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Age and sex-specific associations of visit-to-visit variability of glycated hemoglobin A1c with all-cause mortality in patients with diabetes

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Abstract

Background: Visit-to-visit variability (VVV) of glycated hemoglobin (HbA1c) levels have been found to be associated with prognosis of diabetes. However, little is known about whether or to what extent sex and age may modify the effects of VVV.

Methods: To investigate age- and sex-specific rates of mortality from all causes and relative hazards of mortality in association with VVV of HbA1c levels, 47,145 patients with diabetes and prescription of any antidiabetic agents >6 months were identified from outpatient visits of a tertiary medical center in northern Taiwan during 2003–2018. VVV of HbA1c was measured by quartiles of standard deviation (SD), coefficient of variation (CV), and average real variability (ARV), respectively. The study subjects were linked to Taiwan's National Death Registry to identify all-cause mortality. The person-year approach with the Poisson assumption was used to assess the all-cause mortality rates, and Cox proportional hazard regression model was used to evaluate the relative hazards of all-cause mortality concerning various levels of VVV of HbA1c.

Results: The lowest all-cause mortality rate was found in either the first or second quartile of various measures for VVV of HbA1c, but the highest mortality rate was consistently observed in the fourth quartile of VVV, regardless of SD, CV, or ARV across ages and sexes. Increased hazards of overall all-cause mortality were noticed from the second to fourth quartile of VVV of HbA1c. In detailed age- and sex-stratified analyses, elevated risk of mortality was seen in the fourth quartile of those aged <50 years while in those aged >69 years, increased risk of mortality was noticed in the third and fourth quartiles of any VVV of HbA1c irrespective of sex. In those aged 50–69 years, incremental increased hazards of mortality were consistently observed in the second to fourth quartiles of VVV of HbA1c.

Conclusion: HbA1c variability whether it was SD, CV, or ARV could strongly predict the risks of all-cause mortality. The extent of the relationship between VVV of HbA1c and all-cause mortality in different age groups was comparable between both sexes. Given the importance of long-term glucose fluctuation, the inclusion of HbA1c variability calculated from the standardized method should be considered by clinical guideline policymakers as part of the biochemical panel in daily diabetes management.

Abbreviations: ARV = average real variability, CI = confidence interval, CKD = chronic kidney disease,Cr = creatinine, CV = coefficient of variation, eGFR = estimated glomerular filtration rate,FEMH = Far Eastern Memorial Hospital,FPG = fasting plasma glucose,Hb = hemoglobin, HbA1 = glycated hemoglobin, HR = hazard ratio,ICD-CM = International Classification of Diseases Clinical Modification,LDL = low density lipoprotein,PIN = personal identification number,PY = patient-years, SD = standard deviation,VI = variation independent of the mean, VVV = visit-to-visit variability.

Keywords: diabetes mellitus, glycated hemoglobin, mortality, visit-to-visit variability

1. Introduction

Lowering glycated hemoglobin (HbA1c), which reflects average glucose over approximately 3 months,[1] may reduce the risk of micro- and macrovascular complications in patients with type 1[2] and/or type 2 diabetes.[3] However, the Diabetes Control and complications trial noted a higher risk of retinopathy progression in patients in the conventional treatment group than in the

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The study was approved by the Institutional Review Board of Far Eastern Memorial Hospital (110033-F) with no informed consent required.

The authors have no conflicts of interest to disclose.

The data that support the findings of this study are available from a third party, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are available from the authors upon reasonable request and with the permission of the third party.

The datasets analyzed during the current study are not publicly available because of information governance restrictions.

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intensive group with similar HbA1c levels and suggested intermittent hyperglycemic excursions, that is, glycemic variability might be related to adverse outcomes.[4] Long-term glycemic variability refers to fluctuations of blood glucose over several months or years and is most commonly assessed by visit-to-visit variability (VVV) of HbA1c.[5]

There is no standardized method of measurement or definition to evaluate the VVV of HbA1c. Most of the previous reports used standard deviation (SD) and coefficient of variation (CV) to identify glycemic variability.[6–11] A few studies investigated additional measurements like variation independent of the mean (VIM) and average real variability (ARV) of HbA1c in relationship to all-cause mortality.[8,11] In these studies so far, there is inconsistency as to which of the VVV of HbA1c best predicts the risk of all-cause mortality; this may be due to a limited number of study subjects,[6,7] short period of follow-up,[6,9] only baseline HbA1c measurement obtained,[9–12] study subjects restricted to elder patients only,[9,11] or certified death by just questionnaire.[7] Only the Hong Kong study[8] differentiated the risk estimates of all-cause mortality in the study subjects with ages <65 and ≥65 years; however, the authors did not further analyze the different risk estimates between each sex in those aged groups. To our best knowledge, studies that explored the risk difference of VVV of HbA1c in those aged <50 years are also scarce in the literature.

Our study aimed to assess the relationships between various VVVs of HbA1c and all-cause mortality and to compare the risk estimates among different VVV measures of HbA1c in patients with diabetes of specific age and sex stratifications receiving antidiabetic treatment in Far Eastern Memorial Hospital (FEMH) from Jan 1, 2003, to Dec 31, 2018. Because VIM needs extra estimation, which can generate bias,[13] we selected SD, CV, and ARV as the VVV of HbA1c in our study. We also evaluated the relative risk estimates associated with VVV of HbA1c in various age- and sex stratifications with adjustment of medications, comorbidities, and various laboratory results in the statistical model.

2. Methods

2.1. Study design and subjects

This was a cohort study designed to assess the all-cause mortality concerning VVV of HbA1c among patients with diabetes and treated at FEMH, a tertiary medical center located in New Taipei City, the northern part of Taiwan. In FEMH, average annual outpatient patients with diabetes are more than 20,000, the fourth largest number among 19 medical centers in Taiwan.[14] Twelve endocrinologists take care of nearly 50% of all outpatient patients with diabetes while the rest of the patients are attended by various specialists, mostly cardiologists, neurologists, nephrologists, and family medicine physicians.

Since Jan 1, 2001, the FEMH has established its electronic medical database of inpatient and outpatient visits including the dataset of each patient's age, sex, hospital chart number, personal identification number (PIN), dates of admission and discharge, length of hospital stay, up to six International Classification of Diseases Clinical Modification, 9th or 10th version (ICD-9/10-CM) diagnosis codes, prescribed medications, and laboratory reports.

We identified the study patients by diagnostic codes of ICD-9-CM: 250.xx or ICD-10-CM: E10 or E11. Type of diabetes was classified into type 1 diabetes (ICD-9-CM 250.x1 or ICD-9-CM 250.x3; ICD-10-CM: E10) or type 2 diabetes (ICD-9-CM 250.x0 or ICD-9-CM 250.x2; ICD-10-CM: E11) at outpatient database. The duration of the study period was from Jan 1, 2003, to Dec 31, 2018. Our study had approval from the FEMH's institutional Review Board with no informed consent required (IRB#: 110033-F).

