Identifying and visualising temporal trajectories of hospitalisations for traditional and non-traditional complications in people with type 2 diabetes: a population-based study

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Summary

Background People with type 2 diabetes are increasingly susceptible to complications that are not specific to diabetes. We aimed to examine the temporal trajectories of hospitalisations for traditional and non-traditional complications in people with type 2 diabetes.

Methods We included 758,254 people with incident type 2 diabetes between 2002 and 2018 in Hong Kong, followed up until 2019. We included hospitalisations for 72 selected diseases and all-cause deaths. We derived the temporal trajectories of hospitalisations based on pairs of disease associations and identified trajectory clusters using Markov Cluster Algorithm.

Findings During a median follow-up of 7.8 (IQR: 4–12) years, 57.6% of people experienced a hospitalisation for any of the 72 selected diseases and 22.6% of people died. Among the 5184 directional disease pairs, 95 were identified as having a significant and directional association. The three most common disease pairs were hospitalisations for urinary tract infection followed by pneumonia, ischemic heart disease followed by heart failure, and ischemic stroke followed by pneumonia. Cardiovascular and kidney diseases were predominant in the hospitalisation trajectories. However, these traditional complications had complex associations both among themselves and with various non-traditional complications across multiple systems. Three distinct trajectory clusters were identified, with heart failure/chronic kidney disease, pneumonia, and urinary tract infection as central diseases.

Interpretation Cardiovascular and kidney diseases interacted with a broad set of non-traditional complications to influence the overall patterns of hospitalisation progression in people with diabetes, highlighting the need to broaden diabetes care to consider complications beyond the traditional focus.

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Keywords: Trajectories; Hospitalisation; Type 2 diabetes

Introduction

Type 2 diabetes is a complex metabolic disorder that can lead to complications affecting multiple organ systems.[1] Cardiovascular and kidney diseases are traditional complications and leading causes of hospitalisations in people with type 2 diabetes.[2,3] However, with advances in the management of diabetes and the associated increase in life expectancy, the landscape of diabetes-

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Research in context

Evidence before this study

People with type 2 diabetes are increasingly susceptible to complications that are not specific to diabetes. We performed a systematic search in PubMed and Web of Science from database inception to April 23, 2024, using the terms "Diabetes" AND "Hospitalisation" AND "Trajectory". Previous studies on diabetes have predominantly focused on traditional complications, and no studies have reported the interactions between traditional and non-traditional complications in the hospitalisation trajectories of people with type 2 diabetes.

Added value of this study

This is the first study to examine the disease association-based time sequences of hospitalisations for a wide range of diabetes-related complications using territory-wide data in Hong Kong. We found that traditional cardiovascular and kidney diseases interacted with a broad set of non-traditional complications to influence the overall patterns of hospitalisation progression in people with diabetes. Additionally, we identified distinct trajectory clusters that provided new insights into the progression patterns of hospitalisations in people with type 2 diabetes.

Implications of all the available evidence

Our results highlight the need to broaden diabetes care to consider complications beyond the traditional focus, which are increasingly contributing to the hospitalisation burden in people with type 2 diabetes. The identification of complex trajectory clusters underscores the importance of developing an integrated system to detect, treat and control early in type 2 diabetes to prevent the progression of multiple complications and reduce hospitalisations.

related complications is changing. People with type 2 diabetes are increasingly susceptible to a broader set of complications that are not specific to diabetes.[4] Notably, in some regions, conditions such as cancers and respiratory tract infections have even surpassed traditional complications as primary causes of hospitalisations in people with diabetes.[5,6]

Most existing studies on diabetes have predominantly focused on traditional complications and have treated them as independent events when assessing hospitalisation risks.[5,7] However, this approach overlooks the interconnected nature of diabetes-related complications. Many of these complications might share common risk factors and pathological pathways and tend to develop sequentially, where one condition can significantly influence the risk and progression of subsequent diseases.[8,9] The emergence of non-traditional complications has significantly increased the complexity of managing diabetes. However, it remains largely unknown whether there are complex associations between traditional and non-traditional complications of type 2 diabetes, and how these complications interact and cluster to influence overall hospitalisation patterns. Furthermore, the chronological sequence of hospitalisations for different complications in people with type 2 diabetes has not been well explored.

In this study, we aimed to use large population-based data to 1) identify and visualise temporal trajectories of hospitalisations for a wide range of traditional and non-traditional complications of type 2 diabetes, and 2) identify trajectory clusters that represent common hospitalisation patterns in people with newly diagnosed type 2 diabetes.

