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Peripheral monocyte count is an independent predictor of all-cause mortality in type 2 diabetes with macro-vascular complications

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Abstract

The relationship between monocyte count and mortality seemed to be varied in different diseases, and it remains unclear in type 2 diabetes (T2D). We conducted a prospective study to investigate whether monocyte count predict all-cause mortality in patients with T2D.

In this prospective study, a total of 1073 patients with T2D were enrolled at baseline and 880 patients completed the follow up. The median follow-up time was 47 months. At baseline, clinical characteristics including height, weight, waist circumference, blood pressure were recorded. Biochemical parameters including counts of white blood cells (WBCC), neutrophil (NC) and monocyte (MC), lipid profiles, glycated hemoglobin (HbA1c), serum creatinine were measured. Charlson comorbidity index (CCI) was calculated based on age and comorbidities. Participants were stratified into low, median, and high tertiles according to the baseline MC. Regression models were used to analyze the associations of peripheral MC and the all-cause mortality.

Compared to the survived subjects, the baseline MC was significantly higher in patients who deceased during the follow-up (0.45 ± 0.16 vs $0.37 \pm 0.15 \times 10^9$/L, $P = .003$). In the multivariate Cox hazard models, subjects in higher MC tertile showed higher risks of all-cause mortality (low tertile as the reference, hazard ratio [HR] 95%CI 2.65 [0.84,8.31] and 3.73 [1.14,12.24] for middle and high MC tertile, respectively) after adjusted for gender, body mass index, CCI, duration of T2D, history of hypertension and metabolic syndrome, drugs, levels of high-sensitivity C-reactive protein, systolic blood pressure, HbA1c, WBCC, and NC. In T2D patients with macro-vascular complications at baseline, 1-SD increment of MC resulted in 1.92-fold higher risk of all-cause mortality. However, the relationship disappeared in subjects without macro-vascular complications at baseline (1.13 [0.72, 1.78], $P = .591$).

Peripheral monocyte count is an independent predictor of all-cause mortality in T2D, especially for subjects with macro-vascular complications.

Abbreviations: ACEi = angiotensin converting enzyme inhibitor, ARBs = angiotensin receptor blockers, BMI = body mass index, CCI = Charlson comorbidity index, CHD = coronary heart disease, Cr = creatinine, DBP = diastolic blood pressure, DKD = diabetic kidney disease, DPN = diabetic peripheral neuropathy, DR = diabetic retinopathy, eGFR = estimated glomerular filtration rate, HbA1c = glycated hemoglobin, HDL-c = high-density lipoprotein cholesterol, hs-CRP = high-sensitivity C-reactive protein, HT = hypertension, LDL-c = low-density lipoprotein cholesterol, Neutrophil (%) = neutrophils percentage, OAD = oral antidiabetic drugs, PAD = peripheral arterial disease, SBP = systolic blood pressure, T2D = type 2 diabetes, TC = total cholesterol, TG = triglyceride, WBCC = white blood cell, WC = waist circumference.

Keywords: all-cause mortality, monocyte count, type 2 diabetes

1. Introduction

The prevalence of diabetes has increased substantially in recent decades.[1–3] Compared to subjects without diabetes, patients with diabetes had a two-fold higher risk of all-cause mortality. Apart from cardiovascular diseases, diabetes was also associated with increased mortality from non-cardiovascular diseases such

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as cancer and infection.[4] Exploring risk factors of all-cause mortality is important for diabetes management.

Monocyte is the largest type of leukocyte, and it can differentiate into macrophage and myeloid lineage dendritic cell. The main functions of monocyte (including macrophage and dendritic-cell) include phagocytosis, antigen presentation, and cytokine production. Previous studies suggested that monocyte count was an independent predictor of death in elderly adults, patients with hemodialysis or cervical cancer, and patients admitted to the emergency department.[5–8] However, a prospective study showed that monocyte count was not associated with all-cause mortality in females.[9] Another study enrolled patients with acute decompensated heart failure. After adjustment for baseline potential confounders, monocyte count was not predictive of all-cause mortality, cardiovascular mortality or heart failure hospitalization. But patients with increased monocyte count tended to have an increased ejection fraction and were less likely to have a history of diabetes or coronary revascularization.[10] Roles of monocytes are complicated, and the relationship between monocyte count and mortality seemed to be varied in different diseases.

