# Hematocrit, Independent of Chronic Kidney Disease, Predicts Adverse Cardiovascular Outcomes in Chinese Patients With Type 2 Diabetes

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**OBJECTIVE** — Anemia and chronic kidney disease (CKD) are risk factors for cardiovascular diseases in diabetes. We examined the association between hematocrit, stratified by the presence of CKD, and cardiovascular events in a cohort of Chinese subjects with type 2 diabetes.

**RESEARCH DESIGN AND METHODS** — A total of 3,983 patients who underwent assessment for diabetes complications were recruited. Subjects were categorized into five groups. Group I included subjects with hematocrit below the normal sex-specific range. The cutoff points for groups II–V were selected to represent the distribution of the hematocrit for each sex. CKD was defined by the estimated glomerular filtration rate <60 ml/min per 1.73 $m^2$. Cardiovascular events were defined as cardiovascular mortality and morbidity, including new onset of myocardial infarction, acute coronary syndrome, revascularization, heart failure, and stroke requiring hospitalization.

**RESULTS** — A total of 294 subjects (7.4%) developed cardiovascular events during the median of 36.4 months. The rate of cardiovascular events was highest in subjects with low hematocrit (group I, 18.6%) compared with group V (3.4%, $P < 0.001$). The multivariate-adjusted hazard ratio for cardiovascular events diminished with increasing hematocrit (group I, 1.0; group II, 0.73 [95% CI 0.51–1.04]; group III, 0.57 [0.39–0.83]; group IV, 0.61 [0.39–0.95]; and group V, 0.36 [0.17–0.79]). After stratifying by the presence of CKD, the previously observed reduction in the risk of developing cardiovascular events with increasing hematocrit was abolished in the cohort with CKD but persisted in the non-CKD cohort.

**CONCLUSIONS** — In Chinese subjects with type 2 diabetes, low levels of hematocrit and the presence of CKD are associated with increased risk of developing adverse cardiovascular events.

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**Abbreviations:** AER, albumin excretion rate; ARB, angiotesin II receptor blocker; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Diabetes is a leading cause of end-stage renal disease and cardiovascular diseases, with 60% of the global diabetic population coming from Asia (1). Approximately 26 million people are estimated to have diabetes in China (2). Growing evidence confirms the predictive role of chronic kidney disease (CKD) on cardiovascular morbidity and mortality (3,4). This is due to the constellation of conventional and nonconventional risk factors in patients who develop CKD, such as anemia, inflammation, and abnormal bone metabolism (5,6). In this regard, hematocrit is a risk factor for cardiovascular disease and all-cause mortality in patients with CKD (7), patients with left ventricular dysfunction (8), and the general population (9).

Despite the close associations between CKD and diabetes, there is a paucity of information on the relationship between levels of hematocrit, CKD, and clinical outcomes in patients with type 2 diabetes. In the present study, we examined the association between hematocrit, stratified by the presence of CKD, and the development of cardiovascular events in a cohort of Chinese type 2 diabetic subjects.

## RESEARCH DESIGN AND METHODS

— Patients with diabetes were referred from general practitioners, general medical clinics, and other specialist clinics of the hospital to the Diabetes Centre, Prince of Wales Hospital and underwent comprehensive assessment of complications and risk factors based on the European DiabCare protocol (10). Between 1995 and 2000, 4,231 patients underwent assessments with measurement of hematocrit. Patients with type 1 diabetes ($n = 248$), defined as acute presentation with diabetic ketoacidosis, heavy ketouria (>3+), or continuous requirement of insulin within 1 year of diagnosis, were excluded from this analysis. A total of 3,983 subjects were included in the final analysis. Informed consent was obtained from all patients at the time of assessment to allow use of data for re-

search purpose. The study was approved by the Chinese University of Hong Kong Clinical Research Ethics Committee.

Details of the assessment and laboratory measurement of metabolic parameters were described previously (11). Fasting plasma glucose, lipids (including total cholesterol, HDL cholesterol, triglyceride, and calculated LDL cholesterol), renal and liver functions, complete blood count, and $HbA_{1c}$ (A1C) were measured. A timed urinary collection (4 or 24 h) was obtained to document albumin excretion rate (AER) after exclusion of urinary tract infection. Nonalbuminuria was defined as urinary AER <20 μg/min. Albuminuria was defined as AER ≥20 μg/min. Estimated glomerular filtration rate (eGFR; expressed in milliliters per minute per 1.73 $m^2$) was calculated using the abbreviated Modification of Diet in Renal Disease Study Group formula (12).

