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What is the best predictor of mortality in patients with type 2 diabetes and chronic kidney disease: mean, variability of HbA1c or HbA1c-Hemoglobin ratio?

Seng-Wei Ooi[1†], Ming-Tsang Lee[2†], Yung-Yueh Chang[1,3], Chin-Huan Chang[1] and Hua-Fen Chen[1,4,5,6*]

Abstract

Aim Limitations in the measurement of glycated hemoglobin (HbA1c) in patients with type 2 diabetes (T2D) and chronic kidney disease (CKD) result in uncertainty about the best predictor of mortality among these patients. Our study aimed to determine the association between the mean and average real variability (ARV) of HbA1c, as well as HbA1c-hemoglobin (HH) ratio with mortality among patients with T2D and CKD.

Materials and methods We identified 16,868 T2D patients with stage 3 or above CKD from outpatient visits during 2003–2018. We ascertained all-cause and cardiovascular mortality through linkage to Taiwan's National Death Registry. Mortality rates were estimated using the Poisson distribution, and we conducted Cox proportional hazards regressions to assess relative risks of mortality corresponding to the mean HbA1c, ARV of HbA1c and HH ratio.

Results Compared to patients with a mean HbA1c of 7.0–7.9%, a mean HbA1c < 7.0% was persistently associated with highest risk of all-cause but not cardiovascular mortality after adjusting for confounders. On the contrary, patients with HbA1c-ARV in the second to fourth quartiles and HH ratios in the higher quartiles showed increased risk of all-cause and cardiovascular mortality compared to those in the first quartiles.

Conclusions HbA1c-ARV was more effective than mean HbA1c or HH ratio in predicting mortality in T2D patients with CKD. Apart from optimal glucose control, multidisciplinary care focusing on glycemic variability is essential for reducing mortality in these patients.

Keywords Type 2 diabetes mellitus, Glycated Hemoglobin A, Mortality

[†]Seng-Wei Ooi and Ming-Tsang Lee contributed equally to this work.

*Correspondence:
Hua-Fen Chen
hfchen@mail.femh.org.tw
[1] Division of Endocrinology, Department of Internal Medicine, Far-Eastern Memorial Hospital, Taipei, Taiwan
[2] Division of Endocrinology, Department of Internal Medicine, Far-Eastern Polyclinic, Taipei, Taiwan
[3] Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan
[4] School of Medicine, College of Medicine, Fujen Catholic University, New Taipei City, Taiwan
[5] Department of Public Health, College of Medicine, Fujen Catholic University, New Taipei City, Taiwan
[6] Department of Endocrinology, Far Eastern Memorial Hospital, Nanya S. Rd, New Taipei City, No.21, Sec. 2, Banqiao Dist 220, Taiwan

Introduction

Chronic kidney disease (CKD) is prevalent in patients with type 2 diabetes (T2D), and approximately 36% of patients without cardiovascular or renal disease develop CKD within 4.5 years on average [1]. In that multinational study, CKD was associated with all-cause and cardiovascular mortality, with a hazard ratio [HR] of 2.05 (95% confidence interval [CI]: 1.75–2.33) [1]. Although the American Diabetes Association and Kidney Disease: Improving Global Outcome (KDIGO) recommend regular assessment of glycated hemoglobin A1c (HbA1c) to evaluate long-term glycemic control, [2] the optimal HbA1c level for patients with T2D and CKD has not been clearly established.

Previous studies observed that the association between HbA1c and mortality was U-shaped [3, 4], but another study did not see this relationship between HbA1c and mortality among patients with diabetes and CKD [5]. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, intensive glucose lowering in patients with CKD was significantly associated with higher all-cause (HR: 1.31; 95% CI 1.07–1.89) and cardiovascular mortality (HR: 1.41; 95% CI: 1.05–1.89) when compared to those on standard therapy, bringing into question the rationale behind aggressive glucose control in T2D patients with CKD [6]. In a Taiwanese study, Kuo et al. found that among diabetic patients with stage 3 or 4 CKD, elevated risk of all-cause mortality noted with highest quartile of HbA1c was only significant in patients whose hemoglobin (Hb) was ≥ 10 g/dL but not in those with Hb < 10 g/dL [7]. Similarly, among diabetic patients on maintenance hemodialysis, lower HbA1c unrelated to malnutrition and anemia was not associated with decreased survival [8]. This indicates that anemia might be a major confounding factor in the relationship between HbA1c and mortality.