In patients with diabetes, the role of monocyte count remains undetermined. A cross-sectional study found that in subjects with type 2 diabetes (T2D), monocyte count was positively correlated with intima-media thickness of the common carotid artery (CCA-IMT), which is a sign of macro-vascular complications.[11] Another study enrolled 134 diabetic patients with severe coronary artery disease, and the result showed that an increased circulating monocyte count was significantly associated with a good coronary collateral growth,[12] which is a protective factor of cardiovascular disease and death.[13]

Considering these inconsistent results, we established a prospective study to investigate the relationship between monocyte count and all-cause mortality in patients with T2D.

2. Materials and methods

2.1. Study design and participants

This study was conducted at the First Affiliated Hospital of Chongqing Medical University, China, from June 2013 to December 2018 (Chongqing Diabetic Registry, NCT03692884). Type 2 diabetes was diagnosed based on an oral glucose tolerance test or the medical records. Patients with T2D and agreed to participate in the follow-up were included. Exclusion criteria: individuals with age <20 or >85; individuals with hs-CRP > 5 mg/L; severe heart failure (New York Heart Association Class III–IV); severe liver impairment (liver enzyme ALT ≥ 3-fold the upper limit of normal range); severe renal dysfunction (estimated glomerular filtration rate [eGFR] < 15 mL/min/1.73 m^2). This study was approved by the ethical committee of the First Affiliated Hospital of Chongqing Medical University, and all procedures were performed in accordance with our local guidelines and clinical regulations.

Informed consent was obtained from all participants at baseline. Of the 1073 T2D patients recruited at baseline, 156 participants were lost and 37 withdraw during the follow-up. A total of 880 patients completed the follow-up, with a median time of 47 months. The flow chart of study population is shown in Figure 1.

2.2. Clinical procedures and laboratory measurements

Medical and social history were collected and recorded. The Charlson comorbidity index (CCI)[14] was calculated, incidence of metabolic syndrome[15] was recorded. All subjects underwent physical anthropometry measurements including height, weight, waist circumference (WC), systolic blood pressure (SBP), and diastolic blood pressure (DBP). Body mass index (BMI) was calculated by dividing weight by the square of height. After fasting for at least 8 h overnight, all patients underwent fasting vein blood collection the next morning and were sent to the laboratory within 1 h after blood collection. Blood routine was tested by automatic hematology analyzer (Sysmex xt-4000). Total leukocyte count and its subtypes (including monocyte count) were measured. Automatic enzyme analyzer (model 7080; Hitachi, Tokyo, Japan) were used to determined serum lipid, including total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-c) and low-density lipoprotein cholesterol (LDL-c). The reagent was purchased from Leadman

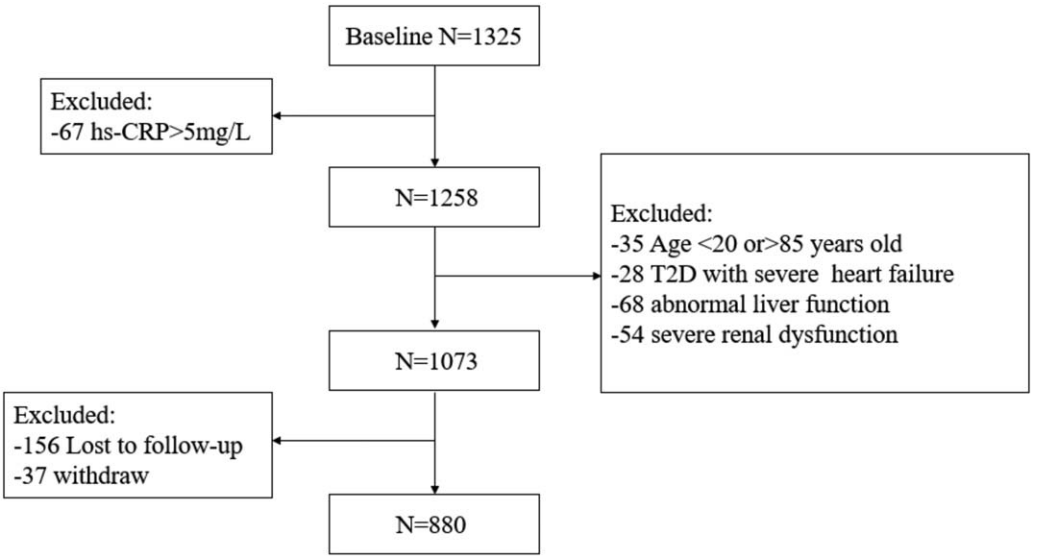

Figure 1. Flow chart of study population.