$GFR = 186 \times [S_{CR} \times 0.011]^{-1.154} \times [age]^{-0.203} \times [0.742$ if female], where $S_{CR}$ is serum creatinine expressed as micromoles per liter. CKD was defined as eGFR <60 ml/min per 1.73 $m^2$ (13). In Hong Kong Chinese, the reference ranges of hematocrit for male and female individuals were ≥39 to <50 and ≥32 to <43%, respectively.

Given the bell-shaped distribution of hematocrit in the cohort, the approach of dividing the cohort into quintiles was not appropriate. It would include subjects with very different hematocrit within the same category of the quintiles. Hence, subjects were categorized into the following five groups on the basis of the sex-specific hematocrit value: group I, male <39%, female <32%; group II, male ≥39 to <43%, female ≥32 to <36%; group III, male ≥43 to <47%, female ≥36 to <40%; group IV, male ≥47 to <50%, female ≥40 to <43%; and group V, male ≥50%, female ≥43%.

Group I included subjects with hematocrit below the normal sex-specific range. The cutoff points for groups II–V were selected to represent the distribution of the hematocrit for each sex in this cohort of subjects.

On 31 December 2000, all registered patients were censored using mortality data from the Hong Kong Death Registry. Details of all medical admissions with primary and secondary diagnosis using the ICD-9 codes and last available serum creatinine results within 12 months of the date of the censor were retrieved from the Hospital Authority Central Computer System. All causes of death were further ascertained by review of case notes by an endocrinologist. Cardiovascular events were defined as cardiovascular mortality and morbidity, including new onset of myocardial infarction, acute coronary syndrome, revascularization (coronary arterial bypass grafting, percutaneous transluminal coronary angioplasty, and aorto-femoral bypass), heart failure, and stroke requiring hospitalization.

### Statistical analysis

The analysis was performed using the SPSS (version 11.5) package. Triglyceride, white blood cell count, creatinine, eGFR, and albuminuria were logarithmically transformed due to skewed distributions. All data are expressed as means ± SD or median (interquartile range), as appropriate. Student's *t* test or ANOVA was used for between-group comparisons for continuous variables and $\chi^2$ test for categorical variables. Cox multivariate regression analysis was used to examine association between CKD and hematocrit for cardiovascular events expressed as hazard ratios (HRs) and 95% CIs. Independent variables included in the model were age, sex, duration of diabetes, smoking history (current and former), BMI, mean arterial pressure, A1C, white blood cell count, HDL cholesterol, LDL cholesterol, triglyceride, and prevalent macrovascular disease. The incidence of cardiovascular events was analyzed using Kaplan-Meier analyses according to different categories of hematocrit. A *P* value <0.05 (two tailed) was considered significant.

**RESULTS** — In this study, 3,983 subjects with type 2 diabetes (mean [±SD] age 59.1 ± 13.5 years, 43.8% male) were followed for a median of 36.4 months (interquartile range 19.1–50.5). The distributions of hematocrit were lower in women than men (38.6 ± 3.8 vs. 43.3 ± 4.3%, $P < 0.001$). Table 1 compares the clinical characteristics and metabolic parameters of patients according to the five groups of hematocrit. A higher hematocrit was associated with younger age, female preponderance, a shorter duration of diabetes, lower systolic blood pressure, and lower AER. In contrast, subjects with hematocrit below the normal range (group I) had lower BMI, triglyceride, LDL cholesterol, and eGFR compared with individuals with higher hematocrit. Furthermore, lower hematocrit was associated with higher frequencies of smoking, vascular complications, and the use of ACE inhibitors or angiotesin II receptor blockers (ARBs) at baseline.

During the study period, 294 subjects (7.4%) developed cardiovascular events. The rate was highest in group I (18.6%) and decreased progressively with increasing value of hematocrit (group II 9.6%, group III 5.6%, group IV 5.2%, and group V 3.4%, $\chi^2 = 93.3$, $P < 0.001$).

