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Retrospective cohort study to investigate the 10-year trajectories of disease patterns in patients with hypertension and/or diabetes mellitus on subsequent cardiovascular outcomes and health service utilisation: a study protocol

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ABSTRACT

Introduction Hypertension (HT) and diabetes mellitus (DM) and are major disease burdens in all healthcare systems. Given their high impact on morbidity, premature death and direct medical costs, we need to optimise effectiveness and cost-effectiveness of primary care for patients with HT/DM. This study aims to find out the association of trajectories in disease patterns and treatment of patients with HT/DM including multimorbidity and continuity of care with disease outcomes and service utilisation over 10 years in order to identify better approaches to delivering primary care services.

Methods and analysis A 10-year retrospective cohort study on a population-based primary care cohort of Chinese patients with documented doctor-diagnosed HT and/or DM, managed in the Hong Kong Hospital Authority (HA) public primary care clinics from 1 January 2006 to 31 December 2019. Data will be extracted from the HA Clinical Management System to identify trajectory patterns of patients with HT/DM. Complications defined by ICPC-2/ International Classification of Diseases-Ninth Revision, Clinical Modification diagnosis codes, all-cause mortality rates and public service utilisation rates are included as independent variables. Changes in clinical parameters will be investigated using a growth mixture modelling analysis with standard quadratic trajectories. Dependent variables including effects of multimorbidity, measured by (1) disease count and (2) Charlson's Comorbidity Index, and continuity of care, measured by the Usual Provide Continuity Index, on patient outcomes and health service utilisation will be investigated. Multivariable Cox proportional hazards regression will be conducted to estimate the effect of multimorbidity and continuity of care after stratification of patients into groups according to respective definitions.

Ethics and dissemination This study was approved by the institutional review board of the University of Hong Kong—the HA Hong Kong West Cluster, reference no: UW 19–329. The study findings will be disseminated through peer-reviewed publications and international conferences.

Trial registration number NCT04302974.

Strengths and limitations of this study

► Large population-based data collected in routine clinical practice reflects hypertension (HT)/diabetes mellitus (DM) care in the real-world setting.
► Comprehensive approach to examine trajectory patterns of the clinical and treatment profiles for patients with HT/DM.
► Few studies to date have investigated the impact of continuity of care on Chinese patients who tend to 'doctor shop'.
► Linked electronic health record data allows for follow-up and examination of long-term outcomes associated with multimorbidity and continuity of care.
► Use of retrospective clinical data may lead to misclassification of diagnosis, recording bias and omission of non-routine data.

INTRODUCTION

As part of the global trend, chronic noncommunicable diseases (NCDs) have become a major disease burden in China. It is most apparent in urban populations like Hong Kong. By 2039, Hong Kong's population is predicted to expand to around 9 million with one-third of the population aged 65 years or over.[1] A significant challenge in maintaining the health of an ageing population is the management of chronic NCD. In 2013, there were over 1.3 million Hong Kong residents with an NCD, constituting 19.2% of the total population, the most common being hypertension (HT, 9.9% of the population), diabetes mellitus (DM, 4.4%) and heart disease (2.0%).[2] Chronic NCD and their complications have been implicated as

major causes for hospitalisation and long-term care,[3] and accounted for approximately two-thirds of all deaths.[4]

Primary care is essential in a healthcare system. Evidence has shown that healthcare systems that are more reliant on primary care produce better population health outcomes, reduce premature mortality, improve continuity and access to care, have high patient satisfaction and reduced health-related disparities at lower costs.[5] A qualitative study conducted in Hong Kong found many patients with chronic disease prefer to receive their ongoing care in the public (ie, Hospital Authority (HA)) system, even if they had a regular private family doctor, because of better perceived standards of training of service providers, fixed and lower costs and ease of access to specialists and other services.[6] An estimate of 80% of patients with HT/DM in Hong Kong are managed in the HA public primary care clinics.[7 8]

In Hong Kong, prior to 2010, usual care of patients with HT/DM in public primary care clinics typically consisted of treatments initiated by the doctor (with follow-up every 3–4 months), and an annual assessment for complications arranged at the discretion of the consulting doctor. However, there was significant variability in the quality of care between doctors and clinics, and despite the introduction of management guidelines and key performance indicators there was a wide range of standard in patient outcomes with a high proportion not achieving the target standard.[9]