During 2003–2018, there were 74,888 patients with diabetes diagnoses. We excluded 4213 patients without any prescription of oral or parenteral antidiabetic agents, and 23,530 patients with a duration of total outpatient visit at FEMH less than 6 months. The final diabetes cohort comprised 47,145 patients. The first date of oral or parenteral antidiabetic agents prescribed in FEMH during 2003–2018 was set as the index date of each patient.

2.2. Follow-up, study endpoint, and covariates

The follow-up period was from the index date to the occurrence of all-cause mortality or censoring. If the patients did not encounter death during the study period, and his/her HbA1c value was detected beyond Dec 31, 2018, they were censored at the end of the study (i.e., Dec 31, 2018). For the others, the dates of their last outpatient visit to FEMH were set as their censored dates. The study endpoint was all-cause mortality. The ages of the patients were computed from the difference in time between the index date and the date of birth.

The information on antidiabetic (sulphonylureas, meglitinides, metformin, thiazolidinediones, α-glucosidase inhibitors, dipeptidyl peptidase 4 inhibitors, sodium-glucose cotransporter 2 inhibitors, insulin [basal insulin only, premixed insulin or basal-bolus insulin], and glucagon-like peptide 1 receptor agonists), antihypertensive (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β-blockers, calcium-channel blockers, and diuretics), and antilipid (statins and fibrates) medications were gathered from the outpatient electronic medical records between the index date and the end of follow-up, which is either death or censoring.

The details of various cardiovascular comorbidities and risk factors, including coronary artery disease, heart failure, hypertensive disease, cerebrovascular disease, and peripheral artery disease, were selected from the outpatient medical records during the study periods. Other diabetic microvascular complications like diabetic nephropathy, neuropathy, retinopathy, and skin complications were also retrieved as potential confounders. Table 1, Supplementary Digital Content, http://links.lww.com/MD/G986, presents the details of respective ICD-9 and ICD-10 codes[15] for various comorbidities and complications compiled in this study.

Each study participant's laboratory results of HbA1c, fasting plasma glucose (FPG), low-density lipoprotein (LDL), creatinine (Cr), and hemoglobin (Hb) level available throughout the study period were also collected. The measurement of the HbA1c assay in FEMH has been certified by the National Glycohemoglobin Standardization Program (NGSP). We evaluated the estimated glomerular filtration rate (eGFR) by Modification of Diet in Renal Disease (MDRD) Study equation using Cr standardized to reference methods.[16] If the patients had more than one result in a quarter, we selected the highest HbA1c, FPG, Cr, eGFR, and LDL of each quarter for his/ her representative HbA1c, FPG, Cr, eGFR, and LDL, respectively; and then calculated the mean of 4 quarter-specific data for that specific year. If the follow-up period in a year is not full, only the available quarter-specific data were used to calculate the annual mean. We then computed the mean of the annual mean for the whole study period. Mean eGFRs analyzed were further classified according to the staging of chronic kidney disease (CKD): stages 1–2, stage 3a, stage 3b, stage 4, and stage 5 CKD if mean eGFR ≥60, 45–59, 30–44, 15–29, and <15 mL/min/m^2, respectively, as recommended by American Diabetes Association.[17] Every year's lowest Hb was collected for the calculation of total mean Hb to prevent overestimation of Hb value after blood transfusion. Mean Hb levels were also divided into 3 groups: ≥11, 9–10.9, <9 g/dL. Hypoglycemia was identified in patients with fasting or postprandial plasma or point-of-care glucose values <70 mg/dL[1] on any occasion during the study period.

2.3. Exposure to VVV

The primary exposure of interest in our study was the intraindividual VVV of HbA1c. The VVV of HbA1c metrics analyzed in our study included (1) the standard deviation (SD) across visits; (2) the coefficient of variation (CV), which was calculated as the SD divided by the mean; (3) average real variability (ARV) as the average of the absolute differences between consecutive HbA1c measurements.[8,11,13] We calculated each patient's annual SD, CV, or ARV separately, and the mean of annual HbA1c-SD, HbA1c-CV, or HbA1c-ARV during the whole study period was computed from the average of each annual values. Patients with diabetes were stratified into four groups by quartiles of HbA1c-SD, HbA1c-CV, and HbA1c-ARV values.

2.4. Statistical analysis

We linked this electronic database to Taiwan's National Death Registry, which contains information on age, sex, dates, and causes of death, for the deceased with a unique PIN. There was obligatory registration of all deaths in Taiwan, and the government will impose a fine if family or co-inhabitants do not complete the death registration within 30 days. The overall agreement rates between the reviewer and coders according to the three- and two-digit categories of ICD-9 were 80.9% and 83.9%, respectively.[18]

The overall, age- and sex-specific incidence density estimates were calculated with person-years as the denominator under the Poisson assumption according to quartiles of HbA1c-SD, HbA1c-CV, and HbA1c-ARV. The independent association of each quartile of VVV of HbA1c with the hazard of all-cause mortality was assessed by Cox proportional hazard regression model using the first quartile as a reference range. The association between HbA1c's VVV and all-cause mortality was further analyzed according to various ages (<50, 50–69, >69 years) and sex (men vs. women) to assess the potential effect-modification by age and sex. We did step-wise adjustment of potential confounding factors in the regression models. In model 1, we adjusted the type of diabetes, age, and sex. In model 2, apart from the variables in model 1, we further adjusted antidiabetic, antihypertensive, and antilipid medications prescription described above. Additional adjustments of selected comorbidities and diabetic complications together with laboratory results to the regression models were made in model 3. All statistical analyses were performed with SAS (version 9.4; SAS Institute, Cary, NC). A P value <.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics of the patients

Table 1 describes the baseline characteristics of the study subjects according to different quartiles of HbA1c-SD, HbA1c-CV, and HbA1c-ARV, respectively. Type 1 diabetes accounted for a higher proportion in higher quartiles of VVV of HbA1c. The mean age of the lowest quartile of VVV of HbA1c was older while younger patients (<50 years) were observed to account for more than 30% of the highest quartile of various VVV measures. A higher percentage of women patients was in the lower quartiles than in the higher ones.

Except for metformin and sodium-glucose cotransporter 2 inhibitors, the prescription of oral or parenteral antidiabetic agents was more frequent in higher quartiles. Both antihypertensive and statin were, in general, more common at lower quartiles, except fibrates which were prescribed more in the higher quartiles.

There was no considerable discrepancy in the prevalence of cardiovascular diseases all across VVV quartiles, but microvascular complications were more prevalent in higher quartiles. In contrast, hypoglycemia was more common in the third quartile than in the lower and higher quartiles of all VVV measures. Patients with a higher quartile of VVV of HbA1c had a higher mean of HbA1c, FPG, and LDL, respectively. More advanced CKD and severe anemia were most prevalent in those with the highest quartile of VVV.

During the mean follow-up of around 7 years, the excessive risk of all-cause mortality (~33%) was encountered in those with the highest VVV of HbA1c while those with the lowest VVV of HbA1c had the least risk of all-cause mortality (~16%).

