may be attributed to several reasons. First, the observation period during the COVID-19 pandemic was much longer in our study (February 2020 to February 2021) during which Hong Kong experienced four local waves with cyclical implementation and easing of social distancing & other containment measures than that of the Danish study (March 12 to May 20, 2020) when strict social distancing was in place at all times. Second, we used a much longer pre-pandemic period between 2012 and 2019 to account for the trends prior to the pandemic than that used in the Danish study (March 12 to May 20, 2019). Third, the population in our study included patients with bronchitis (chronic bronchitis, acute bronchitis, and bronchiectasis), COPD, and asthma, while the Danish study only included patients with COPD.

We found the nonrespiratory mortality rate was higher than the pre-pandemic level throughout the pandemic period. Recent





**FIGURE 1** | Association of COVID-19 pandemic with the incidences rate of mortality and morbidity among patients with chronic respiratory diseases in Hong Kong, January 2012 to December 2021  
Shaded areas represent 95% CI. COPD: chronic obstructive pulmonary disease.

**TABLE 2** | Comparison of incidences rate of mortality and morbidity among patients with CRD during COVID-19 pandemic periods versus pre-COVID-19 pandemic period.

Outcomes <sup>a</sup>	IRR (95% CI) <sup>b</sup>	p Value
<b>All-cause mortality</b>		
Initial COVID-19 pandemic period: immediate impact	0.966 (0.871, 1.071)	0.510
Initial COVID-19 pandemic period: progressive impact	1.005 (0.991, 1.020)	0.478
Post-initial COVID-19 pandemic period: immediate impact	0.952 (0.870, 1.042)	0.287
Post-initial COVID-19 pandemic period: progressive impact	1.019 (1.005, 1.034)	0.007
<b>Respiratory-related mortality</b>		
Initial COVID-19 pandemic period: immediate impact	0.927 (0.789, 1.088)	0.353
Initial COVID-19 pandemic period: progressive impact	1.013 (0.989, 1.037)	0.280
Post-initial COVID-19 pandemic period: immediate impact	0.947 (0.867, 1.034)	0.224
Post-initial COVID-19 pandemic period: progressive impact	1.032 (1.018, 1.045)	0.000
<b>Nonrespiratory-related mortality</b>		
Initial COVID-19 pandemic period: immediate impact	1.004 (0.902, 1.118)	0.935
Initial COVID-19 pandemic period: progressive impact	1.020 (1.006, 1.033)	0.004
Post-initial COVID-19 pandemic period: immediate impact	1.137 (1.058, 1.223)	0.001
Post-initial COVID-19 pandemic period: progressive impact	1.009 (1.000, 1.018)	0.062
<b>Asthma attack</b>		
Initial COVID-19 pandemic period: immediate impact	0.594 (0.498, 0.708)	0.000
Initial COVID-19 pandemic period: progressive impact	1.024 (1.001, 1.048)	0.044
Post-initial COVID-19 pandemic period: immediate impact	0.745 (0.674, 0.823)	0.000
Post-initial COVID-19 pandemic period: progressive impact	1.059 (1.045, 1.072)	0.000
<b>AECOPD</b>		
Initial COVID-19 pandemic period: immediate impact	0.607 (0.506, 0.728)	0.000
Initial COVID-19 pandemic period: progressive impact	1.013 (0.986, 1.040)	0.356
Post-initial COVID-19 pandemic period: immediate impact	0.698 (0.630, 0.773)	0.000
Post-initial COVID-19 pandemic period: progressive impact	1.026 (1.012, 1.041)	0.000
<b>Pneumonia</b>		
Initial COVID-19 pandemic period: immediate impact	0.645 (0.546, 0.762)	0.000
Initial COVID-19 pandemic period: progressive impact	1.003 (0.976, 1.032)	0.819
Post-initial COVID-19 pandemic period: immediate impact	0.573 (0.505, 0.650)	0.000
Post-initial COVID-19 pandemic period: progressive impact	1.050 (1.034, 1.066)	0.000
<b>Acute respiratory failure</b>		
Initial COVID-19 pandemic period: immediate impact	0.634 (0.553, 0.726)	0.000
Initial COVID-19 pandemic period: progressive impact	1.032 (1.014, 1.049)	0.000
Post-initial COVID-19 pandemic period: immediate impact	0.878 (0.761, 1.012)	0.073
Post-initial COVID-19 pandemic period: progressive impact	1.040 (1.008, 1.073)	0.014