To address the challenges of chronic disease care, in 2012, a series of population-based programmes for HT and DM were developed and implemented in the HA's public primary care clinics to enhance and better standardise care with evidence-based assessments and protocol-driven interventions to achieve better outcomes for the patients. Results from our previous studies have shown encouraging findings on the effectiveness and cost efficiency of these programmes in reducing complications and total mortality,[10 11] yet variability in outcomes and standard of care remains, which deserves further research on the long-term trajectories of HT/DM-related clinical parameters, multimorbidity and continuity of care on the disease complications due to HT/DM, all-cause mortality as well as service needs of patients with HT and DM.

There is mounting evidence to support the value of continuity of care for patients with chronic diseases, especially those with multimorbidity commonly defined as coexistence of more than one chronic medical condition, in terms of service utilisation and health outcomes,[12–14] and this may be a potential area for further quality enhancement in public primary care. Continuity of care is a multifaceted concept that encompasses three key areas.[15] First, relational continuity refers to a longitudinal ongoing relationship between the provider and patient. Second, informational continuity that refers to the accessibility to information on prior events that may be of relevance to the patient's care. Third, management continuity that refers to the coherency of care from different providers looking after the patient. Up to

now, the majority of studies on continuity of care have focused on the effect of relational continuity of care on the reduction of health service utilisation and healthcare cost, particularly among older patients.[12 13 16 17] Survival benefits of increased continuity of care was recently shown for HT/DM patients. A nationwide study based on the Korean National Health Insurance database found that lower indices of continuity of care in patients with newly diagnosed HT, diabetes, and hypercholesteraemia were associated with higher all-cause and cardiovascular mortality, cardiovascular events, healthcare cost.[14] The Korean study focused on relational continuity of care using index measures that measured the concentration of visits with the clinician most often seen and the dispersion across clinicians.

Public primary care in Hong Kong is universally provided by the HA that has good informational continuity and management continuity through its shared Clinical Management System (CMS) and management guidelines, but relational continuity cannot be assured. As HA primary care patients have a variety of clinic options (including regular daytime clinics, or out-of-hours evening, weekend and public holiday clinics), they may see different providers in the same or different clinics. Some patients with HT/DM usually consult the same HA primary care clinic for all their needs, with that clinic serving as their 'Primary Care Home'. Others, however, tend to use an assortment of primary care clinics at different times and for the same or different problems. It is unknown whether better relational continuity of care in the context of the 'Primary Care Home' service delivery model[12 13] has any effect on the outcomes and disease burden of patients with HT/DM in our busy public primary care setting where the average consultation time is 7 min.

Aims and objectives

This is a retrospective cohort study planned to monitor patients with HT/DM in public primary care clinics between 2006 and 2019. The overall aim of this study is to examine the trajectories of disease patterns in patients with HT/DM, and determine the factors that are associated with these disease outcomes and service utilisation. The results can inform policy and practice on strategies to deliver primary care services more effectively and efficiently to achieve the best performance and outcomes for patients with HT and DM. Specifically, the objectives are to retrospectively investigate: (1) the 10-year trajectory patterns of the clinical and treatment profiles in HA primary care patients with HT and/or DM; (2) the effect of multimorbidity on the outcomes and service utilisation costs in HA primary care patients with HT and/or DM and (3) the effect of relational continuity of care using the 'Primary Care Home' service delivery model on outcomes and service utilisation costs in HA primary care patients with HT and/or DM.

METHODS AND ANALYSIS
Study design
A 10-year retrospective study on all HA primary care patients with HT and/or DM receiving care from 2006 to 2019, to explore the trajectory patterns for clinical and treatment profiles, specifically the impact of multimorbidity and continuity of care on disease outcomes and health service utilisation.