3.2. Overall, age- and sex-specific all-cause mortality rate by different VVV of HbA1c levels

The overall all-cause mortality rates were lower in those patients in the first and second quartiles of HbA1c-SD (27.24 and 25.95/1000 patient-years [PY]), HbA1c-CV (26.77 and 24.30/1000 PY), and in HbA1c-ARV, (25.08 and 25.35/1000 PY, respectively) (Table 2). It became incrementally increased in the third and fourth quartiles regardless of VVV measures, and the highest ones were consistently observed in those in the fourth quartile (55.46–59.53/1000 PY).

In further age- and sex-stratifications, the lowest all-cause mortality rates generally were observed at the first quartile of each VVV of HbA1c in those aged ≥50 years in both sexes except in women aged >69 years in whom those in the second quartile of HbA1c-CV had the lowest all-cause mortality. In those aged <50 years, however, the lowest mortality rate was seen in those with the second quartile of each VVV regardless of sex (Table 3). The highest all-cause mortality rate was persistently noticed in those with the highest quartile of each VVV in all age- and sex groups (Table 3), and the highest all-cause mortality rate was seen in men aged >69 years in the fourth quartile of HbA1c-CV (131.82/1000 PY) (Table 3).

3.3. Overall, age- and sex-specific relative hazards of all-cause mortality by different VVV of HbA1c levels

Table 2 presents the overall relative hazards of all-cause mortality by various VVV of HbA1c levels in different statistical models. In model 1, the hazard ratio (HR) of all-cause mortality was low in those with the second quartile of HbA1c-SD (HR: 0.92; 95% confidence interval [CI] 0.87–0.98) and HbA1c-CV (HR: 0.87; 95% CI 0.82–0.93), but not in HbA1c-ARV. Additional adjustment of antidiabetic, antihypertensive, and antilipid medications in model 2 altered the estimates of HRs, and more elevated HRs of all-cause mortality were observed in second to fourth quartiles of either SD, CV, or ARV of HbA1c. Model 3 attenuated the HRs, but there was a consistent dose–response relationship between all-cause mortality and higher quartiles of any VVV of HbA1c, and there was no substantial difference in the relative risk estimates among HbA1c-SD, HbA1c-CV, and HbA1c-ARV.

Because of a significant interaction of HbA1c-SD, HbA1c-CV, and HbA1c-ARV with age and sex (P < .0001), we performed a stratified analysis to evaluate the age- and sex-specific HRs to specific VVV of HbA1c levels (Table 3 and Fig. 1). In model 1, lower HRs were observed in the second quartiles of HbA1c-CV and HbA1c-ARV in those aged <50 years of both sexes, and of HbA1c-CV in women aged >69 years. After additional adjustment of medications in model 2, higher quartiles of VVV persistently increased the risk of all-cause mortality. Further adjustment of comorbidities and laboratory results in model 3 slightly attenuated the relative risk estimates, but the statistical significance remained in the highest quartile.

In both sexes, only those <50 years showed a significant association of all-cause mortality with the fourth quartile but not the other higher quartiles. In those aged 50–69 years, however,

Table 1

Characteristics of the study subjects according to different visit-to-visit variabilities of HbA1c.

Variables*,†	HbA1c variability HbA1c-SD				HbA1c-CV				HbA1c-ARV			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
	≤0.31	>0.31	>0.54	>0.8	≤4.36	>4.36	>6.91–1	>10.	≤0.37	>0.37	>0.64	>1.05
Total	10,423	10,422	10,423	10,422	10,422	10,423	10,423	10,422	10,449	10,424	10,402	10,415
		%/Mean ± SD				%/Mean ± SD				%/Mean ± SD		
General Characteristics												
Type of diabetes												
Type 1	0.35	0.95	1.25	1.60	0.47	1.15	1.23	1.30	0.36	0.91	1.24	1.64
Type 2	99.65	99.05	98.75	98.40	99.53	98.85	98.77	98.70	99.64	99.09	98.76	98.36
Age (y)	60.55 ±11.81	58.18 ±12.40	57.12 ±13.17	55.90 ±14.42	60.26 ±11.83	57.77 ±12.44	57.14 ±13.21	56.60 ±14.46	60.17 ±11.73	58.19 ±12.49	57.30 ±13.20	56.10 ±14.48
<50	16.83	24.53	28.60	33.30	17.36	25.50	28.79	31.60	17.52	24.71	28.13	32.92
50–69	61.38	57.73	53.94	49.11	61.64	57.52	53.71	49.28	61.85	57.32	53.96	49.00
>69	21.79	17.75	17.46	17.59	21.00	16.98	17.50	19.12	20.63	17.96	17.91	18.09
Sex												
Women	50.23	48.07	46.83	40.51	50.64	48.54	45.96	40.50	50.43	48.09	46.76	40.35
Men	49.77	51.93	53.17	59.49	49.36	51.46	54.04	59.50	49.57	51.91	53.24	59.65
Antidiabetic medications												
Sulphonylurea	44.87	74.28	81.18	79.94	46.48	74.81	80.30	78.67	46.03	74.04	80.50	79.77
Meglitinide	12.59	19.84	22.43	23.32	12.38	19.56	22.48	23.76	12.46	19.81	21.97	23.97
Metformin	87.27	88.38	88.30	85.91	87.72	89.03	88.04	85.07	87.91	88.47	87.96	85.51
TZD	11.10	24.19	28.60	20.45	12.37	25.75	27.87	18.35	11.60	24.51	27.75	20.51
AGi	10.48	19.67	23.86	19.53	11.15	20.86	23.07	18.45	10.48	20.01	23.91	19.16
DPP4i	36.86	57.99	59.46	50.22	37.91	57.84	58.93	49.85	38.42	58.00	58.88	49.27
SGLT2i	7.60	12.88	12.44	8.04	8.22	12.87	12.38	7.49	7.85	12.90	12.19	8.03
Insulin												
Basal only	2.25	10.31	17.31	15.65	3.01	11.64	16.73	14.12	2.45	11.06	16.58	15.45
Basal bolus	2.72	8.82	17.37	22.32	3.47	10.64	17.09	20.02	2.89	9.05	17.42	21.91
Premixed	4.95	16.80	30.78	34.51	6.23	19.39	30.40	31.02	5.05	17.22	30.58	34.26
GLP-1	0.40	2.01	2.82	2.13	0.52	2.16	2.92	1.77	0.50	2.21	2.65	2.01
Antihypertensives												
ACEi	16.19	21.26	23.56	19.40	16.50	21.67	23.24	19.00	15.89	21.26	23.40	19.88
ARB	63.11	68.38	68.76	59.27	63.25	68.42	69.15	58.71	62.94	68.04	68.97	59.59
Beta-blockers	50.55	50.07	50.24	41.87	50.39	50.00	50.48	41.84	49.29	50.27	49.94	43.23
CCB	56.14	58.98	59.21	51.24	55.50	58.96	59.25	51.85	55.39	58.49	59.48	52.20
Diuretics	42.59	49.51	52.91	48.20	42.54	49.42	53.09	48.16	41.56	49.55	52.97	49.15
Antilipids												
Statin	71.86	73.44	74.34	68.30	72.38	74.29	74.48	66.79	72.70	73.52	74.61	67.11
Fibrates	16.16	23.53	27.77	24.21	16.36	24.33	28.00	22.97	15.97	23.74	27.57	24.40
Comorbidities and complications												
Coronary artery disease	34.72	33.75	32.47	26.62	34.69	33.90	32.59	26.38	33.36	33.14	33.10	27.95
Heart failure	10.72	11.18	13.76	12.92	10.53	11.32	13.80	12.93	10.03	11.38	13.73	13.45
Hypertension	74.57	77.24	76.67	69.55	74.16	77.34	76.71	69.81	74.27	77.06	76.64	70.05
Cerebrovascular disease	14.66	15.71	16.68	14.62	14.66	14.98	17.01	15.03	14.55	15.48	16.85	14.80
Peripheral artery disease	3.36	5.48	5.70	4.90	3.38	5.44	5.84	4.78	3.40	5.10	5.89	5.05
Diabetic nephropathy	20.48	35.06	43.57	40.28	20.68	36.10	43.14	39.47	21.50	35.30	42.97	39.66
Diabetic retinopathy	28.09	40.98	45.50	37.59	28.70	42.69	44.82	35.94	29.64	41.01	44.26	37.28
Diabetic neuropathy	14.00	21.44	24.77	22.99	14.26	22.08	25.09	21.77	14.25	21.37	24.36	23.24
Diabetes with skin complications	0.59	0.88	1.14	1.49	0.56	0.93	1.20	1.42	0.56	0.88	1.20	1.47
Hypoglycemia	9.50	22.12	28.93	22.87	9.65	22.85	28.85	22.05	10.04	22.63	28.24	22.53
Laboratory results												
HbA1c (%)	6.89 ±0.86	7.47 ±0.95	8.07 ±1.15	8.72 ±1.43	7.03 ±1.01	7.62 ±1.11	8.03 ±1.22	8.46 ±1.41	6.90 ±0.84	7.47 ±0.96	8.05 ±1.15	8.72 ±1.44
FPG (mg/dL)	127.5 0 ±26.8 7	142.6 1 ±30.6 0	157.0 7 ±37.3 4	171.2 4 ±47.9 4	130.4 3 ±31.0 9	145.2 6 ±33.3 9	156.28 ±37.5 6	166.2 0 ±46.9 1	127.6 5 ±25.9 3	142.5 2 ±30.7 0	156.7 4 ±36.6 5	171.6 8 ±48.9 3
LDL (mg/dL)	104.60 ±22.85	103.1 7 ±22.1 1	104.4 7 ±23.6 0	108.6 3 ±28.2 3	105.0 5 ±22.9 4	103.5 1 ±22.0 9	104.5 1 ±23.7 9	107.8 1 ±28.1 3	104.5 0 ±22.4 1	102.9 7 ±21.8 8	104.5 8 ±23.9 0	108.8 5 ±28.5 0
eGFR (mL/min/m²)	56.92 ±8.64	55.52 ±10.4 7	54.18 ±11.5 1	53.66 ±11.9 2	56.99 ±8.52	55.76 ±9.99	54.08 ±11.6 3	53.42 ±12.2 7	57.10 ±8.28	55.53 ±10.3 6	54.16 ±11.5 2	53.46 ±12.2 4
≥60	67.77	60.11	54.22	55.44	68.22	60.27	53.80	55.25	68.44	59.94	54.39	54.68
45–59	25.03	28.91	30.91	27.74	24.77	29.37	31.09	27.29	24.72	29.15	30.63	28.13
30–44	4.08	6.04	8.56	9.64	4.01	5.86	8.69	9.76	3.99	6.01	8.77	9.55