Biochemistry Co., LTD. (Beijing, China). Glycated hemoglobin (HbA1c) was determined by boric acid affinity high performance liquid chromatography (Trinity Biotech, ultra-2, Trinity Biotech, Dublin, Ireland). Serum creatinine (Cr) was tested by automatic biochemical analyzer (modular DDP, Roche).

2.3. Chronic diabetic complications assessment

The evaluation for chronic diabetic complications included diabetic peripheral neuropathy (DPN), diabetic retinopathy (DR) and diabetic kidney disease (DKD), peripheral arterial disease (PAD), coronary heart disease (CHD), and stroke. The history of CHD was defined according to previous coronary angiography results or experienced physician's diagnosis. The history of stroke was defined as cerebral hemorrhage or cerebral infarction in the past. Other evaluation methods of chronic complications were described in previous publications.[16,17] DKD, DPN, and DR were classified as micro-vascular complications. CHD, PAD and stroke were classified as macro-vascular complications.

2.4. Primary outcome

The primary outcome is the all-cause mortality, which is defined as any causes of death and determined by discharge records and death records of patients. The occurrence and timing of all cause death were collected during follow-up.

2.5. Statistical analysis

SPSS 22.0 statistical software was used for data analysis. The measurement data was represented by mean ± standard deviation (SD), and the counting data were represented by number and percentage. Independent sample t test or Pearson Chi-square test was used for the comparison between two groups. After parameters were standardized by *z*-score, univariate Cox regression analyses were used to evaluate the correlation between parameters and death. Participants were stratified into tertiles according to low, median, and high by baseline monocyte count. Multivariable Cox regression analyses were used for the evaluation of all-cause mortality and monocyte count tertiles. *P* values of <.05 was considered statistically significant.

3. Results

A total of 880 patients were included for the final analysis. After a median follow-up of 47 months, 33 participants died. The main causes of death were cardiovascular diseases (11 patients), cancer (7 patients), and renal failure (4 patients).

At baseline, compared to the survived group, the deceased group was older and showed a higher ratio of CHD history (36.36% vs 14.59%, $P=.001$), stroke history (24.24% vs 9.88%, $P=.001$), and increased levels of SBP (144.18 ± 20.47 vs 137.33 ± 19.55 mm Hg, $P=.049$), serum creatinine (102.03 ± 48.01 vs 75.74 ± 28.73 μmol/L, $P=.005$), neutrophilic granulocyte percentage (66.59 ± 9.73% vs 63.09 ± 8.99%, $P=.031$), CCI (6.52 ± 1.86 vs 4.78 ± 1.81, $P<.001$), and monocyte count (0.45 ± 0.16 vs 0.37 ± 0.15 × 10^9/L, $P=.003$). However, there was no significant difference between the two groups in the ratio of metabolic syndrome and the use of angiotensin converting enzyme inhibitor/angiotensin receptor blockers (ACEi/ARBs) and insulin (Table 1).

In the univariate Cox regression analysis, parameters such as an increased monocyte count (HR 1.44 95%CI [1.16–1.79]), elder (3.30 [2.17–5.1]), and history of CHD (3.27 [1.61–6.65]) were shown to be significantly associated with a higher risk of all-cause mortality. In T2D patients with macro-vascular complication, monocyte count was also a risk factor of all-cause mortality (1.92 [1.28–2.89]). However, the relationship between monocyte count and all-cause mortality disappeared in patients without macro-vascular complications (1.13 [0.72–1.78]) (Table 2).

Table 1

Comparison of baseline characteristics by all-cause mortality.