Subjects
All patients age 18 years or above with a documented doctor-diagnosed HT or DM who are managed in the HA General Out-Patient Clinics (GOPC) and Family Medicine Clinics between 2006 and 2019. Patients will be identified from the HA CMS database using ICPC-2 codes of T89 (Diabetes insulin dependent), T90 (Diabetes non-insulin dependent); K86 (HT uncomplicated) or K87 (HT complicated).

Sample size calculation
The study intends to detect a difference in the 10-year relative risk of HT/DM-related complications between patients with and without continuity of care as a primary outcome. A previous study in Korea showed that the incidence of stroke and all-cause mortality was 1.2 and 11.5 per 1000 person-year, respectively, in patients with continuity of care, and was 2.0 and 15.4 per 1000 person-year, respectively, in patients without continuity of care.[14] Using the more conservative results from the Korean study and assuming a constant incidence rate, we estimated a 0.6 relative 10-year risk of stroke in patients with continuity of care compared with those without. Thus, the minimum total sample size is 30 224 subjects (15 112 subjects per group) to detect a significant difference in the relative risk of stroke between patients with and without continuity of care with a 0.1 absolute error of relative risk and at 5% level of significance.

Data collection
The research team will collaborate with the HA to extract and analyse data from the HA CMS database. Anonymised data on all eligible subjects (identified by diagnosis codes ICPC-2 or International Classification of Diseases-Ninth Revision, Clinical Modification (ICD-9CM)) from 1 January 2006 to 31 December 2019 will be extracted by the HA statistics team from the HA CM database in mid-2020. Person-time for each patient will be counted from their baseline date, determined as the first date of attendance at GOPC or diagnosis of HT/ DM within the inclusion period, to the occurrence of the outcome event all-cause mortality, last follow-up appointment or the end of follow-up period (31 December 2019), whichever happens first. Data will include sociodemographics, HT/DM-related clinical parameters, disease duration and control, drugs and other treatment modalities, HA primary care clinic utilisation patterns (including consultations from the same or difference doctors, attendance at the same or different clinics, and regular day-time clinic vs out-of-hours evening/Sunday/holiday clinics), HA service utilisation, disease complications and other comorbidities. Mortality data will be obtained from the Hong Kong Death Registry.

Data processing and analysis
Outcome measures
1. The incidence of HT/DM-related complications, all-cause mortality rate and public service utilisation rates over 10 years among patients with HT/DM.
2. The 10-year incidence of all-cause mortality and public service utilisation rates among patients with and without multimorbidity, defined by disease count and the Charlson's Comorbidity Index (CCI).
3. The 10-year incidence of HT/DM-related complications, all-cause mortality rate and public service utilisation rates among patients with and without continuity of care.

Case definitions of HT/DM-related complications and mortality

The primary outcomes of our study are HT/DM-related complications (including cardiovascular disease (CVD), end-stage renal disease (ESRD), peripheral vascular diseases, retinopathy, neuropathy and all-cause mortality.[18–21]
1. CVD is defined as the presence of any of coronary heart disease (CHD), heart failure or stroke.
   a. CHD includes all ischaemic heart diseases, myocardial infarction (MI), coronary death or sudden death as indicated by any of the ICPC-2 codes of K74 to K76 or ICD-9-CM 410.x to 414.x, 798.x.
   b. Heart failure is defined as ICPC-2 codes of K77 or ICD-9-CM 428.x.
   c. Stroke (fatal and non-fatal stroke) is defined as ICPC-2 codes of K89 to K91 or ICD-9-CM codes of 430.x to 438.x.
   d. Peripheral vascular disease is defined as ICPC-2 codes of K92 or ICD-9-CM codes of 250.6x, 440.2x, 997.2, or 997.6x
2. ESRD is defined by any of the ICD-9-CM codes of 249.40, 249.41, 250.40–43, 585.3, 585.4, 585.5, 585.6, or 586.x or an estimated glomerular filtration rate (eGFR) <15 mL/min/1.73 m^2, according to the definition of the National Kidney Foundation.[22]
3. Retinopathy is defined as ICPC-2 codes of F83 or F94, or ICD-9-CM codes of 249.5x, 362.0x, 362.02, 362.07 or 369x.
4. Neuropathy is defined as ICPC-2 codes of N94 or ICD-9-CM codes of 249.6x, 250.6x, 337.1x, 355.x, or 357.2.
5. Mortality is defined as a documented death in the Hong Kong Death Registry.

