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Hemoglobin, Albumin, Lymphocyte, and Platelet Score Correlates with the Occurrence and Prognosis of Diabetic Kidney Disease Patients: Data from Two Large Cohorts

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Abstract: This study is intended to explore the relationship between the HALP score and the incidence as well as mortality of DKD in type 2 diabetes. We also evaluated whether reversing the HALP score could reduce mortality outcomes. This study included 25,750 type 2 diabetes patients from NHANES (1999–2018) and Southwest China (2013–2022). HALP score was calculated as [hemoglobin (g/L) × albumin (g/L)×lymphocytes (/L)]/platelets (/L). DKD was diagnosed based on ACR ≥30 mg/g and/or eGFR <60 mL/min/1.73m². The relationship between HALP score and DKD was explored using logistic regression model, and Cox regression models were used to evaluate its association with all-cause and cause-specific mortality. Subgroup analyses explored the effects of dietary fiber intake and NSAIDs use on HALP score and mortality. Higher HALP score were significantly associated with a lower risk of DKD (NHANES, HR 0.502; Southwest China, HR 0.528) in an antagonist manner. Additionally, higher HALP score was related to decreased all-cause (HR 0.765, p <0.001) and CVD-related mortality（HR 0.667, p <0.001）.We also discovered the same outcome in DKD patients with low dietary fiber intake (HR 0.695, p <0.001) or NSAIDs use (HR 0.733, p <0.001). The magnitude of associations was not materially altered in any of the sensitivity analyses. High HALP score was independently associated with risk of DKD and its all-cause and cardiovascular mortality. Regular HALP monitoring could aid in risk stratification and clinical decisions for DKD in type 2 diabetes.

Keywords: hemoglobin, albumin, lymphocyte, and platelet score; risk management; all-cause mortality; cardiovascular mortality; diabetic kidney disease; type 2 diabetes

1. Introduction

TheDKD is a common complication of type 2 diabetes. Its progression is driven by mechanisms such as polyol pathway enhancement and protein kinase C activation [1–3], which contribute to chronic inflammation, malnutrition, and increased all-cause and cardiovascular-related mortality [4–7]. Chronic inflammation, closely linked to malnutrition, exacerbates insulin resistance and β-cell dysfunction [8], impairing blood glucose control and accelerating DKD progression [9]. Therefore, chronic inflammation and malnutrition may contribute to the onset and progression of DKD. Comprehensive and regular evaluation of nutritional and inflammatory levels to manage the risk and progression of DKD is necessary.

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HALP score is a simple, convenient indicator requiring only a complete blood count and albumin value, reflecting both inflammation and nutritional status. Compelling evidence suggests that the HALP score is an effective predictor of mortality, especially in patients with kidney cancers and stroke survivors [10,11]. Notably, HALP score was proved to be independently associated with cardiovascular and all-cause mortality in both hemodialysis patients and the general population [12,13]. A recent study indicates that the HALP score has an L-shaped correlation with the risk of diabetic retinopathy (DR) [14], suggesting it may be associated with complications of type 2 diabetes.

Current studies suggest that increased dietary fiber intake may reduce DKD incidence, while anti-inflammatory drugs like pentoxifylline can improve glycemic control, enhance insulin sensitivity, and relieve inflammation, thereby slowing subclinical atherosclerosis progression in patients with type 2 diabetes and chronic kidney disease [15,16]. However, evidence regarding the role of HALP in the incidence and mortality of patients with DKD remains insufficient. Adequate consumption of dietary fiber and the use of anti-inflammatory drugs such as NSAIDs could enhance the HALP score, but it remains unclear whether they modify the influence of the HALP score on the mortality of DKD.

To address this gap, we aim to evaluate the association of the HALP score with the incidence and mortality in DKD patients with type 2 diabetes from the National Health and Nutrition Examination Survey (NHANES) 1999–2018 and the Southwest China cohort 2013–2022.

2. Materials and Methods

2.1. Study Population

The This is a multicenter retrospective study utilizing data from NHANES 1999–2018 [17] and Southwest China 2013-2022 (the Big Data Intelligence Platform jointly built by Chongqing Medical University and Yidu Cloud Company) [18]. Written informed consent was obtained, and the ethics were approved by the Ethics Review Board of the National Center for Health Statistics and the Ethics Committee of Chongqing Medical University. A total of 135,310 people from NHANES and 50,000 people from Southwest China were included at the time of enrollment. In the end, a total of 25,750 patients with type 2 diabetes were included in this study according to the inclusion and exclusion criteria.

2.2. Ascertainment of Outcomes

For the association of DKD with the HALP score in NHANES and Southwest China, DKD was diagnosed based on urine albumin to creatinine ratio (ACR) ≥30 mg/g and/or estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m² [19]. eGFR was calculated using the CKD-EPI algorithm in NHANES and the cystatin C-based CKD-EPI equation combined with serum creatinine (CKD-EPIscr-cys) in Southwest China [20,21].

For the relationship of the HALP score with all-cause and cause-specific mortality for DKD in NHANES, the primary outcome was all-cause mortality, while secondary outcomes were cause-specific mortality, including CVD-related, malignancy-related, and cerebrovascular-related mortality. Mortality data were obtained from the 2019 Public-Use Linked files of the National Death Index (1999–2019) [22].

2.3. Assessment of Exposure

The exposure variable was the HALP score, which was calculated using the following formula: [hemoglobin (g/L) × albumin (g/L)×lymphocytes (/L)]/platelets (/L) [10]. Classification of patients was based on the different thresholds using the triplet method: 1) ≤35.85(Q1), 2) 35.85 to 64.88(Q2), and 3) >64.88(Q3) in the NHANES, while 1) ≤30.19(Q1), 2) 30.19 to 70.53(Q2), 3) >70.53(Q3) in the Southwest China.

2.4. Assessment of Covariates

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The data for baseline demographic characteristics and laboratory values were obtained from NHANES and Southwest China, respectively. Structured questionnaires were conducted to collect information about age, sex, ethnicity, drinking status, smoking status, weight, height, systolic blood pressure, diastolic blood pressure, and body mass index (BMI). Chronic kidney disease (CKD) was defined as eGFR < 60 mL/(1.73 m^2 * min). In addition, strict laboratory analyses were performed, including the assessment of hemoglobin, albumin, lymphocyte, platelet, fasting glucose, HbA1c, white blood cell, serum creatinine, uric acid, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, eosinophilic granulocyte, neutrophilic granulocyte, monocyte, and red blood cell. Examined prescription NSAIDs include common drugs like ibuprofen, naproxen, and diclofenac, as well as less common ones like diflunisal and meclofenamate sodium (Supplementary Table 1-2). Dietary intake was assessed using two 24-hour recalls, with fiber intake calculated from the USDA's Food and Nutrient Database, either averaged over two recalls or based on one recall when only a single recall was available. Further details of these covariates were documented in the NHANES Laboratory Medical Technologists Procedures Manual [17] and the Dynamically Updated Big Data Intelligence Platform Using Electronic Medical Records [18].

