Original Article

L-shaped association between the ratio of serum albumin to globulin and the risk of all-cause mortality among adults with kidney stones: a national cohort study

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Background: Kidney stones are a common urological disease with rising global prevalence and are influenced by immune, metabolic, and nutritional factors. The ratio of serum albumin to globulin, a marker of inflammation and nutritional status, has been linked to various inflammatory and chronic conditions, but its role in kidney stone risk and outcomes remains unclear. We aimed to determine the association between ratio of serum albumin to globulin and risk of kidney stones, as well as the impact of ratio of serum albumin to globulin on all-cause mortality in participants with kidney stones.

Methods: Multivariable logistic regression was used to explore the association between ratio of serum albumin to globulin and the risk of kidney stones. Multivariate Cox regression and restricted cubic spline (RCS) were performed to clarify the relationship between ratio of serum albumin to globulin and the risk of all-cause mortality.

Results: Among 31,091 study participants, 2,955 (9.5%) individuals had kidney stones. Multivariable logistic models demonstrated that each standard deviation (SD) increase in the ratio of serum albumin to globulin (SD =0.30) was associated with a 6% reduction in kidney stone risk. A total of 387 (13.1%) participants with kidney stones died for any reasons during a median follow-up of 6.2 years. The multivariable Cox model showed a significantly lower risk of all-cause mortality in the quartile (Q)2, Q3, and Q4 groups as compared to Q1 [Q2: adjusted hazard ratio (aHR) =0.84, 95% confidence interval (CI): 0.63–1.11; Q3: aHR =0.65, 95% CI: 0.48–0.86; Q4: aHR =0.63, 95% CI: 0.46–0.86; P for trend =0.04].

Conclusions: A lower ratio of serum albumin to globulin was associated with an increased risk of kidney stones. Additionally, our study showed that at a cutoff point of 1.5, the association between ratio of serum albumin to globulin and all-cause mortality in participants with kidney stones was nonlinear L-shaped. However, due to the observational nature of the study, our study results should be interpreted with caution.

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Keywords: Kidney stones; ratio of serum albumin to globulin; all-cause mortality; National Health and Nutrition Examination Survey (NHANES); prospective cohort study

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Introduction

Kidney stones are a common urological disease, with the prevalence increasing globally in recent decades (1,2). Emerging evidence suggests that anatomical characteristics of the urinary system, immune and metabolic status, and nutritional factors play a significant role in kidney stone formation (3). Serum albumin and serum globulin, which constitute approximately 85% of total serum protein, are used to calculate the ratio of serum albumin to globulin. This ratio has been used as a biomarker for assessing inflammation and nutritional status in individuals (4-6). Recent studies have found that the ratio of serum albumin to globulin is also associated with risk of inflammatory conditions including inflammatory bowel disease, rheumatoid arthritis, systemic lupus erythematosus, and chronic kidney disease (7-10). Moreover, patients with a low ratio of serum albumin to globulin were associated with an increased risk of inflammatory diseases. Meanwhile, several studies have indicated that ratio of serum albumin to globulin might serve as noninvasive prognostic indicators for patients with diabetes, acute ischemic stroke, and malignancy (11-19), with it being reported that patients with a low ratio of serum albumin to globulin are associated with poorer survival.

However, the association between the ratio of serum albumin to globulin and risk of kidney stones remains unknown. Given the role of chronic inflammation and nutritional status in the pathogenesis of kidney stones (20-22), we hypothesized that the ratio of serum albumin to globulin is an independent risk factor for kidney stones and potentially associated with long-term outcomes in individuals with kidney stones.

Therefore, this study used a nationwide database to determine the association of the ratio of serum albumin to globulin with the risk of kidney stones and all-cause mortality in participants with kidney stones. We present this article in accordance with the STROBE reporting checklist (23) (available at https://tau.amegroups.com/article/view/10.21037/tau-2025-127/rc).

Highlight box

Key findings

- A decreased ratio of serum albumin to globulin correlates with a higher likelihood of developing kidney stones.
- At a cutoff point of 1.5, the ratio of serum albumin to globulin evidenced a nonlinear L-shaped association with all-cause mortality in individuals with kidney stones.

What is known and what is new?

- It is known that the ratio of serum albumin to globulin serves as a marker for inflammation and nutritional status and is associated with various inflammatory diseases and chronic conditions.
- This study adds evidence regarding the relationship between the ratio of serum albumin to globulin and kidney stone risk, as well as its prognostic value for all-cause mortality among patients with kidney stones.

What is the implication, and what should change now?

- The ratio of serum albumin to globulin may serve as a noninvasive biomarker for identifying individuals at higher risk of kidney stones and poor outcomes.
- Our findings suggest that maintaining a relatively high ratio of serum albumin to globulin can help reduce the risk of kidney stones and improve long-term outcomes.

Methods

Study design, population, and data source

The study population was drawn from the National Health and Nutrition Examination Survey (NHANES) database, which has been described previously elsewhere (24-26). The data could be accessed on the NHANES official website (https://www.cdc.gov/nchs/nhanes/). In brief, the NHANES is an ongoing, biannual survey designed to monitor the health and nutritional status of the United States (US) population through a complex, multistage probability sampling method. The data used in this study spanned from 2007 to 2018, covering six survey cycles (including 2007–2008, 2009–2010, 2011–2012, 2013–2014, 2015–2016, and 2017–2018), and were collected via face-