	Deceased (n = 33)	Survived (n = 847)	*P*
Male gender	25 (75.75%)	491 (57.76%)	.041
Age (years)	73.61 ± 7.69	63.93 ± 9.16	<.001
History of CHD	12 (36.36%)	124 (14.59%)	.001
History of stroke	8 (24.24%)	84 (9.88%)	.016
History of HT	24 (72.73%)	541 (63.72%)	.290
Alcohol consumption	12 (36.36%)	287 (33.96%)	.775
Smoking	18 (54.55%)	326 (38.67%)	.067
Duration of T2D (year)	12.21 ± 9.03	9.67 ± 6.85	.12
BMI (kg/m^2)	24.17 ± 3.65	25.09 ± 3.13	.102
SBP (mm Hg)	144.18 ± 20.47	137.33 ± 19.55	.049
DBP (mm Hg)	76.64 ± 10.22	78.14 ± 11.60	.464
HbA1c (%)	8.22 ± 2.08	8.32 ± 2.19	.791
Cr (μmol/L)	102.03 ± 48.01	75.74 ± 28.73	.005
hs-CRP (mg/L)	1.86 ± 1.96	1.54 ± 1.91	.367
WBCC (×10^9/L)	6.41 ± 1.46	6.36 ± 1.48	.856
Neutrophil (×10^9/L)	4.33 ± 1.48	4.05 ± 1.23	.209
Neutrophil (%)	66.59 ± 9.73	63.09 ± 8.99	.031
Monocyte (×10^9/L)	0.45 ± 0.16	0.37 ± 0.15	.003
TC (mmol/L)	4.29 ± 1.02	4.22 ± 1.10	.721
TG (mmol/L)	1.76 ± 1.07	1.86 ± 1.62	.742
HDL-C (mmol/L)	1.13 ± 0.48	1.15 ± 0.34	.785
LDL-C (mmol/L)	2.62 ± 0.88	2.56 ± 0.94	.722
CCI	6.52 ± 1.86	4.78 ± 1.81	<.001
Metabolic syndrome	25 (75.8%)	587 (69.3%)	.429
Treatment with ACEi/ARBs	18 (54.5%)	424 (53.6%)	.915
Treatment with insulin	20 (60.6%)	493 (62.3%)	.842
Treatment with OAD	28 (84.8%)	728 (86.3%)	.797

Data are mean ± SD or %.

ACEi = angiotensin converting enzyme inhibitor, ARBs = angiotensin receptor blockers, BMI = body mass index, CCI = Charlson comorbidity index, CHD = coronary heart disease, Cr = creatinine, DBP = diastolic blood pressure, HbA1c = glycosylated hemoglobin, HDL-C = high density lipoprotein cholesterol, hs-CRP = high-sensitivity C-reactive protein, HT = hypertension, LDL-C = low density lipoprotein cholesterol, OAD = oral antidiabetic drugs, SBP = systolic blood pressure, T2D = type 2 diabetes, TC = total cholesterol, TG = triglyceride, WBCC = white blood cell.

In the multivariable Cox regression analyses, model 1 was unadjusted; model 2 adjusted for gender, BMI; model 3 adjusted for model 2+ CCI, metabolic syndrome, History of HT, duration of T2D, ACEi/ARBs, insulin, oral antidiabetic drugs (OAD), hs-CRP, SBP, HbA1C, WBCC, neutrophils percentage. Compared to patients in the low tertile of monocyte count (as reference), patients in higher baseline monocyte count tertiles showed higher risks of all-cause mortality (2.65 [0.84,8.31] for middle tertile; 3.73 [1.14,12.24] for high tertile) after adjusted for multiple confounders (model 3) (Table 3 and Fig. 2A). The results of subgroup analyses were similar with the univariate Cox regression analyses for monocyte count (Fig. 2B).

4. Discussion

In this prospective study, we are the first to report that a higher peripheral monocyte count is independently associated with an increased risk of all-cause mortality in patients with T2D,

Table 2

Univariate analyses of Cox regression models for predicting all-cause mortality in the type 2 diabetes total population and the subgroups of type 2 diabetes with/without macro-vascular disease.

Univariate	(total T2D) Hazard ratio (95% CI)	P	(T2D with macro-vascular disease) Hazard ratio (95% CI)	P	(T2D without macro-vascular disease) Hazard ratio (95% CI)	P
Gender	1.49 (1.00–2.21)	.051	0.33 (0.11–1.01)	.053	0.55 (0.17–1.72)	.3
Age	3.30 (2.17–5.1)	<.001	1.93 (1.14–3.25)	.014	3.76 (2.07–6.83)	<.001
History of CHD	3.27 (1.61–6.65)	.001	1.07 (0.40–2.84)	.898	–	–
History of stroke	2.90 (1.31–6.44)	.009	1.04 (0.41–2.63)	.939	–	–
History of HT	1.50 (0.70–3.23)	.3	0.99 (0.29–3.42)	.986	1.07 (0.38–3.00)	.901
Duration of T2D	1.39 (1.02–1.89)	.037	1.81 (1.20–2.73)	.004	0.69 (0.38–1.24)	.214
SBP	1.39 (1.02–1.91)	.039	1.46 (0.94–2.25)	.092	1.15 (0.70–1.88)	.582
HbA1c	0.95 (0.67–1.35)	.782	1.24 (0.83–1.88)	.298	0.74 (0.41–1.35)	.327
Monocyte	1.44 (1.16–1.79)	.001	1.92 (1.28–2.89)	.002	1.13 (0.72–1.78)	.591
CCI	2.52 (1.65–3.08)	<.001	1.43 (0.92–2.22)	.110	2.43 (1.49–3.95)	<.001
Cr	1.50 (1.25–1.79)	<.001	1.44 (1.05–1.97)	.024	1.46 (1.15–1.86)	.002
WBCC	1.05 (0.74–1.49)	.776	1.65 (1.02–2.69)	.043	0.55 (0.32–0.95)	.031
Neutrophil (%)	1.54 (1.06–2.23)	.022	2.13 (1.24–3.65)	.006	1.02 (0.62–1.69)	.929
LDL-C	1.06 (0.75–1.50)	.736	1.40 (0.88–2.22)	.151	0.89 (0.52–1.52)	.665