2.5. Statistical Analyses

Baseline characteristics were summarized as mean ± SD for normally distributed continuous variables, medians (interquartile ranges) for non-normally distributed variables, and frequencies (percentages) for categorical variables. The difference among groups was assessed using t-tests, ANOVA, or Kruskal-Wallis tests, and missing data were imputed using multiple imputation with chained equations. The missing rates of covariates were summarized (Supplementary Table 3). Spearman's rank correlation was used to evaluate the relationship between HALP score and selected parameters.

Univariate and multivariate logistic regression models were used to evaluate the association between the HALP score and DKD, with estimated odds ratios (OR) and 95% confidence intervals (CI). Linear regression examined the relationship between HALP score and eGFR. Mediation and interaction models were employed to explore the relationship among type 2 diabetes, HALP score, and eGFR. The bootstrap method was employed to evaluate the significance of mediation effects. Nonlinear associations between HALP score and DKD were evaluated using restricted cubic spline (RCS) models, and logistic regression further examined the contribution of hemoglobin, albumin, lymphocytes, and platelets, both as continuous and categorical variables.

Kaplan-Meier curves and log-rank tests were employed to assess the relationship between HALP score and all-cause or cause-specific mortality in DKD patients. Cox regression models, adjusted for confounders, were used to evaluate the independent effect of HALP score on mortality, with proportional hazards being tested by Schoenfeld residuals. Nonlinear associations were explored using restricted cubic splines and two-piecewise linear regression models, and the influence of dietary fiber intake and NSAIDs use on HALP score and mortality outcomes was examined through subgroup analyses. Hazard ratios (HRs) and 95% CIs were computed for these associations.

All statistical analyses were conducted using SPSS (version 27.0), GraphPad Prism (version 9.5.1), or R software (version 4.3.1). P value of <0.05 was considered statistically significant.

2.6. Sensitivity Analyses

Several sensitivity analyses were conducted: (i) To reduce potential bias from the COVID-19 pandemic, diabetes patients in Southwest China were reanalyzed before and after January 15, 2020 using logistic regression; (ii)Subgroup analyses were conducted to evaluate whether the association between HALP score and DKD remained consistent; (iii) The association between HALP score and cause-specific mortality was reanalyzed after excluding participants who died from cause-specific events within the first year of follow-up. To minimize reverse causality, Cox models were reanalyzed with additional adjustments for baseline illnesses, followed by restricting the sample to participants without baseline cardiovascular risks.(iv) To account for the competing risks between all-cause and cause-specific mortality, the main analyses were repeated using a competing risk model [23]; (v) As

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renal morphology changes in diabetes patients have not been confirmed by biopsy, a decline in eGFR was used as an indicator of DKD. Given the controversy over eGFR cut-off values for defining DKD, different calculation formulas and thresholds were applied to the NHANES and Southwest China datasets, incorporating race and gender-specific parameters [20,21]; (vi) The main analyses were repeated after defining HALP score as a continuous variable; (vii) The robustness and potential variations in the association between HALP score and all-cause and cause-specific mortality were tested across different subgroups.

3. Results

3.1. Baseline Characteristics

The screening strategy for participants is shown in Figure 1.A total of 7,252 participants from NHANES (50.3% female, mean age: 61.51 years) and 18,498 participants with type 2 diabetes from Southwest China (47.9% female, mean age: 69.65 years) were included in the baseline analysis. In NHANES, 2,802 patients died, 4,276 survived, and 174 had missing follow-up data. Significant differences were observed in ethnic composition, drinking status, and smoking status across HALP tertiles. The lowest HALP tertile (<35.85) had significantly lower eGFR ($p < 0.001$), indicating a greater decline in renal function. This group also had the lowest levels of HGB, ALB, and LYM, and the highest PLT levels compared to other tertiles (Table 1). Additionally, Spearman's rank correlation analysis revealed a positive correlation between eGFR and HALP score (Supplementary Table 4). HALP score distributions for NHANES and Southwest China are shown in Supplementary Figure. 1.

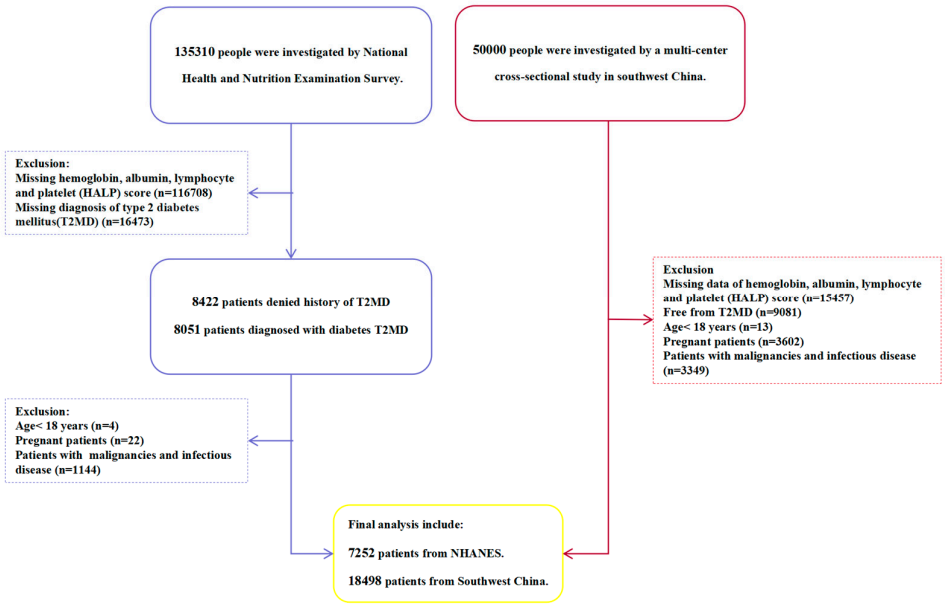

Figure 1. Flowchart of the current study. HALP score, hemoglobin, albumin, lymphocyte, and platelet score; T2DM, type 2 diabetes mellitus.

Table 1. Baseline characteristics of people with type 2 diabetes by category of HALP score in NHANES and Southwest China.