The group of subjects with hematocrit less than the sex-specific normal range for Hong Kong Chinese (group I) was used as the reference group in the analysis of the association between hematocrit and cardiovascular events. After adjustment for age and other confounding factors, there was a reduction in HRs for cardiovascular events in subjects of group III (0.57 [95% CI 0.39–0.83], $P = 0.03$), group IV (0.61 [0.39–0.95], $P = 0.029$), and group V (0.36 [0.17–0.79], $P = 0.01$) compared with group I (Fig. 1). The cumulative event-free probability of cardiovascular outcomes is shown in Fig. 2. The curves separate and continue to diverge throughout the study period (log-rank score = 391, $P < 0.001$).

The relationship between the risk of developing cardiovascular events and hematocrit was further analyzed by stratification of each category of hematocrit into those with or without CKD (Table 2). For subjects with CKD, the previously observed reduction in the risk of developing cardiovascular events with increasing hematocrit was abolished by the presence of CKD. Among those without CKD, there were further reductions in the risk of cardiovascular events with increasing hematocrit compared with those with hematocrit below the normal range (group I). When the association was examined with hematocrit as a continuous variable, hematocrit was not selected as an independent predictor of cardiovascular events for subjects with CKD. In contrast, higher hematocrit was associated with a lower risk of developing cardiovascular events (HR 0.92 [95% CI 0.88–0.96], $P < 0.001$) in the non-CKD cohort.

**CONCLUSIONS** — This study demonstrates that hematocrit is associated with the development of adverse cardiovascular outcomes in Chinese patients with type 2 diabetes. After adjustment for other cardiovascular risk factors, the risk of developing cardiovascular events was highest among subjects with hematocrit below the normal range and decreased with increasing hematocrit. The presence of CKD eliminated the protective effect of

**Table 1—*Baseline clinical and biochemical characteristics of 3,983 Chinese type 2 diabetic patients stratified according to their baseline hematocrit values***

| | Group I | Group II | Group III | Group IV | Group V |
|---|---|---|---|---|---|
| *n* | 366 | 809 | 1,612 | 904 | 292 |
| Male | 66.4 | 58.5 | 43.9 | 28.0 | 22.6* |
| Ex- or current smoker | 43.8 | 34.2 | 27.6 | 21.2 | 28.6* |
| Use of ACE inhibitors or ARB treatment | 17.8 | 16.1 | 12.4 | 9.0 | 8.6* |
| Age (years) | 66.6 ± 12.2 | 66.2 ± 12.7† | 58.0 ± 13.2† | 56.5 ± 13.3† | 54.8 ± 13.5† |
| Duration of diabetes (years) | 10.2 ± 7.2 | 8.7 ± 6.7‡ | 7.1 ± 6.4† | 6.0 ± 6.0† | 5.5 ± 5.5† |
| BMI (kg/m$^2$) | 23.9 ± 3.5 | 24.7 ± 4.1§ | 25.1 ± 3.9† | 25.5 ± 4.0† | 25.2 ± 4.1† |
| Waist circumference (cm) | | | | | |
| Male | 86.0 ± 9.4 | 87.9 ± 10.3 | 88.2 ± 9.6§ | 89.5 ± 9.4‡ | 87.7 ± 8.5 |
| Female | 82.4 ± 10.4 | 83.4 ± 10.2 | 83.1 ± 9.8 | 83.9 ± 10.0 | 83.2 ± 9.6 |
| Systolic blood pressure (mmHg) | 144 ± 24 | 138 ± 22† | 135 ± 21† | 135 ± 20† | 135 ± 20† |
| Diastolic blood pressure (mmHg) | 76 ± 13 | 76 ± 11 | 77 ± 11 | 79 ± 11† | 80 ± 11† |
| Mean arterial pressure (mmHg) | 99 ± 15 | 96 ± 13§ | 96 ± 13§ | 98 ± 13 | 99 ± 13 |
| A1C (%) | 7.49 ± 1.80 | 7.63 ± 1.82 | 7.74 ± 1.79 | 7.87 ± 1.84‡ | 8.38 ± 2.10† |
| Fasting plasma glucose (mmol/l) | 8.52 ± 6.57 | 8.71 ± 3.77 | 8.78 ± 3.13 | 9.16 ± 3.36§ | 10.00 ± 3.79† |
| Total cholesterol (mmol/l) | 5.03 ± 1.32 | 5.21 ± 1.22† | 5.41 ± 1.20† | 5.58 ± 1.08† | 5.74 ± 1.20† |
| HDL cholesterol (mmol/l) | | | | | |
| Male | 1.20 ± 0.38 | 1.18 ± 0.34 | 1.17 ± 0.31 | 1.18 ± 0.32 | 1.13 ± 0.28 |
| Female | 1.25 ± 0.39 | 1.26 ± 0.41 | 1.33 ± 0.36 | 1.34 ± 0.35 | 1.36 ± 0.36 |
| LDL cholesterol (mmol/l) | 3.07 ± 1.00 | 3.26 ± 1.05‡ | 3.35 ± 0.91† | 3.50 ± 0.95† | 3.62 ± 1.01† |
| Triglycerides (mmol/l) | 1.2 (0.9–1.9) | 1.3 (0.9–2.0) | 1.4 (1.0–2.0) | 1.4 (1.0–2.2)§ | 1.4 (1.0–2.2)§ |
| Serum creatinine (μmol/l) | | | | | |
| Male | 107 (85–154) | 89 (78–105)† | 83 (74–94)† | 83 (73–92)† | 83 (72–89)† |
| Female | 105 (66–213) | 77 (60–101)† | 64 (56–76)† | 62 (56–72)† | 63 (55–71)† |
| Mean hematocrit (%) | | | | | |
| Male | 35.6 ± 3.3 | 41.2 ± 1.1† | 44.9 ± 1.2† | 48.1 ± 0.8† | 51.3 ± 1.3† |
| Female | 29.2 ± 2.7 | 34.4 ± 1.1† | 38.1 ± 1.1† | 41.2 ± 0.9† | 44.4 ± 1.3† |
| White blood cell count (10$^9$/l) | 7.0 (6.0–8.7) | 6.9 (5.7–8.2) | 6.8 (5.0–8.0) | 7.2 (6.2–8.5) | 7.6 (6.4–9.0) |
| eGFR (ml/min per 1.73 m$^2$) | 62 (36–88) | 79 (61–97)† | 91 (75–107)† | 94 (80–109)† | 94 (81–110)† |
| AER (μg/min) | 105 (16–1310) | 34 (11–185)† | 17 (9–72)† | 16 (8–56)† | 17 (9–54)† |
| Micro- and macroalbuminuria | 66.9 | 52.9 | 37.2 | 36.2 | 37.1* |
| Retinopathy | 48.9 | 34.5 | 22.8 | 18.1 | 18.2* |
| Neuropathy | 56.5 | 40.1 | 29.5 | 25.6 | 21.3* |
| Macrovascular disease | 30.3 | 19.8 | 11.8 | 10.2 | 8.6* |
| CKD | 48.2 | 24.1 | 9.9 | 6.5 | 5.9* |

