



Differential Health Care Use, Diabetes-Related Complications, and Mortality Among Five Unique Classes of Patients With Type 2 Diabetes in Singapore: A Latent Class Analysis of 71,125 Patients

Diabetes Care 2020;43:1048–1056 | <https://doi.org/10.2337/dc19-2519>

Jun Jie Benjamin Seng,¹ Yu Heng Kwan,²
Vivian Shu Yi Lee,³ Chuen Seng Tan,⁴
Sueziani Binte Zainudin,⁵
Julian Thumboo,^{2,3,6} and
Lian Leng Low^{3,7,8,9}

OBJECTIVE

With rising health care costs and finite health care resources, understanding the population needs of different type 2 diabetes mellitus (T2DM) patient subgroups is important. Sparse data exist for the application of population segmentation on health care needs among Asian T2DM patients. We aimed to segment T2DM patients into distinct classes and evaluate their differential health care use, diabetes-related complications, and mortality patterns.

RESEARCH DESIGN AND METHODS

Latent class analysis was conducted on a retrospective cohort of 71,125 T2DM patients. Latent class indicators included patient's age, ethnicity, comorbidities, and duration of T2DM. Outcomes evaluated included health care use, diabetes-related complications, and 4-year all-cause mortality. The relationship between class membership and outcomes was evaluated with the appropriate regression models.

RESULTS

Five classes of T2DM patients were identified. The prevalence of depression was high among patients in class 3 (younger females with short-to-moderate T2DM duration and high psychiatric and neurological disease burden) and class 5 (older patients with moderate-to-long T2DM duration and high disease burden with end-organ complications). They were the highest tertiary health care users. Class 5 patients had the highest risk of myocardial infarction (hazard ratio [HR] 12.05, 95% CI 10.82–13.42), end-stage renal disease requiring dialysis initiation (HR 25.81, 95% CI 21.75–30.63), stroke (HR 19.37, 95% CI 16.92–22.17), lower-extremity amputation (HR 12.94, 95% CI 10.90–15.36), and mortality (HR 3.47, 95% CI 3.17–3.80).

CONCLUSIONS

T2DM patients can be segmented into classes with differential health care use and outcomes. Depression screening should be considered for the two identified classes of patients.

¹Duke-NUS Medical School, Singapore

²Program in Health Services and Systems Research, Duke-NUS Medical School, Singapore

³SingHealth Regional Health System, Singapore Health Services, Singapore

⁴Saw Swee Hock School of Public Health, National University of Singapore and National University Health System, Singapore

⁵Department of General Medicine (Endocrinology), Sengkang General Hospital, Singapore

⁶Department of Rheumatology and Immunology, Singapore General Hospital, Singapore

⁷Department of Family Medicine and Continuing Care, Singapore General Hospital, Singapore

⁸SingHealth Duke-NUS Family Medicine Academic Clinical Program, Singapore

⁹Outram Community Hospital, SingHealth Community Hospitals, Singapore

Corresponding author: Lian Leng Low, low.lian.leng@singhealth.com.sg

Received 16 December 2019 and accepted 17 February 2020

This article contains Supplementary Data online at <https://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc19-2519/-/DC1>.

© 2020 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. More information is available at <https://www.diabetesjournals.org/content/license>.

Type 2 diabetes mellitus (T2DM) is a growing global health problem that afflicts more than 425 million (8.8%) adults in 2017 (1). It has been projected by the International Diabetes Federation to affect 693 million adults worldwide by year 2045 (1). The global cost of T2DM is high, costing governments USD 1.3 trillion in 2015, and this is estimated to increase to USD 2.3 trillion by 2030 (2).

With aging populations, rising complexity of medical care, and mounting economic costs from T2DM, the administration and delivery of health care at the population level have become more challenging (3,4). Population health, which is defined as “the health outcomes of a group of individuals, including the distribution of such outcomes within the group,” has been gaining traction in recent years due to finite health care resources and the impracticability of designing patient-specific care delivery models tailored for every individual (5). Consequently, population segmentation has been suggested as an avenue for policymakers and health care administrators to develop more cost-efficient and targeted population health-related policies and care models. This process segregates a heterogeneous patient population into unique subgroups with relatively similar anthropological clinical or psychosocial characteristics and/or health care requirements (6). For example, a recent study involving primary care users identified six distinct classes of patients, and patients in the “metabolic disease and multi-organ complications” group were found to have the highest level of health care use and risk of mortality (7).

Among both patients with type 1 diabetes and T2DM patients, a landmark cluster analysis of 5,795 Swedish patients identified five subtypes of patients with diabetes with a varying likelihood of developing diabetes-related complications and differing disease progression (8). Specifically, in T2DM patients, another study in North America identified four distinct subclasses of patients with differing clinical trajectories and health care use. Of note, patients in the high comorbidity and high insulin use group had the highest risk of diabetic nephropathy progression and annual frequency of health care visits (9).

The prevalence of diabetes in Singapore is among the highest within Southeast Asia (13.7% vs. regional prevalence

of 8.5%) (1). This multiethnic Asian country also has one of the highest diabetes-related lower-extremity amputation (LEA) rates among all Organization for Economic Cooperation and Development (OECD) countries (10). Currently, there remains sparse data pertaining to the usage of population segmentation methodologies for evaluating health care use, risk of diabetes-related complications, and mortality among different subgroups of T2DM patients in Asia, as the majority of studies were conducted in Europe and America. It is also important to note that Asians have a markedly increased predisposition for the development T2DM compared with their white counterparts, which arises from a complex interplay between genetics, environmental, lifestyle, and dietary-related factors (11). Therefore, we aim to segment T2DM patients into unique and relatively homogenous classes and evaluate whether health care use, diabetes-related complications, and mortality vary among the different patient subgroups.