Anemia is common in patients with CKD, with a prevalence of 1% in stage 3 CKD, 9% in stage 4 CKD, and 33–67% in stage 5 CKD [9]. The association between HbA1c and fasting glucose is strongest in patients without anemia, and weakest in patients with anemia [10]. Considering the limitations of measuring of HbA1c in T2D patients with CKD, long-term glycemic variability based on visit-to-visit (VVV) measurements of HbA1c [11], has been proposed as a better predictor of all-cause or cardiovascular mortality. Previous analyses observed that VVV of HbA1c could predict development of CKD in patients with diabetes [12], but the association of HbA1c VVV with all-cause and cardiovascular mortality in patients with T2D and CKD is, to the best of our knowledge, still unclear. Recently, a newly proposed HbA1c-Hb (HH) ratio was a better predictor of 90-day and 1-year mortality as well as postoperative adverse outcomes in patients undergoing cardiac surgery [13]. However, the utility of this ratio in T2D patients is still unknown.

This study aimed to evaluate the association between mean HbA1c, VVV of HbA1c and HH ratio with all-cause and cardiovascular mortality among T2D patients with CKD who were treated at Far Eastern Memorial Hospital (FEMH) during 2003–2018.

Methods

The FEMH, a tertiary medical center, has built up its inpatient and outpatient electronic medical database since Jan. 1, 2001. The details of our electronic database, including collection of comorbidities and laboratory data have been published in our previous studies [14–16]. This study was approved by the Research Ethics Review Committee of the FEMH (110282-F), which waived the need for informed consent.

This study included T2D patients with an eGFR < 60 ml/min/m^2 from outpatient clinics, that were cared for by both endocrinologists and non-endocrinologists. We selected 74,888 subjects who were diagnosed with diabetes (ICD-9-CM: 250.xx or ICD-10-CM: E10 or E11) during outpatient visits. We excluded 4,213 patients who were not taking hypoglycemic agents, 23,530 patients with a total outpatient visit duration of less than 6 months at FEMH, 29,807 patients with an eGFR > 60 ml/min/m^2, and 470 patients with type 1 diabetes, for a final study cohort of 16,868 patients with both T2D and CKD (stage 3–5). The index date for each patient was the first date at which hypoglycemic agents were prescribed at FEMH during Jan 1, 2003 and Dec 31, 2018. Each patient's age was calculated as the difference between the index date and their date of birth.

From the index date to the last year of follow-up, the annual mean HbA1c was categorized into < 6.0, 6.0–6.9, 7.0–7.9, 8.0–8.9, 9.0–9.9 and ≥ 10.0%, with a mean HbA1c of 7.0–7.9% as the reference group in analyses since less stringent glycemic control is recommended for diabetic patients with established vascular complications [17]. We calculated each patient's annual intra-individual average real variability of HbA1c (HbA1c-ARV), and then took the mean of the annual HbA1c-ARV during the whole study period to represent the VVV of HbA1c [14]. We chose the HbA1c-ARV to represent the VVV of HbA1c because in our previous study, ARV was a significant predictor of all-cause mortality in both sexes in all ages [14]. Lastly, we also computed the HH ratio [13] by dividing each patient's mean HbA1c by mean Hb level. We divided HbA1c-ARV and HH ratio into quartiles and used the first quartile as the reference group.

We retrieved data on each patient's prescribed oral hypoglycemic agents, as well as insulin,

antihypertensive including angiotensin converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARB), and antilipid medications during the study period. Data on various diabetic complications such as coronary artery disease, heart failure, cerebrovascular disease [15, 16] and hypoglycemia [17], were also collected from the outpatient medical records and treated as potential confounders.

Using a unique PIN, we linked FEMH's electronic database to Taiwan's National Death Registry for the study period. Our outcomes of interest were all-cause and cardiovascular related mortality [15, 16]. For patients who did not experience death during the study period between Jan 1, 2003 and Dec 31, 2018, they were censored at the end of the study follow-up on December 31, 2018. Each patient was followed up from their index date to their date of death, or the December 31, 2018, whichever came first.