Data are percent, means ± SD, or median (interquartile range). Group I hematocrit values: male <39%, female <32%; group II: male ≥39 to <43%, female ≥32 to <36%; group III: male ≥43 to <47%, female ≥36 to <40%; group IV: male ≥47 to <50%, female ≥40 to <43%; and group V: male ≥50%, female ≥43%. *$P < 0.001$ by $\chi^2$ test. †$P < 0.001$, ‡$P < 0.01$, §$P < 0.05$ vs. group I.

higher hematocrit on future cardiovascular events. These results indicate that hematocrit and CKD coalesce to modulate the development of cardiovascular outcomes in Chinese patients with type 2 diabetes.

In the present cohort, subjects with hematocrit below the lower limit of the normal range (group I) were less obese, had better glycemic control, and had more favorable lipid profiles compared with those with normal hematocrit. Despite the apparently better metabolic profile, subjects with low hematocrit had higher rates of diabetes complications at baseline and increased risk of developing cardiovascular events at follow-up. The paradoxical association between conventional cardiovascular risk factors and the presence of diabetes complications are not inconsistent with the concept of reverse epidemiology, a phenomenon that is commonly observed in patients with CKD (14–16). Furthermore, impaired renal function will cause a reduction in the clearance of insulin and oral antidiabetes agents, resulting in improved glycemic control. The lower BMI and cholesterol levels could be related to a degree of malnutrition, which is common among subjects with impaired renal function.