	NHANES(n=7252)	Southwest China(n=18498)

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Variables	Total	HALP≤35.85	35.85<HALP<64.88	HALP≥64.88	*p* value	Total	HALP≤30.19	30.19<HALP<70.53	HALP≥70.53	*p* value
Clinical characteristics										
Age, years	61.51±14.31	63.34±14.76	61.14±14.25	60.51±13.80	<0.001	69.65±13.98	72.60±14.07	69.21±13.73	67.57±13.90	0.033
Sex					<0.001					<0.001
Male	3606(49.70)	733(40.40)	1751(48.30)	1122(61.90)		9639(52.10)	2353(50.90)	4548(49.20)	2738(59.20)	
Female	3646(50.30)	1080(59.60)	1875(51.70)	691(38.10)		8859(47.90)	2271(49.10)	4701(50.80)	1887(40.80)	
Race					<0.001					<0.001
1	1674(23.10)	364(20.10)	847(23.40)	463(25.20)		18290(98.90)	4578(99.00)	9152(99.00)	4560(98.60)	
2	524(7.20)	99(5.50)	284(7.80)	141(7.80)		85(0.50)	24(0.50)	34(0.40)	27(0.60)	
3	2609(36.00)	674(37.20)	1262(34.80)	673(37.10)		30(0.20)	7(0.20)	13(0.10)	10(0.20)	
4	1867(25.70)	558(30.80)	922(25.40)	387(21.30)		21(0.10)	7(0.20)	11(0.10)	3(0.10)	
5	578(8.00)	118(6.50)	311(8.60)	149(8.20)		72(0.40)	8(0.20)	39(0.40)	25(0.50)	
Drinking status					<0.001					<0.001
Never drinkers	2922(40.30)	827(45.60)	1444(39.80)	651(35.90)		13347(72.10)	3378(73.10)	6807(73.60)	3162(68.40)	
Ever drinkers	4330(59.70)	986(54.40)	2182(60.20)	1162(64.10)		5151(27.80)	1246(26.90)	2442(26.40)	1463(31.60)	
Smoking status					<0.001					<0.001
Never smokers	3228(44.50)	903(49.80)	1627(44.90)	698(38.50)		12337(66.70)	3120(67.90)	6398(69.20)	2819(61.00)	

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Ever smokers	4024(55.50)	910(50.20)	1999(55.10)	1115(61.50)		6161(33.30)	1504(32.10)	2851(30.80)	1806(39.00)	
SBP, mmHg	134.13±21.84	135.71±23.31	133.90±21.57	133.02±20.75	<0.001	136.53±36.12	137.54±41.95	137.20±30.03	134.18±40.58	0.039
DBP, mmHg	68.94±14.99	66.45±16.04	69.34±14.61	70.62±14.33	<0.001	78.78±16.42	77.61±13.42	79.55±16.92	78.40±17.96	<0.001
BMI, kg/m2	31.60±7.33	31.57±8.03	31.55±7.20	31.72±6.84	0.733	25.61±3.86	24.66±3.59	25.58±3.89	25.83±4.20	0.639
CKD history					<0.001					<0.001
Suffer from CKD	2509(34.60)	850(46.90)	1164(32.10)	495(27.30)		15140(82.20)	3473(75.60)	7709(83.60)	3958(85.90)	
Free from CKD	4743(65.40)	963(53.10)	2462(67.90)	1318(72.70)		3281(17.80)	1120(24.40)	1513(16.40)	648(14.10)	
Laboratory data										
HGB, g/L	133.00(120.00,146.00)	119.00(101.00,133.00)	135.00(123.00,146.00)	143.00(130.00,157.00)	<0.001	136.77±40.96	116.93±28.55	136.24±28.21	157.68±53.95	<0.001
ALB, g/L	40.85±3.78	38.93±4.12	41.16±3.34	42.24±3.48	<0.001	46.27±67.47	35.40±9.28	41.51±7.33	66.66±132.05	<0.001
LYM, 10^9/L	2.21±1.06	1.59±0.56	2.17±0.62	2.90±1.61	<0.001	1.69±11.21	0.99±0.53	1.58±0.53	2.61±22.38	<0.001
PLT, 10^9/L	249.10±74.82	289.64±85.83	249.65±63.53	207.44±59.80	<0.001	183.35±75.67	220.36±90.63	186.70±60.49	139.67±63.84	<0.001
GLU, mmol/L	8.58±5.05	9.08±5.17	9.65±5.19	9.82±5.18	<0.001	11.32±25.78	11.82±18.22	11.07±30.08	11.34±22.72	<0.001
HbA1c, %	8.60(6.80,11.54)	9.10(6.80,11.54)	8.50(6.80,11.54)	8.40(6.87,11.54)	<0.001	16.10(10.00,22.05)	14.99(10.00,21.09)	15.89(10.00,21.84)	17.47(10.00,23.36)	0.002
WBC, 10^9/L	7.60±2.32	7.03±2.26	7.49±2.05	8.39±2.65	<0.001	15.10±262.25	22.09±475.26	13.20±142.37	11.93±93.22	0.035

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SCR, mg/dL	1.08±0.83	1.26±1.14	1.03±0.74	1.00±0.57	<0.001	0.92(0.76,1.17)	1.00(0.80,1.30)	0.90(0.74,1.12)	0.90(0.76,1.10)	<0.001
UA, umol/L	335.67±96.58	341.76±108.03	332.10±93.09	336.70±90.88	<0.001	342.91±119.47	341.60±138.80	339.70±114.32	350.63±107.79	<0.001
TG, mmol/L	1.99±1.76	1.90±1.90	1.92±1.63	2.23±1.83	0.002	1.69(1.02,2.69)	1.54(0.95,2.53)	1.67(1.01,2.59)	1.91(1.15,3.02)	<0.001
HDL-C, mmol/L	1.24±0.38	1.30±0.40	1.25±0.38	1.16±0.35	<0.001	1.18(0.98,1.44)	1.22(1.03,1.53)	1.19(1.01,1.44)	1.11(0.93,1.34)	<0.001
LDL-C, mmol/L	2.82±1.05	2.74±1.08	2.83±1.04	2.86±1.06	0.001	2.78(2.06,3.50)	2.66(1.98,3.44)	2.82(2.10,3.51)	2.82(2.11,3.53)	0.189
EOS, 10^9/L	0.22±0.17	0.21±0.17	0.22±0.17	0.23±0.18	<0.001	0.20(0.10,0.30)	0.20(0.10,0.30)	0.20(0.10,0.30)	0.20(0.10,0.30)	0.036
NEU, 10^9/L	4.52(3.19,5.39)	4.84(3.90,7.35)	4.31(3.15,5.09)	3.98(2.80,4.84)	<0.001	4.30(3.40,5.50)	4.30(3.30,5.50)	4.30(3.30,5.45)	4.40(3.53,5.60)	0.032
MON, 10^9/L	0.58±0.20	0.54±0.20	0.57±0.20	0.63±0.22	<0.001	0.41±0.23	0.44±0.26	0.40±0.21	0.38±0.22	<0.001
RBC, 10^9/L	4.60±0.54	4.33±0.54	4.62±0.49	4.83±0.50	<0.001	7.74±402.15	16.25±799.17	5.09±64.18	4.54±8.94	<0.001
eGFR, mL/min/1.73 m2	81.43±36.15	72.04±35.75	83.39±36.32	86.90±34.45	<0.001	92.8±10.52	78.7±12.45	97.1±9.72	98.3±9.78	<0.001

Notes: Data are presented as n (%), mean ± SD, or median (interquartile range). **Abbreviations**:NHANES, National Health and Nutrition Examination Survey; Southwest China, A multi-center cross-sectional study in Southwest China; the race in NHANES include 1, Mexican American people, 2, other Hispanic people, 3, non-Hispanic White people, 4, non-Hispanic Black people, 5, multi-racial people; the race in Southwest China include 1, the Han ethnic group, 2, the Tujia ethnic group, 3, the Miao ethnic group, 4, the Hui ethnic group, 5, other ethnic minorties; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; CKD, chronic kidney disease; HGB, hemoglobin; ALB, albumin; LYM, lymphocyte; PLT, platelet; Glu, glucose; HbA1c, glycated hemoglobin A1c; WBC, white blood cell; SCR, serum creatinine; UA, uric acid; TG, triglyceride; HDL-C, high lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; EOS, eosinophile; NEU, neutrophile; MON, monocyte; RBC, red blood cell; eGFR, estimated glomerular filtration rate.

