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# Baseline glycemic status and mortality in 241,499 Korean metropolitan subjects: A Kangbuk Samsung Health Study

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ABSTRACT

*Objective.* Diabetes and prediabetes subjects have increased risk for mortality. We analyzed the mortality risk due to all causes, cardiovascular disease (CVD) and cancer in Korean subjects participating in a health-screening program according to baseline glycemic status and HbA1c levels.

*Materials/methods.* Among 241,499 participants of a health-screening program between 2005 and 2012, the risk of death from all causes, CVD, and cancer was calculated based on the baseline glycemic status (normoglycemia, prediabetes, and diabetes) and HbA1c levels. Uncontrolled diabetes was defined as HbA1c ≥ 7.0%. Vital status and confirmation of the cause of death were based on the analysis of death certificate records from the National Death Index.

*Results.* During 923,343.1 person-years of follow-up, 877 participants died. The multivariable-adjusted hazard ratios (HR) of subjects with controlled and uncontrolled diabetes to normoglycemic subjects for all-cause mortality were 1.58 (95% CI 1.24–2.03) and 2.26 (95% CI 1.78–2.86), respectively. The HRs of subjects with controlled and uncontrolled diabetes to normoglycemic subjects for mortality due to cancer were 1.75 (95% CI 1.23–2.48) and 1.67 (95% CI 1.13–2.45). However, glycemic status was not significantly associated with the risk of mortality due to CVD. The subjects with HbA1c higher than 6.5% showed more than 2-fold increased risk for all-cause mortality and the subjects with HbA1c lower than 5.2% showed increased HR (1.45, 95% CI 1.06–1.97) compared with those with HbA1c of 5.5% in subjects not taking anti-diabetic medications.

*Conclusions.* Mortality risk from all causes and cancer significantly increased in diabetes subjects regardless of the glucose control status. In subjects not taking anti-diabetic medications, both high and low HbA1c resulted in increased risk for all-cause mortality.



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## 1. Introduction

The goal for optimal glucose control of HbA1c < 7.0% was largely unquestioned until the Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation (ADVANCE), and Veterans Affairs Diabetes Trial (VADT) studies could not confirm that tight blood control under the conventionally recommended cutoff values reduced the risk for macrovascular complications or mortality in patients with a long history of type 2 diabetes and high risk for cardiovascular disease (CVD) [1–3]. Furthermore, other studies reported a U-shaped risk with both low and high glucose levels, indicating increased risk for mortality from all causes and from CVD [4,5]. From these results, the joint position statement from ADA and the European Association of Study of Diabetes (EASD) suggested a more flexible glucose control for patients with diabetes, focusing on individual conditions and co-morbidities [6].

The Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study reported significantly increased risk of death from all causes and from CVD in prediabetes subjects [7,8]. The Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Asia (DECODA) study reported similar results among Asians [9]. These two studies commonly showed that 2-hour plasma glucose was superior to fasting plasma glucose (FPG) in the prediction of mortality from all causes and from CVD. In the Atherosclerosis Risk in Communities (ARIC) study, HbA1c level was associated with the risk of diabetes and even more strongly with the risk of CVD and death from all causes compared with fasting glucose in subjects without diabetes [4]. However, only a few large-scale well-designed studies have evaluated the association between HbA1c and mortality in Asians.

Individuals with established diabetes have an increased risk of developing cancer compared with those without diabetes [10–14]. This increased risk is due to several conditions, including hyperinsulinemia, hyperglycemia, increased systemic inflammation, and altered concentrations of endogenous hormones [15–17]. Although the association between hyperglycemia and increased cancer risk in diabetes subjects is clear, the association between hyperglycemia and cancer incidence in subjects without diabetes remains controversial. However, a few studies have reported that hyperglycemia in subjects with and without diabetes can directly affect the development of cancer [12].

In this study, we analyzed the risk for mortality from all causes, CVD, and cancer in 241,499 Koreans participating in a health-screening program. We analyzed the risk for mortality in patients with different glycemic status in 10,950 diabetes patients. Additionally, we analyzed the mortality risk in patients with distinct HbA1c levels after excluding those taking anti-diabetic medications to assess the direct effects of hyperglycemia on mortality risk apart from the effects of medications.

## 2. Methods

### 2.1. Study Population

The Kangbuk Samsung Health Study is a retrospective cohort study of Korean men and women who underwent a comprehensive annual or biennial health examination at the Kangbuk Samsung Hospital Health Screening Centers in Seoul and Suwon, South Korea. The study population consisted of examinees who participated in a comprehensive health-screening examination between 2005 and 2012 (N = 276,239) at the Kangbuk Samsung Hospital Total Healthcare Center (or clinics) in Seoul and Suwon, South Korea. The Seoul Health Exam Center is located in the Jongno-Gu district, in the center of Seoul, South Korea. The Suwon Health Exam Center is located at Youngtong in Suwon, a developing city located about 30 miles from Seoul. During the study period, 196,925 subjects were examined at the Seoul Center and 79,314 subjects were examined at the Suwon Center. The characteristics of the participants from Seoul or Suwon Center are presented in Supplementary Table 1. More than 80% of the participants and their spouses were employees of various companies and local governmental organizations. In Korea, annual or biennial health-screening examinations of employees are required by the Industrial Safety and Health Law. The remaining participants voluntarily attended the health checkup program.

We excluded 34,740 subjects based on the following criteria: unknown vital status (N = 1); missing data on glucose or HbA1c levels (N = 5020); or missing data on other covariates, including smoking status, alcohol consumption, and physical activity (N = 30,177). The final sample included 267,155 participants. Because some individuals met more than one exclusion criterion, the total number of patients eligible for the study was 241,499 (Fig. 1). The institutional review board of the Kangbuk Samsung Hospital approved this study. The requirement of informed consent was waived because we did not use patient-identifiable data routinely collected during the health-screening process.

Among the subjects with diabetes, 4467 subjects were taking anti-diabetic medication. Therefore, the analyses that were performed after excluding participants with the use of blood glucose lowering agents were performed after exclusion of these participants.

### 2.2. Data Collection

All examinations were conducted at the Kangbuk Samsung Hospital Health Screening Center clinics in Seoul and Suwon.