The association between CKD and adverse cardiovascular events is well recognized (3,4,6,8,17). Effective erythropoiesis is dependent on the production of erythropoietin by the kidneys. Thus, low hematocrit or anemia could be a proxy for CKD. Furthermore, prolonged use of ACE inhibitors, and to some extent ARBs, has been associated with reduction in hemoglobin (18–20). The higher percentage of ACE inhibitor or ARB treatment in subjects with low hematocrit may therefore confound the association between hematocrit and adverse cardiovascular events. However, hematocrit remained an independent predictor for cardiovascular events after adjustment for CKD, albuminuria, and other conventional risk factors, as well as the use of ACE inhibitors or ARB treatment (Table 2). Taken to-

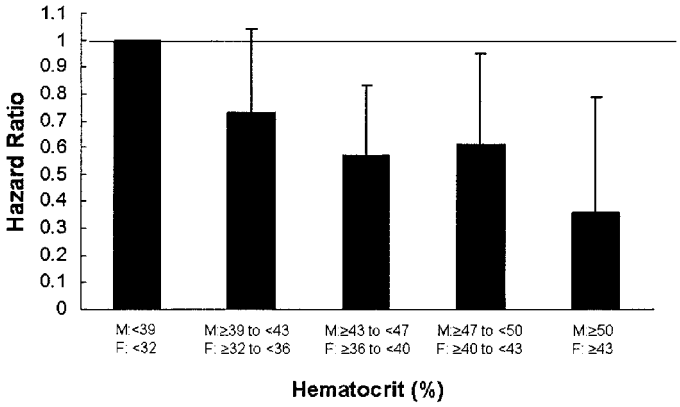


**Figure 1—***Hazard ratios of cardiovascular events according to categories of hematocrit levels in 3,983 Chinese type 2 diabetic patients after a median follow-up period of 3 years using Cox regression analysis. Covariates included age, sex, duration of diabetes, smoking, BMI, mean arterial pressure, HDL cholesterol, LDL cholesterol, triglycerides, A1C, white blood cell count, use of ACE inhibitors or ARB treatment at baseline, prevalent macrovascular diseases, and CKD (defined as eGFR <60 ml/min per 1.73 m$^2$). F, female; M, male.*

gether, our results indicate that low hematocrit may exert an independent effect on the development of cardiovascular events, at least in Chinese subjects with type 2 diabetes.

Anemia is a common finding in subjects with diabetes. About 20% of ambulatory patients with type 2 diabetes were noted to have anemia (hemoglobin <130 g/l in men and <120 g/l in women) (21). Previous studies have shown that low hematocrit value was a risk factor for cardiovascular disease in the general population, in patients with CKD, and in patients with heart failure (7,8). Anemia is also associated with increased risk of retinopathy in a cross-sectional survey involving diabetic patients in Finland (22). In patients with known CKD, reduced levels of hemoglobin, even within the normal range, identify patients at increased risk for further progression of renal disease including Asian type 2 diabetic patients (23–25). In this connection, anemia has now been shown to be an independent risk factor for cardiovascular events not only in subjects with kidney disease (7) and those with left ventricular dysfunction (8) but also in the general population (9). In a meta-analysis of community-based population studies, anemia interacts with CKD to increase the risk of coronary heart disease, stroke, and all-cause mortality among subjects with diabetes (26). In the present study, our results confirm the independent association of hematocrit with cardiovascular events, regardless of the presence of CKD, in subjects with type 2 diabetes.

Several mechanisms may contribute to the association between low hematocrit and adverse clinical outcomes. First, low hematocrit may predispose to chronic myocardial hypoxia, left ventricular dilatation and dysfunction, and lead to increased frequency of cardiovascular disease (17,27–29). Second, anemia is associated with increased oxidative stress since erythrocytes are a major antioxidant component in the blood (30). Third, low–molecular weight advanced glycation end products are associated with declining hemoglobin in type 2 diabetic patients with normal renal function (31). Indeed, correction of anemia in both diabetic and nondiabetic patients with CKD has been shown to reduce hospitalization rate and hospital stay (32,33). Given the high prevalence of anemia and CKD in our diabetic population, there is a need to conduct interventional studies to examine whether optimization of the internal milieu, including correction of anemia, will reduce cardiovascular and renal risk (34).