3.2. HALP Score and Risk of DKD in Type 2 Diabetes

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Logistic regression was performed to examine the association between HALP score and DKD in type 2 diabetes. The confounding factors and HALP, identified through univariate screening ($p < 0.05$) (Supplementary Table 5), would be utilized to construct Model 3. Participants in the middle HALP tertile had a significantly reduced risk of DKD compared with the lowest tertile in Model 3 (NHANES: HR 0.611, 95% CI 0.513–0.713; Southwest China: HR 0.612, 95% CI 0.554–0.676). A further reduction in risk was observed in the highest tertile (NHANES: HR 0.502, 95% CI 0.478–0.530; Southwest China: HR 0.528, 95% CI 0.451–0.617). Trend analysis confirmed a decreasing risk of DKD with increasing HALP score in both cohorts (all p for trend <0.001) (Table 2). Besides, nonlinear dose-response relationships between HALP score and DKD were evident in NHANES (p for nonlinearity <0.05), with a similar linear pattern in males. This relationship was not observed across different age groups (<64 and >64) (Supplementary Figure. 2), and a threshold effect was identified only in males (Supplementary Table 6).

In the NHANES cohort, HALP score was positively correlated with eGFR in both DKD ($r = 0.0327$) and non-DKD populations ($r = 0.1172$). Mediation analysis indicated no significant mediation effect of HALP score on the relationship between type 2 diabetes and DKD ($\beta = -0.323$, $p = 0.752$). However, a significant interaction between HALP score and eGFR was observed in the diabetic population (p for interaction <0.001) (Figure 2).

An analysis of the association of four components of HALP score and the decline in renal function in patients with type 2 diabetes was added. After adjusting for variables, HGB (NHANES, OR 0.668, 95% CI 0.631–0.707; Southwest China, HR 0.808, 95% CI 0.772–0.846) and ALB (NHANES, HR 0.732, 95% CI 0.696–0.770; Southwest China, HR 0.706, 95% CI 0.676–0.718) were independently associated with DKD. LYM showed a weaker association in Southwest China (HR 0.958, 95% CI 0.917–1.000, $p = 0.051$), while PLT had no significant correlation (all $p > 0.05$) (Supplementary Tables 7-10).

Table 2. This Association between HALP score and risk of diabetic kidney disease in type 2 diabetes patients.

HALP Score	NHANES					
	Model 1		Model 2		Model 3	
	OR(95%CI)	*p* value	OR(95%CI)	*p* value	OR(95%CI)	*p* value
Q1	reference		reference		reference	
Q2	0.536(0.477-0.601)	<0.001	0.573(0.506-0.650)	<0.001	0.611(0.513-0.713)	<0.001
Q3	0.425(0.370-0.489)	<0.001	0.479(0.412-0.556)	<0.001	0.502(0.478-0.530）	<0.001
	Southwest China					
HALP Score	Model 1		Model 2		Model 3	
	OR(95%CI)	*p* value	OR(95%CI)	*p* value	OR(95%CI)	*p* value
Q1	reference		reference		reference	
Q2	0.609(0.558-0.664)	<0.001	0.588(0.539-0.642)	<0.001	0.612(0.554-0.676)	<0.001
Q3	0.508(0.456-0.565)	<0.001	0.478(0.429-0.533)	<0.001	0.528(0.451-0.617)	<0.001

Notes:NHANES: Q1(HALP ≤ 35.85), Q2(35.85 < HALP ≤ 64.88), Q3(HALP > 64.88). Model 1 adjusted for none; Model 2 adjusted for age and sex; Model 3 adjusted for age, sex, Race, Drinking status, SBP, DBP, BMI, HbAlc,

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LYM, WBC, PLT, SCR, UA, TG, EOS, NEU, MON, RBC and HALP. Southwest China: Q1(HALP ≤ 30.19), Q2(30.19 < HALP ≤ 70.53), Q3(HALP > 70.53). Model 1 adjusted for none.; Model 2 adjusted for age and sex.; Model 3 adjusted for age,sex,SBP,HGB,PLT,HbAlc,SCR,UA and EOS. **Abbreviations:**NHANES, National Health and Nutrition Examination Survey; Southwest China, A multi-center cross-sectional study in southwest china; OR,odds ratios; 95% CI,95% confidence intervals; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; HGB, hemoglobin; LYM, lymphocyte; PLT, platelet; HbA1c, glycated hemoglobin A1c; WBC, white blood cell; SCR, serum creatinine; UA, uric acid; TG, triglyceride; EOS, eosinophile; NEU, neutrophile; MON, Monocyte; RBC, red blood cell; eGFR, estimated glomerular filtration rate; HALP score, hemoglobin, albumin,lymphocyte, and platelet score.