CCI = Charlson comorbidity index, CI = confidence interval, Cr = creatinine, CHD = coronary heart disease, HT = hypertension, LDL-C = low-density lipoprotein cholesterol, SBP = systolic blood pressure, T2D = type 2 diabetes, WBCC = white blood cell.

Table 3

Multivariable Cox regression analyses of all-cause mortality according to the tertile of monocyte groups.

Model	Low HR (95%CI)	Median HR (95%CI)	P	High HR (95%CI)	P
1	Reference	2.06 (0.70,6.03)	.187	3.49 (1.29,9.47)	.014
2	Reference	2.19 (0.75,6.43)	.153	3.53 (1.29,9.69)	.014
3	Reference	2.65 (0.84,8.31)	.095	3.73 (1.14,12.24)	.030

Model 1. Unadjusted; Model 2. Adjusted for gender, BMI; Model 3. Adjusted for Model 2+ Charlson Comorbidity Index, metabolic syndrome, history of HT, duration of T2D, ACEi/ARBs, insulin, OAD, hs-CRP, SBP, HbA1c, WBCC, neutrophils percentage.

ACEi = angiotensin converting enzyme inhibitor, ARBs = angiotensin receptor blockers, BMI = body mass index, CI = confidence interval, HbA1c = glycated hemoglobin, HR = hazard ratio, HT= hypertension, hs-CRP = high-sensitivity C-reactive protein, OAD = oral antidiabetic drugs, SBP = systolic blood pressure, T2D = type 2 diabetes, WBCC = white blood cell.

especially for those with macro-vascular complication. These findings remained the same when adjusted for potential confounders such as gender, BMI, CCI, metabolic syndrome, history of HT, duration of T2D, ACEi/ARBs, insulin, OAD, hs-CRP, SBP, HbA1C, WBCC, neutrophils percentage. Our findings point out that monocyte count may be a predictor of all-cause mortality in patients with T2D.

Cardiovascular mortality and cancer mortality are the leading causes of death in patients with diabetes. A cross-sectional study recruited 484 patients with T2D, and the results showed that monocyte counts were positively correlated with both mean CCA-IMT and maximum CCA-IMT, a sign of atherosclerosis.[11] Other studies suggested that a higher level of circulating monocyte count was not only associated with increased risks of cardiovascular diseases,[18–20] but also related to the incident and mortality of cancer.[21] Furthermore, different studies showed that monocyte count was an independent predictor of death in elderly adults, in patients with hemodialysis or cervical cancer, and in patients admitted to the emergency department.[5–8] Consistent with those studies, our data found monocyte count to be significantly associated with all-cause mortality after adjusted for potential confounders.

It should be noticed that functions of monocytes are complicated, and the relationship between monocyte counts and mortality seemed to be varied in different diseases. A prospective study, which enrolled 8447 participants from Taiwan, revealed a positive association between monocyte count and mortality from all diseases, cancers and CVD in men, while none of those relationship existed in women.[9] Nevertheless, in the post hoc analysis of the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST), patients with higher monocyte count showed an increased ejection fraction and a decreased risk for diabetes, hypercholesterolemia, or coronary revascularization. Monocyte count was not significantly associated with all-cause mortality or cardiovascular mortality after adjustment for potential confounders.[10] Furthermore, in diabetic patients with severe CHD, an increased circulating monocyte count was significantly associated with a good coronary collateral growth which is a protective factor of cardiovascular disease and death.[12] It seemed that a higher monocyte count may contribute a good prognostic value to diabetic patients, which is inconsistent with other populations such as elderly adults and patients with hemodialysis.