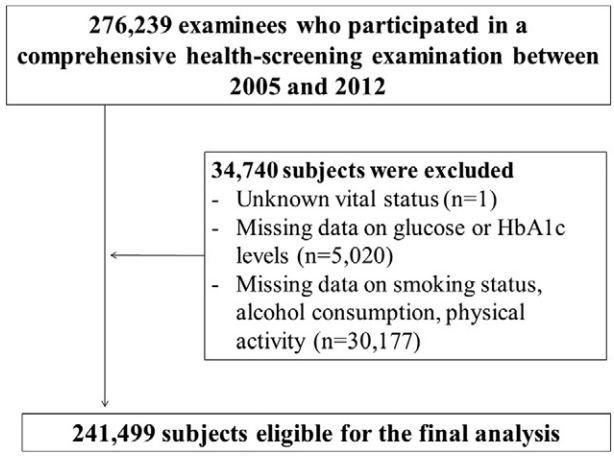



**Fig. 1 – Selection of study subjects.**

At each visit, demographic characteristics, smoking status, alcohol consumption, regular exercise, medical history, and medication use were recorded using a standardized, self-administered questionnaire. Smoking status was categorized into never, former, and current smokers. Alcohol consumption was categorized into none, moderate (≤20 grams/day), and high (>20 grams/day). The weekly frequency of moderate- and vigorous-intensity physical activity was also assessed. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Sitting blood pressure (BP), height, and weight were measured by trained nurses. Obesity was defined as BMI ≥ 25 kg/m$^2$ (the cutoff proposed for Asian populations) [18]. Hypertension was defined as systolic blood pressure of ≥140 mm Hg, diastolic blood pressure of ≥90 mm Hg, self-reported history of hypertension, or current antihypertensive medication use. Prediabetes was defined as a fasting serum glucose level of 100–125 mg/dl or HbA1c of 5.7–6.4%. Diabetes was defined as a fasting serum glucose level of ≥126 mg/dl or HbA1c of ≥6.5%, self-reported diabetes history, or current anti-diabetic medication use according to the diagnostic criteria established by ADA [19]. Diabetes subjects were classified into those with controlled diabetes (HbA1c < 7.0%) or with uncontrolled diabetes (HbA1c ≥ 7.0%).

### 2.3. *Laboratory Analyses*

Blood specimens were obtained from the antecubital vein after at least 10 hours of fasting. Laboratory analyses were performed at the Laboratory Medicine Department of the Kangbuk Samsung Hospital in Seoul, South Korea. Serum levels of glucose, total cholesterol, LDL-C, triglycerides, HDL-C, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyl transferase (GGT) were measured using Bayer Reagent Packs on an automated chemical analyzer (Advia 1650™ Autoanalyzer; Bayer Diagnostics, Leverkusen, Germany). Serum high sensitivity-C reactive protein (hs-CRP) levels were determined using a particle-enhanced immunoturbidimetric assay on a Modular Analytics P800 apparatus (Roche Diagnostics). Serum insulin level was measured using an electrochemiluminescence immunoassay on a Modular Analytics E170 apparatus (Roche Diagnostics), and serum fasting glucose level was measured using the hexokinase method on a Cobas Integra 800 apparatus (Roche Diagnostics; Rotkreuz, Switzerland).

HbA1c determination using the Cobas Integra 800 (Roche Diagnostics, Rotkreuz, Switzerland) is based on the turbidimetric inhibition immunoassay for hemolyzed whole blood (reference range 4.4–6.4%). HbA1c measurements were standardized to the reference method aligned with the Diabetes Control and Complications Trial and the National Glycohemoglobin Standardization Program standards. The intraassay coefficient of variation was 2.3% and interassay coefficient of variation was 2.4%, both of which are within the acceptance range of the aforementioned standardization program [20]. Insulin resistance was assessed with the homeostatic model assessment — insulin resistance (HOMA-IR) equation: fasting blood insulin (μU/ml) × fasting blood glucose (mmol/L)/22.5 [21].

The Laboratory Medicine Department of the Kangbuk Samsung Hospital has been accredited by the Korean Society of Laboratory Medicine (KSLM) and the Korean Association of Quality Assurance for Clinical Laboratories (KAQACL), and participates in the CAP (College of American Pathologists) Survey Proficiency Testing.

### 2.4. *Mortality Follow-up*

Mortality follow-up between January 1, 2005 and December 31, 2012 was based on nationwide death certificate data from the Korea National Statistical Office. All deaths in Koreans are reported to the Statistics Korea and death certificate data for Korean adults are virtually completed. Cancer deaths were identified by codes C00–C97 from the 10th revision of the International Classification of Disease (ICD) as the underlying cause of death on the death certificates [22]. Cardiovascular disease mortality was defined as ICD-10 codes I00 to I99.

### 2.5. *Statistical Analysis*

The characteristics of the study participants were evaluated according to the baseline glycemic status. To test for linear trends, category numbers were used as continuous variables in the regression models.

We used Cox proportional hazard models to estimate the hazard ratios (HRs) for deaths from all causes, from cancer, and from CVD. The models were initially adjusted for age and sex and further adjusted for study center (Suwon, Seoul), year of screening examination, regular exercise, alcohol intake, smoking, and BMI. The analysis was further adjusted for history of cancer, history of CVD, family history of diabetes, and hypertension. To determine the linear trends of risk, the number of categories was used as a continuous variable and tested on each model. For tests of quadratic trend, the linear trend variable was squared after centering it on the median. The proportional hazards assumption was assessed by examining graphs of estimated log(−log)(*SURVIVAL*).

All p-values were two-tailed and values of $p < 0.05$ were considered statistically significant. STATA software version 13.1 (Stata, College Station, TX) was used for data analysis.

## 3. Results

Table 1 presents the baseline participant characteristics. The median follow-up period was 3.8 years. The mean age (SD) of the population at baseline was 39.7 (10.2) years and the mean BMI was 23.3 (3.2) kg/m$^2$. The prevalence rates of prediabetes and diabetes were 35.7% and 4.6%, and almost 50% of the cases of diabetes were uncontrolled diabetes (HbA1c > 7.0%). In general, diabetes and prediabetes subjects showed relatively higher mean BMI and worse metabolic parameters compared with normoglycemic subjects. The subjects with uncontrolled diabetes had worse metabolic parameters than those with controlled diabetes.