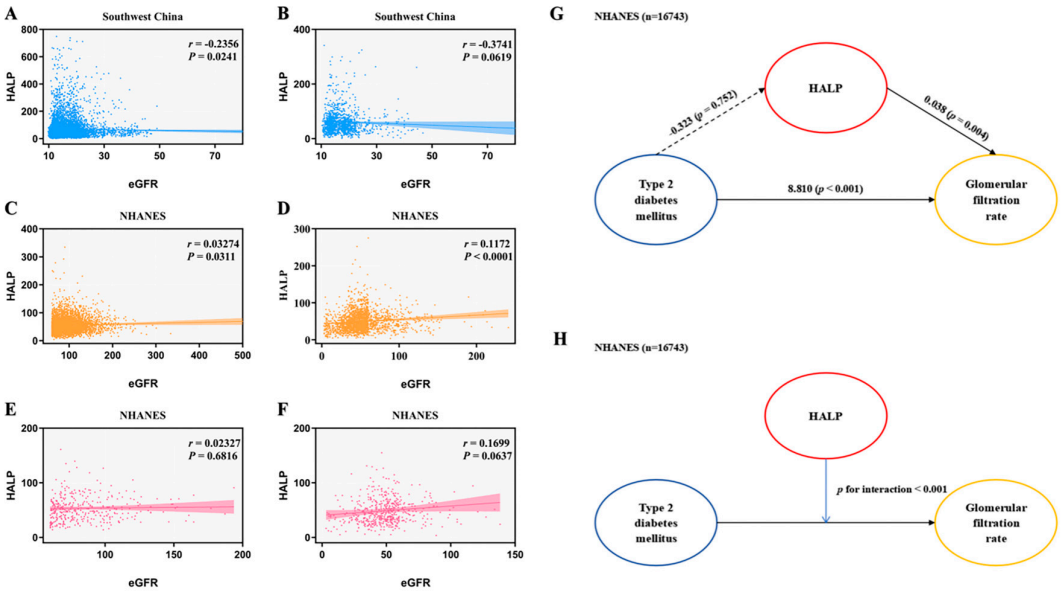

Figure 2. Association of type 2 diabetes, HALP score and glomerular filtration rate. **(A)** Relationship between HALP and eGFR in type 2 diabetes patients from Southwest China ; **(B)** Relationship between HALP and eGFR in diabetic kidney disease patients from Southwest China; **(C)** Relationship between HALP and eGFR in type 2 diabetes patients from NHANES ; **(D)** Relationship between HALP and eGFR in diabetic kidney disease patients from NHANES; **(E)** Relationship between HALP and eGFR in type 2 diabetes patients from NHANES(CVD-related mortality in type 2 diabetes patients) ; **(F)** Relationship between HALP and eGFR in diabetic kidney disease patients from NHANES(CVD-related mortality in diabetic kidney disease patients); **(G)** Mediation analysis model; **(H)** The interaction between type 2 diabetes and HALP score.

3.3. HALP Score and Risk of Mortality with DKD in Type 2 Diabetes

During a median follow-up of 90 months (interquartile range 45, 149), all-cause mortality developed in 2,802 participants, including 893 cases of CVD-related mortality, 408 cases of malignancy-related mortality, and 173 cases of cerebrovascular-related mortality. Kaplan-Meier curves showed significant differences in risk of adverse outcomes among different age and gender groups (Figure 3 and Supplementary Figure. 3).

Confounding factors and HALP score, identified through univariate Cox regression analysis screening (p <0.05) (Supplementary Table 11), were used to construct Model 3. Multivariable-adjusted Cox regression analysis showed that, compared with participants in the lowest HALP tertile, those in the midrange tertile had a reduced risk of all-cause mortality (HR 0.765, 95% CI 0.675–0.867), CVD-related mortality (HR 0.667, 95% CI 0.538–0.827), malignancy-related mortality (HR 0.524, 95% CI 0.275–0.999), and cerebrovascular-related mortality (HR 0.597, 95% CI 0.375–0.950). For participants

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in the highest HALP tertile, the corresponding HRs were 0.833 (95% CI 0.709–0.977), 0.610 (95% CI 0.464–0.801), 0.460 (95% CI 0.231–0.917), and 0.568 (95% CI 0.317–1.016) (Table 3).

Linear dose-response relationships of HALP score with all-cause mortality and CVD-related mortality were demonstrated (all p for non-linearity <0.05), except for CVD-related mortality in the younger group(age <64 years).There was only a weak correlation between HALP score and malignancy-related or cerebrovascular-related mortality (Supplementary Figure 4–5).

Threshold effect analysis identified critical inflection points influencing the correlation between variables. We then evaluated the relationships between independent and dependent variables before and after these points. Significant threshold effects were observed in different models for all-cause and CVD-related mortality (Supplementary Table 12).

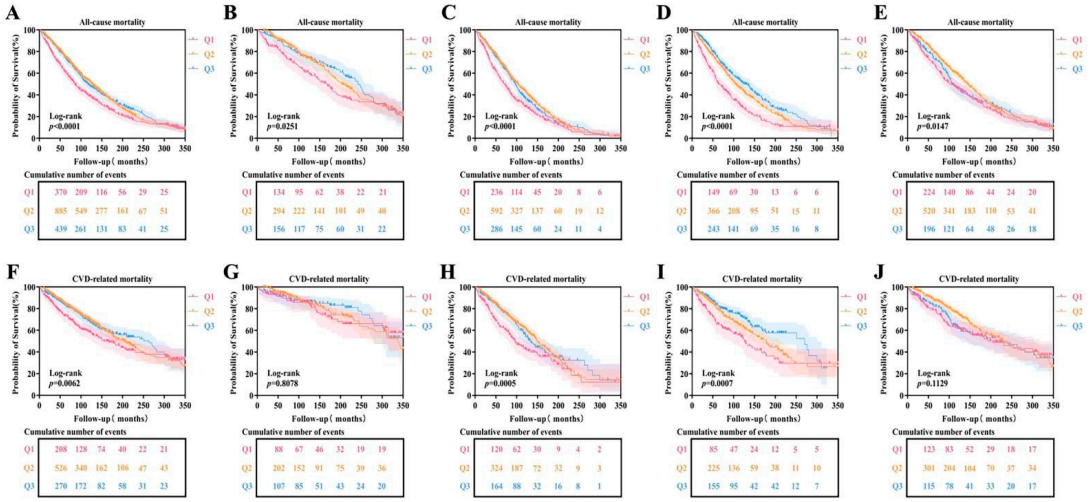

Figure 3. Kaplan-Meier curves of all-cause mortality and CVD-related mortality based on HALP score. Patients were divided into three categories: Q1 (HALP ≤ 32.12), Q2 (32.12 < HALP ≤ 60.43), and Q3 (HALP > 60.43). **(A)** Kaplan-Meier curves of all-cause mortality; **(B)** Kaplan-Meier curves of all-cause mortality in patients under 64 years of age ; **(C)** Kaplan-Meier curves of all-cause mortality in patients over 64 years of age; **(D)** Kaplan-Meier curves of all-cause mortality in male patients; **(E)** Kaplan-Meier curves of all-cause mortality in female patients; **(F)** Kaplan-Meier curves of CVD-related mortality; **(G)** Kaplan-Meier curves of CVD-related mortality in patients under 64 years of age; **(H)** Kaplan-Meier curves of CVD-related mortality in patients over 64 years of age; **(I)** Kaplan-Meier curves of CVD-related mortality in male patients; **(J)** Kaplan-Meier curves of CVD-related mortality in female patients.

Table 3. Multivariate Cox analysis of all-cause and cause-specific mortality in patients with diabetic kidney disease.