Case definitions of multimorbidity

Two methods will be used to measure multimorbidity:
1. Disease count is the most commonly used measure of multimorbidity.[23] HT and DM will be considered as comorbidities of each other. In addition, cancers and 18 other conditions that have been identified as most commonly encountered in primary care in Hong

Kong[24] will be included. These conditions include: (1) lipid disorder; (2) prostate problems; (3) anxiety; (4) arthritis; (5) bursitis/tendinitis/synovitis; (6) gout; (7) hypothyroidism; (8) dermatitis; (9) cerebrovascular disease; (10) haemorrhoids; (11) allergic rhinitis; (12) depression; (13) osteoporosis; (14) dyspepsia; (15) low back pain; (16) COPD/chronic bronchitis; (17) asthma; (18) ischaemic heart disease will be used to define morbidity. This list of conditions was derived from our 2008 Hong Kong Primary Care Morbidity Survey.

2. CCI will also be used to measure multimorbidity.[25] A validated index that recognises and uses 19 conditions to evaluate the impacts on outcomes such as mortality, hospital length of stay and healthcare cost.

Each condition will be defined by the relevant doctor diagnosis coding by ICPC-2 and ICD-9-CM. As there is no clear definition for the cut-off of number of conditions for multimorbidity, all patients will be divided into four groups initially: 1, 2–3, 4–5 and >5 conditions. The actual number of groups used will depend on the distribution of numbers of conditions in the final dataset. If the number of patients in a group is low, the subjects in that group will be combined with another group.

Indicators of continuity of care

The effect of relational continuity of care with the same doctor and with the same clinic will be investigated. Based on a review of the methods for measuring continuity of care,[12 14 16 17 26 27] the Usual Provider Continuity Index (UPCI) was identified as the most commonly used indicator of continuity of care and will be used as the main index measure for continuity of care in this study. The UPCI is defined as the proportion of a patient's doctor visits that is their most regularly seen clinician/clinic. Other measurements including the Modified Continuity Index, Continuity of Care Index and Sequential Continuity Index will be used as secondary indices.[27]

Data analysis

Subject characteristics including social demographics, clinical parameters, treatment modalities, service utilisation in each year will be summarised using descriptive statistics (mean and SD for continuous variables, frequency and proportion for categorical variables). The age-and-gender-adjusted incidence of HT/DM-related complications, all-cause mortality rates and respective attendances of primary care clinics, specialist outpatient clinics (SOPC) and accident and emergency departments and hospitalisation in each year will be reported. Direct medical costs will be estimated by the multiplication of the attendances by unit costs of various services. Incidence rates for the outcome events including HT/DM-related complications (including CVD, ESRD, peripheral vascular diseases, retinopathy and neuropathy), and all-cause mortality will be estimated using an exact 95% CI based on a Poisson distribution. Trajectory patterns of the clinical parameters will be investigated using growth mixture modelling. The conventional growth modelling

assumes that all individuals are drawn from a single population with common parameters (eg, means, variances, covariances), but growth mixture modelling relaxes this assumption and allows for differences in growth parameters across unobserved subpopulations.[28] Hence, we select growth mixture modelling to evaluate trajectory patterns of the clinical parameters. Standard trajectories (eg, linear, quadratic, cubic, etc) will be developed to investigate the change in clinical parameters over time. A total of 5000 random sets of start values will be requested for each model and the 100 best retained for final optimisation to avoid local solution.[29] All models converging on a replicated solution can confidently be assumed to have the best maximum likelihood. Goodness-of-fit statistics including Akaike information criterion (AIC), consistent AIC, Bayesian information criterion (BIC) and sample-adjusted BIC will be used with smaller values indicating a better fit of the model. The standard guidance suggests there is strong evidence to a reject k-1-class model by k-class model if the BIC difference between models is larger than 10.[30] An Elbow plot of the indicators of goodness-of-fit statistics will be generated to identify diminishing improvement by estimating additional classes if the indicators tend to decrease in a less pronounced fashion. The classification accuracy of the model will be summarised using Entropy,[31 32] ranging from 0 to 1. A higher value indicates less classification error, and the model will have adequate classification quality if the value is ≥0.80.[28] The Lo-Mendell-Rubin-adjusted likelihood ratio test will be used to compare the k-class model with the k-1-class model.[33] A significant p value will illustrate that the k-class model shows a significant improvement over the k-1-class model.