Abbreviations: AECOPD: acute exacerbations of chronic obstructive pulmonary disease; CI: confidence interval; CRD: chronic respiratory disease; IRR: incident rate ratio.

<sup>a</sup>Change was estimated as the immediate or progressive changes compared with the “Pre-COVID-19 pandemic period” (January 2012–January 2020), “Initial COVID-19 pandemic period” (February 2020–January 2021), and “Post-initial COVID-19 pandemic period” (February 2021–December 2021).

<sup>b</sup>Unit of incidence rate: per 100,000 people.

research has shown that patients with CRD had a higher prevalence of comorbidities compared with those without CRD [23–25]. Comorbidities such as hypertension, diabetes, chronic kidney disease, cerebrovascular disease, cancer, and depression

were prevalent among patients with CRDs [23]. These concurrent chronic diseases require routine medical care for monitoring and management to prevent or delay complications or disease progression [26, 27]. During the pandemic, these patients had

**TABLE 3** | Comparison of healthcare utilization rates among patients with CRD during COVID-19 pandemic periods versus pre-COVID-19 pandemic period.

Outcomes <sup>a</sup>	IRR (95% CI) <sup>b</sup>	p Value
<b>Primary care clinics</b>		
Initial COVID-19 pandemic period: immediate impact	0.832 (0.775, 0.892)	0.000
Initial COVID-19 pandemic period: progressive impact	1.003 (0.991, 1.015)	0.618
Post-initial COVID-19 pandemic period: immediate impact	0.947 (0.893, 1.003)	0.063
Post-initial COVID-19 pandemic period: progressive impact	0.994 (0.984, 1.004)	0.275
<b>SOPC</b>		
Initial COVID-19 pandemic period: immediate impact	0.901 (0.848, 0.957)	0.001
Initial COVID-19 pandemic period: progressive impact	1.009 (0.999, 1.020)	0.077
Post-initial COVID-19 pandemic period: immediate impact	1.055 (0.977, 1.139)	0.170
Post-initial COVID-19 pandemic period: progressive impact	0.999 (0.985, 1.012)	0.831
<b>Hospital admission</b>		
Initial COVID-19 pandemic period: immediate impact	0.739 (0.651, 0.839)	0.000
Initial COVID-19 pandemic period: progressive impact	1.020 (1.001, 1.040)	0.041
Post-initial COVID-19 pandemic period: immediate impact	0.970 (0.923, 1.020)	0.241
Post-initial COVID-19 pandemic period: progressive impact	1.010 (1.001, 1.018)	0.021
<b>A&amp;E</b>		
Initial COVID-19 pandemic period: immediate impact	0.727 (0.621, 0.850)	0.000
Initial COVID-19 pandemic period: progressive impact	1.013 (0.989, 1.038)	0.282
Post-initial COVID-19 pandemic period: immediate impact	0.915 (0.868, 0.964)	0.001
Post-initial COVID-19 pandemic period: progressive impact	1.016 (1.004, 1.029)	0.011

Abbreviations: A&E: Accident and Emergency Department; CI: confidence interval; CRD: chronic respiratory disease; IRR: incident rate ratio; SOPC: specialist outpatient clinics; SOPC: specialist outpatient clinics.