HALP Score	Model 1		Model 2		Model 3	
	HR(95%CI)	*p* value	HR(95%CI)	*p* value	HR(95%CI)	*p* value
All-cause mortality						
Q1	reference		reference		reference	
Q2	0.737(0.654-0.831)	<0.001	0.708(0.628-0.799)	<0.001	0.765(0.675-0.867)	<0.001
Q3	0.737(0.641-0.848)	<0.001	0.714(0.620-0.823)	<0.001	0.833(0.709-0.977)	0.025
CVD-related mortality						

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Q1	reference		reference		reference	
Q2	0.734(0.596-0.903)	0.003	0.674(0.547-0.830)	<0.001	0.667(0.538-0.827)	<0.001
Q3	0.722(0.567-0.920)	0.008	0.678(0.531-0.866)	0.002	0.610(0.464-0.801)	<0.001
Malignancy-related mortality						
Q1	reference		reference		reference	
Q2	0.912(0.634-1.312)	0.621	0.773(0.536-1.113)	0.166	0.524(0.275-0.999)	0.050
Q3	0.812(0.532-1.240)	0.336	0.769(0.501-1.179)	0.228	0.460(0.231-0.917)	0.027
Cerebrovascular-related mortality						
Q1	reference		reference		reference	
Q2	0.723(0.457-1.145)	0.1667	0.617(0.388-0.981)	0.041	0.597(0.375-0.950)	0.030
Q3	0.549(0.308-0.980)	0.0443	0.554(0.307-0.998)	0.049	0.568(0.317-1.016)	0.057

Notes: Divide patients into three groups, Q1(HALP ≤ 32.12), Q2(32.12 < HALP ≤ 60.43), Q3(HALP > 60.43). All-cause mortality: Model 1 adjusted for none. Model 2 adjusted for age and sex. Model 3 adjusted for age, sex, SBP, DBP, BMI, WBC, SCR, UA, NEU, MON, RBC, eGFR and ACR. CVD-related mortality: Model 1 adjusted for none. Model 2 adjusted for age and sex. Model 3 adjusted for age, sex, SBP, DBP, BMI, WBC, SCR, UA, LDL-C, RBC and eGFR. Malignancy-related mortality: Model 1 adjusted for none. Model 2 adjusted for age and sex. Model 3 adjusted for age, sex, Smoking status, SBP, BMI, WBC, UA, RBC and eGFR. Cerebrovascular-related mortality: Model 1 adjusted for none. Model 2 adjusted for age and sex. Model 3 adjusted for age, SBP, BMI, eGFR and ACR. **Abbreviations:**HR, hazard ratios,95% CI,95% confidence intervals; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index； WBC, white blood cell; SCR, serum creatinine; UA, uric acid; NEU, neutrophile; MON, monocyte; RBC, red blood cell; eGFR, estimated glomerular filtration rate; ACR, albumin to creatinine ratio; HALP score,hemoglobin, albumin,lymphocyte, and platelet score.

3.4. HALP Score and Risk of Mortality in Different Dietary Fiber Intake and NSAIDs Groups

In the low dietary fiber intake group, after adjusting for age, sex, and race, a higher HALP score was significantly associated with a reduced risk of all-cause mortality (Q2 vs. Q1: OR 0.695, p <0.001; Q3 vs. Q1: OR 0.780, p =0.002) and CVD-related mortality (Q2 vs. Q1: OR 0.659, p <0.001; Q3 vs. Q1: OR 0.676, p =0.006). These associations were not observed in the high dietary fiber intake group across all multivariate models (all p >0.05). Similar results were seen in different NSAIDs groups (Table 4).

An L-shaped dose-response relationship was identified between HALP score and the risk of CVD-related and all-cause mortality in the low dietary fiber intake group (p overall <0.0001; p for non-linearity <0.01) and the non-NSAIDs group (p for total <0.001; p non-linear <0.0001). No significant dose-response relationship was found in the high dietary fiber intake or NSAIDs groups (Figure 4).

Table 4. The relationship between HALP score and all-cause and CVD-related mortality in patients with diabetic kidney disease in different groups.

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All-cause mortality					CVD-related mortality				
Variables	Model 1		Model 2		Variables	Model 1		Model 2	
	HR(95% CI)	*p* value	HR(95% CI)	*p* value		HR(95% CI)	*p* value	HR(95% CI)	*p* value
High dietary fiber intake(n=463)					High dietary fiber intake(n=281)				
Q1	reference	0.308	reference	0.687	Q1	reference	0.096	reference	0.261
Q2	0.820(0.631-1.067)	0.140	0.893(0.684-1.164)	0.402	Q2	0.623(0.386-1.004)	0.052	0.680(0.419-1.104)	0.119
Q3	0.839(0.608-1.157)	0.284	0.904(0.651-1.256)	0.548	Q3	1.003(0.580-1.734)	0.991	0.933(0.531-1.641)	0.810
Low dietary fiber intake(n=2046)					Low dietary fiber intake(n=1190)				
Q1	reference	<0.001	reference	<0.001	Q1	reference	0.001	reference	<0.001
Q2	0.714(0.632-0.806)	<0.001	0.695(0.614-0.785)	<0.001	Q2	0.687(0.559-0.844)	<0.001	0.659(0.535-0.811)	<0.001
Q3	0.813(0.697-0.950)	0.009	0.780(0.667-0.912)	0.002	Q3	0.739(0.562-0.971)	0.03	0.676(0.511-0.894)	0.006
Use of NSAIDs drugs(n=26)					Use of NSAIDs drugs(n=19)				
Q1	reference	0.358	reference	0.468	Q1	reference	0.177	reference	0.796
Q2	0.521(0.204-1.334)	0.174	1.663(0.453-6.114)	0.444	Q2	0.314(0.093-1.063)	0.063	0.487(0.061-3.915)	0.499
Q3	0.435(0.053-3.541)	0.436	0.355(0.035-3.627)	0.382	Q3	0.000(0.000-0.000)	0.987	0.001(0.000-0.000)	0.994
Non-use of NSAIDs drugs(n=2483)					Non-use of NSAIDs drugs(n=1452)				
Q1	reference	<0.001	reference	<0.001	Q1	reference	0.005	reference	0.001
Q2	0.741(0.662-0.830)	<0.001	0.733(0.654-0.821)	<0.001	Q2	0.724(0.595-0.881)	0.001	0.692(0.569-0.843)	<0.001
Q3	0.821(0.712-0.946)	0.006	0.794(0.688-0.917)	0.002	Q3	0.836(0.655-1.068)	0.151	0.775(0.605-0.993)	0.044

Notes: Model 1 adjusted for none; Model 2 adjusted for age,sex and race. High dietary fiber intake was defined fiber intake ≥ 21.30 g/day and low dietary fiber intake was defined fiber intake < 21.30 g/day. Divide patients into three groups, Q1(HALP ≤ 32.12), Q2(32.12 < HALP ≤ 60.43), Q3(HALP > 60.43). **Abbreviations:**HR (95% CI), hazard ratios and 95% confidence interval. NSAIDs, non-steroidal antiinflammatory drugs.