(*Continued*)

Table 1

(*Continued*)

Variables*,†	HbA1c variability HbA1c-SD				HbA1c-CV				HbA1c-ARV			
15–29	1.89	2.89	4.06	5.06	1.80	2.81	4.06	5.25	1.81	3.03	3.95	5.13
<15	1.23	2.05	2.25	2.13	1.19	1.69	2.35	2.45	1.04	1.87	2.26	2.52
Hb (g/dL)	13.22 ± 1.	12.99	12.80	12.69	13.23	13.03	12.80	12.63	13.26	12.98	12.80	12.66
	90	±2.05	±2.15	±2.33	±1.89	±2.01	±2.16	±2.35	±1.88	±2.06	±2.16	±2.33
≥11	87.64	82.89	79.23	74.80	87.92	83.85	79.18	73.59	88.25	82.95	78.89	74.52
9–10.9	9.63	13.51	16.14	18.87	9.39	12.95	16.17	19.63	9.25	13.35	16.38	19.14
<9	2.73	3.60	4.63	6.33	2.68	3.20	4.65	6.78	2.50	3.70	4.73	6.34
Outcome												
All-cause mortality	16.81	20.50	25.21	32.44	16.71	19.74	25.16	33.36	15.70	19.97	25.50	33.82
Mean follow-up period (y)	6.17	7.90	7.95	5.85	6.24	8.12	7.90	5.60	6.26	7.88	7.80	5.93
	±4.12	±4.66	±4.64	±4.31	±4.16	±4.69	±4.59	±4.20	±4.17	±4.67	±4.65	±4.33

*Data are % or mean (±SD); Q = Quartiles.

†ACEi = angiotensin converting enzyme inhibitors, AGi = alpha-glucosidase inhibitors, ARB = angiotensin receptor blockers, ARV = average real variability, CCB = calcium-channel blockers, CV = coefficient of variation, DPP4i = dipeptidyl peptidase-4 inhibitor, eGFR = estimated glomerular filtration rate, FPG = fasting plasma glucose, GLP-1 = glucagon-like peptide-1 receptor agonist, Hb = hemoglobin, HbA1c = glycated hemoglobin, LDL = low density lipoprotein, SD = standard deviation, SGLT2i = sodium-glucose cotransporter-2 inhibitors, TZD = thiazolidinediones.

higher hazards of mortality were consistently observed in second to fourth quartiles of VVV except in men with HbA1c-CV in whom only those with third and fourth quartiles of HbA1c-CV showed increased mortality. On the contrary, in those aged >69 years, an elevated risk of mortality was noticed only in the third and fourth quartiles of any VVV of HbA1c irrespective of sex. Male patients had slightly higher HRs than female patients, and those aged 50–69 years in the fourth quartile had the highest risks irrespective of types of VVV.

4. Discussion

Long-term VVV of HbA1c, regardless of SD, CV, or ARV, could equally and robustly predict all-cause mortality in all patients with diabetes especially in those aged 50-69 years of both sexes even after adjustment for potential confounders. We also found out that the association of incremental increase in all-cause mortality with higher HbA1c variability depended on age, but was comparable between sexes.