<sup>a</sup>Change was estimated as the immediate or progressive changes compared with the “Pre-COVID-19 pandemic period” (January 2012–January 2020), “Initial COVID-19 pandemic period” (February 2020–January 2021), and “Post-initial COVID-19 pandemic period” (February 2021–December 2021).

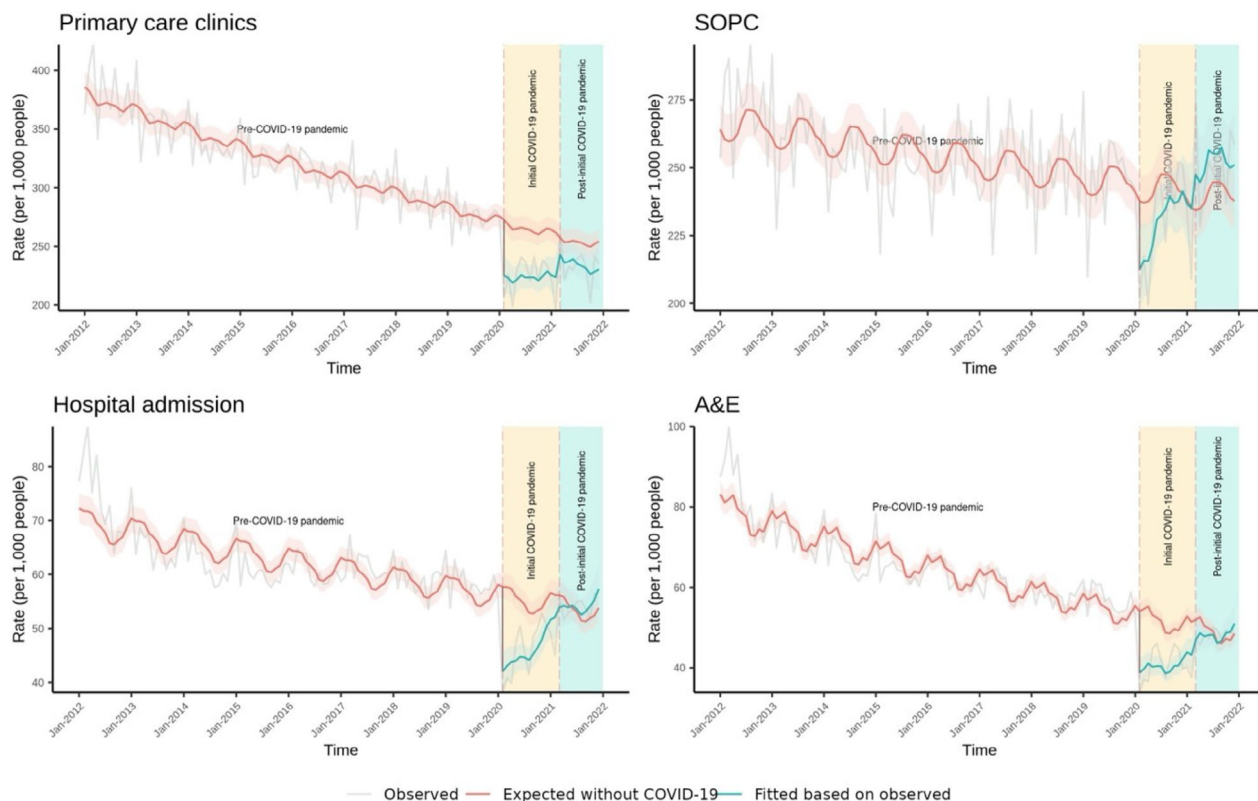
<sup>b</sup>Unit of incidence rate: per 1000 people.

to postpone or cancel regular doctor consultations and check-ups due to restricted access to healthcare and fear of infection [28]. The disrupted routine healthcare may have led to suboptimal disease control and/or delayed detection and treatment for complications. Consequently, this may elevate their risk of mortality. Therefore, we recommend the need to maintain continuing healthcare for patients with CRD, particularly those with concurrent morbidities.

