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Association between Hemoglobin–albumin–lymphocyte–platelet score and all-cause or cardiovascular mortality in patients with diabetes or prediabetes: mediated effects of renal function

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Abstract

Objective Hemoglobin–albumin–lymphocyte–platelet (HALP) score is considered to be a comprehensive indicator of inflammation and nutrition. We aimed to investigate the relationship of HALP score and the risk of all-cause and cardiovascular disease (CVD) mortality in patients with diabetes (DM) or prediabetes (PDM).

Methods 6,869 participants with DM or PDM from the National Health and Nutrition Examination Survey (NHANES) 2005 to 2018 were enrolled. The colleration of HALP score with all-cause and CVD mortality was evaluated using Kaplan-Meier, Cox regression and restricted cubic spline (RCS) methods. The predictive value of HALP score for mortality was evaluated by time-dependent-receiver-operating-characteristic (ROC) curves. Finally, subgroup and interaction analysis were performed.

Results 1203 deaths from all-cause and 399 deaths from CVD were observed. Cox regression analyses showed that the HALP score was negatively correlated with both all-cause and CVD mortality risk. RCS curves showed a nonlinear relationship between HALP score and all-cause or CVD mortality risk, and both the dose-response curves are L-shaped. For all-cause mortality risk, the AUC was 0.805, 0.799, and 0.816 for 3, 5, and 10 years survival, respectively, and for CVD mortality risk, the AUC was 0.839, 0.850, and 0.837 for 3, 5, and 10 years of survival, respectively. Mediation analysis showed that serum creatinine and urea nitrogen partially mediate the relationship between HALP and mortality risk.

Conclusion HALP score is negatively correlated with all-cause and CVD mortality risk, and serves as a valuable predictor of all-cause and CVD mortality risk in patients with DM or PDM.

Clinical trial number Not applicable.

Keywords Hemoglobin–albumin–lymphocyte–platelet, Diabetes mellitus, Prediabetes mellitus, All-cause mortality, Cardiovascular mortality

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Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder that significantly contributes to the development of cardiovascular disease (CVD), which remains the leading cause of death globally [1]. In 2019, over 250 million people were diagnosed with DM, and CVD accounted for more than 6.5 million deaths worldwide [2]. Individuals with DM or prediabetes (PDM) are at an elevated risk of both CVD-related and all-cause mortality [3, 4]. In 2018, mortality rates from all causes and CVD in male DM patients were 27.8 and 7.5 per 1,000 person-years, respectively, compared to 29.5 and 7.1 per 1,000 person-years for females [5]. These statistics highlight the urgent need to identify strategies that can mitigate the risk of CVD in individuals with DM.

Diabetic patients have a higher risk of CVD, with their inherent glucose metabolism abnormality being an independent risk factor for CVD. Other traditional factors such as hypertension (HTN), lipid metabolism disorders, and smoking also increase the risk of CVD in diabetic patients [6], recent research suggests that inflammation plays a crucial role in the progression of both DM and CVD D [7, 8]. Chronic low-grade inflammation is now recognized as a key factor that exacerbates the risk of CVD events in diabetic patients [7]. Several inflammatory markers, such as the monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), and systemic immune-inflammation index (SII), have been identified as potential biomarkers for assessing inflammation in DM and PDM [7, 9, 10]. These markers correlat with an increased risk of CVD and poor clinical outcomes. Specifically, NLR and PLR have been associated with the severity of coronary artery disease and patient outcomes [11–13], and MLR has been linked to cardiac insufficiency in U.S. adults [14]. However, while these markers offer valuable insight into inflammation and CVD risk, they do not assess nutritional status, which also significantly influences clinical outcomes, a retrospective study shows that malnutrition increases the risk of death by 69% in diabetic patients, and this risk exceeds that of other chronic diseases such as heart failure and chronic kidney disease [15], another study showed that moderate to severe malnutrition increased the risk of all-cause mortality and CVD mortality in patients with DM or PDM after adjusting for confounding factors such as age, subgroup analysis further suggested that this relationship remained significant in diabetic or prediabetic patients under 65 years of age [16].

The hemoglobin–albumin–lymphocyte–platelet (HALP) score is a novel, easily calculated index that integrates both inflammatory and nutritional status [17]. It has been shown to be a strong predictor of survival in patients with various cancers, such as esophageal [18], gastric [19], prostate [20], breast [21] and renal cell carcinoma [22]. A recent study has also demonstrated that HALP can be used as a marker for the brief assessment of diabetic nephropathy [23]. In addition, the HALP score has been associated with improved survival outcomes in the general population [17]. Despite its utility as an indicator of inflammation and nutritional status, the HALP score has not been extensively studied in patients with DM or PDM. Although the HALP score is not a modifiable risk factor like traditional lifestyle interventions (e.g., diet, exercise), it serves as a comprehensive marker of disease status and could potentially inform risk stratification and patient management.

This study aims to investigate the association between the HALP score and the risk of all-cause and CVD mortality in individuals with DM or PDM, using data from the National Health and Nutrition Examination Survey (NHANES). Through this research, we hope to provide further insight into the prognostic value of the HALP score in this high-risk population.

Subjects and methods

Data sources

Data were extracted from subjects participating in NHANES from 2005 to 2018, which was designed to assess the metabolic health of adults and children in the U.S. The National Center for Health Statistics (NCHS) and the Ethics Review approved the NHANES protocol, and all participants provided written informed consent [24].The research procedures for all subjects adhered to the ethical standards outlined in the 1964 Declaration of Helsinki and its subsequent revisions. A detailed description is available at https://www.cdc.gov/nchs/nhanes/.

Subjects

Participants were excluded if they were under 20 years of age or lacked data on inflammatory indices or covariates. While NHANES does not explicitly exclude individuals with transient acute conditions, its community-based sampling framework minimizes the inclusion of hospitalized or acutely ill individuals which is consistent with the intended use of the HALP score in non-acute populations [17]. After applying these rigorous exclusion criteria, a total of 6,869 participants were enrolled in this study (Fig. 1 presents the STROBE flowchart).