Methods

Data source and study population

Hong Kong is a special administrative region of China. The Hong Kong Hospital Authority (HA) is a statutory body that governs all public hospitals and the majority of specialist and general outpatient clinics.[10–12] Due to the highly-subsidised public healthcare system, the HA provides approximately 90% of total health services in Hong Kong. In 2000, the HA implemented a territory-wide electronic medical record (EMR) system to routinely collect clinical information for all people attending hospitals and clinics in the public sector. In this study, we included all people (n = 758,254) with incident type 2 diabetes between 1st January 2002 and 31st December 2018, who were aged between 18 and 99 years at diabetes diagnosis in the HA EMR system. No additional inclusion or exclusion criteria were applied for population selection. The sample size of the study population provided ≥80% power to detect a minimum effect size of 10% for 93.8% of all disease pair associations at a significance level of $\alpha = 0.05/5184$ after Bonferroni correction. Incident type 2 diabetes was identified using a validated algorithm based on physician diagnoses, laboratory results, and medication prescriptions. Details on the ascertainment of type 2 diabetes have been reported in our previous publication.[11]

Follow-up and outcome ascertainment

The study population was followed from the date of their diabetes diagnosis until 31st December 2019 or the date of death, whichever came first. We included hospitalisations for 72 selected diseases listed as principal diagnoses at hospital discharge and all-cause deaths

(Supplementary Table S1). These diseases included traditional complications of type 2 diabetes with well-established causal relationships and emerging complications with increasing evidence of a higher risk in people with type 2 diabetes.[4,7] They spanned seven broad disease systems and each selected disease accounted for >1% of total hospital admissions within its respective disease system, including infection (International Classification of Diseases, Ninth Revision [ICD-9]: 001–139), neoplasms (ICD-9: 140–239), mental health disorders (ICD-9: 290–319), circulatory system (ICD-9: 390–459), respiratory system (ICD-9: 460–519), digestive system (ICD-9: 520–579), and genitourinary system (ICD-9: 580–629). Hospitalisation records and all-cause death data were obtained from the HA EMR system.

Statistical analysis

We examined the temporal trajectories of hospitalisations after a diagnosis of type 2 diabetes based on pairs of significant and directional disease associations, using the method developed by S Brunak and colleagues (Fig. 1).[13,14] Initially, a total of 5184 directional disease pairs (e.g., hospitalisation for Disease 1 [D1] → Disease 2 [D2]) were identified based on all possible combinations of the 72 diseases and the event of death, which included 5112 disease–disease pairs and 72 disease–death pairs. For pairs with D1, we randomly selected 10,000 comparison groups who experienced hospitalisation for any other diseases but did not have D1, matched for age (±2 years), sex, diabetes duration (±2 years), and year of hospital admission (±2 years). These confounders were selected based on the modified disjunctive causa criterion.[15] However, variables that might be shared risk factors contributing to hospitalisations within a trajectory or that lie on the pathways of hospitalisation trajectories were not included as confounders to avoid overadjustment and to maintain the descriptive nature of hospitalisation trajectories. We examined the association for each pair using relative risk (RR) by the formula: $RR = \frac{C_{exposed}}{\frac{1}{N}\sum_i C_i}$, where C_{exposed} represents the number of people who experienced a hospitalisation for D1 followed by D2, C_i represents the number of people in each matched comparison group who had a hospitalisation for D2, and N represents the number of comparison groups (which is 10,000). We

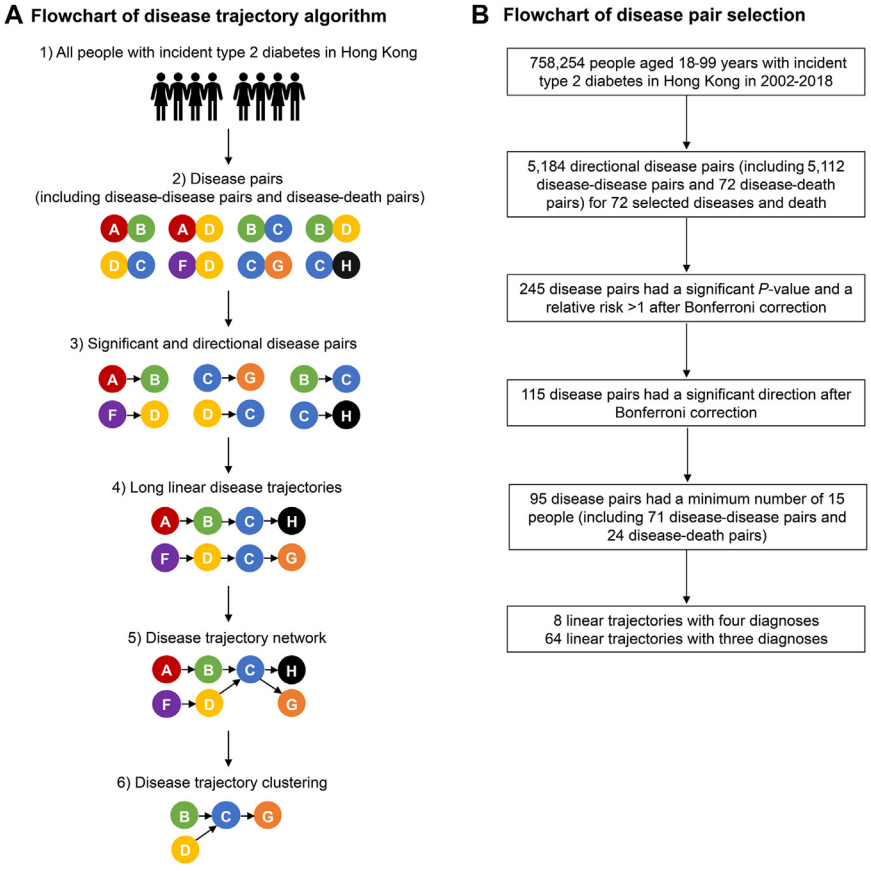

Fig. 1: **Flowcharts illustrating the disease trajectory algorithm and disease pair selection.**