Under the Poisson assumption, we calculated all-cause and cardiovascular mortality rates for each patient using person-years as the denominator. We utilized Cox proportional hazards regression models, then examined the association of mean HbA1c, HbA1c-ARV and HH ratio with the relative risks of all-cause or cardiovascular mortality. We adjusted for potential confounders in each regression model as follows: In Model 1, we adjusted for age and sex. Model 2 included all variables in Model 1, and added prescribed antidiabetic, antihypertensive including ACEi or ARB and antilipid medications. Model 3 further included patients' comorbidities, mean systolic blood pressure (SBP) and diastolic blood pressure (DBP), duration of CKD and laboratory results including mean HbA1c, different quartiles of HbA1c-ARV and HH ratio simultaneously. All statistical analyses were performed with SAS (version 9.4, SAS institute, Cary, NC). A p-value < 0.05 was considered statistically significant.

Results

Baseline characteristics

Among 16,868 participants with T2D and CKD, most were middle aged (50–69 years) (55.45%) with a mean age of 63.61 ± 11.84 years. Proportions of male and female were almost equal. In addition, 44.96% of patients were prescribed insulin (Table 1). The mean HbA1c of most patients (58.90%) was around 6.0–7.9%. Furthermore, 68.85% of patients had stage 3a CKD, 58.54% of patients had anemia, and 29.36% had low mean albumin levels < 3.5 g/dL. During a mean follow-up period of 8 years, 6,857 (40.65%) and 1,357 (8.04%) patients experienced all-cause or cardiovascular mortality, respectively (Table 1).

Effect of mean HbA1c on all-cause and cardiovascular mortality

Supplemental Table 1 shows the overall rates and relative hazard ratios of all-cause and cardiovascular mortality by different mean HbA1c levels. Mortality rates were the lowest in those with a mean HbA1c of 7.0–8.9% (44.00–47.71/1,000 patient-years (PY) for all-cause mortality; 9.4/1,000 PY for cardiovascular mortality). The highest rate of all-cause mortality was seen in T2D patients with a mean HbA1c of $< 6\%$ (81.91/1,000 PY), while those with a mean HbA1c of $\geq 10.0\%$ had the highest cardiovascular mortality rate (13.54/1,000 PY).

Compared to T2D and CKD patients with a mean HbA1c of 7.0–7.9%, those with a mean HbA1c of $\geq 9.0\%$ had comparable risks of all-cause mortality, but those with a mean HbA1c 8.0–8.9% had the lowest risk of all-cause mortality after adjustment of confounders including quartiles of HbA1c-ARV and HH ratio. Patients with T2D and CKD with a mean HbA1c of $< 7.0\%$, on the contrary, had significant risks of all-cause mortality after further adjustment for several covariates in model 3. Any levels of mean HbA1c, however, were not associated with cardiovascular mortality (Supplemental Table 1). Overlapping CIs between model 1 and model 2 of Fig. 1 indicated that the addition of medications in model 2 did not consequentially change the risk estimates of all-cause or cardiovascular mortality, but adjustment of comorbidities, laboratory results including HbA1c-ARV and HH ratio in model 3 magnified or diminished the significant role of lower ($< 7.0\%$) or higher ($\geq 9.0\%$) mean HbA1c and respective all-cause mortality, but not cardiovascular mortality.

Effect of HbA1c-ARV on all-cause and cardiovascular mortality

All-cause mortality rate was the lowest in T2D patients in the second quartile of HbA1c-ARV (37.44/1,000 PY), but in those patients with HbA1c-ARV in the fourth quartile, all-cause mortality rate (70.14/1,000 PY) was the highest. Similarly, we observed the highest cardiovascular mortality rates in those with HbA1c-ARV in the fourth quartile (13.66/1,000 PY), and the lowest rates occurred in the first quartile of HbA1c-ARV (7.77/1,000 PY) (Supplemental Table 2).