Assessment of diabetes and prediabetes

Subjects were defined as suffering from PDM if they met any of the follows criteria: a previous diagnosis of PDM with or without 100 mg/dL ≤ fasting plasma glucose (FPG) < 126 mg/dL and 5.7% ≤ glycosylated hemoglobin (HbA1c) < 6.5%. Subjects were defined as suffering from DM if they met any of the follows criteria: previous

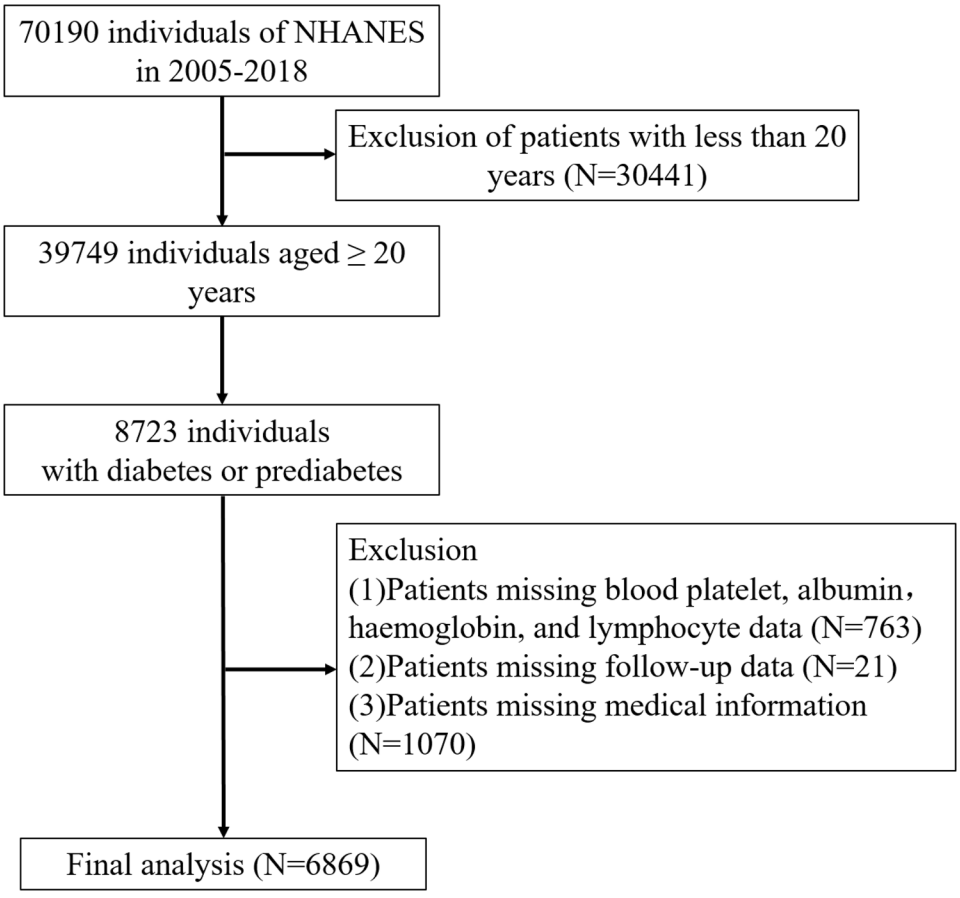

Fig. 1 Flowchart of the study design

use of oral hypoglycemic drugs, FPG ≥ 126 mg/dL, and HbA1c ≥ 6.5% [25].

Assessment of HALP score and study participants grouping

HALP = (hemoglobin (g/L) × albumin (g/L) × lymphocytes (10^9/L))/ platelets (10^9/L).

The participants were categorized into the Q1, Q2, Q3 and Q4 groups according to the HALP quartiles.

Data collection

The study collected data from the NHANES database, including gender, age, height, weight, BMI, poverty income ratio (PIR), race, education levels, with or without HTN, smoking status, drinking alcohol, and married status. Smoking status was defined as "Not at all," "Former," or "now". Drinking alcohol was categorized as "Not at all," "Former," "Mild," "Moderate," or "Severe" based on previous literature [25].

In addition, aspartate-aminotransferase (AST), alanine-aminotransferase (ALT), gamma- glutamyltransferase (GGT), hemoglobin, albumin, total protein (TP), triglycerides (TG), cholesterol (Chol), high-density-lipoprotein-cholesterol (HDL-C), serum creatinine (SCr), blood urea nitrogen (BUN), uric acid (UA), total bilirubin (TB), lactate dehydrogenase (LDH), HbA1c, and FPG were collected and recorded.

Outcome measurements

Death from CVD was defined as CVD mortality. The outcome indicators of the study were all-cause and CVD mortality. Survival data were collected from the NHANES public-use linked mortality file, as of 31 December 2019,and were linked to the NCHS and the National Death Index (NDI) using a probability matching algorithm.

Statistical methods

Each analysis was performed using the R software (version 4.3.3). Based on NHANES guidelines, sample weights, clustering and stratification were performed. Categorical variables were presented as frequency and percentages, while continuous variables were reported using the mean ± standard deviations or medians (first quartile and third quartile) as appropriate for the variable type, and differences were compared using chi-square tests, one-way analysis of variance, and Kruskal-Wallis test, respectively.

Differences in survival rates among subjects in Q1, Q2, Q3, and Q4 groups were assessed using Kaplan-Meier curves. The association of HALP score with mortality was evaluated using Cox regression models. Model 1 was unadjusted for covariates, while model 2 was adjusted for gender, race, and age. Model 3 was adjusted for gender, race, age, education level, smoking status, drinking alcohol, married status, with or without HTN, BMI, PIR, TG, Chol and HDL-C [25].

Furthermore, the dose-response relationship of HALP score with all-cause or CVD mortality in participants was assessed by the restricted cubic spline (RCS) curve, with four knots. A two-step Cox regression model was used to explain the nonlinearity between all-cause and CVD mortality and HALP score. Subgroup and interaction analyses were conducted to further examine the sensitivity of the association of HALP score with all-cause and CVD mortality.

Mediation analysis was performed using the "mediation" package in R. Survival models were constructed using the "surverg" function, with the seed was randomized to 1234. Mediated effects were estimated through a quasi-Bayesian approach with 100 simulations to account for the uncertainties in the estimates.

Results

Baseline characteristics of weighted participants

The baseline characteristics table (Table 1) provides valuable insights into the demographics and health indicators of the study population. The weighted and unweighted sample sizes for each characteristic are reported. Significant differences were observed in variables such as age, BMI, AST, ALT, GGT, TP, TG, HDL, SCR, BUN, UA, STB, LDH, and gender distribution across the four quartiles (Q1-Q4). Moreover, notebal variations were found in the prevalence of HTN, smoking status, education levels, married status, and diabetes status across the quartiles. Additionally, the mortality and survival rates significantly differed among the quartiles. These findings highlight the importance of accounting for these baseline characteristics when analyzing the study's outcomes.

Relationship between HALP score and mortality risk in participants with DM or PDM

Participants in the Q1 group had significantly higher risk of all-cause and CVD mortality compared to those in the Q2, Q3, and Q4 groups (all $p < 0.05$) (Fig. 2A and B).