4.1. All-cause mortality rate associated with VVV of HbA1c

To our best knowledge, the association of mortality with various VVV measures of HbA1c has been very scarcely assessed. Hong Kong study[8] reported that the overall all-cause mortality rate was 3.17/1000 person-years (95% CI, 3.01–3.34), which was much lower than our estimates of various kinds of VVV of HbA1c. A low proportion of insulin use (0.7%) in their patients compared with >20% use of insulin in ours indicated that they recruited less complicated study subjects. In addition, the prevalence of CKD in their study was 11.4% which was much lower than that of our patients. The authors did not collect other comorbidities, nor presented mortality rates according to VVV of HbA1c. Disparate baseline characteristics of study subjects

Table 2

Incidence rates and relative hazards of all-cause mortality in association with visit-to-visit variabilities of HbA1c.

HbA1c* Variabilities	All-cause mortality No. of patients	No. of mortality	Rates (per 1000 patient-years) (95% CI)†	Model 1 Adjusted HR (95% CI)‡	Model 2 Adjusted HR (95% CI)‡	Model 3 Adjusted HR (95% CI)‡,§
HbA1c-SD						
Q1	10,423	1752	27.24 (25.96–28.51)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	10,422	2136	25.95 (24.85–27.05)	0.92 (0.87–0.98)‖	1.17 (1.10–1.25)¶	1.14 (1.06–1.22)#
Q3	10,423	2628	31.70 (30.49–32.91)	1.18 (1.11–1.25)‖	1.54 (1.44–1.64)¶	1.45 (1.35–1.57)#
Q4	10,422	3381	55.46 (53.60–57.33)	2.35 (2.22–2.50)‖	2.71 (2.54–2.89)¶	2.16 (2.00–2.34)#
HbA1c–CV						
Q1	10,422	1741	26.77 (25.51–28.03)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	10,423	2057	24.30 (23.25–25.35)	0.87 (0.82–0.93)‖	1.08 (1.01–1.15)¶	1.09 (1.01–1.17)#
Q3	10,423	2622	31.82 (30.61–33.04)	1.19 (1.12–1.26)‖	1.46 (1.36–1.55)¶	1.37(1.27–1.47)#
Q4	10,422	3477	59.53 (57.55–61.51)	2.46 (2.33–2.61)‖	2.55 (2.40–2.72)¶	2.11 (1.96–2.27)#
HbA1c–ARV						
Q1	10,449	1641	25.08 (23.86–26.29)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	10,424	2082	25.35 (24.26–26.44)	0.96 (0.90–1.02)‖	1.18 (1.11–1.26)¶	1.13 (1.05–1.21)#
Q3	10,402	2652	32.68 (31.44–33.92)	1.28 (1.21–1.36)‖	1.63 (1.53–1.74)¶	1.45 (1.35–1.57)#
Q4	10,415	3522	57.01 (55.12–58.89)	2.56 (2.42–2.72)‖	2.77 (2.60–2.96)¶	2.18 (2.02–2.35)#

*ARV = average real variability, CV = coefficient of variation, HbA1c = glycated hemoglobin, Q = quartiles, SD = standard deviation.

†Based on Poisson assumption, CI = confidence interval.

‡HR = hazard ratio, CI = confidence interval. Blue color: lower HR, Red color: higher HR.

§*P* values for the interaction of HbA1c-SD, HbA1c-CV, HbA1c-ARV with age and sex were <.0001, <.0001, <.0001, respectively.

‖Based on Cox proportional hazard regression with adjustment for general characteristics (i.e., type of diabetes, age, and sex).

¶Based on Cox proportional hazard regression with adjustment for the general characteristics adjusted in Model 1 plus antidiabetic, antihypertensives, and antilipids medications presented in Table 1.

#Based on Cox proportional hazard regression with all covariates included in Model 2 plus comorbidities, complications, and laboratory results presented in Table 1.

Table 3

Age- and sex-specific rates and relative hazards of all-cause mortality in association with visit-to-visit variabilities of HbA1c.