When the HRs for mortality from all causes, from CVD, and from cancer were analyzed according to the glycemic status, the risk for all-cause mortality significantly increased in diabetes subjects (Table 2). The subjects with uncontrolled diabetes showed higher HR for all-cause mortality compared with those with controlled diabetes. The HR for all-cause

**Table 1 – Baseline characteristics of the study participants by diabetes status.**

| Characteristics | Overall | Diabetes status | | | | p for trend |
|---|---|---|---|---|---|---|
| | | Normal | Prediabetes | Controlled diabetes | Uncontrolled diabetes | |
| Number (%) | 241,499 | 144,415 (59.8) | 86,134 (35.7) | 6219 (2.6) | 4731 (2.0) | |
| Age (years) [a] | 39.7 (10.2) | 37.4 (8.7) | 42.1 (10.8) | 51.7 (11.4) | 51.4 (11.2) | <0.001 |
| BMI (kg/m$^2$) | 23.3 (3.2) | 22.7 (3.0) | 24.1 (3.3) | 25.4 (3.3) | 25.6 (3.4) | <0.001 |
| Male (%) | 54.6 | 51.6 | 57.9 | 67.2 | 69.3 | <0.001 |
| Current smoker (%) | 26.4 | 25.3 | 27.5 | 27.8 | 35.9 | <0.001 |
| Alcohol intake (%) [b] | 17.3 | 14.5 | 20.9 | 25.6 | 25.8 | <0.001 |
| Vigorous exercise [c] | 16.0 | 15.0 | 16.8 | 24.3 | 21.2 | <0.001 |
| Obesity (%) | 28.6 | 21.7 | 37.1 | 51.7 | 53.3 | <0.001 |
| Seoul center (%) | 71.6 | 71.1 | 71.3 | 80.3 | 78.9 | <0.001 |
| Hypertension (%) | 14.9 | 9.4 | 19.9 | 48.1 | 45.8 | <0.001 |
| history of CVD | 6.0 | 5.5 | 6.0 | 14.8 | 11.6 | <0.001 |
| History of cancer (%) | 1.5 | 1.2 | 1.9 | 3.4 | 2.1 | <0.001 |
| Family history of diabetes (%) | 14.2 | 12.2 | 15.8 | 26.3 | 31.2 | <0.001 |
| Systolic BP (mm Hg) [a] | 113.0 (14.2) | 110.9 (13.2) | 115.3 (14.7) | 121.7 (15.8) | 122.7 (15.7) | <0.001 |
| Diastolic BP (mm Hg) [a] | 72.7 (9.9) | 71.4 (9.5) | 74.3 (10.2) | 77.8 (10.0) | 78.0 (9.8) | <0.001 |
| Total cholesterol (mg/dl) [a] | 192.4 (34.2) | 187.5 (32.3) | 199.2 (35.1) | 198.8 (38.9) | 206.3 (42.9) | <0.001 |
| Fasting glucose (mg/dl) | 95.1 (16.0) | 89.3 (6.2) | 99.0 (9.1) | 120.5 (19.4) | 168.1 (49.9) | <0.001 |
| HbA1c (%) | 5.6 (0.5) | 5.3 (0.2) | 5.7 (0.3) | 6.3 (0.4) | 8.3 (1.4) | <0.001 |
| LDL-C (mg/dl) [a] | 113.2 (30.7) | 108.7 (28.9) | 119.8 (31.6) | 118.1 (34.2) | 122.6 (35.5) | <0.001 |
| HDL-C (mg/dl) [a] | 55.9 (13.6) | 57.2 (13.6) | 54.5 (13.2) | 50.5 (12.4) | 48.4 (11.0) | <0.001 |
| Triglycerides (mg/dl) [d] | 96 (68–143) | 87 (63–126) | 109 (76–161) | 137 (94–200) | 159 (110–233) | <0.001 |
| AST (U/L) [d] | 22 (18–26) | 21 (18–25) | 22 (18–27) | 25 (20–32) | 26 (20–35) | <0.001 |
| ALT (U/L) [d] | 20 (14–29) | 19 (14–26) | 21 (15–32) | 26 (19–40) | 29 (21–46) | <0.001 |
| GGT (U/L) [d] | 20 (12–35) | 17 (11–29) | 23 (14–42) | 34 (20–62) | 39 (23–71) | <0.001 |
| High-sensitivity C-reactive protein (mg/L) | 0.5 (0.1–1.0) | 0.4 (0.1–0.8) | 0.5 (0.3–1.1) | 0.8 (0.4–1.6) | 1.0 (0.5–2.2) | <0.001 |
| HOMA-IR [d] | 1.66 (1.10–2.30) | 1.55 (1.03–2.08) | 1.79 (1.16–2.54) | 2.53 (1.74–3.64) | 3.51 (2.35–5.03) | <0.001 |

Abbreviations: ALT, alanine aminotransferase; BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; HDL-C, high-density lipoprotein-cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance.
[a] Data are means (standard deviation).
[b] ≥20 g/day.
[c] ≥3 times/week.
[d] Data are medians (interquartile range), or percentages.

mortality was not higher in prediabetes subjects compared with that in normoglycemic subjects.

The HR for mortality due to CVD increased slightly in diabetes subjects after adjusting for age and sex (Table 2). However, this significance was lost after adjusting for other potential confounders.

With regard to mortality due to cancer, diabetes subjects showed significantly increased HR compared with those with normoglycemia in an age–sex adjusted model and multivariable-adjusted model. The subjects with uncontrolled diabetes showed slightly lower risk for cancer mortality compared to those with controlled diabetes (Table 2).

When the HRs for mortality from all causes, CVD, and cancer were analyzed according to HbA1c quintiles in 10,950 diabetes subjects, all-cause mortality risk significantly increased more than two-fold in subjects in the highest quintile (≥8.1%) compared with those in the 3rd quintile (6.7%–7.0%) as the reference (Table 3).

The HR for mortality due to CVD and cancer did not increase in any of the HbA1c quintile groups.