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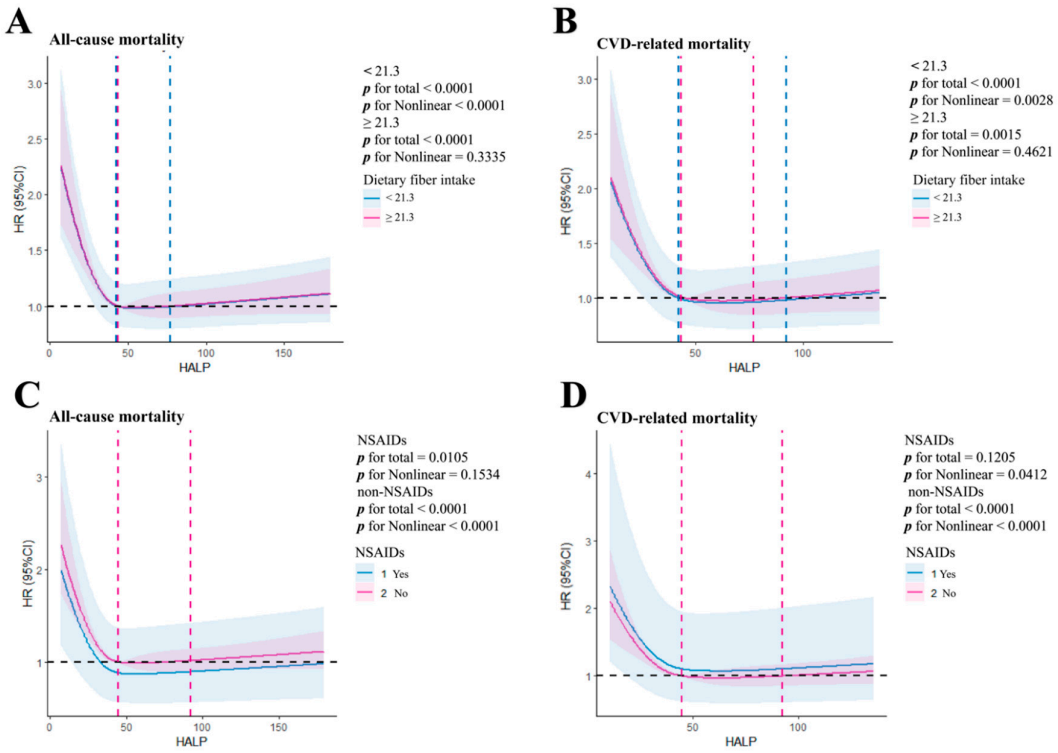

Figure 4. Restricted spline curves for the associations between HALP score with mortality in different groups. Lines represent the HR (hazard ratio), and transparent areas represent the 95% confidence intervals. HR (95% CI) were adjusted for various adverse events in Cox analysis using age,sex and race. **(A)** Restricted spline curves for the associations between HALP score and all-cause mortality in high and low dietary intake groups; **(B)** Restricted spline curves for the associations between HALP score and CVD-related mortality in high and low dietary intake groups; **(C)** Restricted spline curves for the associations between HALP score and all-cause mortality in the NSAIDs and non-NSAIDs groups; **(D)** Restricted spline curves for the associations between HALP score and CVD-related mortality in the NSAIDs and non-NSAIDs groups.

3.5. Sensitivity Analyses

Most results remained consistent across all sensitivity analyses. For example, the association between HALP score and DKD in type 2 diabetes persisted after censoring data up to January 15, 2020, when COVID-19 emerged in Southwest China (Supplementary Tables 13–15). In stratified analyses, the association was stronger among participants from other racial groups, including the Tujia, Miao, Hui, and other ethnic minorities (p for interaction <0.001). Consistent results were found in analyses stratified by age, sex, drinking, smoking, and BMI (all p for interaction >0.05) (Supplementary Figure 6). The findings still held after excluding participants with cardiovascular and cerebrovascular diseases at baseline (Supplementary Figure 7–8, Supplementary Tables 16–18), excluding participants whose cause-specific death occurred within the first two years of follow-up (Supplementary Table 19), and performing competing risk analyses for cause-specific deaths (Supplementary Table 20). While the association between HALP score and mortality from malignant neoplasms and cerebrovascular diseases was slightly attenuated when HALP was redefined as a continuous variable, the overall results remained robust (Supplementary Tables 21–32). Similar findings were observed in the stratified analyses of HALP score associations with all-cause and cause-specific mortality (Figure 5 and Supplementary Table 33).

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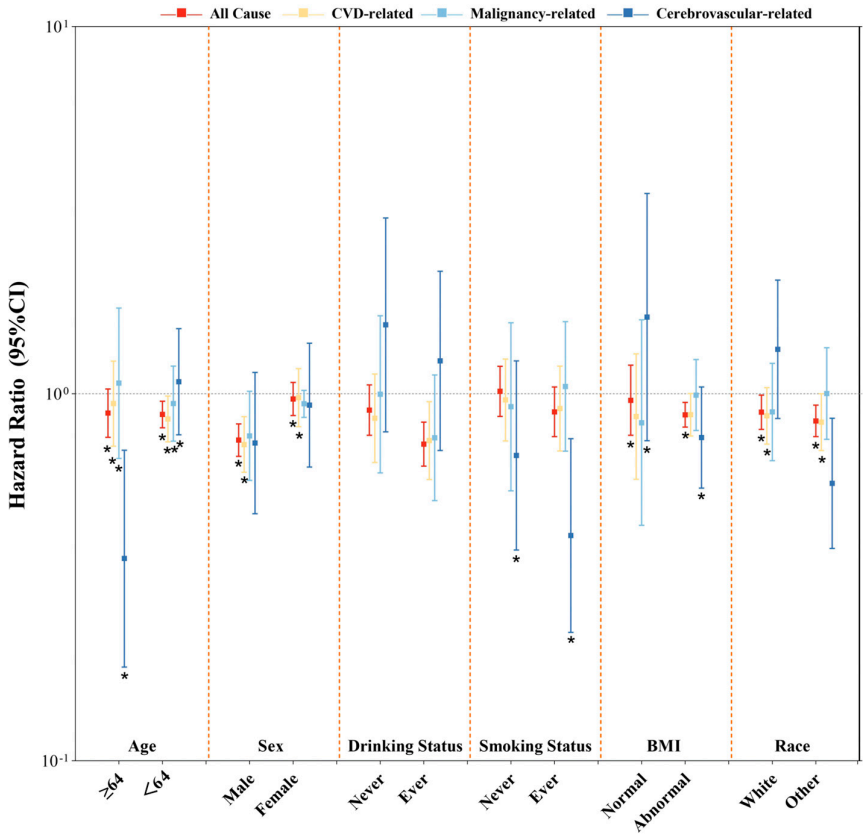

Figure 5. Stratified analyses of the associations of HALP score wtih all-cause mortality and cause-specific death in T2DM with impaired kidney function in NHANES.The Hazard Ratio was derived using Cox proportional hazard regression. *P for interaction <0.05.

4. Discussion

Our study used data from the 1999–2018 NHANES multicenter retrospective cohort and the 2013–2022 Southwest China multicenter cross-sectional study to investigate the relationship between HALP score, renal function impairment in type 2 diabetes, and all-cause and cause-specific mortality in DKD patients. The findings suggest that HALP score was inversely associated with DKD incidence in type 2 diabetes. Although HALP score was not identified as a mediator in DKD, it significantly impacted the progression of DKD. Among the four HALP components, hemoglobin and albumin, key markers of nutritional status, showed the strongest association with renal impairment. Furthermore, higher HALP score were associated with decreased all-cause and CVD-related mortality in DKD. Additionally, this relationship may be modified by NSAIDs use and dietary fiber intake.