This study revealed a noteworthy reduction in asthma exacerbations and AECOPD during the initial COVID-19 pandemic period in 2020, which was consistent with studies in New Zealand [7], the United Kingdom [6, 29], France [10], and Singapore [30]. In the post-initial COVID-19 pandemic period, no significant trend changes in AECOPD incidence rates were observed in this study, with rates remaining lower than those in the pre-COVID-19 pandemic period. This finding was largely consistent with recent literature reporting the admission rates for AECOPD in 2021 remained lower than those before the pandemic in France and Korea [31, 32]. Respiratory viruses have been recognized as triggers for pneumonia in patients with CRD [33, 34]. During the COVID-19 pandemic, Hong Kong has implemented strict measures to control the transmission of SARS-CoV-2, including

social distancing and universal mask-wearing [13]. In early 2020, the percentage of people wearing facemasks in Hong Kong was over 90% [35]. Prior studies suggested social distancing was associated with significant declines in various respiratory virus infections, such as influenza [36, 37]. A retrospective study in Hong Kong has reported the incidence of pneumonia decreased among the general population during the first year of the pandemic when the strict public health policy was implemented [38]. The reduction in pneumonia incidences among people with CRD in the current study could partly be associated with these containment measures. Nevertheless, it is possible that while the incidence of respiratory complications decreased, the severity of cases might have been higher. Due to the unavailability of data on disease severity, we were unable to evaluate changes in the severity of respiratory complications before and during the pandemic. Further studies with disease severity are required to investigate the underlying mechanism.

Despite the overall decrease in the incidence rate of complications during the initial COVID-19 pandemic period, we did not observe significant changes in respiratory-related mortality rates in this period. This could be explained by the increase in in-hospital mortality for respiratory diseases during the first year worldwide [10,



**FIGURE 2** | Association of COVID-19 pandemic with the healthcare utilization rates among patients with chronic respiratory diseases in Hong Kong, January 2012 to December 2021  
Shaded areas represent 95% CI. SOPC: specialist outpatient clinics; A&E: Accident and Emergency Department.

39, 40]. A cohort study in the United States including 8,448,758 admissions showed that mortality in the 30 days after admission due to pneumonia, COPD, and respiratory failure increased by 42%, 24%, and 19% throughout the first year of the pandemic, respectively [41]. The rise in in-hospital mortality could be attributed to more severe disease at admission. Delayed seeking of medical care due to restricted access to healthcare services and fear of infection in hospital settings result in sicker illness and higher risks of mortality at admission [42, 43]. Moreover, we found an increasing trend of respiratory-related mortality during the vaccination period, which can be attributed to the rebound of incidences of asthma exacerbations, pneumonia, and acute respiratory failure in the same period.

This study has several strengths and limitations. First, this study revealed that the disrupted healthcare from the pandemic may have increased the risk of all-cause mortality in this population, especially those with comorbidities. The findings of this study can inform policymakers about post-pandemic recovery and clinical management for future public health crises among patients with CRD. Second, this current study used a territory-wide dataset with a large sample size of 587,049 individuals, allowing us to present the population-level effect of the pandemic in patients with CRD and without COVID-19. However, some limitations should also be acknowledged. First, we might not be able to exclude all COVID-19 cases since some COVID-19 cases were undiagnosed or asymptomatic. This could have introduced bias into this study, but the possibility was low during the initial