RESEARCH DESIGN AND METHODS

Study Setting

Singapore is a multiethnic Asian country, which is comprised of a Chinese majority and minority ethnic groups such as Malay and Indians. The delivery of public health care is achieved through three integrated, regional health care clusters, namely, SingHealth Regional Health System (SRHS), National Healthcare Group, and National University Health Systems. Each health care cluster is supported by a network of general hospitals, tertiary care specialist centers, community hospitals, and polyclinics. Among the three clusters, SRHS forms the largest cluster, and its primary and tertiary health care facilities aid in catering to the health care needs of residents in both south-central and eastern regions of Singapore (12). While health care in the public sector is heavily subsidized by the government, the Community Health Assist Scheme (CHAS) enables residents from lower- to middle-income families to seek subsidized medical treatment for chronic conditions at accredited private general practitioner (GP) clinics near their home. Citizens will qualify for CHAS orange and CHAS blue subsidies if their monthly household income falls between USD 870 and 1,450 and less than USD 870, respectively (13).

Study Design

A retrospective cohort study was conducted involving all patients who were diagnosed with T2DM in or before 2012, were Singapore residents aged ≥ 21 years (the age of majority in Singapore), and had at least one visit in an SHRS health care institute or accredited CHAS GP clinic in year 2012. Patients who were noncitizens or did not have a visit in any SHRS institute were excluded, as they were unlikely to be on long-term medical follow-up in the SHRS. We excluded patients who were diagnosed with T2DM after 2012, as the analyses were to be conducted using patients' baseline characteristics in 2012.

De-identified patient data from an administrative database (Ministry of Health, Singapore) containing details of 71,125 T2DM patients were extracted. These included details on patients' baseline sociodemographic characteristics (age, ethnicity, sex), their comorbidities, CHAS subsidy class (orange, blue, or none) in year 2012, and data pertaining to their health care use, development of diabetes-related complications, and all-cause mortality from 2013 to 2016. CHAS subsidy class was used as a surrogate marker of the financial status of patients, while the comorbidities in the database were coded based on ICD-10.

The details of health care use included the total number of primary outpatient clinic, private general practitioner clinic, specialist outpatient clinic (SOC), and accident & emergency (A&E) visits and the number of inpatient admissions in year 2012. Diabetes complications examined included myocardial infarction, stroke, end-stage kidney disease requiring initiation of dialysis, and LEA. Myocardial infarction and stroke were coded based on ICD-10, while end-stage disease requiring initiation of dialysis and LEA were coded based on Ministry of Health, Singapore, Table of Surgical Procedures (TOSP) codes. The TOSP comprises a list of procedures claimable under MediSave (mandatory national medical savings scheme) or MediShield (a public health insurance for low-income Singapore citizens) (14). Details pertaining to clinical comorbidities, health care use, and diabetes-related complications were aggregated from data across public health care institutions from all three regional health systems in Singapore.

Ethics Approval and Consent to Participate

The study was approved by the Centralized Institutional Review Board in SingHealth (reference number: CIRB 2016/2294). Waiver of consent was obtained and approved by the committee for this study. Permission was also obtained from the hospitals and polyclinics for access to de-identified data from patient medical records.

Statistical Analysis

Latent class analysis (LCA) is a statistical approach used to derive groups of relatively homogenous individuals within a heterogeneous population (7,15). The latent class indicators used included patients' age (<65 years old, ≥65 years old), ethnicity (Chinese, Malay, Indians, and others), duration of diabetes (<5 years, 5–10 years, and >10 years), and clinical comorbidities of patients (Supplementary File 1). We fitted a series of latent class models starting from $k = 1$ (where k is the number of classes) onward. We stopped fitting a model with an additional class when the previous model's smallest class size was <1.5% of the study population (7). The rationale for selecting this cutoff was to ensure that the size of each class consists of a proportion of the study population sufficient to ensure practicality in the design of class-specific health care policies. The selected optimal value for k in the LCA model was determined using both model-fit indices that assess the fit and clinical interpretability of the classes. Indices used included the Akaike information criterion, Bayesian information criterion (BIC), sample size-adjusted BIC, and entropy, for which higher entropy and smaller values of Akaike information criterion, BIC, and sample size-adjusted BIC indicate better model fit (16). The clinical relevance and interpretability of the classes were evaluated by an endocrinologist within the research team and in relation to current clinical guidelines (17).

In this study, the mean \pm SD and number (percentage) were used to summarize continuous and categorical variables respectively. To profile the classes obtained from LCA, we compared the classes with the patients' sociodemographic and clinical characteristics and their health care use using one-way ANOVA or χ^2 tests for continuous and categorical variables, respectively.

To evaluate the discriminative properties of the derived classes on total health care use and the risk of diabetes related-complications from years 2013–2016, we excluded deceased patients in year 2012 from these analyses. For assessment of the relationship between health care use and class membership with adjustment for confounders, multivariable negative binomial regression was performed where appropriate, and the incidence rate ratios (IRRs) are reported with 95% CIs. To assess the relationship of class membership with 4-year risk of developing diabetes-related complications and all-cause mortality, we performed Cox proportional hazards regression analyses, and the hazard ratios (HRs) are reported with 95% CIs. The regression analyses were adjusted for the patients' age, sex, ethnicity, CHAS status, and duration of T2DM.

R, version 3.60, software (Foundation for Statistical Computing, Austria) was used for the latent class analyses, while Stata 15.0 software (2016) (StataCorp, College Station, TX) was used for all other statistical analyses.

Data and Resource Availability

The data sets generated and/or analyzed during the current study are not publicly available due to institutional restrictions but are available from the corresponding author on reasonable request.