employed a binomial model as a pre-filtering step and conducted a single binomial test to approximate the probability distribution of D2 occurring after D1. The probability distribution of D2 is given by: $\Pr(D2) = \frac{1}{n}\sum_{i=1}^{n}\frac{c_i}{n_{match,i}}$, where n is the number of people with D1, c_i is the number of people with D2 in the *i*-th comparison group, and $n_{match,i}$ is the number of potentially matching hospitalisations for the *i*-th individual with D1 in their respective comparison group. We used a Bonferroni-corrected *P*-value <0.001/5004 as the threshold for selection.[13] The *P* values for RRs were calculated using the formula: $P = \frac{1}{N}\{i|C_i \geq C_{exposed}\}$.

Pairs that had both an RR greater than one and a significant *P*-value <0.05/245 after Bonferroni correction for one or both directions (e.g., D1→D2 and/or D2→D1) were tested for directionality. We used one-tailed binomial tests to determine whether a significantly greater number of people experienced a hospital admission for one disease before the other (D1→D2), or vice versa (D2→D1) for each pair. Pairs with a Bonferroni corrected *P*-value <0.05/359 in the directionality test were considered to have a significant directional association. We merged pairs that had significant directionality and overlapping diagnoses into long linear disease trajectories consisting of three or more diagnoses. Using this approach, each subsequent disease in the trajectory followed the preceding one in a significant and directional pattern. We combined all trajectories into a disease trajectory network that reflects the temporal associations and progression patterns of hospitalisations over time in people with type 2 diabetes after diagnosis. To ensure statistical robustness, only trajectories followed by a minimum of 15 people, as determined by bootstrap value calculations, were included in the final analysis.

In long liner trajectories with three or more diagnoses, we applied Markov Cluster Algorithm to identify trajectory clusters based on their shared diagnoses. A trajectory cluster is a group of disease trajectories that tend to occur together more frequently than would be expected by chance and represents common patterns of hospitalisation progression. Jaccard Index was used to measure the similarity between different sets of diagnoses, which calculated the degree of similarity by comparing the number of diagnoses shared by different trajectories against the total number of unique diagnoses across these trajectories. Trajectories with a higher number of shared diagnoses received higher Jaccard similarity scores and were grouped together into the same cluster. Within each trajectory cluster, we identified a central disease, which is the diagnosis that appears most frequently in the trajectory and serves as a key marker in the hospitalisation progression. To verify that a disease is central to the cluster, we calculated the RR by comparing the frequency of its occurrence between all diagnoses preceding and succeeding it within the cluster.[13,14] To further assess the impact of the central disease on hospitalisation progression, we calculated the RR for all subsequent diseases associated with the central disease within each long linear trajectory.

All analyses were performed using R software, version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

Ethical approval

This study was approved by the Chinese University of Hong Kong-New Territories East Cluster Clinical Research Ethics Committee (CREC Ref. No. 2020.032).

Role of the funding source

The Direct Grant for Research from The Chinese University of Hong Kong had no role in study design, data collection, data analysis, data interpretation, or writing of the report but supported the presentation of this work at an international conference.

Results

Baseline characteristics of the study population

Among the 758,254 people included in this analysis, 51.6% (n = 391,500) were men (Table 1). At the time of diabetes diagnosis, the mean age was 62.8 (standard deviation [SD]: 13.1) years, the mean HbA1c was 7.6% (SD: 2.1%), 61.2% (n = 464,334) of people were using blood pressure-lowering drugs, and 20.7% (n = 157,041) were using lipid-lowering drugs. Within one year following diabetes diagnosis, 52.5% (n = 398,421) of people were initiated on oral glucose-lowering drugs and 5.8% (n = 44,213) were on insulin.

Disease pairs as basis for hospitalisation trajectories

During a median follow-up of 7.8 (interquartile range: 4–12) years, 57.6% (n = 436,878) of people experienced a hospitalisation for any of the 72 selected diseases, and 22.6% (n = 171,052) of people died. Among all the 5184 pairs, a total of 95 pairs with at least 15 people were identified as having a significant and directional association (Fig. 1). They included 71 disease–disease pairs and 24 disease–death pairs. Among the 95 pairs, 91 (95.8%) had an RR greater than 1.10, suggesting a clinically important increase in hospitalisation risk.