There are limitations in an observational study. First, the duration of follow-up was relatively short. Nevertheless, the number of cardiovascular events was enough to reveal differences in the predictive power of different categories of hematocrit. Second, there may be selection bias in recruiting patients from a single

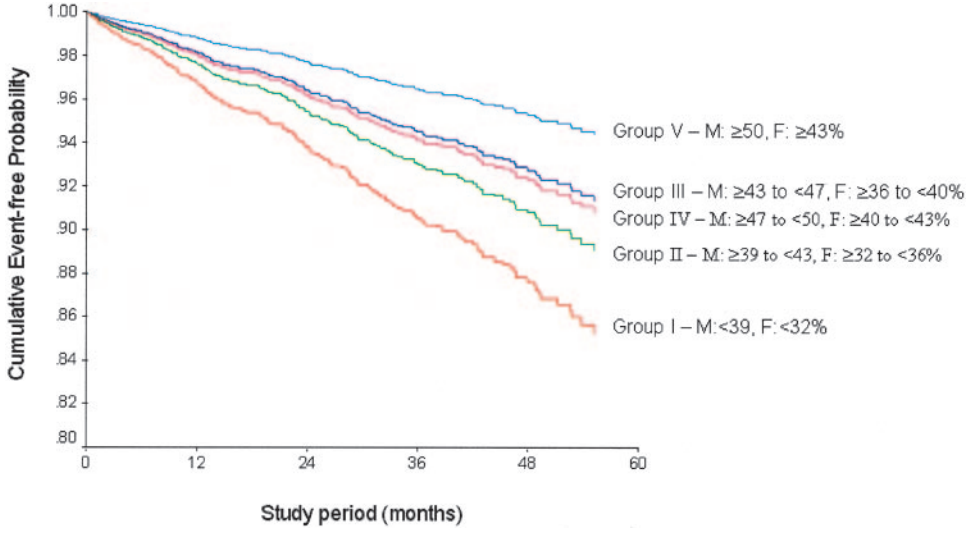


**Figure 2—***Kaplan-Meier curves of cardiovascular events among Chinese type 2 diabetic patients according to categories of hematocrit. Covariates included age, sex, duration of diabetes, smoking, BMI, mean arterial pressure, HDL cholesterol, LDL cholesterol, triglycerides, A1C, white blood cell count, use of ACE inhibitors or ARB treatment at baseline, prevalent macrovascular diseases, and CKD (defined as eGFR <60 ml/min per 1.73 m$^2$). F, female; M, male.*

**Table 2—*Multivariate-adjusted HRs (95% CIs) of cardiovascular events in patients with type 2 diabetes stratified according to hematocrit and CKD defined as eGFR <60 ml/min per 1.73 m$^2$***

| | Group I | Group II | Group III | Group IV | Group V |
|---|---|---|---|---|---|
| With CKD | | | | | |
| *n* | 176 | 195 | 160 | 58 | 17 |
| HR (95% CI) | 1.00 | 1.37 (0.86–2.18) | 0.83 (0.46–1.50) | 0.97 (0.44–2.14) | 0.99 (0.29–3.33) |
| *P* value | Ref. | 0.187 | 0.538 | 0.943 | 0.985 |
| Without CKD | | | | | |
| *n* | 189 | 613 | 1,450 | 841 | 272 |
| HR (95% CI) | 1.00 | 0.37 (0.22–0.63) | 0.37 (0.23–0.60) | 0.39 (0.23–0.69) | 0.20 (0.07–0.53) |
| *P* value | Ref. | <0.001 | <0.001 | 0.001 | 0.001 |

Group I hematocrit values: male <39%, female <32%; group II: male ≥39 to <43%, female ≥32 to <36%; group III: male ≥43 to <47%, female ≥36 to <40%; group IV: male ≥47 to <50%, female ≥40 to <43%; and group V: male ≥50%, female ≥43%. Covariates included age, sex, duration of diabetes, smoking, BMI, mean arterial pressure, HDL cholesterol, LDL cholesterol, triglycerides, A1C, white blood cell count, use of ACE inhibitors or ARB treatment at baseline, and prevalent macrovascular diseases.

center. In Hong Kong, most patients with chronic diseases including diabetes are managed at public hospitals. Hence, the present cohort is a representative sample of Chinese patients with diabetes in Hong Kong. Lastly, all covariates were measured once at baseline. The variability of measurements may lead to underestimation of the confounding effect of covariates on outcomes. Nonetheless, our results demonstrated the benefit of having these measurements on a single occasion in identifying high-risk subjects in clinical practice.

In conclusion, low levels of hematocrit and the presence of CKD are associated with increased risk of developing adverse cardiovascular events. While these findings call for routine monitoring of hematocrit in subjects with type 2 diabetes to identify high-risk subjects for cardiovascular complications, interventional studies are required to confirm the causal nature of these associations.

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P.C.Y.T. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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