Title: Indirect Effect of COVID-19 Pandemic on Cardiovascular Diseases Incidence, Mortality, and Healthcare Use among Patients with Hypertension but without SARS-CoV-2 Infection in Hong Kong: An Interrupted Time Series Analysis

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ABSTRACT

This study investigated the effects of the COVID-19 pandemic on cardiovascular disease (CVD) incidence among hypertensive patients without SARS-CoV-2 infection by changes in CVD incidence, all-cause mortality, blood pressure (BP) control, and healthcare utilization rates among this population from Hong Kong. Individuals diagnosed with hypertension from January 2010 to January 2020 were followed up until death, SARS-CoV infection, or April 2022. Interrupted time series analyses on 1,318,907 patients with hypertension, comparing outcomes across four periods: pre-pandemic (January 2012-January 2020), early pandemic (February 2020-February 2021), interwave (March-December 2021), and Omicron outbreak (January-April 2022). A significant increase in out-of-hospital mortality was found when the early pandemic started. Overall all-cause mortality increased progressively during the interwave period. CVD incidence decreased immediately in the early pandemic period, followed by a progressive increase, and surpassed the pre-pandemic level at the beginning of the interwave period. The proportion of patients with office-measured BP ≤140/90 mmHg remained below pre-pandemic levels across the pandemic periods. Healthcare utilization declined immediately in February 2020, while most utilization rebounded to the pre-pandemic level after March 2021 and declined again during the Omicron outbreak. Healthcare disruptions during the early pandemic likely delayed CVD diagnosis and treatment, driving an immediate rise in out-of-hospital mortality. When healthcare services gradually recovered in the interwave period, CVD incidence rebounded and both in and out-of-hospital all-cause mortality increased with a lag, possibly related to delayed treatment. (229 words)

Keywords: hypertension; cardiovascular disease; access to healthcare; indirect impact; COVID-19

Introduction

The coronavirus disease 2019 (COVID-19) pandemic had a significant effect on the health and healthcare use of patients with hypertension [1,2]. While the direct effects of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection on hypertension have been well-studied [3,4], its indirect effects, which may have arisen from disrupted health service delivery and an unwillingness to seek care due to concerns of being infected, are not fully understood. Patients with hypertension rely on regular medical consultations for disease monitoring and management [5,6], therefore, the disruption to routine follow-up visits during the pandemic may have contributed to unmet care needs and suboptimal hypertension control and management among this population, contributing to elevated risk of cardiovascular disease (CVD) and mortality. Previous studies reported an increased all-cause or CVD mortality risk among patients with hypertension after the pandemic started [7-10], however, these studies mainly focused on the short-term influence of the first COVID-19 wave, without showing the mid- and long-term effects. Moreover, although Hong Kong modeled China's 'zero-COVID' policy until 2023, its policies were more flexible and less strict, for example, the Hong Kong government-enforced mandatory testing to close contact groups without broad lockdowns [11-13]; by timely adjusting its policy according to the community transmission rate, the government successfully controlled four waves in 2020 and maintained a low infection-level in 2021. The flat and stable pandemic curve enables us to explore whether there was a rebound in healthcare utilization and any delayed trends of CVD and mortality over time. Therefore, to learn a lesson from the pandemic, we aim to investigate the indirect effect of the pandemic on hypertensive population without SARS-CoV-2 infection in Hong Kong by the changes in all-cause mortality, CVD incidence, blood pressure (BP) control, and healthcare service utilization after the

pandemic started, comparing to its historical trend using interrupted time series analysis (ITSA) on population-based and longitudinal data, hoping to improve preparedness in clinical management for future public health emergencies.

Materials and methods

Data Source

We collected longitudinal electronic medical data from the Hong Kong Hospital Authority Clinical Management System (HKHA CMS), which was linked to the Hong Kong Death Registry, between 1st January 2010, and 30th April 2022. HKHA is government-run statutory body that provides public healthcare services across 7 geographical clusters in Hong Kong [14]. All clusters follow standardized clinical protocols and practices, share a unified electronic health record system (CMS), and implement consistent quality assurance programs. Moreover, HKHA CMS covers approximately 90% of inpatient services and hospital admissions, 50% of specialist outpatient clinics (SOPC) visits, and 30% of first-contact outpatient services [15-17]. Such a centralized nature and territory-wide coverage of HKHA may minimize potential center-specific variations and loss to follow-up among those who utilize public health services and the data has demonstrated a high accuracy [16,17]. Data on demographics, diagnosis records, laboratory, and physical examinations, treatment details, death information, and healthcare utilization, including primary care clinics, SOPCs, hospital admissions, and Accident & Emergency department (A&E) visits were aggregated at an individual-monthly level.