Compared with patients in the first quartile, patients with HbA1c-ARV in the third and fourth quartiles had higher risks of all-cause mortality in model 1 and 2. In Fig. 2, there were overlapping of CIs between model 1 and model 2 suggesting that the effect estimates between these two models were inconsequential. Although the statistical significance of second quartile of HbA1c-ARV was not evident in model 1 and

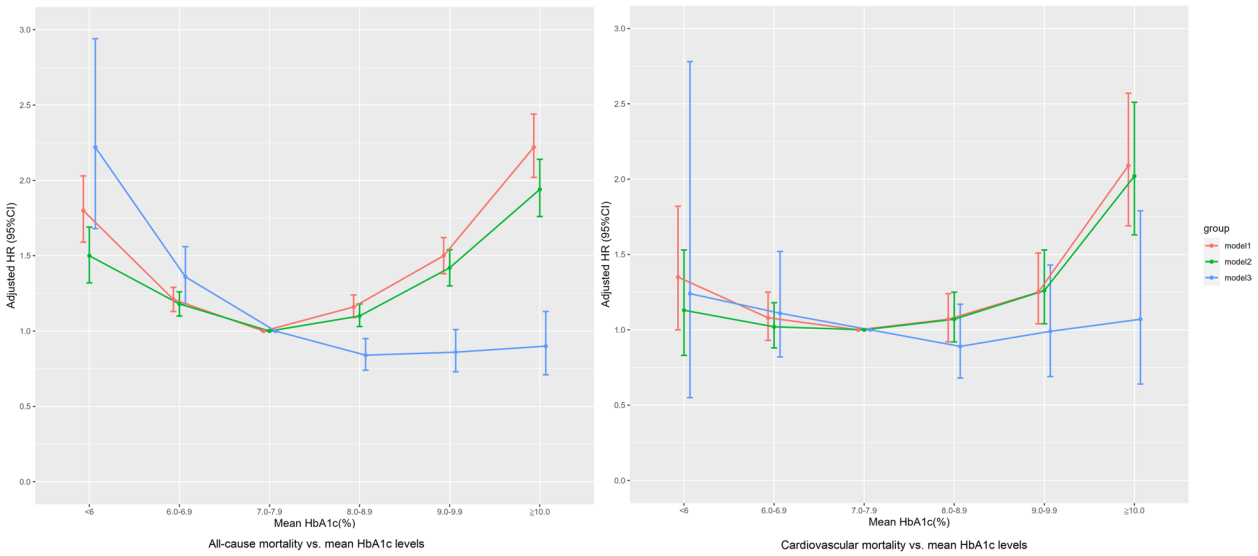

Fig. 1 Relative hazards of all-cause and cardiovascular mortality according to mean HbA1c levels in patients with type 2 diabetes and stage 3–5 chronic kidney disease