To evaluate the effect of multimorbidity on disease complications, all-cause mortality rates and service utilisation rates, patients will be stratified to groups based on their number of morbidities. Patient characteristics will be summarised using descriptive statistics and grouped into one of four multimorbidity subgroups based on number of morbidities (1, 2–3, 4, 5 and >5 conditions). The cumulative incidences of disease complications, mortality rate and public service utilisation rates will be reported. Incidence rates including HT/DM-related complications (including CVD, ESRD, peripheral vascular diseases, retinopathy and neuropathy), and all-cause mortality will be estimated with an exact 95% CI based on a Poisson distribution. Multivariable Cox proportional hazards regressions adjusted for all common patient's characteristics including age, gender, smoking status, body mass index, fasting glucose, low-density lipoprotein cholesterol, eGFR, charlson's index, the usages of antihypertensive drugs, antidiabetic drugs and lipid-lowering agents will be conducted to estimate the effect of multimorbidity (independent variable) on complications and all-cause mortality (dependent variable). Cox proportional hazards regression is a common method for investigating the effect of exposure on the time a specified event takes to happen. Proportional hazards assumption will

be checked by examining plots of the scaled Schoenfeld residuals against time for the covariates. The presence of multicollinearity will be assessed using the variance inflation factor. To test whether the linear association between the number of comorbidities and complication or mortality, the number of comorbidities will be treated as continuous variables and used in the restricted cubic splines with three knots in the Cox models. Both univariate and multivariable Poisson regression will be used to evaluate the effect of multimorbidity on the frequency of use of each type of service. If the count outcomes are overdispersed, negative binomial regression models will be conducted. Data analysis will be carried out using the CCI as well as the total number of chronic conditions as indicators of multimorbidity.

To evaluate the effect of relational continuity of care on HT/DM-related complications, all-cause mortality and service utilisation, patients will be stratified into two groups based on their UPCI. Subjects with low continuity of care will be defined as those UPCI <median; and subjects with high continuity of care will be defined as those with a UPCI ≥median. Descriptive and subgroup analysis will be performed to summarise the patient characteristics in each group. Multivariable Cox proportional hazards regressions models adjusting for all common patient characteristics including age, gender, smoking status, body mass index, fasting glucose, low-density lipoprotein cholesterol, eGFR, the Charlson's index, the usages of antihypertensive drugs, antidiabetic drugs and lipid-lowering agents will be used to compare the incidences of HT/DM-related complications and all-cause mortality (dependent variable) between the groups (independent variable). A Poisson regression adjusting for all common patient's characteristics including age, gender, smoking status, body mass index, fasting glucose, low-density lipoprotein cholesterol, eGFR, the Charlson's index, the usages of antihypertensive drugs, antidiabetic drugs and lipid-lowering agents will be used to evaluate the effect of the continuity of care (independent variable) on the frequency of service utilisation (dependent variable). Poisson regression is a common model to evaluate the analysis of counts of events. If the count outcomes are overdispersed, a negative binomial regression models will be conducted.

Patient and public involvement
Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research

DISCUSSION
The prevalence of HT and DM will be ever-increasing in an ageing population,[1 2] threatening the sustainability of the public healthcare system in many Asian populations including that of Hong Kong. More effective and cost-effective primary care to prevent complications is the solution to cope with the increasing service demand from patients with HT and/or DM. Thus, serving as the springboard to a large-scale cohort study, the identification of clinical outcomes and healthcare service utilisation rates of patients with DM and HT in the past 10 years in this study can provide a solid understanding on recent situation in a public primary healthcare system. Further, by focusing on factors that influence the trajectory and the outcome of patients with HT/DM, specifically multimorbidity and continuity of care, it allows us to explore for a better approach to provide efficient and cost-effective primary healthcare in the future.