Study Population

We included patients with a documented diagnosis of hypertension from January 2010 to January 2020, who were identified using the International Classification of Primary Care, Second Edition (ICPC-2) and the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) (**Supplementary Table 1)**. The index date was defined as the first date of hypertension documentation. The baseline date was defined as the date starting observation for outcomes of interest. We applied a 6-month washout period to exclude patients who died or had health outcomes of interest within 6 months after the baseline date to avoid confounders introduced by patients who died shortly after the baseline date [18]. Longitudinal data on eligible patients would be retrieved until 1) the month before documented SARS-CoV-2 infection, 2) the death date, or 3) 30 April 2022, the end of the study period, whichever came first.

Outcome Measures

The primary outcomes were monthly incidence rates of all-cause mortality and CVD. As the HKHA mandated that all patients undergo SARS-CoV-2 testing (either polymerase chain reaction tests or rapid antigen tests) before and during hospital admission until December 2022 [19], the in-hospital records of all-cause mortality, and CVD incidence which was mainly diagnosed in hospitals, were believed to be minimally affected by undiagnosed infected cases. Deaths that occurred during hospitalization in hospitals managed by HKHA were defined as in-hospital mortality and others were out-of-hospital deaths [20]. CVD incidence was defined as the first occurrence of coronary heart disease (CHD), stroke, or heart failure (HF) documented in the HKHA CMS. Detailed definitions are shown in **Supplementary Table 1**. The secondary outcomes were healthcare utilization rates, including primary care clinics, SOPCs, hospital admissions, A&E attendance, and prescription rate of anti-

hypertensive agents along with its mean length of dispensing duration (days), monthly proportion (%) of patients who achieved systolic blood pressure (SBP)≤140mmHg and diastolic blood pressure (DBP)≤90mmHg for patients with recorded office measured blood pressure [21], among all patients with office-measured BP records in each specific month. All rates, mean length of dispensing duration, and proportions of patients achieved above BP control targets were sex- and age-standardized to the patient group in 2019 [17] to account for different sex and age distributions across follow-up years.

Statistical Analysis

In the ITSA, we applied segmented quasi-Poisson regression models [22,23] with seasonality adjustment using harmonic terms (sines and cosines with 3-, 6- and 12-month periods) as rates were overdispersal (**Supplementary Table 6**). The first breakpoint was designated as February 2020, given that the first confirmed case of COVID-19 was on 23rd January 2020, and Hong Kong has started to implement stringent control measures [12]. The second breakpoint was set as March 2021, when the fourth wave of COVID-19 ended and infection levels in Hong Kong were relatively low until the Omicron outbreak [24,25]. The third breakpoint was set as January 2022, when Omicron variants started to spread through the community [26] and began the most significant wave in Hong Kong [27,28] (**Supplementary Figure 1**). Therefore, the overall observation period was divided into four subperiods: 'pre-pandemic period' (months 1-97, January 2012-January 2020), 'early pandemic period' (months 98-110, February 2020-February 2021, covering the 1st wave through the 4th wave), 'interwave period' (months 111-120, March 2021-December 2021), and 'Omicron outbreak period' (months 121-124, January 2022-April 2022, covering the peak of the 5th wave). We

introduced step (level) and slope (trend) variables as regressors in the model to estimate immediate changes and progressive changes in the monthly outcomes rates at three breakpoints, compared with the pre-pandemic situation (**Supplementary Methods equation 1**). Moreover, we employed Newey-West standard error [29] to adjust for potential autocorrelation and heteroskedasticity of the residuals. The presence of autocorrelation was confirmed using the *Breusch-Godfrey* test and the maximum significant lag orders were defined by partial autocorrelation function, while heteroskedasticity was detected using the *Breusch-Pagan* test. The association between anti-hypertensive prescription rate and dispensing duration, %patients achieved SBP/DBP ≤140/90mHg, all-cause mortality and CVD incidence was further estimated by using the similar multivariable quasi-Poisson model as the ITSA but adjusted healthcare utilization rates (**Supplementary Methods equation 2**).

Subgroup analyses were conducted based on sex (male and female), three age groups within each year (20-44, 45-64, ≥65), and age-adjusted Charlson Comorbidity Index (ACCI) within each year (ACCI: 0-2, 3-4, ≥5) [30,31] (**Supplementary Table 3**). To enhance the robustness of the findings, sensitivity analyses on different washout periods, seasonality, and model type were performed with 1) 0 and 12-month washout periods for health outcomes; 2) 6- and 12-month period seasonality adjustment, and 3) generalized linear models with log-transformed rates and adjusting 3-, 6- and 12-month period seasonality.