RESULTS

A total of 71,125 T2DM patients were included in the analyses (Supplementary File 2). Table 1 depicts the baseline demographic and clinical characteristics of patients in the year 2012, segregated by the latent classes. The majority of patients were of Chinese ethnicity ($n = 49,951$ [70.2%]) and had a moderate (5–10 years) duration of diabetes ($n = 48,911$ [68.8%]). The proportions of male and female patients (48.7% vs. 51.3%, respectively) and of elderly and younger patients (48.3% vs. 51.7%) were similar. Pertaining to socioeconomic status, one-half of the patient population was receiving CHAS subsidies (50.3%).

For the model selection, LCA analyses were performed for $k = 1$ to $k = 7$. A five-class model was selected in view of the better statistical fit and predetermined minimum class sizes. When compared with the model-fit indices and class sizes

of other class models, it had the highest entropy, and the smallest class size was 1.57% (Supplementary File 3).

The five derived classes were as follows, and their terminologies are defined in Supplementary File 4.

1. Class 1: Younger patients with short T2DM duration and "relatively healthy" ($n = 11,133$)
2. Class 2: Younger patients with short-to-moderate T2DM duration and moderate disease burden without end-organ complications ($n = 24,566$)
3. Class 3: Younger females with short-to-moderate T2DM duration and high psychiatric and neurological disease burden ($n = 1,211$)
4. Class 4: Older patients with moderate T2DM duration and moderate disease burden ($n = 26,254$)
5. Class 5: Older patients with moderate-to-long T2DM duration, with depression, dementia, and high disease burden with end-organ complications ($n = 8,051$)

Characteristics of the Classes

Supplementary File 5 depicts the heat map display of the sociodemographic and clinical characteristics of patients across the five classes relative to the overall population. The majority of patients in classes 1, 2, and 3 were ≤65 years old, while the majority of patients in classes 4 and 5 were >65 years old (Table 1). The proportion of females was the highest among patients in class 3 (69.1%). With regard to ethnicity, the proportion of minority ethnic groups (Indians, Malays, and others) was the highest in class 5 (47.0%). (Table 1) Pertaining to the duration of T2DM, patients in class 1 had the shortest mean \pm SD T2DM duration (3.21 ± 2.90 years), while patients in class 5 had the longest mean T2DM duration (8.10 ± 3.10 years). Patients in class 1 had the lowest prevalence of cardiovascular, cerebrovascular, and renal-related comorbidities. Conversely, the prevalence of cardiovascular, cerebrovascular, and renal diseases was highest in patients in class 5. Patients in classes 3 and 5 also had a significantly higher prevalence of depression (13.1%–78.2% vs. 0.6%–1.7%; $P < 0.001$) compared with other classes. Patients in class 3 had the highest overall prevalence of psychiatric diseases, which included general anxiety disorder, major

Table 1—Baseline sociodemographic and clinical characteristics of patients in year 2012, segregated by latent classes

Characteristics	Overall (N = 71,125)	Class 1 (n = 11,133)	Class 2 (n = 24,566)	Class 3 (n = 1,121)	Class 4 (n = 26,254)	Class 5 (n = 8,051)	P
Class label		Younger patients with short T2DM duration and “relatively healthy”	Younger patients with moderate to moderate disease burden without end-organ complications	Younger females with short-to-moderate T2DM duration and high psychiatric and neurological disease burden	Older patients with moderate T2DM duration and moderate disease burden	Older patients with moderate-to-long T2DM duration, with depression, dementia, and high disease burden with end-organ complications	
Age, years	64 ± 12.6	54.4 ± 12.7	55.6 ± 7	60 ± 13	74.2 ± 6.9	70.5 ± 11	<0.001
Age (in year 2012), years							
<65	36,776 (51.7)	9,075 (81.5)	24,566 (100)	775 (69.1)	0 (0)	2,360 (29.3)	<0.001
≥65	34,349 (48.3)	2,058 (18.5)	0 (0)	346 (30.9)	26,254 (100.0)	5,691 (70.7)	
Sex							
Male	34,662 (48.7)	5,959 (53.5)	12,987 (52.9)	268 (23.9)	10,634 (40.5)	4,814 (59.8)	<0.001
Female	36,463 (51.3)	5,174 (46.5)	11,579 (47.1)	853 (76.1)	15,620 (59.5)	3,237 (40.2)	
Race groups							
Chinese	49,951 (70.2)	7,099 (63.8)	16,059 (65.4)	867 (77.3)	21,661 (82.5)	4,265 (53)	<0.001
Indian	7,250 (10.2)	1,548 (13.9)	2,599 (10.6)	157 (14)	1,238 (4.7)	1,708 (21.2)	
Malay	11,352 (16.0)	1,907 (17.1)	4,948 (20.1)	40 (3.6)	2,982 (11.4)	1,475 (18.3)	
Others	2,572 (3.6)	579 (5.2)	960 (3.9)	57 (5.1)	373 (1.4)	603 (7.5)	
CHAS status							
Blue	27,056 (38.0)	3,659 (32.9)	9,158 (37.3)	493 (44.0)	11,057 (42.1)	2,689 (33.4)	
Orange	8,621 (12.1)	1,545 (13.9)	3,926 (16)	120 (10.7)	2,340 (8.9)	690 (8.6)	
None	35,448 (49.8)	5,929 (53.3)	11,482 (46.7)	508 (45.3)	12,857 (49.0)	4,672 (58.0)	
T2DM duration, years	4.9 ± 3.1	3.2 ± 2.9	4.4 ± 2.6	5.0 ± 3.5	5.2 ± 2.7	8.1 ± 3.1	<0.001
T2DM duration, years							
<5	27,848 (39.2)	8,006 (71.9)	10,771 (43.8)	515 (45.9)	7,749 (29.5)	807 (10)	<0.001
5–10	38,424 (54)	2,774 (24.9)	13,291 (54.1)	497 (44.3)	17,296 (65.9)	4,566 (56.7)	
>10	4,853 (6.8)	353 (3.2)	504 (2.1)	109 (9.7)	1,209 (4.6)	2,678 (33.3)	
Prevalence of comorbidities							
Psychiatric diseases							
Anxiety	1,251 (1.8)	59 (0.5)	252 (1.0)	564 (50.3)	132 (0.5)	244 (3.0)	<0.001
General anxiety disorder	39 (0.1)	0 (0)	0 (0)	39 (3.5)	0 (0)	0 (0)	<0.001
Major depression	2,809 (3.9)	174 (1.6)	149 (0.6)	994 (88.7)	438 (1.7)	1,054 (13.1)	<0.001
Schizophrenia	815 (1.1)	129 (1.2)	256 (1.0)	266 (23.7)	125 (0.5)	39 (0.5)	<0.001
Bipolar disorder	250 (0.4)	31 (0.3)	51 (0.2)	102 (9.1)	34 (0.1)	32 (0.4)	<0.001
Metabolic diseases							
Hyperlipidemia	62,462 (87.8)	4,324 (38.8)	24,522 (99.8)	924 (82.4)	24,910 (94.9)	7,782 (96.7)	<0.001
Hypertension	60,778 (85.5)	3,035 (27.3)	22,955 (93.4)	911 (81.3)	25,829 (98.4)	8,048 (100.0)	<0.001
Cardiovascular diseases							
Coronary heart disease	19,782 (27.8)	447 (4.0)	4,582 (18.7)	312 (27.8)	7,294 (27.8)	7,147 (88.8)	<0.001
Previous myocardial infarction	7,013 (9.9)	111 (1.0)	1,653 (6.7)	74 (6.6)	2,183 (8.3)	2,992 (37.2)	<0.001