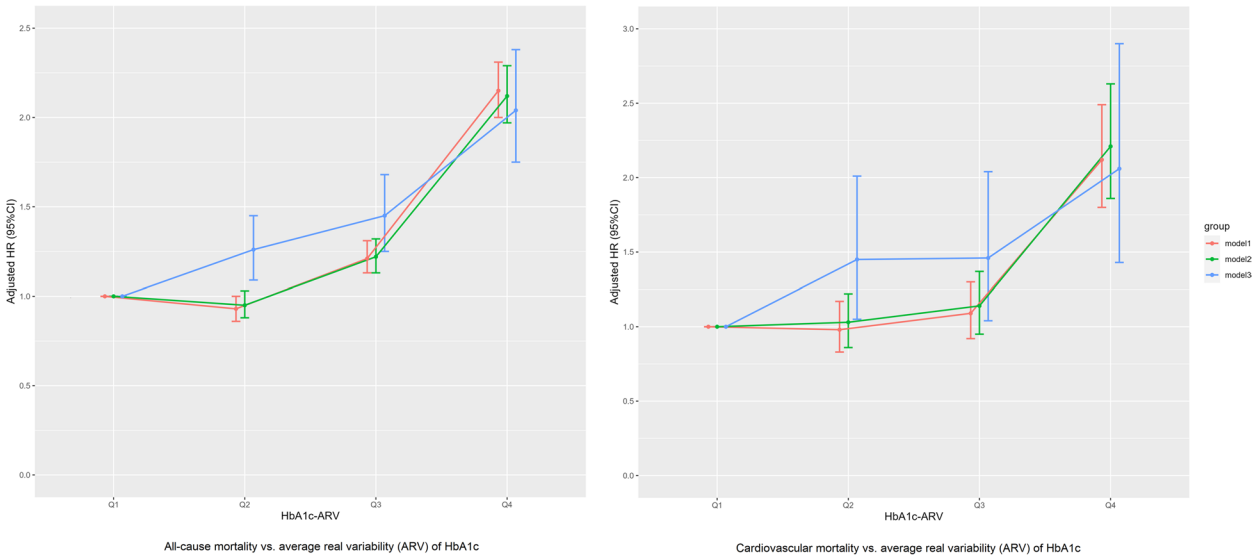

Fig. 2 Relative hazards of all-cause and cardiovascular mortality according to average real variability (ARV) of HbA1c in patients with type 2 diabetes and stage 3–5 chronic kidney disease

2, further adjustment for other covariates in model 3 including mean HbA1c and HH ratio, those in second, third, and fourth quartiles of HbA1c-ARV had significant risks of all-cause mortality (HR 1.26, 1.45 and 2.04, respectively). Similarly, patients with HbA1c-ARV in the second to fourth quartiles had consequential risk of cardiovascular mortality (HR: 1.45, 1.46, and 2.06, respectively in model 3). (Supplemental Table 2).

Effect of HH ratio on all-cause and cardiovascular mortality

All-cause and cardiovascular mortality rates were the lowest in T2D patients with HH ratios in the first quartile, but were the highest in those with HH ratios in the fourth quartile (Supplemental Table 3). Compared with the study subjects in the first quartile, those with HH ratios in the second, third, and fourth quartiles had higher risks of all-cause mortality in models 1 and 2.

However, after adjustment for medications, comorbidities, complications, and laboratory data including mean HbA1c and HbA1c-ARV, only HH ratios in the third and fourth quartiles showed elevated risk of all-cause mortality (HR 1.31 and 1.86, respectively). Likewise, only patients with HH ratios in the fourth quartile had significant risk of cardiovascular mortality in the fully adjusted model 3 (HR: 1.81; 95% CI 1.02–3.21). Fig. 3 revealed that there were statistically discernable HRs with all-cause or cardiovascular mortality in second to fourth quartiles of HH ratio in model 1 and 2. However, adjustment of additional covariates in model 3 lessened the magnitude of their significance, and only those with higher quartiles remained statistically evident.

Discussion

During a mean follow-up of 8 years, among T2D patients with CKD, those with lower mean HbA1c (< 7.0%) experienced significant risks for all-cause mortality after adjustment for various confounding factors, but those with any mean HbA1c was not related to cardiovascular mortality. In contrast, patients with HbA1c-ARV in the second, third and fourth quartile had significant risks of all-cause and cardiovascular mortality, while only patients with HH ratios in the higher quartile had elevated risks of all-cause and cardiovascular mortality.

The mortality rates we estimated in our patients with T2D and CKD were lower than those seen in hemodialysis patients with diabetes from the USA [18] and Korea. [19] Patients with diabetes in chronic hemodialysis may have worse survival. [20] Although some studies of patients with diabetes and stage 3–4 [3] or 3–5 CKD [4], revealed a U-shaped association between baseline HbA1c and mortality, authors of the Seattle Kidney Study did not find any association between baseline HbA1c and mortality after 4.2 years of follow-up. [5] However, different study designs might result in dissimilar results. A single measurement of baseline HbA1c in previous studies[3–5] may not accurately reflect the overall glycemic control in diabetes patients. In addition, duration of follow-up may influence study results. Ishimura et al. reported that the one-year survival rate of diabetic patients in hemodialysis was similar between patients with good and poor glycemic control, but good glycemic control was an independent predictor of a better prognosis after 3–5 years of follow-up. [21].