The HRs for mortality from all causes were analyzed according to the HbA1c levels after excluding participants who used anti-diabetic medications. When an HbA1c level of 5.5% was used as the reference, the HR for all-cause mortality linearly increased as HbA1c increased (Table 4). The HR for all-cause mortality in subjects with HbA1c of 6.5%–6.9% and ≥7.0% was 2.02-fold and 2.73-fold significantly higher than that of subjects with HbA1c of 5.5%, respectively, after adjusting for potential confounders (Fig. 2A). Similarly, the HR for all-cause mortality in subjects with HbA1c of <5.2% was 1.45-fold higher than that of subjects with HbA1c of 5.5%. In contrast, the mortalities due to CVD and cancer did not increase significantly according to HbA1c groups in these subjects who did not take any anti-diabetic medications (Fig. 2B and C).

## 4. Discussion

In this study performed in 241,499 Korean adults, the subjects with diabetes showed significantly increased risk for all-cause mortality with subjects with uncontrolled diabetes having higher HR compared as those with controlled diabetes. The diabetes subjects showed increased risk for mortality due to cancer regardless of the glucose control status. When the risks were analyzed in HbA1c quintiles in 10,950 diabetes subjects, the risk for all-cause mortality increased 2-fold in subjects with HbA1c of >8.1% compared with the reference group with HbA1c between 6.7% and 7.0%. When the analyses

**Table 2 – Risk of death from all causes, cardiovascular disease, and cancer by glycemic status in 241,499 health checkup examinees at Kangbuk Samsung Hospital in 2005–2012.**

| | Mean (SD) of HbA1c (%) | Number of subjects | Person-years | Number of events | ID (per $10^5$ person-years) | Age- and sex-adjusted HRs (95% CI) | Model 1 adjusted HRs (95% CI) | Model 2 adjusted HRs (95% CI) |
|---|---|---|---|---|---|---|---|---|
| All-cause mortality | | | | | | | | |
| Normal | 5.33 (0.21) | 144,415 | 579,770.0 | 342 | 58.8 | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| Prediabetes | 5.71 (0.27) | 86,134 | 300,285.6 | 341 | 113.6 | 1.05 (0.90–1.23) | 1.09 (0.93–1.28) | 1.07 (0.93–1.27) |
| Controlled diabetes | 6.29 (0.44) | 6219 | 24,315.0 | 91 | 374.3 | 1.57 (1.23–2.00) | 1.68 (1.31–2.14) | 1.58 (1.24–2.03) |
| Uncontrolled diabetes | 8.34 (1.41) | 4731 | 18,971.9 | 103 | 542.9 | 2.22 (1.76–2.80) | 2.30 (1.82–2.91) | 2.26 (1.78–2.86) |
| p for trend | | | | | | <0.001 | <0.001 | <0.001 |
| Mortality due to cardiovascular disease | | | | | | | | |
| Normal | 5.33 (0.21) | 144,415 | 579,770.0 | 50 | 8.6 | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| Prediabetes | 5.71 (0.27) | 86,134 | 300,285.6 | 46 | 15.3 | 0.95 (0.63–1.43) | 0.93 (0.61–1.42) | 0.86 (0.56–1.30) |
| Controlled diabetes | 6.29 (0.44) | 6219 | 24,315.0 | 10 | 41.1 | 1.10 (0.55–2.23) | 1.14 (0.56–2.32) | 0.89 (0.43–1.83) |
| Uncontrolled diabetes | 8.34 (1.41) | 4731 | 18,971.9 | 14 | 73.8 | 1.93 (1.03–3.59) | 1.88 (1.00–3.51) | 1.57 (0.83–2.95) |
| p for trend | | | | | | 0.10 | 0.11 | 0.37 |
| Mortality due to cancer | | | | | | | | |
| Normal | 5.33 (0.21) | 144,415 | 579,770.0 | 152 | 26.2 | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| Prediabetes | 5.71 (0.27) | 86,134 | 300,285.6 | 176 | 58.6 | 1.13 (0.90–1.41) | 1.20 (0.95–1.50) | 1.21 (0.97–1.52) |
| Controlled diabetes | 6.29 (0.44) | 6219 | 24,315.0 | 47 | 193.3 | 1.62 (1.15–2.28) | 1.79 (1.27–2.53) | 1.75 (1.23–2.48) |
| Uncontrolled diabetes | 8.34 (1.41) | 4731 | 18,971.9 | 35 | 184.5 | 1.52 (1.04–2.22) | 1.63 (1.11–2.39) | 1.67 (1.13–2.45) |
| p for trend | | | | | | 0.004 | 0.001 | 0.001 |

Cox proportional hazard models were used to estimate the hazard ratios (HRs) and 95 percent confidence intervals (95% CIs); model 1 was adjusted for age, sex, study center, year of screening examination, smoking status, alcohol intake, regular exercise, and BMI; model 2 = model 1 plus history of cancer, history of cardiovascular disease, family history of diabetes, and hypertension.

were performed in 237,032 subjects after excluding those who used anti-diabetic medications, the HR for all-cause mortality significantly increased more than 2-fold in subjects with HbA1c higher than 6.5%, and increased 1.5-fold in subjects with HbA1c lower than 5.2% compared with those with HbA1c of 5.5%. Mortality risk among prediabetes subjects did not increase compared with normoglycemic subjects.

Diabetes has been known for the increased all-cause mortality. The results from UKPDS and EDIC study suggested increased risk for all-cause and diabetes-related mortality in subjects with diabetes [23,24]. Numerous studies reported similar results regarding all-cause mortality in diabetes subjects. In a recent study that analyzed data from Taiwan Triple High Survey during a median follow-up period of 9.7 years, the risk for all-cause mortality in diabetes subjects increased 2.29-fold compared with those without diabetes [25]. In another study performed in English subjects with an average follow-up period of 7 years, the risk for all-cause mortality increased 1.85-fold among subjects with uncontrolled diabetes [26]. Our results confirmed previously reported results on the significantly increased risk for all-cause mortality in diabetes subjects compared with those without diabetes irrespective of the ethnic group. Across the studies, diabetes subjects with high HbA1c or uncontrolled glucose showed increased rates of all-cause mortality, indicating the deleterious effects of hyperglycemia on the survival of diabetes subjects. In our study, the subjects with HbA1c higher than 6.5% showed more than 2-fold higher HR for all-cause mortality compared the reference group with HbA1c of 5.5% in subjects not taking anti-diabetic medications. This result suggests that HbA1c of 6.5% could be suggested as a 'threshold' for increased risk for mortality in subjects not taking anti-diabetic medications.