Continued on p. 1052

Table 1—Continued

Characteristics	Overall (N = 71,125)	Class 1 (n = 11,133)	Class 2 (n = 24,566)	Class 3 (n = 1,121)	Class 4 (n = 26,254)	Class 5 (n = 8,051)	P
Previous coronary artery bypass graft	1,944 (2.7)	24 (0.2)	479 (1.9)	8 (0.7)	621 (2.4)	812 (10.1)	<0.001
Previous percutaneous coronary intervention	5,090 (7.2)	99 (0.9)	1,637 (6.7)	47 (4.2)	1,548 (5.9)	1,759 (21.8)	<0.001
Heart failure	1,944 (2.7)	24 (0.2)	479 (1.9)	8 (0.7)	621 (2.4)	812 (10.1)	<0.001
Kidney diseases							
CKD	56,987 (80.1)	6,226 (55.9)	20,740 (84.4)	957 (85.4)	21,290 (81.1)	7,774 (96.6)	<0.001
End-stage renal disease on dialysis	1,432 (2.0)	51 (0.5)	136 (0.6)	9 (0.8)	8 (0)	1,228 (15.3)	<0.001
Kidney transplant	5 (0)	1 (0)	1 (0)	0 (0)	0 (0)	3 (0)	<0.001
Neurological diseases							
Stroke	6,188 (8.7)	49 (0.4)	1,047 (4.3)	145 (12.9)	2,001 (7.6)	2,946 (36.6)	<0.001
Hemorrhagic stroke	1,238 (1.7)	18 (0.2)	232 (0.9)	43 (3.8)	392 (1.5)	553 (6.9)	<0.001
Ischemic stroke	5,492 (7.7)	34 (0.3)	884 (3.6)	115 (10.3)	1,763 (6.7)	2,696 (33.5)	<0.001
Dementia	1,702 (2.4)	62 (0.6)	29 (0.1)	56 (5.0)	955 (3.6)	600 (7.5)	<0.001
Vascular diseases							
Peripheral vascular disease	2,930 (4.1)	138 (1.2)	389 (1.6)	35 (3.1)	810 (3.1)	1,558 (19.4)	<0.001
Previous LEA	1,296 (1.8)	105 (0.9)	187 (0.8)	4 (0.4)	14 (0.1)	986 (12.2)	<0.001

Data are means ± SD or n (%).

Table 2—Health care use (yearly), incidence of diabetes-related complications from 2013 to 2016, and 4-year all-cause mortality among patients, segregated by latent classes

	Overall	Class 1	Class 2	Class 3	Class 4	Class 5	P
Class label		Younger patients with short T2DM duration and “relatively healthy”	Younger patients with short-to-moderate T2DM duration and moderate disease burden without end-organ complications	Younger females with short-to-moderate T2DM duration and high psychiatric and neurological disease burden	Older patients with moderate T2DM duration and moderate disease burden	Older patients with moderate-to-long T2DM duration, with depression, dementia, and high disease burden with end-organ complications	
Average yearly health care use from 2013 to 2016, mean ± SD							
Polyclinic visits	4.82 ± 4.05	3.51 ± 3.83	5.64 ± 3.90	5.12 ± 5.45	4.91 ± 3.77	3.78 ± 4.73	<0.001
GP visits	1.26 ± 2.86	1.08 ± 2.57	0.81 ± 2.23	1.70 ± 5.52	1.82 ± 3.28	0.97 ± 2.63	<0.001
SOC visits	3.04 ± 3.63	2.57 ± 3.19	2.62 ± 3.35	5.85 ± 6.02	3.18 ± 3.52	4.13 ± 4.43	<0.001
Emergency department visits	0.5 ± 1.09	0.35 ± 0.84	0.38 ± 0.87	1.15 ± 3.64	0.48 ± 0.74	1.00 ± 1.80	<0.001
Inpatient admissions	0.38 ± 0.74	0.24 ± 0.53	0.27 ± 0.63	0.66 ± 1.25	0.4 ± 0.65	0.85 ± 1.18	<0.001
Total no. of patients who developed diabetes-related complications from 2013 to 2016 (%)							
Myocardial infarction	3,157 (4.44)	300 (2.69)	684 (2.78)	52 (4.64)	1,382 (5.26)	739 (9.18)	<0.001
End-stage renal disease requiring dialysis initiation	1,251 (1.76)	128 (1.15)	432 (1.76)	12 (1.07)	397 (1.51)	282 (3.50)	<0.001
Stroke	1,931 (2.71)	198 (1.78)	464 (1.89)	39 (3.48)	936 (3.57)	294 (3.65)	<0.001
LEA	664 (0.93)	83 (0.75)	191 (0.78)	9 (0.80)	184 (0.70)	197 (2.45)	<0.001
4-Year all-cause mortality, n patients (%)	7,670 (10.78)	503 (4.52)	812 (3.31)	134 (11.95)	3,585 (13.66)	2,636 (32.74)	<0.001