In our study, the significant risk for all-cause mortality in those with a low mean HbA1c < 7.0% still significant after adjustment for comorbidities, complications and laboratory results such as anemia and albumin. Patients with CKD usually have anemia due to relative erythropoietin deficiency, shortened erythrocyte survival, disordered iron homeostasis, and uremic-induced inhibitions of erythropoiesis [22], which may have resulted in low HbA1c. After adjustment for these important confounding factors, however, the consequential risks observed in those with higher mean HbA1c (≥ 8.0%) in model 1 and 2 became attenuated, and their risk estimates in model 3 turned out to be comparable to those with a mean HbA1c 7.0–7.9%. Interestingly, the lowest risk of all-cause mortality observed in our T2D patients with CKD was those with a mean HbA1c 8.0–8.9%. On the other hand, HbA1c

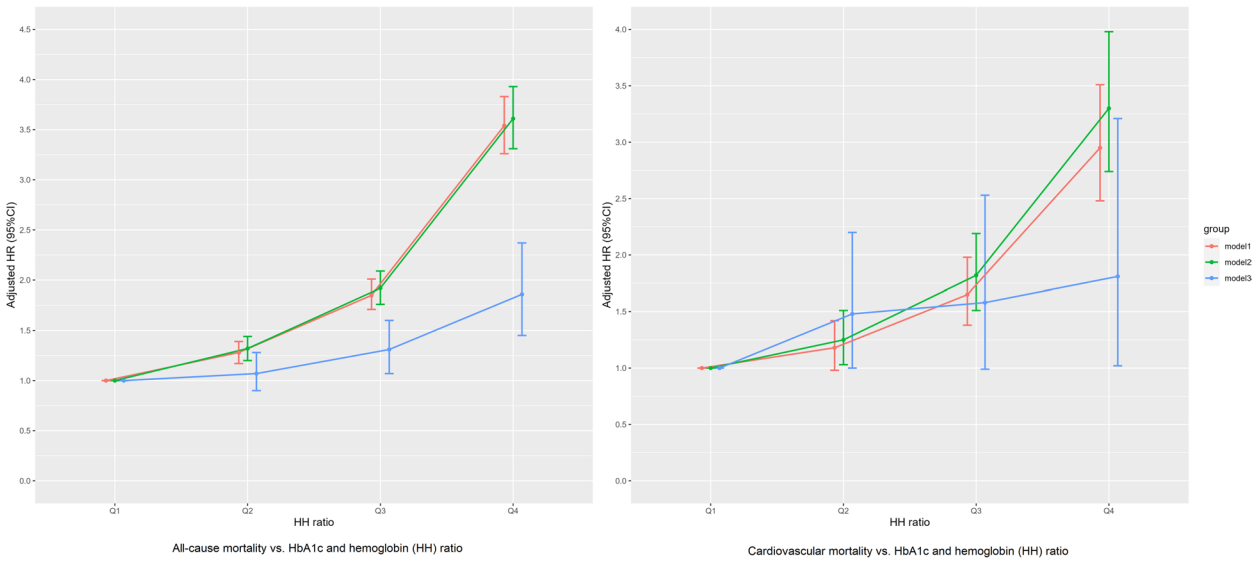

Fig. 3 Relative hazards of all-cause and cardiovascular mortality according to HbA1c and hemoglobin (HH) ratio in patients with type 2 diabetes and stage 3–5 chronic kidney disease

was not associated with cardiovascular mortality in this study.

In the Dialysis Outcomes and Practice Patterns Study (DOPPS), [23] hemodialysis patients with HbA1c < 7.0% and ≥ 9.0% increased all-cause mortality, revealing a U-shaped association. Hypoglycemia might be a worrisome issue in diabetic patients with lowest mean HbA1c, but the percentage of insulin use and frequencies of level 1–3 hypoglycemia episodes in those with mean HbA1c < 7.0% were the lowest among our T2D patients with CKD. In the DOPPS study, 78% of patients with mean HbA1c < 5.0% were also not treated with glucose lowering agents, but associated poor nutritional status demonstrated higher mortality rates for patients with mean HbA1c < 7.0%. Kalantar-Zadeh et al. noted that there might be possible interactions between indexes of glycemic control and factors related to nutrition, inflammation and anemia. They observed that lower A1c that was unrelated to malnutrition or anemia appeared to be associated with improved survival in hemodialysis patients [8], which is similar findings by Kuo et al. [7] Inability to identify malnutrition status might be a limiting factor in our analyses. Additional studies are obligatory to explore the underlying mechanisms between the relationship of low mean HbA1c and all-cause mortality in T2D patients with CKD.