	All-cause mortality					
HbA1c variabilities*	**No. of patients**	**No. of mortality**	**Rates (per 1000 patient-years) (95% CI)†**	**Model 1Adjusted HR (95% CI)‡**	**Model 2 Adjusted HR (95% CI)‡**	**Model 3 Adjusted HR (95% CI)‡**
HbA1c-SD						
Men						
Aged <50 y						
Q1	1057	74	11.17 (8.62–13.71)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	1484	115	9.51 (7.77–11.25)	0.75 (0.56–1.01)§	1.12 (0.83–1.51)‖	1.13 (0.80–1.58)¶
Q3	1815	176	11.55 (9.84–13.25)	0.87 (0.67–1.15)§	1.27 (0.95–1.69)‖	1.19 (0.85–1.65)¶
Q4	2387	385	26.64 (23.98–29.30)	2.38 (1.86–3.06)§	2.76 (2.11–3.62)‖	1.94 (1.41–2.68)¶
Aged 50–69 y						
Q1	3216	419	20.89 (18.89–22.89)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	3153	569	23.06 (21.16–24.95)	0.96 (0.84–1.09)§	1.25 (1.10–1.42)‖	1.26 (1.09–1.46)¶
Q3	2991	727	31.45 (29.17–33.74)	1.30 (1.15–1.46)§	1.78 (1.56–2.03)‖	1.74 (1.50–2.02)¶
Q4	2966	1037	60.94 (57.23–64.64)	2.90 (2.59–3.25)§	3.30 (2.91–3.74)‖	2.71 (2.32–3.15)¶
Aged >69 y						
Q1	909	399	81.51 (73.51–89.50)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	770	401	82.15(74.11–90.19)	0.92 (0.81–1.06)§	1.19 (1.03–1.38)‖	1.14 (0.97–1.34)¶
Q3	727	431	96.39(87.29–105.49)	1.12 (0.97–1.28)§	1.48 (1.27–1.71)‖	1.43 (1.20–1.69)¶
Q4	839	538	128.89(117.99–139.78)	1.69 (1.49–1.93)§	2.32 (2.00–2.68)‖	1.99 (1.65–2.39)¶
Women						
Aged <50 y						
Q1	695	26	5.82 (3.58–8.06)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	1069	46	4.96 (3.52–6.40)	0.70 (0.43–1.14)§	1.15 (0.69–1.87)‖	1.10 (0.60–2.01)¶
Q3	1162	79	7.70 (6.00–9.40)	1.08 (0.69–1.68)§	1.62 (1.02–2.60)‖	1.18 (0.65–2.13)¶
Q4	1079	132	19.79 (16.41–23.16)	3.40 (2.23–5.18)§	3.84 (2.44–6.05)‖	2.27 (1.24–4.16)¶
Aged 50–69 y						
Q1	3175	290	14.17 (12.54–15.80)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	2858	439	18.44 (16.71–20.16)	1.04 (0.90–1.21)§	1.33 (1.14–1.55)‖	1.31 (1.11–1.56)¶
Q3	2623	590	26.41 (24.28–28.54)	1.48 (1.28–1.70)§	1.84 (1.58–2.15)‖	1.70 (1.43–2.02)¶
Q4	2145	649	49.48 (45.67–53.28)	3.33 (2.90–3.82)§	3.46 (2.96–4.05)‖	2.61 (2.16–3.15)¶
Aged >69 y						
Q1	1360	543	70.05 (64.16–75.94)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	1078	566	75.57 (69.34–81.79)	0.94 (0.84–1.06)§	1.10 (0.98–1.24)‖	1.07 (0.93–1.22)¶
Q3	1090	624	84.88 (78.22–91.54)	1.07 (0.95–1.20)§	1.29 (1.14–1.47)‖	1.28 (1.11–1.48)¶
Q4	992	640	118.11 (108.96–127.26)	1.68 (1.50–1.89)§	1.90 (1.68–2.15)‖	1.70 (1.46–1.99)¶
HbA1c-CV						
Men						
Aged <50 y						
Q1	1076	78	11.46 (8.91–14.00)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	1513	118	9.25 (7.58–10.92)	0.69 (0.52–0.92)§	0.95 (0.71–1.28)‖	0.99 (0.71–1.38)¶
Q3	1876	187	11.90 (10.20–13.61)	0.90 (0.69–1.18)§	1.20 (0.91–1.58)‖	1.15 (0.84–1.57)¶
Q4	2278	367	27.93 (25.08–30.79)	2.52 (1.97–3.21)§	2.44 (1.88–3.17)‖	1.86 (1.38–2.52)¶
Aged 50–69 y						
Q1	3179	421	21.05 (19.04–23.06)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	3116	552	22.15 (20.30–24.00)	0.88 (0.78–1.00)§	1.11 (0.97–1.26)‖	1.22 (1.06–1.42)¶
Q3	3010	716	30.78 (28.53–33.04)	1.25 (1.11–1.41)§	1.58 (1.39–1.80)‖	1.57 (1.36–1.82)¶
Q4	3021	1063	63.70 (59.87–67.53)	3.06 (2.73–3.43)§	3.10 (2.75–3.51)‖	2.73 (2.36–3.16)¶
Aged >69 y						
Q1	884	383	79.75 (71.76–87.74)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	729	384	82.68 (74.41–90.95)	0.96 (0.83–1.10)§	1.21 (1.04–1.40)‖	1.16 (0.99–1.37)¶
Q3	737	422	92.23 (83.43–101.03)	1.09 (0.95–1.25)§	1.44 (1.24–1.68)‖	1.31(1.10–1.55)¶
Q4	895	580	131.82 (121.09–142.55)	1.79 (1.58–2.04)§	2.25 (1.95–2.59)‖	1.92 (1.61–2.28)¶
Women						
Aged <50 y						
Q1	732	34	7.20 (4.78–9.63)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	1141	40	3.84 (2.65–5.04)	0.46 (0.29–0.72)§	0.64 (0.40–1.03)‖	0.59 (0.34–1.01)¶
Q3	1120	87	8.90 (7.03–10.77)	1.05 (0.70–1.56)§	1.27 (0.83–1.93)‖	0.87 (0.52–1.45)¶
Q4	1012	122	21.13 (17.38–24.88)	3.17 (2.17–4.65)§	2.98 (1.98–4.48)‖	1.86 (1.11–3.11)¶
Aged 50–69 y						
Q1	3239	302	14.24 (12.63–15.85)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	2874	447	18.27 (16.58–19.97)	1.03 (0.89–1.19)§	1.28 (1.10–1.49)‖	1.27 (1.07–1.50)¶
Q3	2579	577	26.74 (24.56–28.92)	1.52 (1.32–1.75)§	1.73 (1.49–2.01)‖	1.60 (1.35–1.90)¶
Q4	2109	642	51.40 (47.42–55.37)	3.55 (3.09–4.07)§	3.32 (2.85–3.86)‖	2.44 (2.05–2.90)¶
Aged >69 y						
Q1	1302	522	70.11 (64.10–76.13)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	1039	516	69.86 (63.83–75.88)	0.86 (0.76–0.97)§	1.00 (0.88–1.13)‖	1.00 (0.87–1.15)¶

(*Continued*)

Table 3

(*Continued*)

HbA1c variabilities*	All-cause mortality			Model 1Adjusted HR (95% CI)‡	Model 2 Adjusted HR (95% CI)‡	Model 3 Adjusted HR (95% CI)‡
	No. of patients	No. of mortality	Rates (per 1000 patient-years) (95% CI)†			
Q3	1084	632	86.02 (79.31–92.72)	1.09 (0.97–1.23)§	1.29 (1.14–1.46)‖	1.25 (1.09–1.43)¶
Q4	1095	703	120.53 (111.62–129.44)	1.73 (1.54–1.93)§	1.78 (1.58–2.01)‖	1.64 (1.42–1.89)¶
HbA1c-ARV						
Men						
Aged <50 y						
Q1	1,083	74	10.72 (8.28–13.16)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	1502	98	8.05 (6.46–9.65)	0.67 (0.50–0.91)§	0.96 (0.71–1.31)‖	0.99 (0.70–1.41)¶
Q3	1776	181	12.44 (10.63–14.25)	1.00 (0.77–1.32)§	1.42 (1.07–1.88)‖	1.23 (0.89–1.71)¶
Q4	2382	397	26.85 (24.20–29.49)	2.50 (1.95–3.20)§	2.59 (1.98–3.39)‖	1.80 (1.31–2.48)¶
Aged 50–69 y						
Q1	3227	388	19.07 (17.18–20.97)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	3119	565	23.14 (21.23–25.04)	1.05 (0.92–1.20)§	1.32 (1.15–1.51)‖	1.32 (1.14–1.53)¶
Q3	3007	721	31.49 (29.19–33.78)	1.44 (1.27–1.63)§	1.90 (1.67–2.17)‖	1.73 (1.49–2.01)¶
Q4	2973	1078	62.66 (58.92–66.40)	3.28 (2.92–3.68)§	3.54 (3.12–4.02)‖	2.84 (2.44–3.31)¶
Aged >69 y						
Q1	864	371	79.16 (71.11–87.22)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	783	400	81.94 (73.91–89.97)	0.95 (0.82–1.09)§	1.69 (1.01–1.35)‖	1.12 (0.95–1.31)¶
Q3	750	440	95.99 (87.02–104.96)	1.14 (0.99–1.30)§	1.48 (1.28–1.72)‖	1.34 (1.13–1.58)¶
Q4	848	558	130.67 (119.82–141.51)	1.74 (1.53–1.99)§	2.21 (1.92–2.56)‖	1.82 (1.52–2.18)¶
Women						
Aged <50 y						
Q1	746	29	5.82 (3.70–7.94)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	1070	36	3.92 (2.64–5.21)	0.57 (0.35–0.94)§	0.85 (0.51–1.41)‖	0.86 (0.47–1.58)¶
Q3	1148	85	8.54 (6.72–10.36)	1.21 (0.79–1.86)§	1.62 (1.03–2.55)‖	1.12 (0.64–1.97)¶
Q4	1041	133	20.27 (16.83–23.72)	3.50 (2.34–5.23)§	3.72 (2.41–5.74)‖	2.15 (1.20–3.86)¶
Aged 50–69 y						
Q1	3229	274	13.02 (11.48–14.56)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	2849	431	18.08 (16.37–19.79)	1.14 (0.98–1.33)§	1.42 (1.21–1.66)‖	1.32 (1.11–1.57)¶
Q3	2601	585	27.03 (24.84–29.22)	1.67 (1.45–1.93)§	1.96 (1.67–2.29)‖	1.81 (1.52–2.16)¶
Q4	2122	678	51.30 (47.44–55.16)	3.78 (3.28–4.35)§	3.69 (3.16–4.32)‖	2.75 (2.28–3.32)¶
Aged >69 y						
Q1	1289	504	67.88 (61.95–73.81)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	1087	552	73.31 (67.20–79.43)	0.95 (0.84–1.07)§	1.08 (0.96–1.22)‖	1.04 (0.90–1.19)¶
Q3	1111	640	86.09 (79.42–92.76)	1.13 (1.01–1.27)§	1.39 (1.23–1.58)‖	1.30 (1.13–1.50)¶
Q4	1033	677	120.39 (111.32–129.46)	1.81 (1.61–2.03)§	1.90 (1.67–2.15)‖	1.65 (1.42–1.92)¶