Fig. 2 shows the top 20 most common linear disease–disease pairs and the top 10 most common linear disease–death pairs, which accounted for 75.7% and 85.5% of all people in each pair category. The top 20 leading linear disease–disease pairs covered 20 unique diseases that included not only major traditional cardiovascular (e.g., ischemic heart disease, heart failure, and ischemic stroke) and kidney (e.g., chronic kidney disease [CKD]) complications but also a broad range of non-traditional complications of type 2 diabetes (e.g.,

Characteristics	Overall (N = 758,254)
Male sex	391,500 (51.6)
Age at diabetes diagnosis (years)	62.8 (13.1)
Age group	
<40 years	31,031 (4.1)
40–59 years	290,486 (38.3)
60–79 years	359,226 (47.4)
≥80 years	77,511 (10.2)
Year of diabetes diagnosis	
2002–2005	187,946 (24.8)
2006–2009	166,853 (22.0)
2010–2013	178,542 (23.5)
2014–2018	224,913 (29.7)
HbA1c (%)	7.6 (2.1)
Fasting plasma glucose (mmol/L)	7.9 (3.0)
HDL-C (mmol/L)	1.3 (0.4)
LDL-C (mmol/L)	3.1 (1.0)
Triglycerides (mmol/L)	1.5 (1.0, 2.1)
Total cholesterol (mmol/L)	5.1 (1.2)
Estimated GRF (mL/min/1.73 m^2)	78.6 (22.5)
Drug use within one year after diabetes diagnosis	
Any oral glucose-lowering drugs	398,421 (52.5)
Metformin	321,295 (42.4)
Sulfonylureas	228,398 (30.1)
Dipeptidyl peptidase-4 inhibitors	5698 (0.8)
Insulin (>28 days)	44,213 (5.8)
Drug use at diabetes diagnosis	
Lipid-lowering drugs	157,041 (20.7)
Statins	134,959 (17.8)
Blood pressure-lowering drugs	464,334 (61.2)
Renin-angiotensin system inhibitors	156,289 (20.6)

Data are presented as mean (standard deviation) for normally distributed continuous variables, median (interquartile range) for skewed continuous variables, or n (%) for categorical variables. Abbreviations: HDL-C: High-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; GRF: glomerular filtration rate.

Table 1: **Characteristics of study population at diabetes diagnosis.**

urinary tract infection, pneumonia, dementia, and diseases of the digestive system). These pairs showed a significant cross–system association, with over half (55%) of them consisting of diseases that affected different disease systems. Among them, the mean age at hospitalisation varied from 67.0 (SD: 14.3) to 84.1 (SD: 8.0) years, and the mean duration of progression between hospitalisations for each pair ranged from 0.6 (SD: 0.3) to 2.4 (SD: 0.8) years. The three most common linear disease–disease pairs were urinary tract infection followed by pneumonia (n = 5439), ischemic heart disease followed by heart failure (n = 4226), and ischemic stroke followed by pneumonia (n = 4109). Of all people progressing through the three pairs, 51%, 59%, and 43% followed a linear progression without any intervening diseases between them, respectively (Fig. 2). Among the top 10 leading linear disease–death pairs, pneumonia (n = 23,210), heart failure (n = 8120), and lung cancer (n = 7248) were the three most common causes of hospitalisations leading to death, with 52%, 35%, and 80% of people who progressed from them to death following a linear trajectory, respectively. Other leading disease–death pairs included certain cancers (including colon cancer, liver cancer, and pancreatic cancer), septicemia, CKD, pleurisy, and chronic liver disease.

Hospitalisation trajectory network based on disease pairs

Combining the 95 pairs into longer trajectories, we identified eight long linear trajectories with four diagnoses and 64 with three diagnoses. The eight longest trajectories with four diagnoses covered 10 diseases and shared multiple overlapping diagnoses (e.g., heart failure and pneumonia) (Supplementary Figure S1). Notably, six of the eight trajectories included progressions between traditional and non-traditional complications of type 2 diabetes. Fig. 3 shows the trajectory network that represented the overall patterns of hospitalisation progression in people with type 2 diabetes based on the significant temporal associations of all the 95 pairs. Within the network, cardiovascular diseases (e.g., ischemic stroke, ischemic heart disease, cardiac dysrhythmias, and heart failure) and kidney diseases (e.g., CKD) were predominant causes of hospitalisations and were central to the trajectories. These traditional complications had extensive and complex associations both among themselves and with a variety of non-traditional complications across multiple systems (e.g., dementia, urinary tract infection, pneumonia, and septicemia), which together comprised the main components of the trajectories. However, trajectories involving digestive diseases and digestive-related cancers followed a more straightforward pathway, which had fewer associations with diseases from other systems and directly progressed towards death after hospitalisation for cancer.

Hospitalisation trajectory clusters

Among the long linear trajectories with three or more diagnoses, we identified three distinct trajectory clusters, including cardio-renal cluster, pneumonia cluster, and urinary tract infection clusters (Fig. 4). The cardio-renal cluster was the largest and represented hospitalisation trajectories associated with traditional complications of type 2 diabetes, within which heart failure (RR = 8.2 [95% CI: 8.2, 8.2], $P < 0.0001$) and CKD (RR = 8.9 [95% CI: 8.9, 8.9], $P < 0.0001$) were the central diseases (Supplementary Table S2). A variety of cardiovascular diseases (e.g., ischemic heart disease, conduction disorders, and hypertension) converged on heart failure, which then proceeded to kidney diseases (e.g., acute kidney injury, CKD, and renal failure) and other diseases (e.g., septicemia and peritonitis) before leading to death. In the pneumonia cluster, various diseases