When HALP score was treated as a continuous variable, Cox regression analysis showed that HALP score was negatively correlated with all-cause mortality risk in Model 3 (hazard ratio (HR) = 0.997, 95% confidence interval (CI) [0.995, 0.999], $p = 0.004$). When HALP score was treated as a categorical variable, compared to the Q1 group, the adjusted HR for all-cause mortality risk in the Q2, Q3 and Q4 groups were 0.567, 0.591, and 0.578, respectively, in Model 3. The p-value for trend was below 0.05. (Table 2)

Similarly, when HALP score was treated as a continuous variable, Cox regression analysis showed that HALP score was negatively correlated with CVD mortality risk in Model 3 (HR = 0.992, 95% CI [0.987, 0.996], $p < 0.001$). When the HALP score was treated as a categorical variable, compared to the Q1 group, the adjusted HR for CVD mortality risk in the Q2, Q3, and Q4 groups were 0.393, 0.571, and 0.431, respectively, in Model 3. The p-value for trend was below 0.05. (Table 2)

Dose-response relationship between HALP score and all-cause and CVD mortality risk in patients with PDM or DM

After adjusting for gender, race, age, drinking alcohol, smoking status, education levels, with or without HTN, BMI, married status, PIR, TG, Chol, and HDL-C. The RCS curves revealed L-shaped dose-response relationships between HALP score and both all-cause and CVD mortality risk. Inflection point analysis showed that the inflection points for the curves for all-cause and CVD mortality were at HALP scores of 52 and 49, respectively (both p for nonlinear relationship < 0.05) (Fig. 2C and D). Additionally, two-segment Cox regression analysis indicated a negative correlation between the HALP score and the risk of all-cause mortality for HALP score less than 52, and with the risk of CVD mortality for HALP score less than 49 (HR = 0.964 and 0.940, respectively). (Table 3).

We further analyzed the nonlinearity of HALP score in relation to all-cause and CVD mortality risk in prediabetic and diabetic populations.

In patients with PDM, the dose-response curve for the HALP score and all-cause mortality risk was L-shaped, with an inflection point at 58. However no significant correlation was found between the HALP score and the risk of CVD mortality (Fig. 3A and B).

In patients with DM, both the dose-response curves for HALP score and all-cause and CVD mortality risk were L-shaped, with inflection points at a HALP score of 50. (Figure 3C and D).

Predictive power of HALP score for all-cause and CVD mortality in participants with DM or PDM

Time-dependent receiver-operator characteristic curves (ROC) showed that when the HALP score was combined with other covariates to predict the risk of all-cause mortality, the areas under the curves (AUC) at 3, 5, and 10 years were 0.805, 0.799, and 0.816, respectively. (Fig. 4A). For CVD mortality, the AUCs at 3, 5, and 10 years were 0.839, 0.850, and 0.837, respectively. (Fig. 4C). Moreover, time-dependent AUC curves demonstrated the strong predictive power of the HALP score for both all-cause

Table 1 Baseline characteristics of weighted participants

Characteristic	Hemoglobin-albumin-lymphocyte-platelet score				*P*
	Q1 Weighted *N* = 55,509,646 Unweighted *n* = 1,717[1]	Q2 Weighted *N* = 62,645,900 Unweighted *n* = 1,715[1]	Q3 Weighted *N* = 59,870,976 Unweighted *n* = 1,719[1]	Q4 Weighted *N* = 60,506,572 Unweighted *n* = 1,718[1]	
Age	59 ± 15	58 ± 14	56 ± 14	56 ± 14	< 0.001[1]
BMI	33 ± 9	33 ± 8	33 ± 7	32 ± 7	0.501[1]
PIR	2.46 (1.31, 4.56)	2.92 (1.46, 5.00)	3.06 (1.49, 5.00)	2.64 (1.34, 4.60)	< 0.001[2]
HbA1c	6.30 (5.70, 7.00)	6.20 (5.70, 7.10)	6.30 (5.70, 7.30)	6.40 (5.70, 7.50)	0.061[2]
Aspartate Aminotransferase (U/L)	22 (18, 26)	23 (19, 27)	23 (19, 28)	24 (20, 31)	< 0.001[2]
Alanine Aminotransferase (U/L)	19 (15, 26)	22 (17, 29)	24 (18, 32)	25 (19, 35)	< 0.001[2]
Gamma Glutamyl Transferase (IU/L)	20 (14, 33)	22 (16, 33)	25 (17, 38)	27 (18, 42)	< 0.001[2]
Total protein (g/dL)	7.00 ± 0.51	7.05 ± 0.46	7.11 ± 0.44	7.16 ± 0.46	< 0.001[1]
Triglycerides (mg/dL)	135 (92, 197)	141 (94, 215)	158 (108, 229)	172 (113, 255)	< 0.001[2]
Cholesterol (mg/dL)	185 ± 51	188 ± 43	191 ± 44	189 ± 45	0.007[1]
HDL-C (mmol/L)	1.33 ± 0.39	1.30 ± 0.37	1.26 ± 0.42	1.18 ± 0.34	< 0.001[1]
Serum creatinine (mg/dL)	0.87 (0.72, 1.10)	0.86 (0.71, 1.02)	0.86 (0.73, 1.01)	0.89 (0.75, 1.02)	0.140[2]
Blood Urea Nitrogen (mg/dL)	15 (11, 20)	14 (11, 18)	14 (11, 18)	14 (11, 18)	0.028[2]
Uric acid (mg/dL)	5.66 ± 1.67	5.62 ± 1.50	5.72 ± 1.41	5.75 ± 1.43	0.046[1]
Total Bilirubin (mg/dL)	0.60 (0.40, 0.70)	0.60 (0.40, 0.80)	0.60 (0.40, 0.80)	0.60 (0.40, 0.80)	< 0.001[2]
Lactate Dehydrogenase (IU/L)	138 (119, 161)	133 (116, 153)	131 (115, 150)	134 (116, 153)	0.002[2]
Gender					< 0.001[3]
Female	37.0%	44.3%	50.4%	65.0%	
Male	63.0%	55.7%	49.6%	35.0%	
Race					< 0.001[3]
Mexican American	6.8%	7.7%	9.3%	11.0%	
Other Hispanic	5.2%	5.4%	6.3%	5.7%	
Non-Hispanic White	62.9%	66.9%	63.9%	63.5%	
Non-Hispanic Black	17.6%	11.5%	11.7%	10.8%	
Other Race	7.5%	8.5%	8.7%	8.9%	
Drinking status					< 0.001[3]
Not at all	14.6%	12.9%	10.5%	11.0%	
Former	23.2%	20.6%	21.1%	18.6%	
Mild	33.0%	32.3%	33.2%	29.3%	
Moderate	8.1%	12.2%	11.3%	8.9%	
Severe	21.1%	22.1%	23.9%	32.2%	
Smoking status					< 0.001[3]
Not at all	52.1%	55.5%	49.7%	44.0%	
Former	36.0%	33.9%	33.9%	31.7%	
Now	11.9%	10.6%	16.4%	24.3%	
Education levels					0.073[3]