The significance level was set at $p<0.05$, and a 95% confidence interval (CI) was calculated. All analyses were performed using R 4.3.1 (R Core Team, Vienna, Austria)

Results

Description of the study population

A total of 1,318,907 patients diagnosed with hypertension from January 2010 to January 2020 were included in this study; 628,578 (47.7%) of them were male. A total of 310,726 (23.6%) patients died during the study period without a washout period, and 75,719 (5.7%) patients were infected with SARS-CoV-2. Patient characteristics are presented in **Table 1**.

All-Cause Mortality and CVD Incidence

Figure 1 shows all-cause mortality rates and CVD incidence changes due to the pandemic. Compared with the pre-pandemic level, we found that the all-cause mortality rate did not change significantly during the early pandemic period and at the beginning of the interwave period, but with a progressive increase of 1.3% (95% CI: 0.7% to 1.8%) per month afterward; however, the out-of-hospital mortality increased significantly when the early pandemic started (immediate impact 22.0%, 95%CI: 6.9% to 39.1%, **Table 2**). There was a significant drop in CVD incidence at the beginning of the early pandemic period (immediate impact, -15.8%, 95% CI: -26.0% to -4.3%), followed by a significant increase trend (progressive impact, 2.2%, 95% CI: 0.8% to 3.5%) during this period. At the start of the interwave period, the CVD incidence rate was 17.9% (immediate impact, 95%CI: 9.0% to 27.6%) higher than the pre-pandemic period and maintained a higher level (**Table 2** and **Figure 1**).

Similar changes were found in the incidence of all subtypes of CVD during the early pandemic period, but only CHD and stroke rebounded significantly when the interwave

period started (**Supplementary Figure 2 and Supplementary Table 7**). The observed stroke incidence in females, those aged ≥45 years, and those with ACCI≥3 (**Supplementary Figures 4-6**) exceeded the predicted incidence significantly in March 2021. Most results of sensitivity analyses with different seasonality and linear model were similar to the main analyses, however, without applying a washout period we found that the rebound of CVD incidence in March 2021 was not significant especially stroke (**Supplementary Tables 8, 9,10** & **12**).

Healthcare Utilization

As **Table 3** and **Figure 2** present, when the first COVID-19 wave began, all healthcare service utilization rates declined immediately, including SOPC visits (-17.4%, 95%CI: -23.4% to -10.8%), primary care clinics visits (-6.7%, 95%CI: -10.3% to -3.0%), hospital admissions (-23.5%, 95%CI: -30.5% to -15.8%) and A&E visits (-28.8%, 95%CI: -37.5% to -18.9%). Rates of SOPC visits, primary care clinic visits, and hospital admissions recovered gradually afterward and returned to the pre-pandemic level in March 2021, while A&E visits were at significantly lower levels (-11.3%, 95%CI: -14.6% to -7.8%). During the Omicron outbreak period, all healthcare service utilization had a significantly decreasing trend. Sensitivity analyses found similar results (**Supplementary Tables 11 & 13**).

Blood Pressure Control and Prescription

The proportion of people with office-measured BP ≤140/90 mmHg was continuously lower than the pre-pandemic level after the first wave of the COVID-19 pandemic (**Supplementary Tables 7 & Supplementary Figure 3**).

In terms of anti-hypertensive agents, the decline in the prescription rate (immediate impact, -5.3%, 95%CI: -10.6% to -0.1%) was accompanied by an increased dispensing duration (immediate impact, 4.9%, 95%CI: 1.2% to 8.7%) right after the first wave. The dispensing duration increased spontaneously when the prescription rate progressively dropped during the Omicron outbreak period (**Supplementary Table 7**). The results of sensitivity analyses were consistent with the primary analyses **(Supplementary Tables 10-13**).

The Association of Prescription with Blood Pressure Control, CVD Incidence, and All-Cause Mortality

As shown in **Table 4**, prescription rate (relative risk, RR: 1.000, 95%CI: 1.000 to 1.000, p<0.001) and mean length of dispensing duration of anti-hypertensive agents (RR: 1.010, 95%CI: 1.009 to 1.011) were significantly associated with %patients achieved SBP/DBP≤140/90 mmHg; higher proportion was associated with lower CVD incidence (RR: 0.181, 95%CI: 0.153 to 0.214), and lower all-cause mortality (RR: 0.402, 95%CI: 0.328 to 0.494) after adjusting temporal trend, seasonality, healthcare utilization rates and periods.