Apart from mean HbA1c, consistent glycemic control is important for reducing mortality risk in T2D patients [24], and VVV of HbA1c is reported to be an important parameter for evaluating mortality in patients with diabetes. In one Taiwanese study, the authors calculated the HbA1c coefficient of variation (HbA1c-CV) for each individual patient using HbA1c measurements within the first year of the index date. After 10 years of follow-up, diabetic patients with HbA1c-CV in the third, fourth, and fifth quintiles were associated with increased all-cause mortality after multivariate adjustment [25]. Similarly, patients in our study with HbA1c-ARV in the second, third and fourth quartiles also had higher risk of all-cause mortality, even after adjustment for various confounders including hemoglobin and albumin. We used the mean of annual mean of HbA1c-ARV, which appropriately reflected intra-individual variation during the whole study period.

In a Hong Kong Diabetes Registry study, the intrapersonal standard deviation (SD) of serially measured HbA1c (HbA1c-SD) predicted the development of renal and cardiovascular complications [26]. However, in a multicenter cross-sectional analysis of T2D patients in Italy, HbA1c-SD was not significantly higher in subjects with a history of cardiovascular disease [27]. In our analysis, however, T2D patients with HbA1c-ARV in the second to fourth quartiles had higher risk of cardiovascular mortality in model 3. Previous studies revealed that glycemic variability was strongly associated with the progression of CKD and development of end stage kidney disease (ESKD). [28, 29] Higher HbA1c variability, an indicator of previous glucose fluctuation and poor glycemic control, may have activated oxidative stress, damaged microvascular structures and impeded endothelial function [30]. leading to various micro- and macrovascular complications and subsequent increased mortality.

Although HbA1c reflects one's average glycemic control over the past 3 months or so, conditions that affect red blood cell turnover such as hemolytic or other anemia, hemoglobin variants, acute or chronic blood loss, ESKD or pregnancy may result in discrepancies between the measured HbA1c and the patient's true mean glycemia [17]. A recent analysis studied the correlation between HH ratio and postoperative status for cardiac surgery. The authors divided the HH ratio into < 0.5, 0.5–0.7, and > 0.7, and patients with HH ratios of 0.5–0.7 and > 0.7 were associated with higher rates of 90-day mortality (HR: 5.12 and 7.25, respectively) and 1-year mortality (HR: 4.53 and 9.20, respectively). [13] The prevalence of anemia in that study was 30.3%, and the authors concluded that attempting to correct the HbA1c for Hb in the HH ratio might result in better prediction of postoperative mortality. In our study, the prevalence of anemia was higher (58.54%), and only HH ratio > 0.65 or > 0.77, respectively, was significantly associated with increased all-cause and cardiovascular mortality.

We used C index differentiation and r^2 calibration degree to determine the predictive performance of mean HbA1c, HbA1c-ARV and HH ratios and all-cause and cardiovascular mortality. The C index differentiation estimates of all three HbA1c metrics were 0.83 and 0.81 for all-cause and cardiovascular mortality, respectively, while r^2 calibration degree of above HbA1c measures were 0.99 and 0.62 for all-cause and cardiovascular mortality, respectively. This indicated that mean HbA1c, HbA1c-ARV and HH ratios were equally good at risk discriminative performance for our study outcomes.

However, only patients with lower mean HbA1c (< 7.0%) showed highest risk of all-cause mortality in our analysis. The HRs estimated were around 1.36–2.22 while their 95% CI were varying from 1.18–2.94, but none of those with any mean HbA1c was associated with cardiovascular mortality. Similarly, only those with higher quartile of HH ratio revealed significant risk of all-cause and cardiovascular mortality, but their HRs were higher around 1.8 with wider 95% CI especially in cardiovascular mortality (1.02–3.21). On the contrary, those with HbA1c-ARV in the second to fourth quartiles were related with consequential risk of all-cause and cardiovascular mortality, with higher HRs (~ 2)

and narrower 95% CI (1.05–2.90). Interactions of mean HbA1c, HbA1c-ARV, and HH ratio are significant predictors of all-cause ($p < 0.0001$) and cardiovascular ($p < 0.0001$) mortality. Including mean HbA1c, HbA1c-ARV, and HH ratio simultaneously in model 3 altered the HRs of mean HbA1c and all-cause mortality, attenuated the significance of HH ratio with all-cause or cardiovascular mortality, but they had little influence for risk estimates of each quartile of HbA1c-ARV in either all-cause or cardiovascular mortality. From the difference in the effect size of the outcome events among three measures, we speculated HbA1c-ARV was the best predictor for all-cause and cardiovascular mortality. Future studies are still necessary to determine whether mean HbA1c, HbA1c-ARV or the HH ratio is a better predictor of mortality in patients with diabetes and CKD.