Table 1 (continued)

Characteristic	Hemoglobin-albumin-lymphocyte-platelet score				*P*
	Q1 Weighted *N* = 55,509,646 Unweighted *n* = 1,717[1]	Q2 Weighted *N* = 62,645,900 Unweighted *n* = 1,715[1]	Q3 Weighted *N* = 59,870,976 Unweighted *n* = 1,719[1]	Q4 Weighted *N* = 60,506,572 Unweighted *n* = 1,718[1]	
Less than high school	19.9%	17.1%	18.9%	20.6%	
High school or Some College or AA degree	56.7%	55.0%	55.3%	57.5%	
College Graduate above	23.4%	27.9%	25.8%	21.9%	
Married status					0.087[3]
Married/Living with partner	50.4%	55.7%	58.2%	54.9%	
Widowed/Divorced/Separated	41.7%	37.4%	34.4%	36.9%	
Never Married	8.0%	6.9%	7.4%	8.2%	
Hypertension					0.130[3]
With hypertension	63.2%	59.8%	57.4%	58.2%	
Without hypertension	36.8%	40.2%	42.6%	41.8%	
All-cause mortality					< 0.001[3]
Survival	77.2%	87.5%	87.7%	89.0%	
Death	22.8%	12.5%	12.3%	11.0%	
Carviovascular mortality					< 0.001[3]
Survival	91.7%	96.9%	95.6%	96.8%	
Death	8.3%	3.1%	4.4%	3.2%	
Prediabetes or Diabetes					0.002[3]
Prediabetes	24.5%	30.7%	30.7%	24.9%	
Diabetes	75.5%	69.3%	69.3%	75.1%	

BMI = body mass index, PIR = poverty income ratio, HbA1c = glycosycated haemoglobin, HDL-C = high density lipoprotein- cholesterol

[1]One-way ANOVA

[2]Kruskal-Wallis rank sum test

[3]Pearson's Chi-squared test

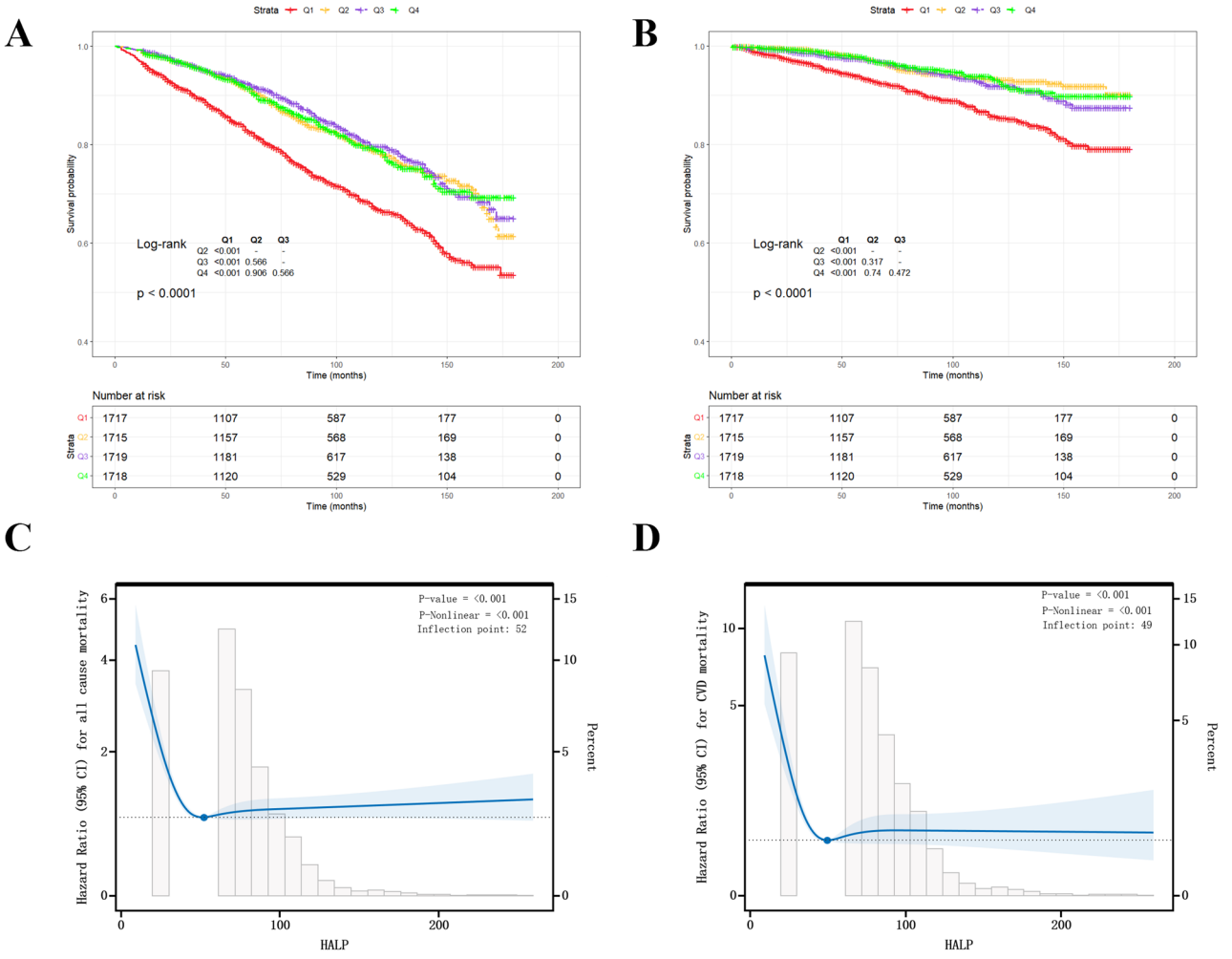

Fig. 2 Association between HALP score and the risk of mortality in participants with diabetes or prediabetes. **A**: Kaplan-Meier curve for all-cause mortality, **B**: Kaplan-Meier curve for CVD mortality, **C**: The nonlinear relationship between the HALP score and all-cause mortality, **D**: The nonlinear relationship between the HALP score and CVD mortality. Adjusted for gender, race, age, drinking alcohol, smoking status, education levels, with or without HTN, BMI, married status, PIR, TG, Chol and HDL-C. HALP, hemoglobin–albumin–lymphocyte–platelet; CVD, cardiovascular disease; BMI, body mass index; PIR, poverty income ratio; TG, triglyceride; Chol, cholesterol, HDL-C, high-density lipoprotein- cholesterol

and CVD mortality at different time intervals (Fig. 4B and D).