Discussion

To our knowledge, this is the first study presenting the change in CVD incidences among uninfected patients with hypertension before and after the COVID-19 pandemic. Using over 10 years of population-based data, we found CVD incidence had an immediate drop when the pandemic began while the out-of-hospital mortality increased. An excessive rebound in March 2021 was also found in CVD incidence, along with an increasing trend in all-cause mortality rate. These changes indicated delayed diagnosis

and treatment of CVD, which was possibly linked to the decline in healthcare service utilization in the early pandemic period and suboptimal BP control throughout the pandemic, and subsequently raised the mortality risk.

We observed the incidence of CVD and its subtypes declined right after the first COVID-19 wave but rebounded and surpassed the pre-pandemic level during the interwave period. Given that the trend in CVD incidence between 2012 and 2019 was stable and a drastic fluctuation in the CVD incidence is biologically implausible among patients with hypertension, indicating that patients who should have been diagnosed with CVD in 2020 'caught up' with diagnoses in 2021. Delayed diagnosis and management of CVD were associated with more extended hospital stays, poorer prognosis, and higher risk of mortality [32]. Notably, we found the incidence of acute and fatal CVD event, AMI, was lower than the pre-pandemic level right after the initial and the Omicron outbreak along with a significantly increased out-of-hospital mortality spontaneously, raising a concern that the potential cases died at home without receiving diagnoses or care [33].

Our study showed no significant change in mortality rates in the early pandemic period, which differed from prior studies suggesting that cardiovascular and all-cause mortality increased by 12.9% [8] and 17.1% to 48.3% [7,34] in 2020 compared with the pre-pandemic period among patients with hypertension, respectively. Such differences could be attributed to different disease control policies and medical care-seeking behaviors between Hong Kong and other countries. Compared to these studies which were at most one-year follow-up, our study had a longer-term follow-up period after 2020, enabling us to observe the lagged effects on mortality. We found an upward trend

of mortality during the interwave period followed the rebound of the CVD incidence, which is probably related to delayed treatment of delayed diagnosed CVD and other diseases, even though healthcare services gradually restored and diagnosis 'catch-up' during the interwave period, delayed CVD treatment increases the mortality risk. Studies with more extended observation are needed to monitor the change in the mortality rates after the Omicron outbreak, which was the most significant wave and caused massive disruption in healthcare services in Hong Kong.

When the first COVID-19 case was confirmed in January 2020 (**Supplementary Figure 1**), the Hong Kong government declared an 'emergency' level. The fear of infection, hospital and clinic shutdown, and stringent medical manpower have discouraged people with underlying CVD from seeking medical care, leading to significant immediate drops in all healthcare service utilization, as observed in our study. The present findings in changes in CVD incidence rates and deterioration in blood pressure control might result from the changes in healthcare-seeking behaviors and healthcare resources provision in patients with hypertension, similar to another study from Hong Kong [20]. A previous study in the United States has similar findings among the general population that visits A&E have declined by 23% for myocardial infarction and 20% for stroke during the national emergency period [35]. Moreover, due to the reallocation of healthcare resources to emergency COVID-19 care [36], SOPCs and primary care services have been reduced in Hong Kong, contributing to disrupted routine medical consultations and health checks. Consequently, asymptomatic patients with CVD could not be identified and diagnosed [37]. Therefore, to reduce treatment delay in future public health crises, it is crucial to maintain necessary outpatient services to ensure regular follow-up and health checks and access

to A&E and hospitalization services, where patients with CVD-related symptoms get evaluated and treated.

Due to the disrupted routine medical care and other pandemic effects [38], there are concerns about suboptimal BP management among patients with hypertension during the pandemic. Most of the current evidence suggested a worse BP control during the early phase of the pandemic [39-41], whereas some studies reported no negative impact of the outbreak on BP control [42,43]. Our study found the proportion of patients with BP targeted to ≤140/90 mmHg after the first wave was lower than the pre-pandemic level, which was the independent contributor to the CVD incidence and all-cause mortality rate in 2021, similar to the previous report [44]. The increased dispensing duration of anti-hypertensive agents reflected the physicians' efforts to maintain treatment adherence when in-person care was disrupted during the first and the Omicron outbreak, but such efforts might be not sufficient. Monitoring BP and evaluating CVD risk through telemedicine [45,46] can help maintain adherence and timely adjust regimens during in-person care disruption.

Perspective of Asia

Asian countries, particularly in urban areas like Hong Kong, implemented longer periods of strict policies, including healthcare disruptions and broad lockdowns [47], to manage the COVID-19 pandemic compared to Western countries. Consequently, the indirect effects of the pandemic on CVD incidence and blood pressure control among patients with hypertension and without SARS-CoV-2 infection may differ, and the strength of these effects may also vary. Further research is needed to confirm the long-

term indirect effects of the COVID-19 pandemic, as well as its impact on other countries, especially in rural areas.