depression, schizophrenia, and bipolar disorder, and the prevalence of neurological diseases was high.

Health Care Use and Incidence of Diabetes-Related Complications From Years 2013–2016

A total of 1,777 (2.5%) patients were excluded from the analyses, as they died in year 2012. Patients in classes 3 and 5 had the highest tertiary health care use with regard to the average number of inpatient admissions and SOC and A&E visits from 2013 to 2016 (Table 2). For primary health care use, classes 2, 3, and 4 had the highest number of polyclinic visits. Overall, class 1 has the lowest overall health care use.

For diabetes-related complications, class 5 had the highest proportion of patients who developed myocardial infarction, end-stage renal disease requiring dialysis initiation, stroke, and LEA (*P* <

0.001). Conversely, class 1 had the lowest proportion of patients who developed diabetes-related complications in 2013.

Multivariable Analyses of Latent Classes With Total Health Care Use, Diabetes-Related Complications From Years 2013–2016, and 4-Year All-Cause Mortality

Class 1 was set as the reference group for analyses. Overall, class membership was predictive of health care use, diabetes-related complications and mortality (*P* < 0.001) (Table 3). With regard to primary health care use pattern across the five classes, patients in classes 2 and 4 had the highest total polyclinic visits (class 2 adjusted IRR 1.53, 95% CI 1.49–1.57; class 4 1.53, 95% CI 1.47–1.59). Pertaining to tertiary health care use, patients in class 3 had the highest total SOC visits (IRR 2.12, 95% CI 1.97–2.29) and total A&E

visits (IRR 3.31, 95% CI 3.04–3.59). Class 5 had the highest total inpatient admissions (IRR 2.82, 95% CI 2.67–2.98).

For diabetes-related complication patterns across the five classes, class 5 patients had the highest hazard for myocardial infarction (HR 12.05, 95% CI 10.82–13.42), end-stage renal dialysis requiring dialysis initiation (HR 25.81, 95% CI 21.75–30.63), stroke (HR 19.37, 95% CI 16.92–22.17), and LEA (HR 12.94, 95% CI 10.90–15.36).

The two classes with the highest hazard for 4 years all-cause mortality were class 3 (HR 2.31, 95% CI 1.94–2.74) and class 5 (HR 3.47, 95% CI 3.17–3.80).

CONCLUSIONS

Overall, our study identified five distinct classes of T2DM patients with unique health profiles, with differential health care use, diabetes complication risk, and mortality patterns. Given the association

Table 3—Adjusted effect of the five latent classes on health care use, diabetes-related complications from years 2013–2016, and 4-year all-cause mortality

	Class 1 ^b	Class 2	Class 3	Class 4	Class 5	Wald χ^2 for class membership
Class label	Younger patients with short T2DM duration and “relatively healthy”	Younger patients with short-to-moderate T2DM duration and moderate disease burden without end-organ complications	Younger females with short-to-moderate T2DM duration and high psychiatric and neurological disease burden	Older patients with moderate T2DM duration and moderate disease burden	Older patients with moderate-to-long T2DM duration, with depression, dementia, and high disease burden with end-organ complications	
Total health care use from 2013 to 2016 ^c						
Polyclinic visits	1.00	1.53 (1.49–1.57)***	1.42 (1.33–1.52)***	1.53 (1.47–1.59)***	1.10 (1.06–1.14)***	2,820***
Private GP visits	1.00	0.97 (0.92–1.02)*	1.28 (1.12–1.45)***	0.91 (0.85–0.98)**	0.73 (0.68–0.79)***	10,345***
SOC visits	1.00	0.97 (0.94–1.00)*	2.12 (1.97–2.29)***	1.17 (1.12–1.22)***	1.41 (1.35–1.47)***	2,214***
Emergency department visits	1.00	1.02 (0.98–1.05)*	3.31 (3.04–3.59)***	1.53 (1.46–1.61)***	2.47 (2.35–2.59)***	6,027***
Inpatient admissions	1.00	1.05 (1.01–1.09)**	2.70 (2.45–2.97)***	1.55 (1.46–1.63)***	2.82 (2.67–2.98)***	5,318***
4-Year risk of diabetes-related complications ^d						
Myocardial infarction	1.00	2.74 (2.47–3.05)***	3.68 (3.01–4.50)***	3.11 (2.79–3.47)***	12.05(10.82–13.42)***	8,086***
End-stage renal disease requiring dialysis	1.00	1.58 (1.33–1.87)***	1.51 (0.96–2.38)*	1.95 (1.60–2.38)***	25.81(21.75–30.63)***	41,417***
Stroke	1.00	2.80 (2.45–3.20)***	7.45 (6.15–9.03)***	3.50 (3.06–4.02)***	19.37(16.92–22.17)***	7,468***
LEA	1.00	0.92 (0.77–1.10)*	0.85 (0.48–1.49)*	0.65 (0.52–0.81)***	12.94(10.90–15.36)***	3,187***
4-Year all-cause mortality ^d	1.00	0.92 (0.83–1.01)*	2.31 (1.94–2.74)***	1.20 (1.10–1.31)***	3.47 (3.17–3.80)***	15,960***