In our study, opposite to our expectations, subjects with prediabetes did not show significantly increased risk for mortality from any cause compared with normoglycemic subjects. This result is in contrast with those of DECODE and DECODA, which ranked the risk of mortality from all causes and from CVD between the groups with and without diabetes [7–9]. However, the two previous studies also confirmed that the increase mortality risk in the prediabetic subjects largely attributed to increased post-prandial glucose, not in subjects with impaired fasting glucose (IFG). Considering that we could have missed some of the subjects with impaired glucose tolerance, the correlation between mortality risk and prediabetes could have been weaker than that observed in subjects with prediabetes and high levels of post-prandial glucose.

Because diabetes is considered a 'vascular disease' or 'CVD equivalent', diabetes subjects show increased risk for CVD and mortality due to CVD [26–28]. The pathophysiological mechanism for the vascular damage in diabetes involves increased levels of advanced-glycation end-products generated

**Table 3 – Risk of death from all causes, cardiovascular disease, and cancer by HbA1c quintiles among 10,950 subjects with diabetes.**

| Quintiles of HbA1c | Mean (SD) of HbA1c (%) | Number of subjects | Person-years | Number of events | ID (per $10^5$ person-years) | Age- and sex-adjusted HRs (95% CI) | Model 1 adjusted HRs (95% CI) | Model 2 adjusted HRs (95% CI) |
|---|---|---|---|---|---|---|---|---|
| All-cause mortality | | | | | | | | |
| Q1 (<6.3%) | 5.33 (0.21) | 2494 | 10,437.2 | 44 | 421.6 | 1.34 (0.80–2.24) | 1.33 (0.80–2.23) | 1.30 (0.78–2.17) |
| Q2 (6.3%–6.6%) | 5.33 (0.21) | 2299 | 8460.4 | 31 | 366.4 | 1.19 (0.69–2.06) | 1.19 (0.69–2.05) | 1.21 (0.70–2.10) |
| Q3 (6.7%–7.0%) | 5.71 (0.27) | 1810 | 6931.9 | 22 | 317.4 | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| Q4 (7.1%–8.0%) | 6.29 (0.44) | 2262 | 9004.4 | 44 | 488.7 | 1.41 (0.84–2.35) | 1.36 (0.82–2.27) | 1.39 (0.83–2.33) |
| Q5 (≥8.1%) | 8.34 (1.41) | 2085 | 8453.0 | 53 | 627.0 | 2.16 (1.31–3.55) | 2.04 (1.24–3.37) | 2.10 (1.27–3.47) |
| p for quadratic term | | | | | | 0.001 | 0.002 | 0.001 |
| Mortality due to cardiovascular disease | | | | | | | | |
| Q1 (<6.3%) | 5.33 (0.21) | 2494 | 10,437.2 | 6 | 57.5 | 1.39 (0.35–5.58) | 1.41 (0.35–5.66) | 1.17 (0.29–4.72) |
| Q2 (6.3%–6.6) | 5.33 (0.21) | 2299 | 8460.4 | 1 | 11.8 | 0.28 (0.03–2.68) | 0.27 (0.03–2.58) | 0.26 (0.03–2.55) |
| Q3 (6.7%–7.0%) | 5.71 (0.27) | 1810 | 6931.9 | 3 | 43.2 | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| Q4 (7.1%–8.0%) | 6.29 (0.44) | 2262 | 9004.4 | 9 | 100.0 | 2.13 (0.58–7.88) | 2.05 (0.55–7.59) | 1.90 (0.51–7.07) |
| Q5 (≥8.1%) | 8.34 (1.41) | 2085 | 8453.0 | 5 | 59.2 | 1.55 (0.37–6.48) | 1.53 (0.36–6.45) | 1.43 (0.34–6.06) |
| p for quadratic term | | | | | | 0.598 | 0.596 | 0.595 |
| Mortality due to cancer | | | | | | | | |
| Q1 (<6.3%) | 5.33 (0.21) | 2494 | 10,437.2 | 24 | 230.0 | 1.98 (0.89–4.41) | 1.96 (0.88–4.39) | 2.00 (0.89–4.47) |
| Q2 (6.3%–6.6%) | 5.33 (0.21) | 2299 | 8460.4 | 17 | 200.9 | 1.81 (0.78–4.19) | 1.82 (0.78–4.21) | 1.88 (0.81–4.36) |
| Q3 (6.7%–7.0%) | 5.71 (0.27) | 1810 | 6931.9 | 8 | 115.4 | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| Q4 (7.1%–8.0%) | 6.29 (0.44) | 2262 | 9004.4 | 16 | 177.7 | 1.40 (0.60–3.28) | 1.38 (0.59–3.23) | 1.41 (0.60–3.31) |
| Q5 (≥8.1%) | 8.34 (1.41) | 2085 | 8453.0 | 17 | 201.1 | 1.91 (0.82–4.42) | 1.82 (0.78–4.24) | 1.89 (0.81–4.42) |
| p for quadratic term | | | | | | 0.471 | 0.564 | 0.512 |

Cox proportional hazard models were used to estimate the hazard ratios (HRs) and 95 percent confidence intervals (95% CIs); model 1 was adjusted for age, sex, study center, year of screening examination, smoking status, alcohol intake, regular exercise, and BMI; model 2 = model 1 plus history of cancer, history of cardiovascular disease, family history of diabetes, and hypertension.

by prolonged hyperglycemia, which leads to systemic inflammation and oxidative stress [29,30], and the metabolic derangements caused by insulin resistance [31]. However, the results of our study did not show any significant increase in the risk of mortality due to CVD. The reason for the discrepancy between these results could be partly explained by the relatively short duration of follow-up in this study compared with the follow-up of 8–10 years in previous studies [26,28]. Additionally, the increased incidence of CVD may not be directly associated with mortality due to CVD because of the marked development of anti-atherosclerotic treatment with excellent effects.