*ARV = average real variability, CV = coefficient of variation, HbA1c = glycated hemoglobin, Q = quartiles, SD = standard deviation.

†Based on Poisson assumption, CI = confidence interval.

‡HR = hazard ratio, CI = confidence interval. Blue color: lower HR, Red color: higher HR.

§Based on Cox proportional hazard regression with adjustment for type of diabetes.

‖Based on Cox proportional hazard regression with adjustment for type of diabetes adjusted in Model 1 plus antidiabetic, antihypertensives, and antilipids medications presented in Table 1.

¶Based on Cox proportional hazard regression with all covariates included in Model 2 plus comorbidities, complications, and laboratory results presented in Table 1.

between General Out-patient clinics and a tertiary medical center like ours might have produced dissimilar outcomes.

In our study, all-cause mortality rates were not much different in the first and second quarters of any sets of HbA1c variability. It became slightly increased in the third quartile, but the mortality rate came to be of considerably greater amounts in the fourth quartile. Similar patterns were observed in the age- and sex-stratified analyses. Diabetic men had higher mortality rates, and in those aged <70 years, there were nearly doubling of mortality rates in the fourth quartile compared with those in the third quartile disregarding of sex.

4.2. Risk of all-cause mortality associated with HbA1c

The risk estimates of all-cause mortality in VVV varied among studies. In some studies, the HR of HbA1c-SD was higher than that of HbA1c-CV,[6,8] but in our study, the hazards of mortality were comparable among HbA1c-SD, HbA1c-CV, and HbA1c-ARV, corresponding to the results of other studies.[7,9–11] Direct comparisons of the association between VVV of HbA1c and risk of all-cause mortality among previous studies and those of ours might be challenging because of differences in baseline demographic status, variations in the ascertainment of HbA1c (mean vs. baseline), dissimilarity in comorbidities, and length of follow-up.

Ma et al, from Taiwan[6] and Wan et al, from Hong Kong[8] treated HbA1c-SD and HbA1c-CV as continuous variables rather than different quartiles stratified as in our study, and the HRs for HbA1c-SD was 1.99 (95% CI, 1.11–3.54) and 1.70 (95% CI, 1.52–1.91), respectively, after full adjustment of all potential confounders. Their HR estimates of mortality in HbA1c-SD were comparable to the results of ours (2.16, 95% CI, 2.00–2.34), but the HRs for HbA1c-CV (1.06 and 1.04, respectively) in their studies were much lower than our risk estimates (HR: 2.11; 95% CI, 1.96–2.27). In the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial,[11] which also analyzed VVV of HbA1c as continuous variables, the HRs estimated among HbA1c-SD, HbA1c-CV, and HbA1c-ARV were similar which was comparable to the findings of our study, but their HRs calculated were lower around 1.31–1.38 in the fully adjusted model.

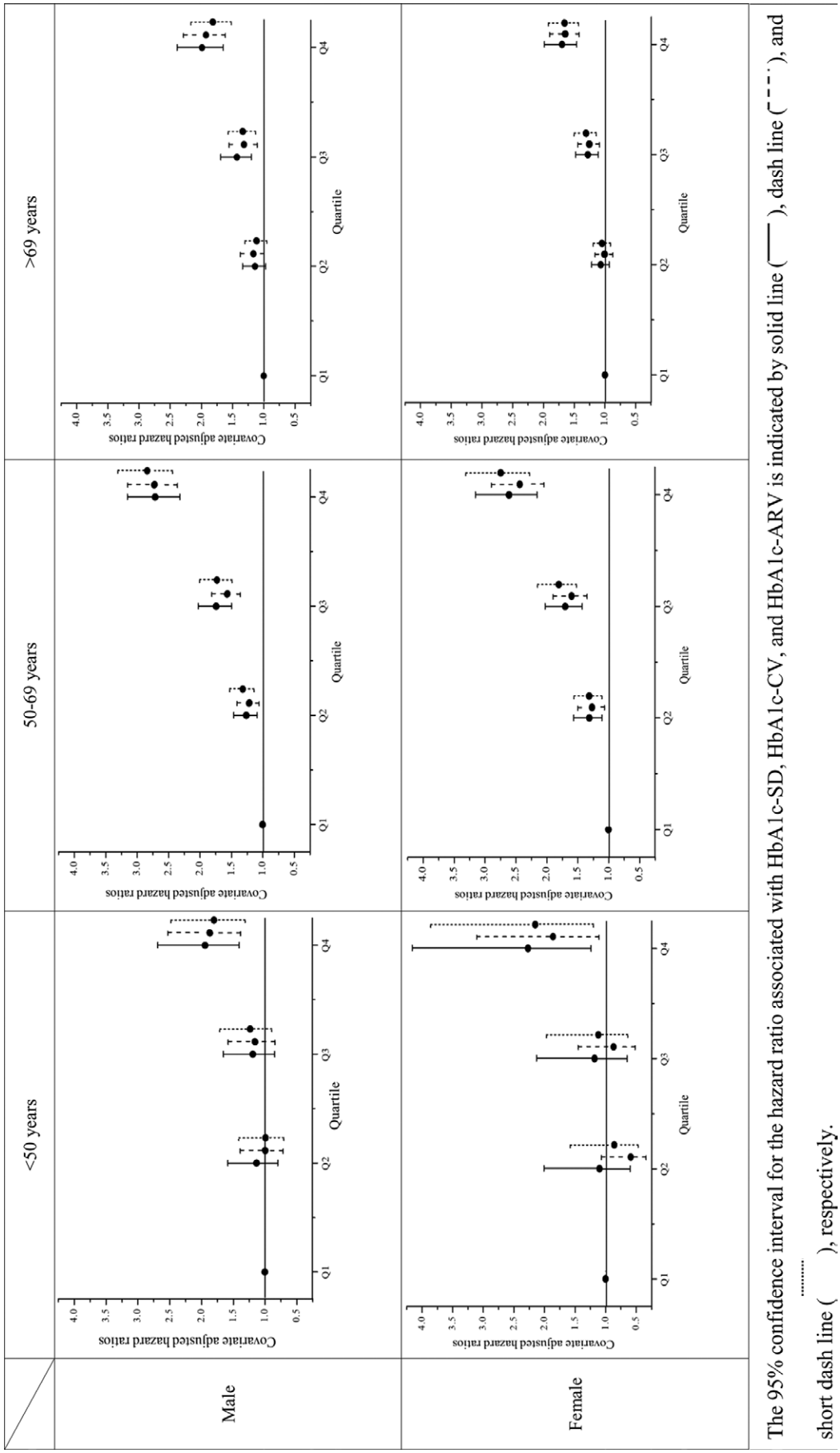

Figure 1. Age- and sex-specific relative hazards of all-cause mortality in association with various measures of visit-to-visit variabilities of HbA1c.