In our study, an increased monocyte count was associated with all-cause mortality in T2D with macro-vascular complication, but not in T2D without macro-vascular complication. On one hand, as an increment of monocyte count led to an increased CCA-IMT[11] and a good coronary collateral growth[12] in patients with diabetes, monocyte may displayed detrimental and protective roles in T2D at the same time. In contrast, compared to patients without macro-vascular complication, the number of death in patients with macro-vascular complication was much higher (18 out of 181 [9.9%] vs 15 out of 641 [2.3%], $P < .001$), so the relationship between monocyte count and all-cause

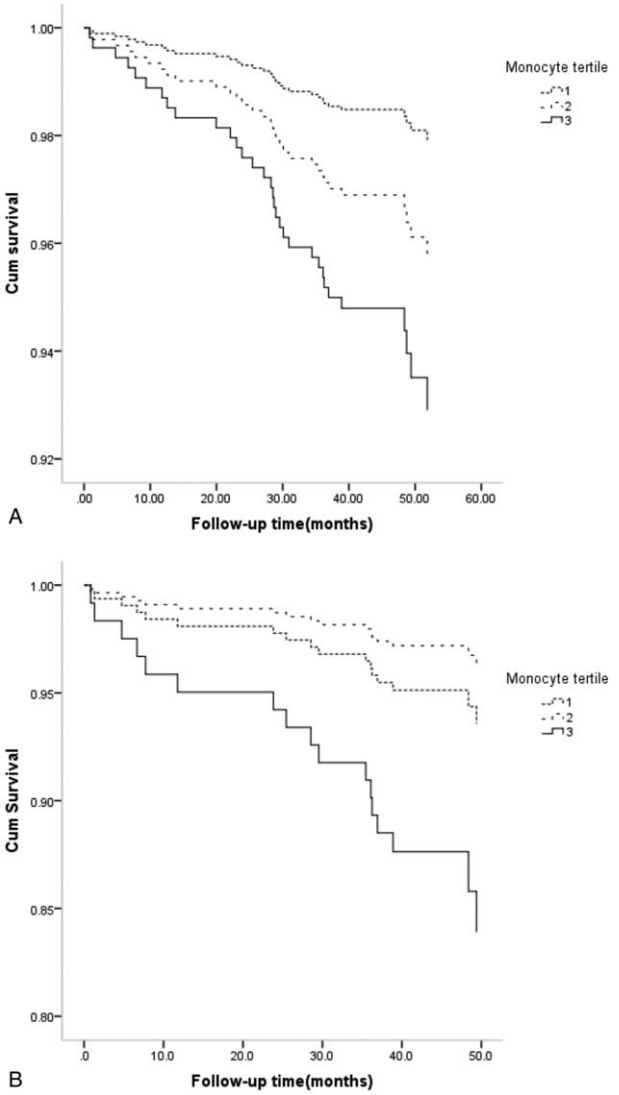

Figure 2. Survival curve of all-cause mortality by monocyte tertile groups in the type 2 diabetes total population (A) and the subgroup with macro-vascular disease (B).

mortality may be more notable. Complicated functions of monocyte and a lower number of death in patients without macro-vascular complication in our study may account for the inconsistent results between T2D with and without macro-vascular complication.

Some limitations need to be mentioned. In the present study, the median follow-up time was not long (47 months) and the number of death was not large (33 people), especially in T2D without macro-vascular complication. The relationship between monocyte count and specific cause of death could not be analyzed because of the limited follow-up time and the number of death. Furthermore, this study was conducted in one Chinese medical center, so the selection bias was inevitable.

5. Conclusions

In conclusion, peripheral monocyte count predicts all-cause mortality in patients with T2D, especially for T2D with macro-vascular complication. These findings should be verified in more prospective studies conducted among different populations.

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Author contributions

L.N.Y. and J.B.H. designed the study, oversaw the data collection, and wrote the manuscript. Z.H.W. and X.J.C. conducted the data analysis and contributed to the writing of the manuscript. Y.W. and S.M.Y. contributed to the study design, provided statistical expertise, and contributed to the writing of the manuscript. T.L. and M.M. contributed to the writing of the manuscript. Q.F.C. and Z.X.X. assisted with the data collection, and contributed to the writing and editing of the manuscript. Z.P. D. and L.L.G. assisted with the data collection. R.L. and Q.F.L. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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