After the release of ACCORD and ADVANCE data in 2008, studies were focused not on the increased mortality risk in diabetic subjects with high HbA1c but in diabetic subjects with low HbA1c [1,2,4,5]. The results of a retrospective study from the UK General Practice Research Database indicated that the adjusted HR for all-cause mortality showed a U-shaped association with increased HR in diabetic subjects with low and high HbA1c [5]. Of note, the study showed that the lowest HR for all-cause mortality was observed in subjects with HbA1c of 7.5%. In another study performed in US adults without diabetes using the data from the National Health and Nutrition Examination Survey III, HbA1c of <4.0% was associated with an increased risk of all-cause mortality compared with HbA1c of 5.0–5.4% and yielded an HR of 2.9 after adjusting for confounding factors [32]. In our study, subjects with HbA1c lower than 5.2% showed significantly increased risk for all-cause mortality compared with those with HbA1c of 5.5% in subjects not taking anti-diabetic medications. This result is in line with those of a previous study in that low HbA1c could be deleterious for survival even in subjects not taking anti-diabetic medications.

The risk for cancer increases among individuals with diabetes [13,14]. The pathogenic mechanism for this association is still unclear but a plausible mechanism involves inflammatory signaling pathways and altered hormonal concentrations due to hyperglycemia and obesity [15–17]. In a recent study by de Beer et al. [11], chronic hyperglycemia as a function of HbA1c levels correlated with increased risk of different types of cancer. In another study performed in participants of the Atherosclerosis in Communities (ARIC) study, non-diabetic women with HbA1c of >5.7% showed increased risk of mortality due to cancer compared with non-diabetic participants with HbA1c of 5.0%–5.6% [12]. These authors also found that diabetic women with good glycemic control (<7.0%) had a lower risk of cancer compared with those with high glucose levels. They found that diabetic women had a higher risk of site-specific cancer mortality for postmenopausal breast cancer compared with non-diabetic women, whereas diabetic men did not have a higher risk of site-specific cancer mortality compared with non-diabetic men. The results of our study were somewhat similar to the results of previous studies in that the subjects with diabetes

**Table 4 – Risk of death from all causes, cardiovascular disease, and cancer by HbA1c levels in 237,032 health checkup examinees at Kangbuk Samsung Hospital in 2005–2012 after excluding participants who used blood glucose lowering agents.**