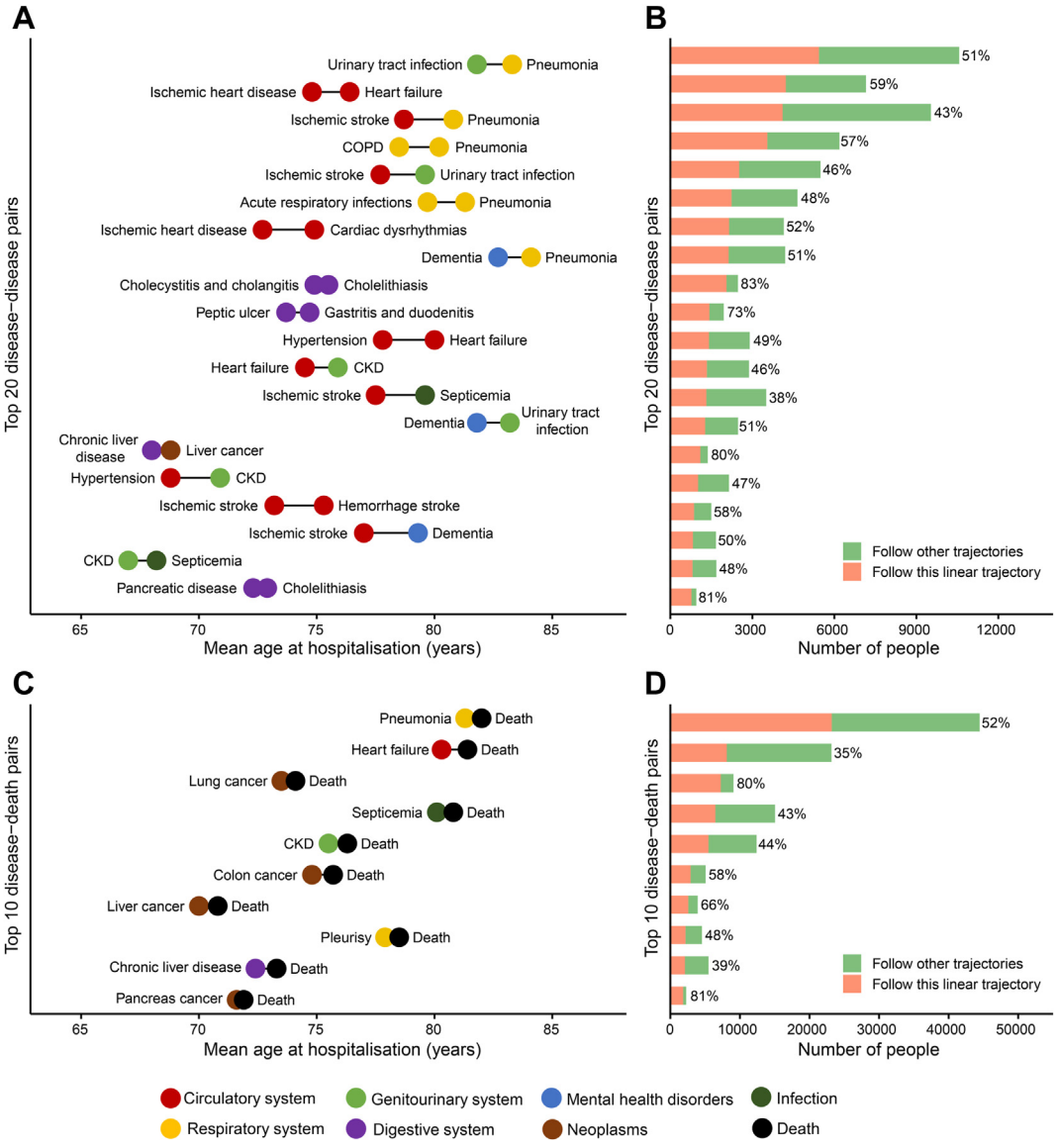

Fig. 2: **Top 20 most common linear disease–disease pairs and top 10 most common linear disease–death pairs**. Panel A and Panel B show the mean age at hospitalisation for diseases in each pair. In Panel B and Panel D, each bar represents the total number of people who progressed from Disease 1 to Disease 2. Within each bar, the red portion indicates the number of people who followed this specific linear disease trajectory directly, while the green portion represents those who followed other trajectories. The number displayed behind each bar indicates the percentage of people who followed this specific linear trajectory (represented by the red portion) out of the total number of people who progressed from Disease 1 to Disease 2 by any trajectory. The pairs are ranked based on the number of people who followed this specific linear trajectory from high to low.

from multiple systems, including urinary tract infection, ischemic stroke, and several respiratory diseases (e.g., acute respiratory infections, asthma, and chronic obstructive pulmonary disease [COPD]), converged on pneumonia (RR = 7.4 [95% CI: 7.4, 7.4], $P < 0.0001$) and subsequently progressed to death. The urinary tract infection cluster advanced from diseases such as ischemic stroke, bladder cancer, and dementia, leading to urinary tract infection (RR = 3.9 [95% CI: 3.9, 3.9], $P < 0.0001$) and then to pneumonia. Compared to people in the pneumonia or urinary tract infection clusters, those in the cardio-renal cluster were diagnosed with diabetes at a younger age, had a higher HbA1c level, a lower eGFR level, and were more likely to use glucose-lowering drugs, lipid-lowering drugs, and blood pressure-lowering drugs (Supplementary Table S3). In