Subgroup and interaction analysis

To assess the effects of other factors on the relationship between HALP score and all-cause or CVD mortality. Subgroups were categorized based on gender, age, BMI, race, education levels, drinking alcohol, smoking status, with or without HTN, married status, and PDM or DM. The analysis revealed a stronger correlation between HALP score and the risk of all-cause mortality in patients under 65 years of age, with BMI ≥ 30 kg/m², or those with HTN, after adjusting for covariates. Similarly, the HALP score showed a stronger association with CVD mortality in individuals aged under than 65 years and with BMI ≥ 30 kg/m², although the differences in correlation strength between subgroups were not statistically significant. Additionally, the results indicated a stronger correlation between the HALP scores and both all-cause and CVD mortality risk in diabetic patients compared to prediabetic patients, although the *p*-values for interaction were both above 0.05 (Fig. 5A and B).

Analysis of mediation effects

Renal function indicators, including SCr and BUN, were found to significantly mediate the relationship between the HALP score and all-cause mortality, Specifically, SCr mediated 10.1% of the total effect (coefficient = 0.0637, 95% CI: 0.0340, 0.0904, $p < 0.001$), while BUN mediated 47.9% of the total effect (coefficient = 0.215, 95% CI: 0.145, 0.280, $p < 0.001$) (Fig. 6A and B). A similar mediation effect was observed in the association between HALP score and CVD mortality, with SCr mediating 3.9% of the total effect (coefficient = 0.116, 95% CI: 0.059,

Table 2 Association between HALP score and all-cause or CVD mortality in participants with diabetes or prediabetes

			Model1			Model 2			Model3		
	N	**Event *N***	**HR[1]**	**95% CI[1]**	***P***	**HR[1]**	**95% CI[1]**	***P***	**HR[1]**	**95% CI[1]**	***P***
All-cause mortality											
HALP (continuous)	6,869	1,203	0.996	0.994, 0.999	0.003	0.998	0.996, 1.000	0.038	0.997	0.995, 0.999	0.004
HALP (standardized)	6,869	1,203	0.884	0.815, 0.958	0.003	0.932	0.871, 0.996	0.038	0.898	0.833, 0.967	0.004
HALP (quartile)											
Q1	1,717	453	—	—		—	—		—	—	
Q2	1,715	261	0.576	0.495, 0.671	< 0.001	0.558	0.479, 0.650	< 0.001	0.567	0.486, 0.661	< 0.001
Q3	1,719	246	0.536	0.459, 0.626	< 0.001	0.616	0.526, 0.720	< 0.001	0.591	0.505, 0.692	< 0.001
Q4	1,718	243	0.568	0.486, 0.664	< 0.001	0.629	0.536, 0.738	< 0.001	0.578	0.491, 0.681	< 0.001
P for trend			< 0.001			< 0.001			< 0.001		
Cardiovascular mortality											
HALP (continuous)	6,869	399	0.991	0.986, 0.996	< 0.001	0.994	0.990, 0.998	0.008	0.992	0.987, 0.996	< 0.001
HALP (standardized)	6,869	399	0.733	0.625, 0.859	< 0.001	0.814	0.699, 0.948	0.008	0.749	0.636, 0.880	< 0.001
HALP (quartile)											
Q1	1,717	169	—	—		—	—		—	—	
Q2	1,715	71	0.420	0.318, 0.554	< 0.001	0.407	0.308, 0.538	< 0.001	0.393	0.297, 0.521	< 0.001
Q3	1,719	88	0.514	0.397, 0.665	< 0.001	0.613	0.472, 0.795	< 0.001	0.571	0.439, 0.743	< 0.001
Q4	1,718	71	0.445	0.337, 0.587	< 0.001	0.506	0.382, 0.672	< 0.001	0.431	0.322, 0.577	< 0.001
P for trend			< 0.001			< 0.001			< 0.001		

[1]HR = Hazard Ratio, CI = Confidence Interval, HALP = Hemoglobin-albumin-lymphocyte-platelet

Model 1: no covariates were adjusted

Model 2: adjusted for gender, race, and age

Model 3: adjusted for gender, race, age, drinking status, smoking status, education levels, married status, with or without HTN, BMI, PIR, TG, Chol, and HDL-C

HTN = hypertension, BMI = body mass index, PIR = poverty income ratio; TG, triglyceride; Chol, cholesterol, HDL-C, high-density lipoprotein- cholesterol

Table 3 Threshold effect analysis of the relationship between all-cause or CVD mortality and HALP score in participants with diabetes or prediabetes

		Adjusted HR(95%CI)	*P*
All-cause mortality			
HALP			
Model 1	One-step cox regression	0.997(0.995–0.999)	< 0.004
Model 2	Two-piecewise cox regression		
	HALP < 52	0.964(0.957–0.971)	< 0.001
	HALP ≥ 52	1.001(1.000-1.002)	0.153
	Likelihood ratio test		< 0.001
CVD mortality			
HALP			
Model 1	One-step cox regression	0.992(0.987–0.996)	< 0.001
Model 2	Two-piecewise cox regression		
	HALP < 49	0.940 (0.927–0.953)	< 0.001
	HALP ≥ 49	1.000(0.997–1.003)	0.955
	Likelihood ratio test		< 0.001

Model 1 and Model 2: adjusted for gender, race, age, drinking status, smoking status, education levels, married status, with or without HTN, BMI, PIR, TG, Chol, and HDL-C

HALP = Hemoglobin-albumin-lymphocyte-platelet, HTN = hypertension, BMI = body mass index, PIR = poverty income ratio, HbA1c, glycosylated hemoglobin; TG, triglyceride; Chol, cholesterol, HDL-C, high-density lipoprotein- cholesterol

0.180, $p < 0.001$) and BUN mediating 47.9% of the total effect (coefficient = 0.426, 95% CI: 0.259, 0.637, $p < 0.001$) (Fig. 6C and D).

Discussion

The important contribution of inflammation and nutritional status in the onset of DM or PDM and CVD is well established [7, 26]. This study, for the first time, revealed a relationship of HALP scores with all-cause and CVD mortality in participants with DM or PDM. The results of ROC suggested that the baseline HALP score is a favorable index for predicting the risk of all-cause and CVD mortality in participants with DM or PDM.