Data are IRR (95% CI) unless otherwise specified. Models were adjusted for age, sex, ethnicity, CHAS status, and duration of T2DM. ^bReference group. ^cNegative binomial regression analyses were performed. ^dCox proportional hazards regression analyses were performed. HRs reported with 95% CI. * $P \geq 0.05$; ** $P < 0.05$; *** $P < 0.001$.

between predictive ability of the classes and future health care use and health outcomes in 2013 among T2DM patients, our findings support the usage of data-driven population segmentation methods among T2DM patients and have significant implications on diabetes care, health policy planning, and resource allocation.

Among class 3 and 5 patients who had the highest tertiary health care use, diabetes-related complications, and mortality, an important unifying characteristic noted was the high prevalence of depression (13.1%–88.7%). This was significantly higher than in the general population (5.8%) (18) and concurred with a systematic review by Roy et al. (19) that showed that the prevalence of depression in the population with diabetes was twice that in the population without diabetes (19.1% vs. 10.7%, respectively). Comorbid depression has significant repercussions on the outcomes of T2DM and has been associated with poorer health-related quality of life, premature mortality, and increased risk of diabetes-related complications

(20). While our study findings support American Diabetes Association guidelines for consideration of depression screening among elderly T2DM patients, there are no recommendations on the specific subgroups of elderly T2DM patients who should be screened (17). With the aging population worldwide and limited health care resources, it is impractical to perform universal screening for all elderly T2DM patients. Importantly, our findings highlight the need for routine screening for depressive symptoms among elderly patients with moderate-to-long duration of T2DM (>5 years), multiple comorbidities, and end-organ complications.

Additionally, we have identified another subgroup of T2DM patients—class 3 (younger females with short-to-moderate T2DM duration and high psychiatric and neurological disease burden)—who may benefit from depression screening. Studies have shown that depressive symptoms and episodes among T2DM patients tend to be persistent, and the rates of relapses are exceptionally high, with a

5-year recurrence rate of 79% (20). Furthermore, another study by Ke et al. (21) also showed that high psychiatric disease burden among young-onset T2DM patients contributed to a significant 36.8% of inpatient admission bed-days. The early identification of these high-need patients, using validated instruments such as the Patient Health Questionnaire-9, may permit implementation of psychological interventions and treatment, which in turn promote disease remission and reduce the financial burden of disease.

For patients in class 5, the prevalence of dementia was also noted to be high (7.5%). Dementia is the most severe stage on the continuum of diabetes-related cognitive deficits and has been associated with poor glycemic control and increased risk of severe hypoglycemia (22). While guidelines have recommended dementia screening among elderly patients, the subtypes of elderly patients to be screened have not been defined (23). Our study suggests that there is a need for routine screening for dementia

among elderly patients, especially with moderate-to-long-standing T2DM and multimorbidities.

For the patients in class 3 with high neurological disease burden, secondary and tertiary disease prevention plays an important role. As these conditions often culminate in significant physical, cognitive, behavioral, and psychosocial problems and limitations, neuro-rehabilitation involving a multidisciplinary team should be considered and incorporated in patient care following diagnosis. There is also little controversy on the benefits of risk factor modification for these patients, in particular tobacco use, lifestyle and dietary modifications, and aggressive treatment of concomitant metabolic diseases such as hyperlipidemia. While trials evaluating the impact of multiple risk factor interventions have shown promising results for health outcomes, the actualization and long-term sustainability of these interventions in real life are often confounded by factors such as treatment compliance (24). As such, more studies are needed on developing sustainable models of care for the optimization of outcomes for these patients.

Pertaining to the study population, it was important to note that the prevalence of concomitant metabolic diseases such as hypertension (85.5%), hyperlipidemia (87.8%), and chronic kidney disease (CKD) (80.1%) was exceptionally high. For hypertension, specifically, the prevalence in this study was among the highest within Asia (40.4%–85.8%) and in the world (25). Likewise, the prevalence of CKD was more than three times that in the U.S. (25%) (26). T2DM patients with CKD have been shown to have poorer glycemic control and higher risk of diabetes-related complications such as neuropathies and cardiovascular disease (27). Consequently, for patients in class 1 who were deemed to be “relatively healthy” and have the lowest health care use, there is still a significant proportion of patients with these diseases. Hence, targeted interventions for these patients as well as patients in classes 2 and 4 with moderate disease burden should encompass themes for disease maintenance, early intervention, and disease prevention. Potential strategies are the use of intensive glycemic control among T2DM patients and education programs. For example, Action in Diabetes and Vascular Disease: Preterax and Diamcron

MR Controlled Evaluation (ADVANCE) showed that intensive glycemic control was able to reduce risk of end-stage kidney disease by 65% and macroalbuminemia by 30% (28). Likewise, a review by Li et al. (29) showed that education programs for diabetic kidney disease patients have a positive influence on their self-management behaviors and knowledge of diabetes.