COVID-19 pandemic in Hong Kong when there was very strict reporting, quarantine, and contact tracing of COVID-19 cases. Additionally, most of the deaths, asthma attacks, AECOPD, pneumonia, and ARF occurred during hospitalization in Hong Kong (Table S16), and all patients admitted to the hospital were required to undergo at least two PCR tests for SARS-CoV-2 infections, maximizing the identification of potential infected cases. Second, as is inherent in ITSA, there are limitations in making firm causal inferences due to the lack of a true control group that did not experience the COVID-19 pandemic. Factors other than COVID-19, such as natural fluctuations in healthcare resources, seasonal variations and policy changes, may have contributed to the observed outcomes, making it challenging to attribute observed outcomes solely to the pandemic. To reduce the impact of the aforementioned issue, we have employed a comparable control group using pre-pandemic data to serve as the counterfactual scenario where the COVID-19 pandemic did not occur. Future studies with more rigorous study designs, such as multiregional controlled studies, are required to examine the indirect effect of the COVID-19 pandemic on mortality, complications, and healthcare utilization among patients with CRD. Third, we were unable to stratify the healthcare utilization data by respiratory-related and nonrespiratory-related since the specified reasons for health services visits are lacking in the raw data. Fourth, the effects of the post-initial COVID-19 pandemic period may continue for a long period, which the short duration of follow-up in the present study may not have fully captured. Future studies with longer observation are warranted to identify the trend and



patterns in mortality, complication, and healthcare utilization effectively, especially considering the varying effects of Omicron variants. Fifth, we were unable to conduct the subgroup analysis stratifying by race and region since these data were unavailable in the raw dataset. According to the Population Census conducted by the Hong Kong government, 92.0% and 91.6% of the population in 2016 and 2021 were Chinese, respectively [44]. Given the high proportion of Chinese in the population in Hong Kong, the race-related confounding should be minimal. Additionally, Hong Kong is a small city with minimal regional variability. Although public hospitals are divided into seven geographical clusters, residents have access to the services from all clusters. All public hospitals in Hong Kong use a centralized electronic health record system and standardized clinical protocols, guidelines, and diagnosis coding, which has minimized regional variability in care quality or coding practices. Sixth, given that Hong Kong has unique healthcare systems, infection control measures during the COVID-19 pandemic, healthcare seeking behaviours, and population characteristics, applying the findings of this study to other regions requires caution. Future studies with multiregional designs should be conducted to comprehensively understand the mortality, complications and healthcare utilization changes of patients with CRD during the pandemic worldwide. Seventh, the shifts in clinical attention to respiratory conditions during the COVID-19 pandemic may have influenced the diagnostic coding for CRD. We analyzed longitudinal trends in CRD diagnoses before and during the COVID-19 pandemic. The stable increasing trend of CRD diagnoses suggests no abrupt inflation in diagnostic coding for CRD during the COVID-19 pandemic. The potential influence of heightened attention on respiratory diagnoses is possible but should be minimal. Lastly, since we cannot access actual clinical records, the accuracy of diagnostic coding for CRD cannot be verified in this study. Moreover, there might be potential misclassification bias in differentiating respiratory and nonrespiratory mortality. Nevertheless, previous validation studies reported a high overall positive predictive value of 85.0%–92.7% for CRD diagnostic coding within the electronic health records in the Hospital Authority in Hong Kong, suggesting the diagnostic coding for CRD was reliable for research [45, 46]. Future studies should consider implementing standardized diagnostic coding practices and verifying data by cross-checking with clinical records, to enhance data accuracy and reliability.

In conclusion, the mortality rates, particularly nonrespiratory mortality, among patients with CRD increased during the first two years of the pandemic, which could have been a result of healthcare disruption and delayed access to care among these high-risk patients. Assurance of sufficient allocation of healthcare resources to patients with CRD, particularly those with comorbidities, should be a priority during future public health crises. Contingency plans on continuing follow-up and monitoring of patients with CRD are needed, for example, teleconsultations, shared primary care, and tele-reminders on red-flag symptoms for patients with CRD, when healthcare services may be disrupted during public health crises.

## Disclosure

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## Ethics Statement

This study was approved by the Severance Hospital Institutional Review Board (IRB No. 4-2022-0248) and the Institutional Review Board of the University of Hong Kong Hospital Authority Hong Kong West Cluster (ref.: UW 21–297).