A study showed that HALP is an independent protective factor for diabetic nephropathy, positively correlated with glomerular filtration rate [23], while another study found that low levels of HALP are an independent risk factor for diabetic retinopathy [27]. In addition, the HALP score has been correlated with long-term CVD mortality in the general population [17]. The present study further explored the finding that the HALP score was independently and negatively correlated with all-cause and CVD mortality in patients with DM or PDM. In addition, a nonlinear relationship between the HALP score and all-cause and CVD mortality risk was observed by the RCS model. The RCS curves showed a L-shaped relationship between the HALP score and both all-cause and CVD mortality risk.The HAPL score was negatively correlated with both all-cause and CVD mortality, when the HAPL score was less than 52 or 49, respectively.

PDM, as a metabolic condition, increases the risk of pre-frailty and frailty in older adults [28, 29] and increasing the risk of death [30, 31]. A growing number of studies in recent years have attempted to dentify new predictors of mortality in people with DM or PDM that differ from traditional risk factors, such as non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio [32], the stress hyperglycemia ratio [33],the serum uric acid to high-density lipoprotein cholesterol ratio [34], and remnant cholesterol [35]. This study showed that the HALP score, a novel and easily calculable index combining inflammatory and nutritional markers, was negatively associated with the risk of all-cause or CVD mortality in patients with DM or PDM.

A systematic review shows that malnourished patients among the diabetic population exhibit low albumin, low hemoglobin, and low BMI [36], this suggests a correlation between malnutrition and hemoglobin levels in diabetic populations. However, studies have indicated that osmotic dehydration caused by hyperglycemia and abnormal red blood cell turnover can lead to elevated hemoglobin levels, potentially masking the nutritional status of diabetic patients [37]. Therefore, hemoglobin alone can partially reflect the nutritional status of diabetic patients, but it has certain limitations, it needs to be combined with albumin, BMI, and inflammatory markers for a comprehensive assessment [37, 38], and albumin is a well-established marker of nutritional status and liver function [39], Lymphocytes are indicative of immune function, and platelets, which are elevated in inflammatory conditions, contribute to the inflammatory response [40]. The HALP score incorporates the aforementioned indicators, providing a better reflection of inflammation and nutritional status. A higher HALP score suggests better nutritional and immune status, whereas a lower score indicates poor nutrition and heightened inflammation, both of which are associated with worse clinical outcomes [41]. For reliable HALP scoring, patients should be in a stable state condition, free from acute infections, trauma, blood disorders, or post-surgery conditions [39, 41].

The mechanism linking the HALP score to CVD risk remains unclear, but immune cells, particularly neutrophils, play a critical role in inflammation-related diseases. Platelets further exacerbate these processes by promoting thrombosis and atherosclerosis [42]. This interaction between neutrophils and platelets leads to the induction of atherosclerosis and thrombosis, ultimately leading to CVD events [43]. However, the role of lymphocytes is

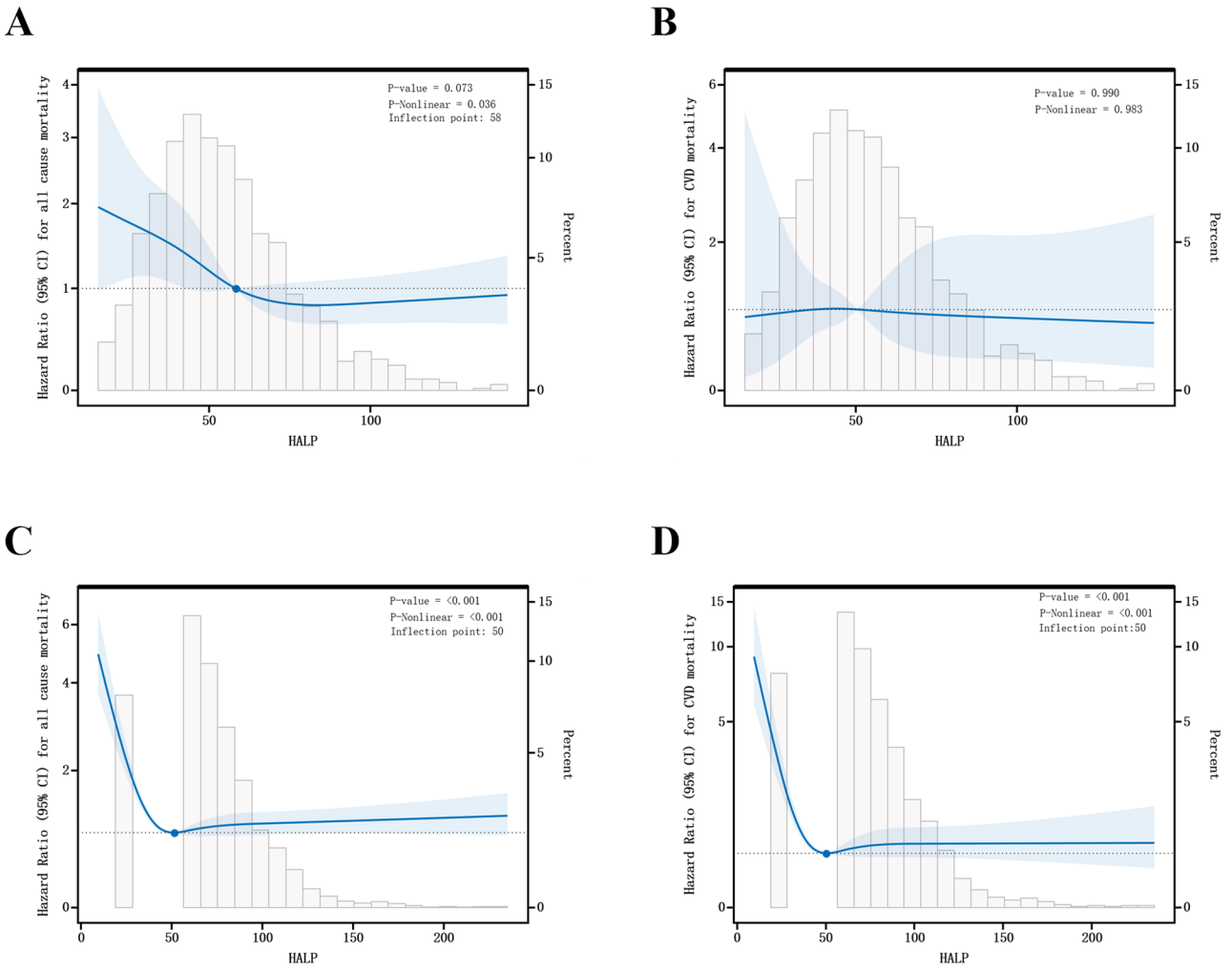

Fig. 3 The nonlinear relationship between the WWI and all-cause and CVD mortality in participants with diabetes or participants with prediabetes, respectively. **A** and **B**: The nonlinear relationship of the HALP with all-cause and CVD mortality risk in participants with prediabetes; **C** and **D**: The nonlinear relationship of the HALP with all-cause and CVD mortality risk in participants with diabetes. Adjusted for gender, race, age, drinking alcohol, smoking status, education levels, with or without HTN, BMI, married status, PIR, TG, Chol and HDL-C

more complex, Regulatory T cells can release interleukin-10 and anti-calcific factors with anti-inflammatory effects, which can limit vascular calcification and atherosclerotic processes [26, 44]. T lymphocytes, particularly Th1 cells, drive endothelial dysfunction and lipid buildup in macrophages, resulting in atherosclerosis [26]. Additionally, albumin acts as an antioxidant, neutralizing reactive oxygen species [45], while hemoglobin, through its role in oxygen transport, helps inhibit vascular permeability and inflammatory mediator production [46].