To quantify and to evaluate the extent of multimorbidity, there are generally three measures: count measure, index measure and cluster measure. Count measure is a commonly used measurement that uses a simple count of conditions to provide a reliable measure of healthcare utilisation.[34] However, this simple count of conditions does not put the weighting of the disease severity and prognosis into consideration. Index measure uses ICD codes and a scale measurement on disease severity to evaluate a weighted measure on the extent of multimorbidity.[23] As this measurement approach has been widely validated and extensively used in a range of setting,[23 34–37] it is more effective to reflect and predict disease outcomes. Cluster measures considers multimorbidity in a wider perspective as it evaluates through analysing common combinations of chronic diseases such as prevalence, cost or statistical methods.[34] Nevertheless, there is a high heterogeneity in the methodological criteria for patterns and combinations and can be different from setting to setting making the measure less ideal due to its decreased comparability.[38] Given the context of our study, the count measure has been more widely used and validated locally,[24 25] and thus, both measures can supplement each other to determine the extent of multimorbidity.

In theory, continuity of care should be defined as a patient receiving healthcare services from the same clinician in the same clinic for a continuous prolonged period, however, it has been noted that different studies have varying approaches to providing services with continuity of care in real life.[12] Real-life situations that hinder the provision of the ideal healthcare service with continuity of care should also be put into consideration. For instance, in the Hong Kong public healthcare system, it is unusual for the same clinician to remain in the same clinic for a prolonged period of time due to training needs, career advancement or retirement. Given these challenges, team-based and clinic-based continuity of care should also be considered. Team-based continuity of care refers to patients managed by a small number of clinicians within the same team, which might take advantage from sharing information within the team. On top of this, the all clinicians within an individual clinic should be using the same treatment protocols. Regular team or clinic meetings can be a platform for healthcare providers to share the same up-to-date practices and information. Hence, apart from clinician-based continuity of care,

the impact of team-based and clinic-based continuity of care might be more applicable to real-world primary care.

There are also several important limitations of this study. The retrospective design of the study does not allow for any inferences be drawn regarding causality. To protect the privacy of our subjects, all data will be extracted anonymously from HA CMS. However, this also limits our capacity to crosscheck, which may lead to confusion and heterogeneity of the dataset. To lower such risks, clinical parameters, diseases characteristics and treatment modalities have been defined between the research and HA staff. Another challenge will be the potential for misclassification bias that may result from the reliance on using diagnosis codes such as ICPC-2 and ICD-9-CM. Nonetheless, as clinicians in Hong Kong practice by, respectively, providing both ICPC-2 and ICD-9-CM codes routinely,[39] it might potentially lower the risk of misclassification bias. A high coding accuracy was previously found for the diagnosis for MI and stroke with positive predictive values of 85.4% (95% CI 78.8% to 90.6%) and 91.1% (95% CI 83.2% to 96.1%), respectively.[40] Another challenge will be missing data from the database. Using multiple imputation to reduce selection bias by accounting the missing data can be used to retain the power and completeness of the dataset if missing data does occur.[41] Finally, outcomes recorded in the study are limited to those within the public healthcare system. Any service utilisation is, therefore, not measured if patients received fee-for-service outpatient services in the private system. However, most patients with chronic diseases and serious complications are treated in the heavily subsidised public system, therefore, HA data should capture nearly all complications in patients with HT or DM.

There is value in better understanding the long-term outcome trajectories and service needs of HT and DM patients to help inform further service planning and optimise quality of care. Understanding whether better relational continuity of care in the context of the 'Primary Care Home' service delivery model has any effect on the outcomes and disease burden of HT/DM patient will also be beneficial to the development of future primary healthcare service model in Hong Kong. Findings from this study will inform healthcare policy and optimise service delivery to make care for patients with the two most common chronic diseases more effectively and efficiently.

ETHICS AND DISSEMINATION

The study was approved by the Institutional Review Board of the University of Hong Kong—the Hospital Authority Hong Kong West Cluster (reference number: UW 19–329). The study findings will be disseminated through peer-reviewed publications and international conferences.

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