Strengths and Limitations

This study had several strengths: first, using population-based data from more than 1.3 million people, we have reported for the first time the in-depth indirect pandemic impact on CVD incidence among patients with hypertension who had never been infected with SARS-CoV-2, providing information for future public health emergency in terms of medical services maintenance and allocation. Second, Hong Kong implemented a mandatory and active case-detection policy and maintained a low infection level (**Supplementary Figure 1**) until the start of the Omicron outbreak period, and the compulsory tests for infection before and during hospital admissions [19], making the SARS-CoV-2 infection records we retrieved reliable and representative. Lastly, Newey-West standard errors and sensitivity analyses could enhance the robustness of our findings, even though there were some results varied from different washout periods, their confidence intervals largely overlapped, suggesting effect sizes are stable between the main analyses and the sensitivity ones; moreover, as our study based on monthly data, it is difficult to detect which one came first, baseline or the index date. Therefore, applying no washout period may overestimate the incidence rates, contributing to the remarkable difference between sensitivity analysis without a washout period and the main one with a 6-month washout period.

This study also has some limitations. We did not include the data from private hospitals. Due to the reallocation of public healthcare services to COVID-19 cases, patients might seek medical care from private hospitals, probably resulting in an underestimated CVD

incidence and in-hospital mortality. However, the public sector serves over 90% of the people with chronic diseases in Hong Kong with considerable governmental subsidies [48,49]. In the territory-wide Hong Kong Population Health Survey 2020-22, there was only 9.9% of patients with hypertension visited private clinics or hospitals for follow-up care [50]. The HKHA database is believed to be population representative. Secondly, we did not reveal the recovery pattern later in the Omicron epidemic period. But we can presume a similar finding as in 2021. Future study with longer follow-up duration is needed to reveal the long-term impact of the pandemic.

Conclusion

In conclusion, healthcare disruptions during the early pandemic likely delayed CVD diagnosis and treatment, driving an immediate rise in out-of-hospital mortality. As healthcare services gradually recovered in the inter-wave period, CVD incidence rebounded, and all-cause mortality increased with a lag, possibly related to 'catch-up' in diagnosis and delayed treatment, respectively. A similar trend in adverse effects was observed during the Omicron period, though the full lag effect remains unclear. These findings highlight the need for contingency plans to maintain routine healthcare services for patients with hypertension in future public health crises.

Acknowledgments

Author contributions

ZH and YKY had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. ZH and YKY collected and prepared the data, ZH and YKY performed the data analysis, and ZH performed the visualization. ZH and YKY wrote the manuscript with feedback from CLKL, EYFW, JQ, KAG, ILM, GKKL, ICKW, DVKC, WWKK, CSL, CLKL, and EYFW. EYFW, CLKL, JQ obtained funding from Hong Kong. All authors interpreted the findings, provided a critical review of important intellectual content, and approved the final version.

Role of the Funder/Sponsor

The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation of the manuscript.

Ethical approval

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).

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Data availability

Data will not be made available to others because the data custodians have not given permission.

Statement

During the preparation of this work, the author(s) did not use any generative AI tools.

Conflict of interest

EYFW has received research grants from the Health Bureau of the Government of the Hong Kong SAR, the Hong Kong Research Grants Council of the Government of the Hong Kong SAR, Narcotics Division, Security Bureau of the Government of the Hong Kong SAR, and National Natural Science Foundation of China, outside the submitted work. ICKW reports research funding from Amgen, Bristol Myers Squibb, Pfizer, Janssen, Bayer, GSK, Novartis, the Hong Kong Research Grants Council of the Government of the Hong Kong SAR, the Hong Kong Health and Medical Research Fund, the National Institute for Health Research in England, the European Commission, and the National Health and Medical Research Council in Australia, consulting fees from IQVIA and World Health Organisation, payment for expert testimony for Appeal Court of Hong Kong and is a non-executive director of Jacobson Medical in Hong Kong, Advance Data Analytics for Medical Science (ADAMS) Limited (HK), Asia Medicine Regulatory Affairs (AMERA) Services Limited and OCUS Innovation Limited (HK, Ireland and UK) a former director of Therakind in England, outside of the submitted work. ICKW reports role as member of Pharmacy and Poisons Board in Hong Kong, the Expert Committee on Clinical Events Assessment Following COVID-19

Immunisation, and the Advisory Panel on COVID-19 Vaccines of the Hong Kong Government.