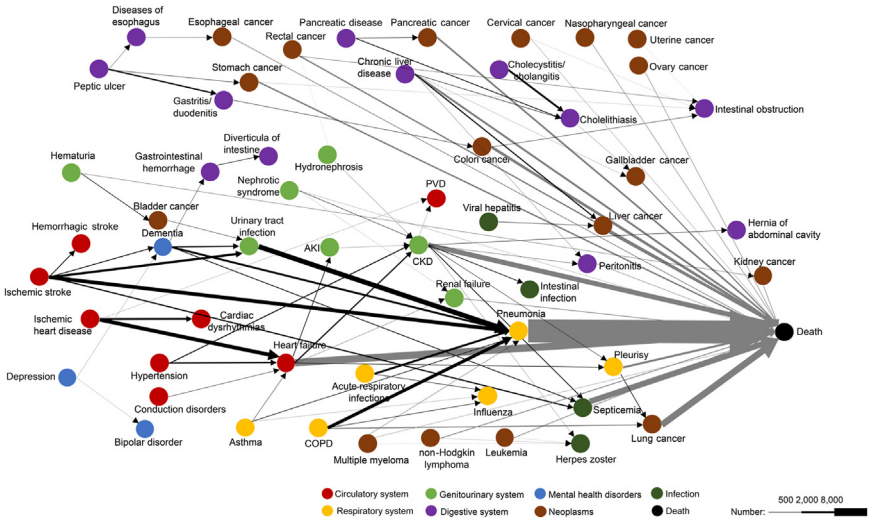

Fig. 3: **Hospitalisation trajectory network in people with newly diagnosed type 2 diabetes**. Each circle represents a specific disease (including death) and each colour corresponds to a different disease system. Each line represents a significant association between the two diseases and each arrow indicates the direction of the association. The width of each line represents the number of people who followed this linear pair. The black lines represent disease–disease pairs and the grey lines represent disease–death pairs. A significant pair of hyperplasia of prostate and prostate cancer is isolated with other diseases and is not included in the network.

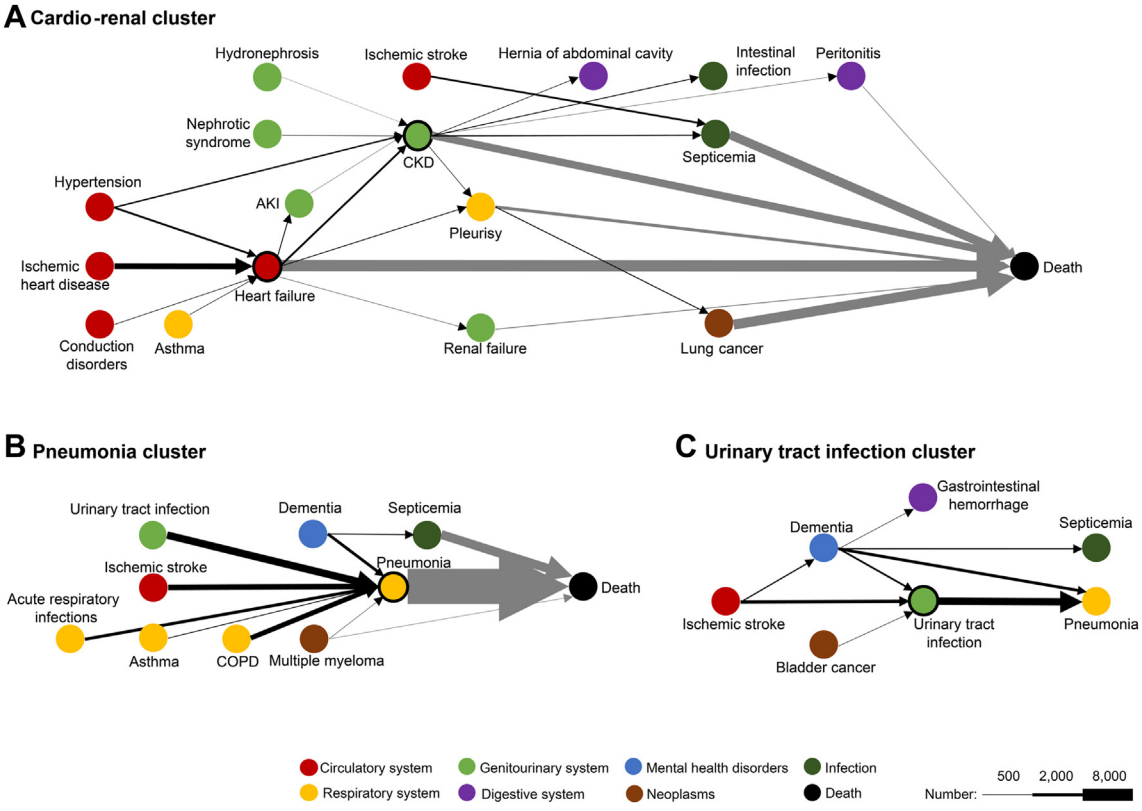

Fig. 4: **Hospitalisation trajectory clusters in people with newly diagnosed type 2 diabetes**. Each circle represents a specific disease (including death) and each colour corresponds to a different disease system. Each line represents a significant association between the two diseases and each arrow indicates the direction of the association. The width of each line represents the number of people who followed this linear pair. The black lines represent disease–disease pairs and the grey lines represent disease–death pairs.

the subgroup analysis by sex, clusters in both men and women contained the same central diagnoses as the overall population but showed slight sex-related differences in the diseases involved (Supplementary Figure S2). For instance, within the pneumonia cluster, COPD and a progression from ischemic stroke to dementia were identified only in men, not in women.