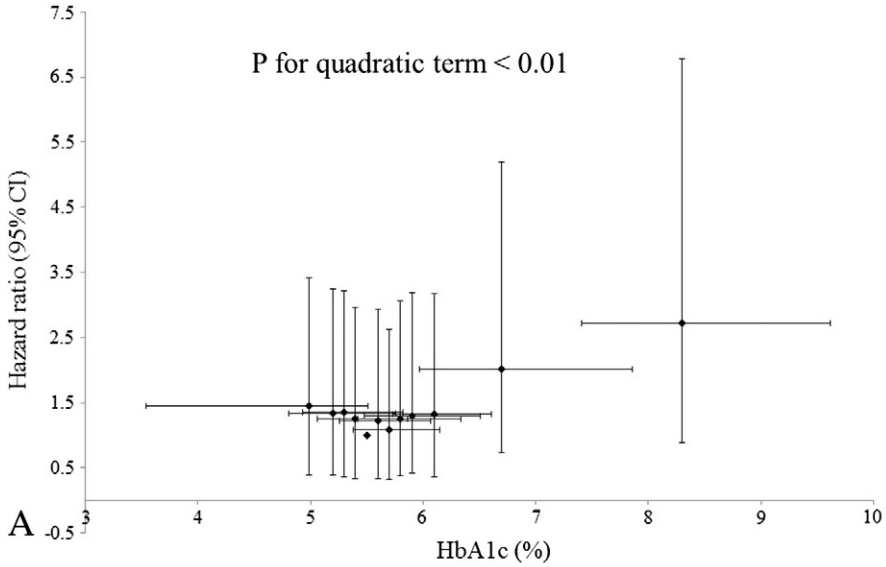
| Categories of HbA1c | Number of subjects | Person-years | Number of events | ID (per $10^5$ person-years) | Age- and sex-adjusted HRs (95% CI) | Model 1 adjusted HRs (95% CI) | Model 2 adjusted HRs (95% CI) |
|---|---|---|---|---|---|---|---|
| All-cause mortality | | | | | | | |
| <5.2% | 29,669 | 154,259.2 | 105 | 68.1 | 1.54 (1.14–2.09) | 1.48 (1.09–2.01) | 1.45 (1.06–1.97) |
| 5.2% | 20,791 | 94,604.6 | 61 | 64.5 | 1.39 (0.98–1.96) | 1.36 (0.96–1.92) | 1.34 (0.95–1.90) |
| 5.3% | 27,301 | 113,894.0 | 78 | 68.5 | 1.38 (1.00–1.91) | 1.37 (0.99–1.89) | 1.35 (0.98–1.87) |
| 5.4% | 31,707 | 120,845.0 | 84 | 69.5 | 1.27 (0.93–1.75) | 1.26 (0.92–1.73) | 1.25 (0.91–1.71) |
| 5.5% | 32,607 | 113,055.1 | 70 | 61.0 | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| 5.6% | 28,832 | 95,000.3 | 79 | 83.2 | 1.22 (0.88–1.68) | 1.23 (0.89–1.70) | 1.23 (0.89–1.70) |
| 5.7% | 22,383 | 71,098.4 | 61 | 85.8 | 1.08 (0.77–1.53) | 1.08 (0.77–1.53) | 1.09 (0.77–1.54) |
| 5.8% | 15,502 | 48,100.4 | 53 | 110.2 | 1.25 (0.87–1.79) | 1.26 (0.88–1.80) | 1.26 (0.88–1.80) |
| 5.9% | 9729 | 30,417.0 | 40 | 131.5 | 1.26 (0.85–1.86) | 1.30 (0.88–1.92) | 1.29 (0.87–1.90) |
| 6.0–6.4% | 14,092 | 47,641.7 | 83 | 174.2 | 1.29 (0.93–1.78) | 1.31 (0.95–1.82) | 1.33 (0.96–1.84) |
| 6.5–6.9% | 2070 | 7786.2 | 27 | 346.8 | 1.99 (1.27–3.11) | 2.13 (1.36–3.35) | 2.02 (1.29–3.18) |
| ≥7.0% | 2349 | 9331.4 | 40 | 428.7 | 2.72 (1.84–4.03) | 2.72 (1.83–4.03) | 2.73 (1.84–4.05) |
| p for quadratic term | | | | | <0.001 | <0.001 | <0.001 |
| Mortality due to cardiovascular disease | | | | | | | |
| <5.2% | 29,669 | 154,259.2 | 16 | 10.4 | 1.75 (0.79–3.88) | 1.69 (0.76–3.77) | 1.66 (0.74–3.73) |
| 5.2% | 20,791 | 94,604.6 | 6 | 6.3 | 1.00 (0.36–2.76) | 0.96 (0.35–2.66) | 1.00 (0.36–2.78) |
| 5.3% | 27,301 | 113,894.0 | 10 | 8.8 | 1.28 (0.53–3.07) | 1.27 (0.53–3.07) | 1.29 (0.54–3.11) |
| 5.4% | 31,707 | 120,845.0 | 12 | 9.9 | 1.28 (0.55–2.96) | 1.28 (0.55–2.95) | 1.29 (0.56–2.99) |
| 5.5% | 32,607 | 113,055.1 | 10 | 8.9 | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| 5.6% | 28,832 | 95,000.3 | 15 | 15.8 | 1.58 (0.71–3.52) | 1.59 (0.71–3.54) | 1.57 (0.70–3.49) |
| 5.7% | 22,383 | 71,098.4 | 7 | 9.9 | 0.83 (0.32–2.19) | 0.84 (0.32–2.22) | 0.85 (0.32–2.23) |
| 5.8% | 15,502 | 48,100.4 | 9 | 18.7 | 1.42 (0.58–3.51) | 1.39 (0.56–3.44) | 1.36 (0.55–3.35) |
| 5.9% | 9729 | 30,417.0 | 5 | 16.4 | 1.04 (0.35–3.06) | 1.05 (0.36–3.10) | 1.01 (0.34–2.97) |
| 6.0–6.4% | 14,092 | 47,641.7 | 10 | 21.0 | 1.01 (0.42–2.45) | 1.00 (0.41–2.42) | 0.98 (0.40–2.38) |
| 6.5–6.9% | 2070 | 7786.2 | 2 | 25.7 | 0.94 (0.21–4.32) | 1.05 (0.23–4.81) | 1.00 (0.22–4.59) |
| ≥7.0% | 2349 | 9331.4 | 7 | 75.0 | 3.04 (1.15–8.03) | 2.85 (1.07–7.54) | 2.90 (1.09–7.70) |
| p for quadratic term | | | | | 0.05 | 0.06 | 0.06 |
| Mortality due to cancer | | | | | | | |
| <5.2% | 29,669 | 154,259.2 | 36 | 23.3 | 0.94 (0.60–1.49) | 0.89 (0.56–1.40) | 0.87 (0.55–1.38) |
| 5.2% | 20,791 | 94,604.6 | 24 | 25.4 | 0.98 (0.59–1.62) | 0.95 (0.57–1.57) | 0.94 (0.56–1.56) |
| 5.3% | 27,301 | 113,894.0 | 35 | 30.7 | 1.11 (0.70–1.75) | 1.08 (0.69–1.71) | 1.07 (0.68–1.69) |
| 5.4% | 31,707 | 120,845.0 | 44 | 36.4 | 1.18 (0.77–1.82) | 1.17 (0.76–1.80) | 1.15 (0.75–1.77) |
| 5.5% | 32,607 | 113,055.1 | 39 | 34.5 | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| 5.6% | 28,832 | 95,000.3 | 36 | 37.9 | 0.97 (0.62–1.53) | 0.98 (0.62–1.55) | 0.98 (0.62–1.55) |
| 5.7% | 22,383 | 71,098.4 | 32 | 45.0 | 0.99 (0.62–1.58) | 0.99 (0.62–1.59) | 1.00 (0.62–1.60) |
| 5.8% | 15,502 | 48,100.4 | 22 | 45.7 | 0.90 (0.53–1.52) | 0.92 (0.54–1.55) | 0.92 (0.54–1.55) |
| 5.9% | 9729 | 30,417.0 | 24 | 78.9 | 1.30 (0.78–2.17) | 1.35 (0.81–2.26) | 1.31 (0.78–2.19) |
| 6.0–6.4% | 14,092 | 47,641.7 | 52 | 109.2 | 1.38 (0.91–2.10) | 1.43 (0.93–2.17) | 1.45 (0.95–2.21) |
| 6.5–6.9% | 2070 | 7786.2 | 13 | 167.0 | 1.62 (0.86–3.05) | 1.76 (0.93–3.31) | 1.58 (0.84–3.00) |
| ≥7.0% | 2349 | 9331.4 | 13 | 139.3 | 1.51 (0.80–2.84) | 1.56 (0.83–2.94) | 1.55 (0.82–2.92) |
| p for quadratic term | | | | | 0.05 | 0.04 | 0.05 |