With regard to interethnic disparities in T2DM outcomes, our findings correlated with findings reported in literature, where class 5, which comprised the highest proportion of Indians and Malays, had the highest risk of diabetes-related complications. A study by Chew et al. (30) noted that Indians with T2DM suffered from increased diabetes-related complications such as LEA and nephropathy compared with Chinese patients. Both Malay and Indian T2DM patients have also been shown to have poorer diabetes control compared with their Chinese counterparts (31). Although the mechanism for ethnic disparities in outcomes is unclear, postulated reasons include a complex interplay between environmental and socioeconomic factors as well as increased genetic predisposition to insulin resistance among Indians and Malays, which may affect their diabetes control. The design of interventions for this class of patients should address these interethnic differences during diabetes care, e.g., education programs tailored for culture-specific dietary habits.

Currently, there exists a myriad of population segmentation frameworks such as Johns Hopkins Adjusted Clinical Groups System and Bridges to Health for population health (32). However, the optimal segmentation framework for T2DM patients has not been established. As such, it is inevitable that there will be interstudy variations pertaining to derived patient clusters, which arise due to the differences in population segmentation methodology used, selection of segmentation variables, and subjectivity in the naming of patient clusters. Nonetheless, our study generally concurred with findings from studies that have used similar or overlapping latent variables within their segmentation approaches. For example, a study by Jiang et al. (9) identified four unique clusters of T2DM patients, for which patients in the “high comorbidity/moderate treatment” class had significantly higher risk for diabetes-related nephropathy and its progression

compared with patients in the “low comorbidity/low treatment” class.

The main strength of the study is that it is one of the largest Asian studies that have evaluated differential health care use, diabetes-related complications, and mortality patterns among subclasses of T2DM patients. Another strength was that the diagnoses of patients made in other public institutions and regional health systems in Singapore were captured within the database, which increases the robustness and generalizability of our findings.

Nonetheless, our study results should be interpreted with the following limitations. First, due to the inherent limitations of data and lack of data granularity available in the administrative database, variables related to patients’ socioeconomic status (e.g., household income), control of diabetes (e.g., HbA_{1c}), diabetes-related retinopathy, and types of anti-diabetes medications, which may affect patients’ health care use and mortality, could not be evaluated. Furthermore, modifiable risk factors such as control of concomitant hypertension and obesity, which play a role in predicting diabetes control and disease trajectories, could not be examined. Given the complexity of diabetes care, the use of data-driven care models may complement risk stratification approaches derived from population segmentation techniques in predicting clinical outcomes of T2DM patients (33,34). An example of a data-driven integrated diabetes care program is the Risk Assessment and Management Programme—Diabetes Mellitus (RAMP-DM), which was shown to reduce cardiovascular disease, nephropathy, and mortality by 30–60% (35). It identifies high-risk T2DM patients using a validated scoring algorithm derived from large data registries and refers these patients for comanagement with nursing personnel and family practitioners for optimization of diabetes control (35). For health care use, we could only evaluate all-cause health care use instead of T2DM-specific health care use, and health care costs could not be assessed. With the rising use of electronic health records, which can capture more comprehensive medical data, future studies should consider exploring the use of socioeconomic and clinical variables as potential latent class indicators for the segregation of patients as well as to assess T2DM-specific

health care use, costs, and mortality. Another limitation of the study was that the patients who used private health care exclusively were not captured in the database. Nevertheless, as the majority (>80%) of the health care demand in Singapore is catered for by the public health care institutions, we expect the number of patients who fall within this group to be small (7). Lastly, we were unable to assess the long-term clinical trajectories and interclass migration of patients, as the longitudinal data for patients were limited within the administrative database. Future studies may wish to explore these using statistical modeling techniques such as latent class growth analysis and follow-up patients for a longer period of time.

Conclusion

Our study identified five distinct subgroups of T2DM patients with differential health care use, diabetes-related complications, and mortality patterns, using routine sociodemographic and clinical data available in clinical practice. There is a need to screen for concomitant psychiatric diseases such as depression among two identified subgroups of T2DM patients. Our findings serve as an important foundation for guiding researchers and policy makers in designing clinical trials and health care policies to optimize the outcomes of T2DM patients, respectively.

Funding. This study is supported by the Singapore Ministry of Health's National Medical Research Council under the Fellowship Programme by SingHealth Regional Health System, Population-based, Unified, Learning System for Enhanced and Sustainable (PULSES) Health Centre Grant (NMRC/CG/C027/2017_SHS).

Singapore Ministry of Health's National Medical Research Council and SingHealth Regional Health System, Population-based, Unified, Learning System for Enhanced and Sustainable (PULSES) Health Centre did not play any role in the study design, data collection, data analysis, data interpretation, manuscript writing, or decision to submit the manuscript for publication.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. L.L.L. was the study's principal investigator and was responsible for the conception and design of the study. J.J.B.S., Y.H.K., V.S.Y.L., C.S.T., S.B.Z., and J.T. were the co-investigators. Access to data was provided by L.L.L. and V.S.Y.L. J.J.B.S., C.S.T., and V.S.Y.L. were responsible for analyzing the data. All authors contributed to the interpretation of data and literature review. J.J.B.S. prepared the initial draft of the manuscript. All authors revised the draft critically for important intellectual content and

agreed to the final submission. L.L.L. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