Apart from glycemic management, optimal management of blood pressure and lipid profiles are more important for reduction of cardiovascular diseases. In our study, we added important confounding factors like mean SBP, mean DBP in addition to comorbidities, complications and laboratory results in model 3 as hypertension is associated with progression of CKD, all-cause mortality and increased risk of cardiovascular disease. [31] Patients with mean DBP > 80 mmHg were persistently associated with higher risk of all-cause and cardiovascular mortality, and the usage of ACEi or ARB consistently reduced the risk of study outcomes. In addition to optimal glycemic control, strict adherence of recommended guidelines for blood pressure management is crucial in preventing cardiovascular events and subsequent mortality.

The strengths of our study were the usage of the FEMH electronic medical records and its linkage with the National Death Registry. This might have minimized selection, non-response, and information biases. We collected patients with prescriptions for oral or parenteral antidiabetic agents, which might have reduced the misclassification bias. We were also able to identify and adjust for cardiovascular risk factors, medications and laboratory results, which might have affected the survival of patients in our study. Most importantly, we were able to adjust for anemia, which is a major limiting factor in interpreting low HbA1c levels. Furthermore, we compared the HRs of mean HbA1c, HbA1c-ARV and HH ratio for all-cause and cardiovascular mortality in T2D patients with CKD, which may be a novel finding in CKD patients.

Our study is not without limitations. We were unable to collect data on BMI and smoking, which may have affected survival in our patients. However, we already adjusted for several comorbidities, medications and laboratory results. Although we could extract Hb data and adjust for it in our model, Hb may have been drawn in different clinical conditions, which may confound the results of our study. Lastly, this study was based on a single tertiary medical center, and the generalizability of our study findings should be confirmed in future trials.

Conclusions

Our study found that in T2D patients with CKD, lower mean HbA1c (< 7.0%) was associated with all-cause but not cardiovascular mortality. HbA1c-ARV could more effectively predict both all-cause and cardiovascular mortality compared to HH ratio. In daily clinical practice, we should implement integrated and multifaceted diabetes care to optimize glucose control and minimize glycemic variability in T2D patients with CKD.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12882-024-03686-9.

Additional file 1. Overall rates and relative hazards of all-cause and cardiovascular mortality according to mean HbA1c levels in patients with type 2 diabetes and stage 3-5 chronic kidney disease.

Additional file 2. Overall rates and relative hazards of all-cause and cardiovascular mortality according to average real variability (ARV) of HbA1c and in patients with type 2 diabetes and stage 3-5 chronic kidney disease.

Additional file 3.Overall rates and relative hazards of all-cause and cardiovascular mortality according to HbA1c and hemoglobin (HH) ratio in patients with type 2 diabetes and stage 3-5 chronic kidney disease.

Authors' contributions

MTL and CHC designed the study. SWO and CHC extracted the database. YYC and HFC analyzed the data. MTL and SWO drafted the manuscript. YYC prepared the figures and tables. HFC contributed to scientific discussion, data interpretations, supervision of the study and the revision of the manuscript. All authors have read and approved the final manuscript.

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Availability of data and materials

The data sets analyzed during the current study are not publicly available because the raw data contains potentially identifying patients' information. The restrictions are imposed by the Research Ethics Review Committee of Far Eastern Memorial Hospital according to Human Subjects Research Act, Laws and Regulations Database, Ministry of Health and Welfare, the Republic of China (Taiwan). (https://law.moj.gov.tw/ENG/LawClass/LawAll.aspx?pcode=L0020176). Application to the Research Ethics Review Committee of Far Eastern Memorial Hospital (contact via irb@mail.femh.org.tw, reference number 110282-F) is available for researchers who meet the criteria for access to confidential data according to Taiwanese Laws and Legislation.

Declarations

Ethics approval and consent to participate

The study was approved by the Institutional Review Board of Far Eastern Memorial Hospital (110282-F) which waived the need for informed consent.

Competing interests

The authors declare no competing interests.

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