Central diseases and hospitalisation risk of subsequent diseases

The presence of central diseases within the trajectory clusters was associated with a significantly increased risk of subsequent diseases (Supplementary Table S4). For instance, in the trajectory from ischemic heart disease to CKD, people with a history of ischemic heart disease who subsequently developed heart failure had a 3.16-fold (95% CI: 2.88, 3.48, $P < 0.0001$) increased risk of CKD compared to those without heart failure. Among people with dementia, the hospitalisation for urinary tract infection was associated with a 2.10-fold (95% CI: 1.99, 2.22, $P < 0.0001$) increased risk of pneumonia.

Discussion

In this territory-wide population-based cohort study, we identified and visualised the temporal trajectories of hospitalisations for a wide range of traditional and non-traditional complications in people with newly diagnosed type 2 diabetes. We found that cardiovascular and kidney complications were predominant in the hospitalisation trajectories. However, these traditional complications had complex associations with a broad set of non-traditional complications across multiple disease systems that together influenced the overall patterns of hospitalisation progression. Within the hospitalisation trajectories, certain diseases were closely associated and tended to follow specific progression patterns that formed trajectory clusters. Three distinct trajectory clusters were identified, with heart failure/CKD, pneumonia, and urinary tract infection as the key diagnoses central to hospitalisation progression in each cluster. Furthermore, pneumonia, heart failure, and cancers were the most common causes of hospitalisations leading to death.

Our study provided a novel perspective on understanding the burden and patterns of hospitalisations in people with type 2 diabetes. Instead of only following the sequence of hospitalisation as observed during the follow-up,[16–18] we derived hospitalisation trajectories based on significant time-dependent disease associations.[13,14,19] This association-based approach not only examined the chronological order of hospitalisations but also provided insights into how multiple diseases interact and influence each other's risk and progression over time. It enabled the identification of complex sequential patterns and indirect pathways that might be missed when diseases are considered in isolation. For instance, we identified a hospitalisation trajectory from ischemic heart disease to septicemia, progressing through multiple intermediary diseases including heart failure, acute kidney injury, and CKD. This trajectory reflected the indirect effects of ischemic heart disease on susceptibility to serious infections through a complex multi-system pathway. However, these effects might not be captured by conventional methods if the follow-up time is insufficient for individuals to develop all intermediary conditions.

Our study confirmed a high burden of hospitalisations due to cardiovascular and kidney diseases in people with type 2 diabetes from a novel angle, which were identified as central to the hospitalisation trajectories. Notably, we also found that these traditional complications were not isolated but had broad effects on a spectrum of non-traditional complications that are less specific to diabetes, particularly respiratory infections, urinary tract infections, and dementia. Hyperglycaemia has detrimental effects on both the innate immune response and adaptive immunity, contributing to increased risks of severe infections requiring hospitalisation.[6,20,21] Evidence also supports an increased risk of dementia in people with diabetes,[22] particularly when coexisting with cardiovascular disease,[23] potentially driven by vascular damage, chronic inflammation, and metabolic dysregulation.[24,25] In addition to infections and mental health disorders, we observed a substantial number of people progressing from various digestive diseases to digestive-related cancers. Diabetes may contribute to digestive diseases through neuropathy and vascular damage,[26] and to cancer through the effects of hyperglycaemia and hyperinsulinaemia on inflammation, oxidative stress, and abnormal cell growth.[27,28] However, the progression from digestive diseases to cancers could be more direct, partially due to the localised pathophysiology of the digestive system.

We found that certain hospitalisation trajectories shared common diseases and formed three trajectory clusters, including cardio-renal, pneumonia, and urinary tract infection clusters. Diseases in the same cluster are closely related through several mechanisms, such as sequential progression, shared risk factors, similar pathophysiology, or treatment effects. Within these clusters, heart failure/CKD, pneumonia, and urinary tract infection acted as central diseases where multiple conditions converged before progressing to subsequent complications. The cardio-renal cluster reflects the interrelated associations between traditional complications of type 2 diabetes, while the pneumonia and urinary tract infection clusters involve progression between non-traditional complications that have not been well reported in previous studies. Diseases in the pneumonia cluster may be linked by impaired immune function, increased aspiration risk, and weakened respiratory defences. These factors can increase the susceptibility to fatal pneumonia, making it one of the

leading causes of death in people with type 2 diabetes.[29] In the urinary tract infection cluster, people with ischemic stroke and dementia might have more difficulty maintaining personal hygiene and managing infections due to factors such as impaired mobility and urinary retention, which can lead to severe urinary tract infection requiring hospitalisation. It is noteworthy that hospitalisation progression from urinary tract infection to pneumonia was identified in both the pneumonia and urinary tract infection clusters. In this connection, our group and others had reported a significant association between glycaemic control and all-site infections.[20]