The HALP score, a novel immune-nutritional marker, has been studied in diabetic complications such as DR [24], while its relationship with DKD remains unexplored [14]. Current research mainly focuses on the predictive value of HALP in cancer and cardiovascular outcomes [25], leaving a gap in its implications for DKD and related mortality. This highlights the need for further research to determine whether the HALP score can serve as a reliable biomarker for assessing the risk of DKD and its associated all-cause and CVD-related mortality.

DKD in type 2 diabetes is closely linked to chronic low-grade inflammation, as elevated glucose and insulin resistance trigger inflammatory responses, further worsening insulin resistance and β-cell dysfunction [26]. Studies have also shown increased macrophage infiltration in the atherosclerotic lesions of DKD patients, likely driven by elevated cytokine levels. Activated

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macrophages release additional cytokines, promoting the synthesis of platelet-activating factors and adhesion molecules, further aggravating atherosclerosis [27]. This highlights the critical role of inflammation as a therapeutic target in managing CVD-related mortality in DKD patients. Additionally, diabetic patients often experience malnutrition due to a poor diet, digestive issues, or medication side effects. This worsens glycemic control, complicates diabetes management, and increases the risk of nephropathy progression [28]. Growing evidence shows that protein malnutrition is closely linked to the development and prognosis of renal disease [29]. Chronic inflammation combined with malnutrition significantly increases the risks of infection and mortality in DKD patients, leading to a poor prognosis [30–32]. The rational use of the HALP score in clinical practice for early assessment of inflammation and nutrition is essential for slowing nephropathy progression and reducing all-cause and CVD-related mortality in DKD patients.

We initially hypothesized that the HALP score might serve as an intermediary between diabetes and diabetic nephropathy; however, our findings did not support a mediating effect. This outcome may be attributed to data limitations, such as insufficient sample size and other contributing factors. Notably, further analysis revealed that HALP score played a significant antagonistic role in the progression of renal function impairment in type 2 diabetes. This may be attributed to the close relationship between the HALP score components (hemoglobin, albumin, lymphocyte count, platelet count) and DKD progression. First, lower hemoglobin levels, common in diabetic nephropathy, reflect impaired renal function due to reduced erythropoietin production and malnutrition in chronic disease states [33,34]. Second, hypoalbuminemia, commonly linked to massive proteinuria in diabetic nephropathy, results from significant protein loss in the urine, leading to decreased serum albumin levels. Hypoalbuminemia not only reflects severely impaired renal filtration but also contributes to edema, malnutrition, and increased infection risk, further accelerating the progression of diabetic nephropathy [35]. Third, changes in lymphocyte count, critical for immune regulation, may reflect immune dysfunction in DKD. Abnormal lymphocyte levels can influence inflammatory responses, infection, and other factors, contributing to the progression of diabetic nephropathy [36]. Accumulating evidence suggests that chronic inflammation and neutrophils play pathogenic roles in DKD. Elevated circulating neutrophil counts are significantly associated with renal abnormalities in patients with type 2 diabetes and DKD, and are also linked to higher all-cause and CVD-related mortality in this population [37]. Fourth, platelet count has limited diagnostic value in identifying patients with type 2 diabetes at risk of developing DKD [38]. The findings align with previous studies, showing that hemoglobin and albumin are stronger indicators of nephropathy progression risk, with lymphocytes playing a secondary role and platelets having a weaker influence.

These findings underscore the critical roles of both nutrition and inflammation in the progression of diabetic nephropathy, highlighting the need to address both factors in managing the disease prognosis. First, adjusting dietary fiber intake supports nutritional management. Previous studies have shown that a high-fiber diet regulates blood glucose, slows carbohydrate digestion, and reduces postprandial glucose spikes, with soluble fibers particularly effective in lowering blood lipids and reducing cardiovascular burden [39]. Second, anti-inflammatory drugs can reduce inflammation, enhance insulin sensitivity, improve glucose control, and lower the risk of complications such as DKD [40]. Our findings support this, showing that HALP is linked to higher all-cause and CVD-related mortality in patients with type 2 diabetes, especially in those with low fiber intake and no NSAIDs use. Thus, our study confirms that the HALP score is a comprehensive indicator of nutritional and inflammatory status, underscoring the importance of assessing anti-inflammatory drug use, such as NSAIDs, and fiber intake to slow disease progression.

This study has significant clinical and public health implications. First, HALP should be incorporated into the routine management of type 2 diabetes, especially in DKD. As a dual indicator, HALP provides a more comprehensive assessment of patients' nutritional and inflammatory status, aiding in early identification of high-risk individuals and enabling timely preventive measures to delay disease progression. Additionally, both nutrition and inflammation are reversible factors. Dietary fiber and anti-inflammatory drugs can modify HALP levels, potentially slowing disease

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progression and reducing adverse outcomes. Monitoring HALP provides an early indication of diabetic nephropathy and serves as a simple, effective biomarker for predicting prognosis.

To the best of our knowledge, this is the first study to demonstrate the association between HALP score and DKD progression, with additional mediation and interaction analyses.It is also the first to assess the HALP score in relation to all-cause and cause-specific mortality in DKD. This multicenter cohort study, conducted in China and the US, included diverse ethnicities, a rigorous design, and large sample sizes. Extensive sensitivity analyses further ensured the robustness of our findings.

This study has several limitations. First, NHANES provides validated diagnoses, but other variables are self-reported, which introduces the potential for bias. Second, causal inference is limited due to the observational nature of the study. Third, despite adjusting for multiple confounders, residual confounding, such as genetic susceptibility and medication use, may remain. Fourth, HALP score was only evaluated at enrollment, with no follow-up assessments over time. Finally, the lack of follow-up data in the Southwest China cohort limits further analysis. NHANES currently does not collect information on OTC medications, which could result in misclassifying participants exposed to OTC NSAIDs but not taking prescription NSAIDs. However, this bias is likely minimal when prescription NSAID use is low (below 35%) compared to OTC NSAIDs use [41].

5. Conclusions

In conclusion, the HALP score is inversely associated with DKD risk in type 2 diabetes, with higher scores linked to lower all-cause and CVD-related mortality. Strategies to raise HALP, such as increased dietary fiber intake and NSAIDs use, may help reduce mortality risks. Regular monitoring of the HALP score could aid in risk stratification and clinical decisions for managing DKD in type 2 diabetes.

Supplementary Materials: The following supporting information can be downloaded at website of this paper posted on Preprints.org, Supplemental Figures: Supplementary Figure 1-8; Supplementary Tables: Supplementary Table 1-33.

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Institutional Review Board Statement: Not applicable

Informed Consent Statement: Patient consent was exempted due to the retrospective nature of

this study.

Data Availability Statement: Publicly available datasets were analyzed in this study. Data from the National Health and Nutrition Examination Survey (NHANES) can be found here: https://www.cdc.gov/nchs/nhanes/index.htm. And data from the Southwest China can be accessed here: https://www.yiducloud.com.cn/research/index.html.

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Conflicts of Interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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