Abbreviations

A&E	Accident and Emergency Department
ACCI	Age-adjusted Charlson Comorbidity Index
AMI	Acute myocardial infarction
BP	Blood pressure
CHD	Coronary heart disease
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CVD	Cardiovascular diseases
DBP	Diastolic blood pressure
HKHA CMS	Hong Kong Hospital Authority Clinical Management System
HF	Heart failure
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICPC-2	International Classification of Primary Care, Second Edition
ITSA	Interrupted time series analyses
LDL-C	Low-density lipoprotein cholesterol
RR	Rate Ratio
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SBP	Systolic blood pressure
SOPC	Specialist outpatient clinics
WHO	World Health Organization

Reference

1. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020;382:1708-20.
2. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. JAMA. 2020;323:2052-9.
3. Pranata R, Lim MA, Huang I, Raharjo SB, Lukito AA. Hypertension is associated with increased mortality and severity of disease in COVID-19 pneumonia: A systematic review, meta-analysis and meta-regression. J Renin Angiotensin Aldosterone Syst. 2020;21:1470320320926899.
4. Zhang J, Wu J, Sun X, Xue H, Shao J, Cai W, et al. Association of hypertension with the severity and fatality of SARS-CoV-2 infection: A meta-analysis. Epidemiol Infect. 2020;148:e106.
5. Whelton Paul K, Carey Robert M, Aronow Wilbert S, Casey Donald E, Collins Karen J, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. Journal of the American College of Cardiology. 2018;71:e127-e248.
6. Lam CL, Ngai K, Lee JP. The Hong Kong Reference Framework for Hypertension Care for adults in primary care settings-translating evidence into practice. Hong Kong Practitioner. 2012.)
7. Anderson KK, Maresh S, Ward A, Koller EA, Connor P, Evans M, et al. The COVID-19 pandemic's impact on all-cause mortality disparities in Medicare: By race, income, chronic health, mental/behavioral health, disability. Gen Hosp Psychiatry. 2023;81:57-67.
8. Hennecken C, Doulamis IP, McLaughlin L, Avgerinos D, Briasoulis A, Kampaktsis PN. Increase in hypertension-related cardiovascular mortality in the United States early in the COVID-19 pandemic. J Cardiovasc Med (Hagerstown). 2023;24:315-6.
9. de Lusignan S, Joy M, Oke J, McGagh D, Nicholson B, Sheppard J, et al. Disparities in the excess risk of mortality in the first wave of COVID-19: Cross sectional study of the English sentinel network. J Infect. 2020;81:785-92.
10. Li L, Hang D, Dong H, Yuan-Yuan C, Bo-Heng L, Ze-Lin Y, et al. Temporal dynamic in the impact of COVID- 19 outbreak on cause-specific mortality in Guangzhou, China. BMC Public Health. 2021;21:883.
11. COVID-19. https://www.news.gov.hk/eng/categories/covid19/index.html. Accessed Jan 18.
12. Together, we fight the Virus! https://www.coronavirus.gov.hk/eng/index.html. Accessed Jan 18.
13. Burki T. Hong Kong's fifth COVID-19 wave-the worst yet. Lancet Infect Dis. 2022;22:455-6.
14. Schoeb V. Healthcare service in Hong Kong and its challenges. The role of health professionals within a social model of health. China Perspectives. 2016;2016:51-8.