- International Diabetes Federation (Ed.). *IDF Diabetes Atlas*. 8th ed. Brussels, Belgium, International Diabetes Federation, 2017
- Bommer C, Sagalova V, Heeseemann E, et al. Global economic burden of diabetes in adults: projections from 2015 to 2030. *Diabetes Care* 2018;41:963–970
- Beard JR, Officer AM, Cassels AK. The world report on ageing and health. *Gerontologist* 2016;56(Suppl. 2):S163–S166
- Eissens van der Laan MR, van Offenbeek MA, Broekhuis H, Slaets JP. A person-centred segmentation study in elderly care: towards efficient demand-driven care. *Soc Sci Med* 2014;113:68–76
- Kindig D, Stoddart G. What is population health? *Am J Public Health* 2003;93:380–383
- Vuik SI, Mayer EK, Darzi A. Patient segmentation analysis offers significant benefits for integrated care and support. *Health Aff (Millwood)* 2016;35:769–775
- Yan S, Seng BJJ, Kwan YH, et al. Identifying heterogeneous health profiles of primary care utilizers and their differential healthcare utilization and mortality - a retrospective cohort study. *BMC Fam Pract* 2019;20:54
- Ahlqvist E, Storm P, Käräjämäki A, et al. Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables. *Lancet Diabetes Endocrinol* 2018;6:361–369
- Jiang R, Law E, Zhou Z, Yang H, Wu EQ, Seifeldin R. Clinical trajectories, healthcare resource use, and costs of diabetic nephropathy among patients with type 2 diabetes: a latent class analysis. *Diabetes Ther* 2018;9:1021–1036
- Ang Y, Yap CW, Saxena N, Lin L-K, Heng BH. Diabetes-related lower extremity amputations in Singapore. *Proceedings of Singapore Healthcare* 2017;26:76–80
- Ma RCW, Chan JCN. Type 2 diabetes in East Asians: similarities and differences with populations in Europe and the United States. *Ann N Y Acad Sci* 2013;1281:64–91
- Seng JJB, Lim VZK, Kwan YH, Thumboo J, Low LL. Outpatient primary and tertiary healthcare utilisation among public rental housing residents in Singapore. *BMC Health Serv Res* 2019;19:227
- CHAS subsidies [Internet], 2019. Available from <https://www.chas.sg/content.aspx?id=636>. Accessed 4 October 2019
- Table of surgical procedures [Internet], 2019. Available from <https://www.moh.gov.sg/docs/librariesprovider5/medisave/table-of-surgical-procedures.pdf>. Accessed 15 September 2019
- Fitzpatrick SL, Coughlin JW, Appel LJ, et al. Application of latent class analysis to identify behavioral patterns of response to behavioral lifestyle interventions in overweight and obese adults. *Int J Behav Med* 2015;22:471–480
- Celex G, Soromenho G. An entropy criterion for assessing the number of clusters in a mixture model. *J Classif* 1996;13:195–212
- Introduction: *Standards of Medical Care in Diabetes—2019*. *Diabetes Care* 2019;42(Suppl. 1):S1–S2

- Chong SA, Abdin E, Vaingankar JA, et al. A population-based survey of mental disorders in Singapore. *Ann Acad Med Singapore* 2012;41:49–66
- Roy T, Lloyd CE. Epidemiology of depression and diabetes: a systematic review. *J Affect Disord* 2012;142(Suppl.):S8–S21
- Holt RIG, de Groot M, Golden SH. Diabetes and depression. *Curr Diab Rep* 2014;14:491
- Ke C, Lau E, Shah BR, et al. Excess burden of mental illness and hospitalization in young-onset type 2 diabetes: a population-based cohort study. *Ann Intern Med* 2019;170:145–154
- Biessels GJ, Despa F. Cognitive decline and dementia in diabetes mellitus: mechanisms and clinical implications. *Nat Rev Endocrinol* 2018;14:591–604
- American Diabetes Association. 2. Classification and diagnosis of diabetes: Standards of Medical Care in Diabetes—2019. *Diabetes Care* 2019;42(Suppl. 1):S13–S28
- Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med* 2008;358:580–591
- Colosia AD, Palencia R, Khan S. Prevalence of hypertension and obesity in patients with type 2 diabetes mellitus in observational studies: a systematic literature review. *Diabetes Metab Syndr Obes* 2013;6:327–338
- Zelnick LR, Weiss NS, Kestenbaum BR, et al. Diabetes and CKD in the United States population, 2009–2014. *Clin J Am Soc Nephrol* 2017;12:1984–1990
- Luk AO, Li X, Zhang Y, et al.; JADE Study Group. Quality of care in patients with diabetic kidney disease in Asia: the Joint Asia Diabetes Evaluation (JADE) Registry. *Diabet Med* 2016;33:1230–1239
- Patel A, MacMahon S, Chalmers J, et al.; ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008;358:2560–2572
- Li T, Wu HM, Wang F, et al. Education programmes for people with diabetic kidney disease. *Cochrane Database Syst Rev* 2011:CD007374
- Chew BH, Mastura I, Lee PY, Wahyu TS, Cheong AT, Zaiton A. Ethnic differences in glycaemic control and complications: the adult diabetes control and management (ADCM), Malaysia. *Med J Malaysia* 2011;66:244–248
- Hong CY, Chia KS, Hughes K, Ling SL. Ethnic differences among Chinese, Malay and Indian patients with type 2 diabetes mellitus in Singapore. *Singapore Med J* 2004;45:154–160
- Low LL, Kwan YH, Liu N, Jing X, Low ECT, Thumboo J. Evaluation of a practical expert defined approach to patient population segmentation: a case study in Singapore. *BMC Health Serv Res* 2017;17:771
- Chan JCN, Lim L-L, Luk AOY, et al. From Hong Kong Diabetes Register to JADE Program to RAMP-DM for data-driven actions. *Diabetes Care* 2019;42:2022–2031
- Wu H, Lau ESH, Ma RCW, et al. Secular trends in all-cause and cause-specific mortality rates in people with diabetes in Hong Kong, 2001–2016: a retrospective cohort study. *Diabetologia* 2020;63:757–766
- Wan EYF, Fung CSC, Jiao FF, et al. Five-year effectiveness of the multidisciplinary Risk Assessment and Management Programme—Diabetes Mellitus (RAMP-DM) on diabetes-related complications and health service uses—a population-based and propensity-matched cohort study. *Diabetes Care* 2018;41:49–59