Some other studies divided VVV of HbA1c into tertiles,[7] quartiles,[9,10] or deciles,[11] and compared the results among them. Those studies that grouped their VVV of HbA1c into quartiles, detected higher risks of all-cause mortality in the third and fourth quartiles, but not in the second quartile of HbA1c-SD and HbA1c-CV, compared with that of the first quartile.[9,10] In a Japanese study, subjects were classified according to tertiles of SD and CV of HbA1c, and the authors observed that the HR of all-cause mortality was significant only in the third tertile compared with that of the first tertile of HbA1c-SD and HbA1c-CV.[7]

In an English study, Critchley et al created 6 categories for HbA1c-CV into 10, 25, 50, 75, and 90 percentiles as cut-off points among patients with type 2 diabetes from 361 general practices.[12] The authors observed that a gradual increase in mortality risk was seen with increasing baseline HbA1c-CV, ranging from HR 1.32 (95% CI, 1.21–1.44) in the 25–50 percentile group to 1.71 (95% CI, 1.53–1.91) in the top 10 percentile category. In the ADVANCE trial,[11] the authors also grouped HbA1c-SD into deciles, and they found out there were significant linear associations between deciles of baseline HbA1c-SD in patients with type 2 diabetes, and the HR associated with the highest vs. lowest tenth comparison was 3.31 (95% CI, 1.57–6.98).

In our study, the significance of mortality in different quartiles of VVV of HbA1c varied with various age groups. In those aged 50–69 years, there was incremental risk elevation of all-cause mortality from the second to the fourth quartile. In patients with diabetes aged >69 years, higher risks of all-cause mortality were observed in the third and fourth quartile of VVV of HbA1c, but not in the second quartile of HbA1c variability, compared with the first quartile. In those aged <50 years, only those in the fourth quartile have a consequential increased risk of mortality. The risk estimates of all-cause mortality were similar among HbA1c-SD, HbA1c-CV, or HbA1c-ARV in different age groups irrespective of sex.

Previous studies scarcely reported the different risk estimates for various age groups. In the Hong Kong study,[8] the authors reported the risk estimates of those patients aged <65 years were higher than those aged ≥65 years in all measures of HbA1c variability. In our study, the HRs of those aged 50–69 years were the highest regardless of VVV measures in both sexes. Despite negligible significance observed in the second and third quartiles of various VVV of HbA1c in those aged <50 years, it cannot be concluded that VVV of HbA1c is a trivial issue in those young age groups. Evidence of young-onset diabetes and excessive risk of premature death and incident complications[19] indicated that we should implement constructive intervention to prevent variability in HbA1c in younger patients with diabetes before they come to middle age when second to fourth quartiles of VVV of HbA1c is consequentially corresponding to increased mortality.

To our best knowledge, the literature regarding various VVV measures of HbA1c and mortality in different age and sex stratifications is scarce. Generally, the HR of women patients was higher than those of male patients aged <50 years in VVV of HbA1c-SD and HbA1c-ARV probably due to relative male excess mortality.[20] In those aged >69 years, however, the HRs of women patients became lower than those of male patients across all VVV measures, which is likely to be a result of the longer life expectancy of women.[21] In those aged 50–69 years, the HRs of male patients and women patients were comparable apart from a few exceptions. The lack of protective effect of endogenously produced estrogens[22] in menopause might increase mortality in women patients[23] of those age groups which might have equalized the risk of mortality in both sexes. Further studies are necessary to verify the accurate estimates of all-cause mortality in relationship with VVV of HbA1c in different sexes.

Several mechanisms might be possible between increased all-cause mortality and worsening of VVV of HbA1c. Glucose fluctuations exhibited a more specific triggering effect on oxidative stress,[24] a central mediator of injury to lipids, proteins, and DNA.[25] Repeated glycemic oscillations increase the levels of proinflammatory cytokines, and induce endothelial dysfunction,[26] epigenetic and gene expression changes.[27] Intermittent high glucose enhances apoptosis in endothelial and human islet beta-cells,[28] accelerates macrophage adhesion to endothelial cells, promotes the formation of fibrotic arteriosclerotic lesions,[29] and subsequent fibrogenesis.[30] In addition, poor compliance with medication, multiple comorbidities, poor quality of life, and lack of social support might be confounding in the analysis of the relationship between VVV of HbA1c and mortality.[5,10]

4.3. Strengths and limitations of our study

Our study has several methodological strengths. First, patients with diabetes were retrieved from the FEMH hospital database, and the chance of nonresponse bias was considered low. In addition, the ascertainment of disease information from the hospital database rather than self-reports might largely reduce the possibility of recall bias. Second, one of the potential advantages of using hospital datasets in clinical research is that we could analyze multiple HbA1c assessments of the study subjects during the whole study period rather than just baseline HbA1c or a limited number of HbA1c measurements, which could provide satisfactory assessment for the effects of VVV of HbA1c on all-cause mortality. Third, we only recruited diabetes patients with oral or parenteral antidiabetic agents which might have reduced the disease misclassification bias in our study. Fourth, we could identify several cardiovascular risk factors, comorbidities complications, antihypertensives, antilipid medications, and laboratory results which might also have influenced the survival of our patients. Adjustment for these factors may have helped reduce the potential confounding.

Despite the above strengths, our study has several limitations. Several factors not detected in our study including BMI, smoking, alcohol consumption, blood pressure, compliance with medications, quality of life, and socioeconomic status,[5,10] might have provided residual confounding in our study. To our best effort, we already adjusted a number of known risk factors for mortality in the models. Identification of comorbidities and complications of our study depended only on ICD codes. In addition, this study was based on a single tertiary medical center, and the baseline characteristics of our study participants might have been different from the general diabetic population. Further studies are required to assess the generalizability of our study results.

5. Conclusion

Our study highlighted the important role of any kind of HbA1c variability whether it was HbA1c-SD, HbA1c-CV or HbA1c-ARV could predict increased risk of all-cause mortality equally in patients with diabetes. The magnitude of association between VVV of HbA1c and all-cause mortality varied in different ages and sexes. We should implement integrated therapeutic strategies to ameliorate HbA1c variability rather than just emphasizing optimal HbA1c targets in routine daily diabetes management.

Author contributions

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