15. Your Health, Your Life: APPENDIX B HONG KONG'S CURRENT HEALTHCARE SYSTEM. In: Health Bureau HKS, China (ed). https://www.healthbureau.gov.hk/beStrong/files/consultation/appendixb_eng.pdf.). Health Bureau2013.
16. Ren QW, Yu SY, Teng TK, Li X, Cheung KS, Wu MZ, et al. Statin associated lower cancer risk and related mortality in patients with heart failure. Eur Heart J. 2021;42:3049-59.
17. Wang Y, Xu W, Mak IL, Chin WY, Yu EYT, Lam CLK, et al. Trends of clinical parameters and incidences of diabetes mellitus complications among patients with type 2 diabetes mellitus in Hong Kong, 2010-2019: a retrospective cohort study. EClinicalMedicine. 2023;60:101999.
18. Kim SM, Jeong Y, Kim YL, Kang M, Kang E, Ryu H, et al. Association of Chronic Kidney Disease With Atrial Fibrillation in the General Adult Population: A Nationwide Population-Based Study. J Am Heart Assoc. 2023;12:e028496.
19. *Quality and Safety Annual Report 2022.* 2022.
20. Xin H, Wu P, Wong JY, Cheung JK, Lau EHY, Leung GM, et al. Hospitalizations and mortality during the first year of the COVID-19 pandemic in Hong Kong, China: An observational study. Lancet Reg Health West Pac. 2023;30:100645.
21. Lim MK, Ha SCN, Luk KH, Yip WK, Tsang CSH, Wong MCS. Update on the Hong Kong Reference Framework for Hypertension Care for Adults in Primary Care Settings-review of evidence on the definition of high blood pressure and goal of therapy. Hong Kong Med J. 2019;25:64-7.
22. Mascha EJ, Sessler DI. Segmented Regression and Difference-in-Difference Methods: Assessing the Impact of Systemic Changes in Health Care. Anesth Analg. 2019;129:618-33.
23. Taljaard M, McKenzie JE, Ramsay CR, Grimshaw JM. The use of segmented regression in analysing interrupted time series studies: an example in pre-hospital ambulance care. Implement Sci. 2014;9:77.
24. Lau SSS, Ho CCY, Pang RCK, Su S, Kwok H, Fung S-f, et al. COVID-19 Burnout Subject to the Dynamic Zero-COVID Policy in Hong Kong: Development and Psychometric Evaluation of the COVID-19 Burnout Frequency Scale. Sustainability. 2022;14:8235.
25. Li X, Tong X, Yeung WWY, Kuan P, Yum SHH, Chui CSL, et al. Two-dose COVID-19 vaccination and possible arthritis flare among patients with rheumatoid arthritis in Hong Kong. Ann Rheum Dis. 2022;81:564-8.
26. Mefsin YM, Chen D, Bond HS, Lin Y, Cheung JK, Wong JY, et al. Epidemiology of Infections with SARS-CoV-2 Omicron BA.2 Variant, Hong Kong, January-March 2022. Emerg Infect Dis. 2022;28:1856-8.
27. Burki T. Hong Kong's fifth COVID-19 wave—the worst yet. The Lancet Infectious Diseases. 2022;22:455-6.
28. Yang B, Lin Y, Xiong W, Liu C, Gao H, Ho F, et al. Comparison of control and transmission of COVID-19 across epidemic waves in Hong Kong: an observational study. The Lancet Regional Health – Western Pacific. 2024;43:
29. Newey WK, West KD. A simple, positive semi-definite, heteroskedasticity and autocorrelationconsistent covariance matrix. 1986.)
30. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. J Clin Epidemiol. 1994;47:1245-51.

31. Huang YQ, Gou R, Diao YS, Yin QH, Fan WX, Liang YP, et al. Charlson comorbidity index helps predict the risk of mortality for patients with type 2 diabetic nephropathy. J Zhejiang Univ Sci B. 2014;15:58-66.
32. Moroni F, Gramegna M, Ajello S, Beneduce A, Baldetti L, Vilca LM, et al. Collateral Damage: Medical Care Avoidance Behavior Among Patients With Myocardial Infarction During the COVID-19 Pandemic. JACC Case Rep. 2020;2:1620-4.
33. Wu J, Mamas MA, Mohamed MO, Kwok CS, Roebuck C, Humberstone B, et al. Place and causes of acute cardiovascular mortality during the COVID-19 pandemic. Heart. 2021;107:113-9.
34. Fornasini M, Sisa I, Baldeon ME. Increased Cardiovascular Mortality in Ecuador during COVID-19 Pandemic. Ann Glob Health. 2023;89:21.
35. Lange SJ, Ritchey MD, Goodman AB, Dias T, Twentyman E, Fuld J, et al. Potential Indirect Effects of the COVID-19 Pandemic on Use of Emergency Departments for Acute Life-Threatening Conditions - United States, January-May 2020. MMWR Morb Mortal Wkly Rep. 2020;69:795-800.
36. Department TIS. Hospital services to be adjusted. https://www.news.gov.hk/eng/2020/02/20200210/20200210_180258_488.html. Accessed 11 June 2024.
37. Wallace ML, Ricco JA, Barrett B. Screening strategies for cardiovascular disease in asymptomatic adults. Prim Care. 2014;41:371-97.
38. Kreutz R, Dobrowolski P, Prejbisz A, Algharably EAE, Bilo G, Creutzig F, et al. Lifestyle, psychological, socioeconomic and environmental factors and their impact on hypertension during the coronavirus disease 2019 pandemic. J Hypertens. 2021;39:1077-89.
39. Gotanda H, Liyanage-Don N, Moran AE, Krousel-Wood M, Green JB, Zhang Y, et al. Changes in Blood Pressure Outcomes Among Hypertensive Individuals During the COVID-19 Pandemic: A Time Series Analysis in Three US Healthcare Organizations. Hypertension. 2022;79:2733-42.
40. Omboni S, Ballatore T, Rizzi F, Tomassini F, Panzeri E, Campolo L. Telehealth at scale can improve chronic disease management in the community during a pandemic: An experience at the time of COVID-19. PLoS One. 2021;16:e0258015.
41. Zhang S, Zhou X, Chen Y, Wang L, Zhu B, Jiang Y, et al. Changes in Home Blood Pressure Monitored Among Elderly Patients With Hypertension During the COVID-19 Outbreak: A Longitudinal Study in China Leveraging a Smartphone-Based Application. Circ Cardiovasc Qual Outcomes. 2021;14:e007098.
42. Feitosa F, Feitosa ADM, Paiva AMG, Mota-Gomes MA, Barroso WS, Miranda RD, et al. Impact of the COVID-19 pandemic on blood pressure control: a nationwide home blood pressure monitoring study. Hypertens Res. 2022;45:364-8.
43. Sornsenee P, Vichitkunakorn P, Choomalee K, Romyasamit C. Effect of the COVID-19 Pandemic and Other Predictors of True Therapeutic Inertia on Patients with Hypertension in a Primary Care Clinic in Thailand. Risk Manag Healthc Policy. 2021;14:3807-16.
44. Zhou D, Xi B, Zhao M, Wang L, Veeranki SP. Uncontrolled hypertension increases risk of all-cause and cardiovascular disease mortality in US adults: the NHANES III Linked Mortality Study. Sci Rep. 2018;8:9418.