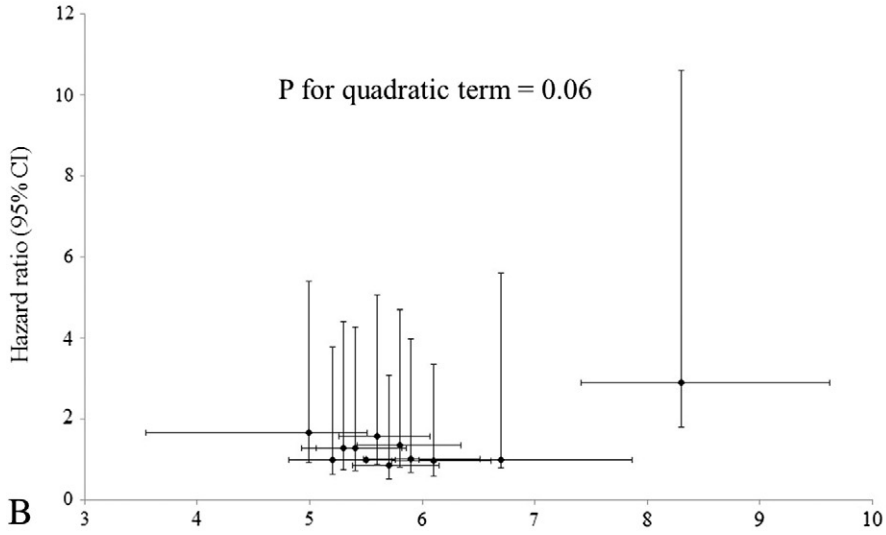
Cox proportional hazard models were used to estimate the hazard ratios (HRs) and 95 percent confidence intervals (95% CIs); model 1 was adjusted for age, sex, study center, year of screening examination, smoking status, alcohol intake, regular exercise, and BMI; model 2 = model 1 plus history of cancer, history of cardiovascular disease, family history of diabetes, and hypertension.

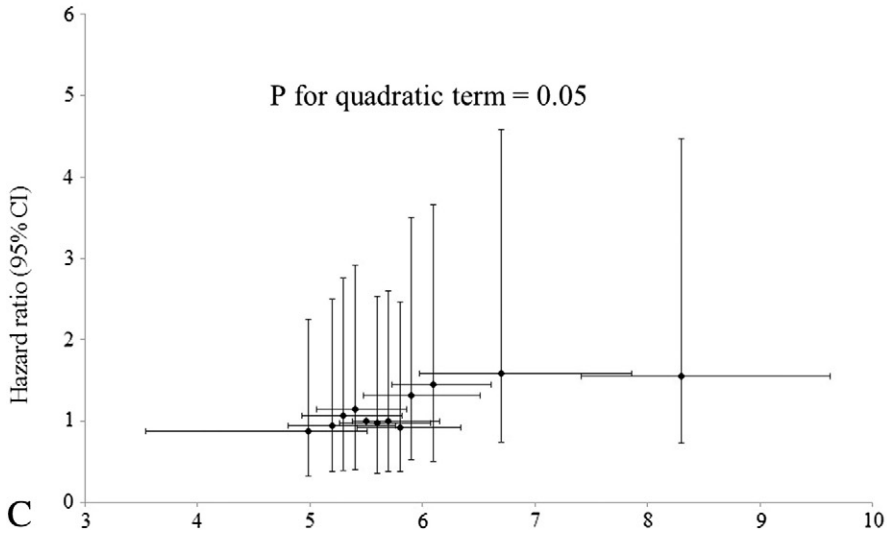
showed increased HR for mortality due to cancer, although the specific types of cancer could not be identified.

In our study, patients with uncontrolled diabetes showed lower risk for cancer mortality. The plausible reason for lower risk for cancer mortality in subjects with uncontrolled diabetes compared to those with controlled diabetes could be assumed from not increased risk for cancer mortality in subjects not taking anti-diabetic medications, suggesting the

**Fig. 2 – Adjusted hazard ratio for all-cause mortality (A), CVD mortality (B) and cancer mortality (C) by HbA1c levels in 237,032 health checkup examinees after excluding subjects on anti-diabetic medications.Cox proportional hazard models were used to estimate the hazard ratios and 95% CIs. The hazard ratios were calculated after adjusting age, sex, study center, year of screening examination, smoking status, alcohol intake, regular exercise, BMI, history of cancer, history of cardiovascular disease, family history of diabetes, and hypertension. CI, confidence interval; BMI, body mass index.**


P for quadratic term < 0.01
Hazard ratio (95% CI)
HbA1c (%)
A


P for quadratic term = 0.06
Hazard ratio (95% CI)
B


P for quadratic term = 0.05
Hazard ratio (95% CI)
C

effects of anti-diabetic medication on cancer. In the previous studies, there are still debates regarding the increased risk for cancer incidence or mortality according to the types of anti-diabetic medications used [33–36]. Therefore, lower risk for cancer mortality in subjects with uncontrolled diabetes could be explained by the possibility of less exposure of anti-diabetic medications in these patient groups compared to those with controlled diabetes. However, this is just the assumption, as the specific types of medications or cancer were not identified in our study. Anyhow, our results are in line with those of previous studies in that diabetes subjects had increased risk for mortality due to cancer.

Our study has limitations. First, prediabetes was defined only by fasting serum glucose and HbA1c but post-challenge glucose was not assessed. Therefore, the true association between IFG or impaired glucose tolerance and mortality from various causes could not be analyzed in this study. However, the performance of an oral glucose tolerance test in this large health-screening cohort was not considered cost effective [37,38]. Because the health-screening program primarily aimed to assess the health status of the participants and we simply analyzed the data from a selected population of the observational cohort, the results have to be interpreted on the basis of the nature of the study cohort. Second, the specific type of cancer causing mortality was not identified; therefore, more thorough analyses of the association between different types of cancer and diabetes could not be performed. Despite these limitations, we demonstrate for the first time that in a large number of metropolitan Asian adults, subjects with diabetes have increased risk for all-cause and cancer mortality at a relatively young age and that the HbA1c levels and mortality showed a J-shaped association with increased risk for mortality in subjects with both low and high HbA1c.

## 5. Conclusions

In conclusion, analysis of 241,499 Koreans participating in a health-screening program indicated that all-cause mortality risk significantly increased among diabetes subjects, and that HR was higher in subjects with uncontrolled diabetes. Furthermore, risk for mortality due to cancer significantly increased in diabetes subjects regardless of the glucose control status. Of note, we demonstrated for the first time in a large Korean population that subjects with HbA1c higher than 6.5% and lower than 5.2% showed significantly increased mortality risk compared with those with HbA1c of 5.5% in subjects not being treated with anti-diabetic medications.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.metabol.2015.10.005.

## Author Contributions

SY and WL had the original idea for this study and designed the study; SY analyzed the data; ER and WL wrote the manuscript; SP and YC commended on the results and helped to finish the manuscript.

## Financial Disclosure

None.

## Conflict of Interest

The authors have no relevant conflict of interest to disclose.

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