The HALP score integrates inflammation and nutritional status, offering higher predictive accuracy for disease survival, as explored in several studies [47]. In the study, a lower HALP score was correlated with increased all-cause and CVD mortality risk in people with DM or PDM and demonstrated good predictive value for both outcomes. This study has several important strengths. The HALP score, as a comprehensive index combining inflammation and nutritional status, provides a simple yet effective tool for evaluating mortality risk in a high-risk population with DM or PDM. Compared to other traditional prognostic assessment tools, the HALP score has the advantage of being easy to use and inexpensive. This simplicity allows for its potential use in a variety of healthcare settings, providing valuable prognostic information that could enhance patient management and improve outcomes for patients with DM and PDM.

The observed inverse association between HALP score and mortality risk in individuals with DM or PDM may be influenced by the inherent heterogeneity of our cohort. While we stratified analyses by diabetes status, unmeasured factors such as diabetes duration, severity of complications, and variations in disease management could modulate the relationship. Patients with prolonged

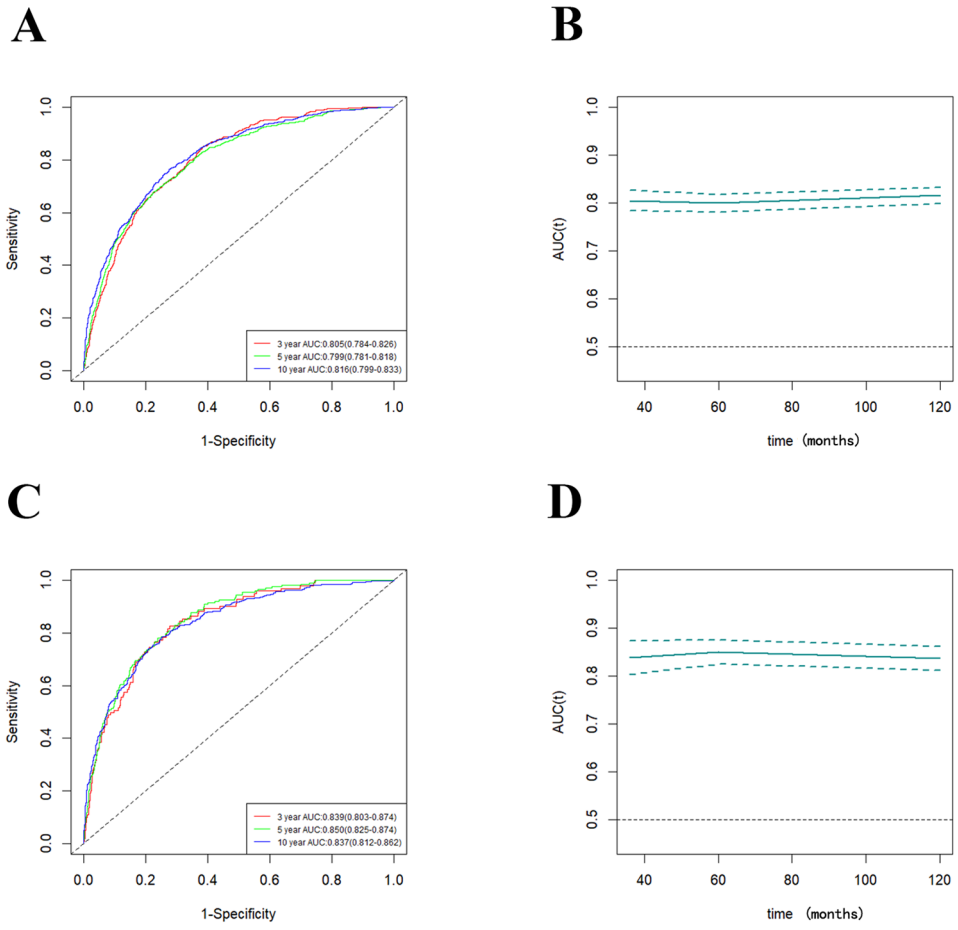

Fig. 4 The predictive power of HALP score for all-cause and CVD mortality. **A**: Time-dependent ROC curves of the HALP score for predicting all-cause mortality; **B**: Time-dependent AUC curves of the HALP score for predicting all-cause mortality. **C**: Time-dependent ROC curves of the HALP score for predicting CVD mortality; **D**: Time-dependent AUC curves of the HALP score for predicting CVD mortality

diabetes duration are more likely to develop chronic low-grade inflammation and malnutrition, both of which may reduce HALP components (e.g., albumin and hemoglobin levels) [7]. This could amplify the observed inverse association between lower HALP scores and mortality, as these individuals inherently face higher baseline risk [9, 26]. Microvascular (e.g., nephropathy) or macrovascular complications (e.g., coronary artery disease) are strongly linked to systemic inflammation and nutritional deficits [10]. For example, diabetic nephropathy may directly lower albumin levels due to proteinuria [45], while advanced CVD could suppress lymphocyte counts through chronic immune activation [43]. These pathways may confound HALP's predictive value, as the score itself partially reflects end-organ damage rather than solely baseline risk [23, 27]. Variations in glucose-lowering therapies (e.g., SGLT2 inhibitors reducing inflammation) or statin use (improving lipid profiles and endothelial function) could indirectly elevate HALP scores by mitigating inflammation or preserving nutritional status [48]. Conversely, aggressive insulin regimens might transiently alter platelet counts or albumin levels [49]. Such unmeasured treatment effects could attenuate or strengthen HALP's association with mortality. The lack of adjustment for these factors suggests that our estimates may represent a conservative measure of HALP's prognostic utility.