## Conflicts of Interest

The authors declare no conflicts of interest.

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**Supplementary Table 16.** Proportion of Complications and Mortality Diagnosed During Hospitalization Among Patients with CRD Over Time.

### Supporting Information

Additional supporting information can be found online in the Supporting Information section.

**Supplementary Table 1.** ICD-9-CM, ICPC-2, and ICD-10-CM Codes Used to Define Patients With CRD and Complications, Cause of Death.

**Supplementary Table 2.** ICD-9-CM Codes Used to Calculate the Charlson Comorbidity Index.

**Supplementary Table 3.** Sensitivity Analysis on Comparison of Incidences of Mortality and Morbidity Among Patients with CRD During the COVID-19 Pandemic Periods Versus Pre-COVID-19 Pandemic Period with 6- and 12-month Periods of Seasonality.

**Supplementary Table 4.** Sensitivity Analysis on Comparison of Healthcare Utilization Rates among Patients with CRD During the COVID-19 Pandemic Periods Versus Pre-COVID-19 Pandemic Period Using 6- and 12-Month Periods of Seasonality.

**Supplementary Table 5.** Sensitivity Analysis on Comparison of Incidences of Mortality and Morbidity Among Patients with CRD During the COVID-19 Pandemic Periods Versus Pre-COVID-19 Pandemic Period Using Generalized Linear Model.

**Supplementary Table 6.** Sensitivity Analysis on Comparison of Healthcare Utilization Rates among Patients with CRD During the COVID-19 Pandemic Periods Versus Pre-COVID-19 Pandemic Period Using Generalized Linear Model.

**Supplementary Table 7.** Sensitivity Analysis on Comparison of Incidences of Mortality Among Patients with CRD During the COVID-19 Pandemic Periods Versus Pre-COVID-19 Pandemic Period with 6-Month Washout Period or No Washout Period.

**Supplementary Table 8.** Sensitivity Analysis on Comparison of Incidences of Mortality Among Patients with CRD During the COVID-19 Pandemic Periods Versus Pre-COVID-19 Pandemic Period with Exclusion of CRD Patients with Pneumonia.

**Supplementary Table 9.** Sensitivity Analysis on Comparison of Incidences of Mortality and Morbidity Among Patients with CRD During the COVID-19 Pandemic Periods Versus Pre-COVID-19 Pandemic Period with Adjustment of the First Breakpoint Time from February 2020 to December 2019.

**Supplementary Table 10.** Subgroup Analysis on Comparison of Incidences of Mortality and Morbidity Among Patients with CRD During the COVID-19 Pandemic Periods Versus Pre-COVID-19 Pandemic Period Stratified by Sex.

**Supplementary Table 11.** Subgroup Analysis on Comparison of Healthcare Utilization Rates Among Patients with CRD During the COVID-19 Pandemic Periods Versus Pre-COVID-19 Pandemic Period Stratified by Sex.

**Supplementary Table 12.** Subgroup Analysis on Comparison of Incidences of Mortality and Morbidity Among Patients with CRD During the COVID-19 Pandemic Periods Versus Pre-COVID-19 Pandemic Period Stratified by Age.

**Supplementary Table 13.** Subgroup Analysis on Comparison of Healthcare Utilization Rates Among Patients with CRD During the COVID-19 Pandemic Periods Versus Pre-COVID-19 Pandemic Period Stratified by Age.

**Supplementary Table 14.** Subgroup Analysis on Comparison of Incidences of Mortality and Morbidity Among Patients with CRD During the COVID-19 Pandemic Periods Versus Pre-COVID-19 Pandemic Period Stratified by CCI.

**Supplementary Table 15.** Subgroup Analysis on Comparison of Healthcare Utilization Rates Among Patients with CRD During the COVID-19 Pandemic Periods Versus Pre-COVID-19 Pandemic Period Stratified by CCI.