Although the prevention and management of cardiovascular and kidney diseases remain priorities in people with type 2 diabetes, the complex interrelations between these traditional complications and emerging non-traditional complications complicate diabetes management, calling for considering conditions beyond the traditional focus. The high burden of hospitalisations for pneumonia highlights the importance of adherence to vaccination schedule, smoking cessation, and respiratory health monitoring especially in older people with type 2 diabetes. Enhanced hygiene support and education of both patients and their carers on symptoms of infections and importance of early action are prudent and may serve to prevent infection-related hospitalisations. The landmark publication of the 44-year legacy effects of the UKPDS reinforced the importance of early glycaemic control and avoiding therapeutic inertia in reducing any-diabetes related endpoints.[30] Given the clustering of these traditional and non-traditional complications in diabetes-related hospitalisations, the development of an integrated system to detect, treat and control early in diabetes cannot be emphasised enough.[1] More importantly, a hospitalisation episode provides an important opportunity to intensify care, education, and surveillance to prevent these clusters and trajectories. To achieve these multiple goals, alignment amongst policy makers, healthcare providers and patients is needed to transform diabetes care through system change and capacity building with ongoing data collection to prove the value and impact of proactive intervention in making healthcare sustainable.[1] While our study focused on hospitalisation trajectories following the diagnosis of type 2 diabetes, hospitalisations prior to diabetes diagnosis may also influence these trajectories. Future studies with accurate data on pre-diagnosis hospitalisations could provide valuable insights into their impact on diabetes development and subsequent hospitalisation patterns.

Strengths and limitations

This study has several strengths, including territory-wide coverage of the population with diabetes in Hong Kong, inclusion of a wide spectrum of diabetes-related complications, completeness of hospitalisation records in the public sector, and a long follow-up period. However, it also has limitations. Firstly, our study was based on an administrative database, which has inherent limitations, such as miscoding and misclassification. Secondly, the conservative use of the Bonferroni correction in both association and directionality tests might have obscured some true but modest hospitalisation associations. However, this approach ensured that we included only the most statistically robust hospitalisation trajectories and minimised the risk of reporting misleading information. Thirdly, we focused only on one direction for each disease pair that people were most likely to follow, which might not fully capture the complex associations between diseases with bidirectional associations. Fourthly, despite matching for the calendar year, changes in medical practice, healthcare access, and treatment technology over the study period might influence hospitalisation patterns. For instance, increasing use of sodium-glucose co-transporter 2 inhibitors and mineralocorticoid receptor antagonist which have been shown to slow the progression of CKD and prevent hospitalisation for heart failure might alter the cardio-renal cluster in the future.[31,32] These factors should be considered when interpreting the study findings. Fifthly, our study did not include hospitalisations that occurred in private healthcare settings, which account for less than 10% of all inpatient services in Hong Kong. Sixthly, hospitalisations were coded using ICD-9, which may limit the comparability of our findings with studies that employ ICD-10. Seventhly, hospitalisation records for people who have moved overseas cannot be captured. However, the impact of this limitation is likely minimal. Eighthly, data on some important confounders (e.g., socioeconomic status) were not available in the HA EMR system, and we were unable to control for them. Ninthly, our study only included diseases listed as the principal diagnosis at hospital discharge. Therefore, conditions that did not frequently require hospitalisation or were recorded as secondary diagnoses may be underrepresented. Lastly, variations in clinical thresholds for hospital admission and coding practices across different settings may affect the generalisability of our findings to other populations.

In conclusion, our study identified the disease association-based time sequences of hospitalisations for a wide range of diabetes-related complications. While cardiovascular and kidney diseases were the major complications in hospitalisation trajectories in people with type 2 diabetes, they interacted and clustered with a broad set of non-traditional complications to influence the overall patterns of hospitalisation progression, highlighting the vulnerability of type 2 diabetes as a multi-system disease. These findings underscore the need to broaden the scope of diabetes care covering complications beyond the traditional focus on cardiovascular and kidney diseases.

Contributors

HW contributed to conception of the article, statistical analysis, interpretation of results, drafting the manuscript, revising the manuscript, and approving the final version. HZ and CH contributed to the method development, interpretation of results, revising the manuscript, and approving the final version. AOYL and JCNC contributed to conception of the article, acquisition of data, interpretation of results, revising the manuscript, and approving the final version. AY and ESHL contributed to statistical analysis, interpretation of results, revising the manuscript, and approving the final version. XZ, JNML, BF, RCWM, APSK, EC, and WYS contributed to revising the manuscript and approving the final version. AOYL is the guarantor of this work, has full access to all the data in the study and takes responsibility for the integrity of the data, the accuracy of the data analysis, and the decision to submit the manuscript.

Data sharing statement

The data underlying the results presented in the study are hosted by the Hong Kong Hospital Authority. Due to local regulation, the data are not available to the public. Request for data can be made via Hong Kong Hospital Authority: https://www3.ha.org.hk/data.

Editor note

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Declaration of interests

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2025.101532.

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