Nevertheless, this study has several limitations. First, some clinical data, including self-reported diabetes status and glucose-lowering medication use, relied on participant recall rather than objective verification, which may introduce information bias. Second, the NHANES dataset lacks granular details on diabetes duration, microvascular/macrovascular complications, and longitudinal treatment regimens (e.g., insulin therapy intensity, statin adherence), limiting our ability to control for these confounders, and although the core objective of NHANES is to focus on risk factors for chronic diseases, potential bias in the results may occur due to the incomplete exclusion of patients with acute infections and other conditions. Third, the potential regression from PDM to normoglycemia during follow-up was not captured,

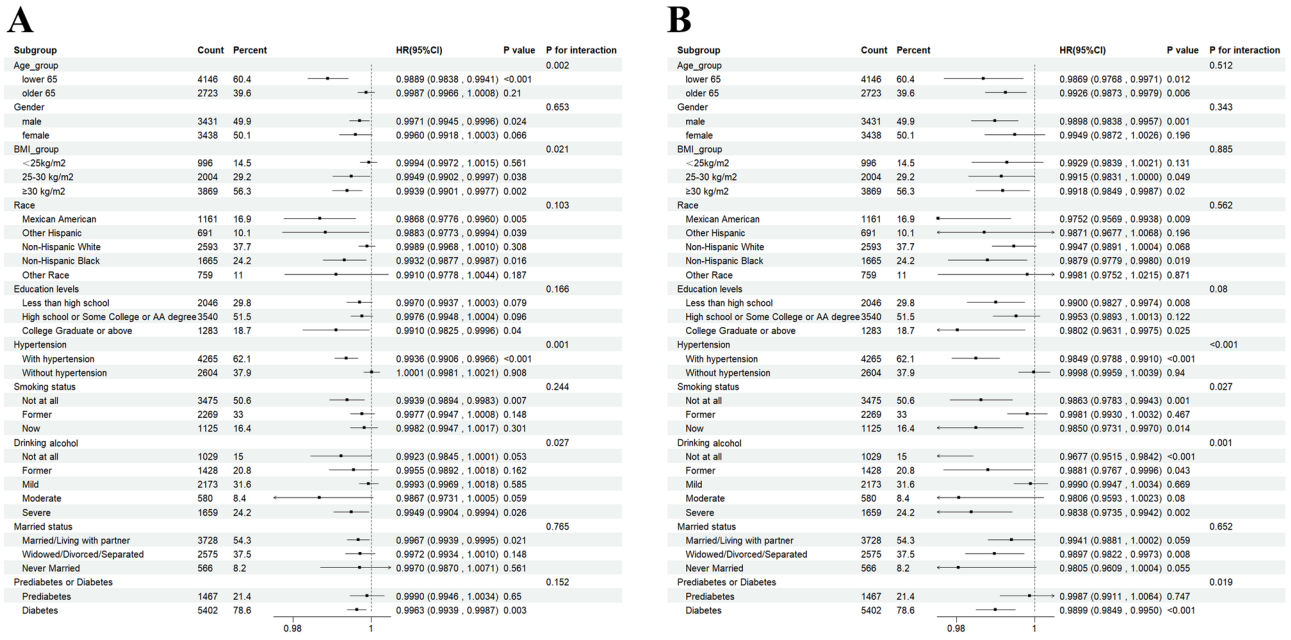

Fig. 5 The relationship between HALP score and all-cause and CVD mortality based on subgroups. **A**: Subgroup and interaction analyses for all-cause mortality, **B**: Subgroup and interaction analyses for CVD mortality. Adjusted for gender, race, age, drinking alcohol, smoking status, education levels, with or without HTN, BMI, married status, PIR, TG, Chol and HDL-C

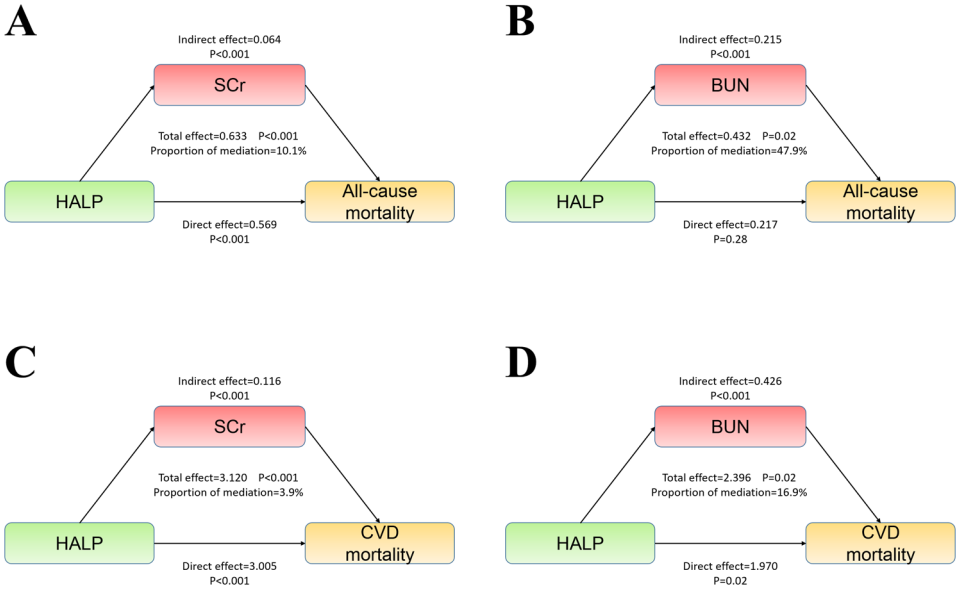

Fig. 6 Analysis of mediation effects. The mediated effects of SCr (**A**), and BUN (**B**) on HALP and all-cause mortality, the mediated effects of SCr (**C**), and BUN (**D**) on HALP and CVD mortality

which may bias mortality estimates. Fourth, only baseline HALP scores were analyzed, and dynamic changes over time potentially reflecting disease progression were not evaluated. Future studies should incorporate longitudinal phenotyping of diabetes subtypes and complications to validate the prognostic utility of HALP in more homogeneous cohorts.

Conclusion

The HALP score was negatively correlated with all-cause and CVD mortality risk and proved to be a valuable index for predicting all-cause and CVD mortality risk in participants with DM and PDM. Renal function may partially mediate the relationship between HALP and mortality risk. The measurement of the HALP score may be useful in assessing mortality risk and predicting prognosis

in individuals with DM or PDM. Future research should explore how altering HALP score impacts patient prognosis.

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Author contributions
Pingping Zhao conceived and designed the study. Pingping Zhao, Zhuang Zhang, Ming Li and Jingqi Hao collected clinical and biochemical data. Pingping Zhao, Zhuang Zhang, Ming Li, Jingqi Hao, and Yirong Wang contributed to the statistical analysis, results interpretation, drafting and revising the paper.

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Data availability
All data can be downloaded from the official NHANES website, and the data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The National Center for Health Statistics and Ethics Review approved the NHANES protocol and all participants provided written informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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