45. Russo V, Cassini R, Caso V, Donno C, Laezza A, Naddei M, et al. Nursing Teleconsultation for the Outpatient Management of Patients with Cardiovascular Disease during COVID-19 Pandemic. Int J Environ Res Public Health. 2021;18:
46. Salisbury C, O'Cathain A, Thomas C, Edwards L, Gaunt D, Dixon P, et al. Telehealth for patients at high risk of cardiovascular disease: pragmatic randomised controlled trial. Bmj. 2016;353:i2647.
47. Ho HK. COVID-19 Pandemic Management Strategies and Outcomes in East Asia and the Western World: The Scientific State, Democratic Ideology, and Social Behavior. Front Sociol. 2020;5:575588.
48. Hong Kong Healthcare System and Healthcare Professionals. In. https://www.healthbureau.gov.hk/download/press_and_publications/otherinfo/180500_sr/e_ch1.pdf.). Hong Kong Health Bureau2016.
49. Lau IT. A Clinical Practice Guideline to Guide a System Approach to Diabetes Care in Hong Kong. Diabetes Metab J. 2017;41:81-8.
50. Report of Population Health Survey 2020-22 (Part I) In. https://www.chp.gov.hk/files/pdf/dh_phs_2020-22_part_1_report_eng_rectified.pdf.). Centre of Health Protection, Department of Health, The Government of Hong Kong SAR 2022.

Point of view

- Clinical relevance

As healthcare services gradually recovered during the interwave period, CVD incidence rebounded, and both in- and out-of-hospital all-cause mortality increased with a lag, potentially related to delayed treatment among patients with hypertension who did not have SARS-CoV-2 infection.

- Future direction

Further research is essential to confirm the long-term indirect effects of the COVID-19 pandemic and to assess its impact in other countries, particularly in rural areas.

- Consideration for the Asian population

Asian countries, particularly in urban areas like Hong Kong, implemented longer periods of strict policies, including healthcare disruptions and broad lockdowns, to manage the COVID-19 pandemic compared to Western countries, which may have led to differing indirect effects on cardiovascular disease incidence and blood pressure control among patients with hypertension who did not have SARS-CoV-2 infection, along with variations in the strength of these effects.

Figure legends

Figure 1 Association of (1) the initial COVID-19 outbreak, (2) the interwave period, and (3) the 'Omicron outbreak' with the monthly age- and sex-standardized incidence rates for all-cause mortality and CVD among patients with hypertension in Hong Kong, January 2012 to April 2022

Note: The grey solid line shows observed data. The blue solid line shows the model estimates based on observed data, and the orange solid line shows the predicted values based on pre-pandemic data using the quasi-Poisson regression. Red and blue shaded areas represent 95%CI. Lag(all-cause mortality)=0, lag(CVD)=2.

Figure 2 Association of (1) the initial COVID-19 outbreak, (2) the interwave period, and (3) the 'Omicron outbreak' with the monthly age- and sex-standardized rates for healthcare utilization among patients with hypertension in Hong Kong, January 2012 to April 2022

Note: The grey solid line shows observed data. The blue solid line shows the model estimates based on observed data, and the orange solid line shows the predicted values based on pre-pandemic data using the quasi-Poisson regression. Red and blue shaded areas represent 95%CI. SOPC: specialist outpatient clinics. A&E: Accident and Emergency Department. Lag(primary care)=2, lag(SOPC) =2, lag(hospital admission)=0, lag(A&E)=0.