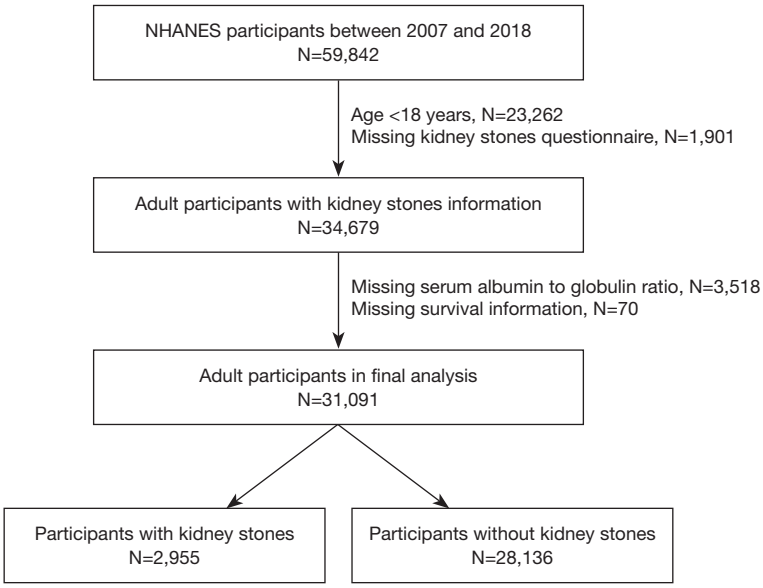

Figure 1 Flowchart of participant selection. NHANES, National Health and Nutrition Examination Survey.

to-face structured interviews, physical examinations, and laboratory tests. All NHANES protocols received approval from the Centers for Disease Control and Prevention National Center for Health Statistics Ethics Review Board, and participants provided informed written consent prior to participation.

We identified 59,842 participants between 2007 and 2018 from the NHANES database. We first excluded participants aged <18 years (n=23,262) and those without information on kidney stone status (n=1,901). Of the 34,679 adult participants, we further excluded those without information on the ratio of serum albumin to globulin (n=3,518) and survival (n=70). Finally, a total of 31,091 participants were included in the analysis (*Figure 1*). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Assessment of the ratio of serum albumin to globulin, kidney stones, and mortality

The ratio of serum albumin to globulin was calculated using the following equation: serum albumin (g/L)/serum globulin (g/L). In this study, we determined the presence of kidney stones among participants via the following questionnaire item: "Have you ever had kidney stones?". Participants were considered to have kidney stones if they responded yes to the question.

The mortality information for each participant in the NHANES database was linked to the National Death Index (NDI) death certificate records until December 31, 2019 (https://www.cdc.gov/nchs/data-linkage/mortality-public.htm). The International Classification of Diseases, 10th revision (ICD-10) diagnosis codes were used to determine the specific cause of death. The primary outcome in this study was all-cause mortality. Cardiovascular (CV) mortality was defined as any death related to heart disease (codes I00–I09, I11, I13, and I20–I51) or cerebrovascular disease (codes I60–I69) (27,28). Cancer mortality was defined as codes C00–C97 (29,30). Deaths from other causes were considered to be non-CV/cancer mortality. Individuals were followed up until the date of death or the end of the maximum follow-up date (December 31, 2019), whichever came first.

Covariates

We collected individuals' sociodemographic information, vital signs, comorbidities, and laboratory serum findings. Specifically, the sociodemographic information included age, sex, race and ethnicity, and education. Vital signs included body mass index (BMI), systolic blood pressure (SBP), and diastolic blood pressure (DBP). Comorbidities included hypertension, diabetes, congestive heart failure, coronary heart disease, and malignancy. Laboratory serum

tests included albumin, globulin, serum creatinine (SCr), triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), glycated hemoglobin A1c (HbA1c), uric acid (UA), blood urea nitrogen (BUN), white blood cell count (WBC), mean cell hemoglobin concentration (MCHC), alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT). The estimated glomerular filtration rate (eGFR) was calculated via the 2021 ethnicity-independent Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (31). Comorbidities were determined through questionnaire items. For example, when a participant was asked "Have you ever been told you have high blood pressure?" by experienced research staff, if the response was yes, we considered the participant to have hypertension; otherwise, hypertension was considered absent.

Handling of missing variables

In the final analysis dataset, data on SCr, eGFR, BUN, GGT, HDL-C, TC, TG, UA, and ALT were missing in fewer than 0.1% of participants, while data on AST, education, HbA1c, WBC, MCHC, BMI, SBP, and DBP were missing in 0.1%, 0.1%, 0.2%, 0.2%, 0.2%, 1.2%, 3.8%, and 3.8% of participants, respectively. We imputed missing values using the random forest imputation method from the "randomForest" R package (The R Foundation for Statistical Computing) (32).

Statistical analysis

Continuous variables are presented as the mean ± standard deviation (SD) or as the median with the 25th and 75th percentiles, and intergroup comparisons were performed using analysis of variance (ANOVA) and the Kruskal-Wallis rank-sum test. Categorical variables are expressed as frequencies (percentages) and were compared using the Chi-squared test.

Multivariable logistic regression was used to examine the association between the ratio of serum albumin to globulin and the risk of kidney stones. Model 1 adjusted for sex, age, and race and ethnicity. Model 2 further adjusted for education, SBP, hypertension, diabetes, congestive heart failure, coronary heart disease, and malignancy. Model 3 (full model) adjusted for, in addition to the variables included in Model 2, BMI, TC, TG, BUN, UA, HbA1c, WBC, eGFR, MCHC, AST, and GGT. The odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) are reported.

In participants with kidney stones, we also performed restricted cubic spline (RCS) Cox regression (adjusted for variables in Model 2) to test for linearity and characterize the dose-response relationships between the ratio of serum albumin to globulin and all-cause mortality. Kaplan-Meier (KM) curves and log-rank tests were employed to assess the cumulative incidence of all-cause mortality across quartile (Q)1 to Q4 for the ratio of serum albumin to globulin. We used multivariable Cox models, with Models 1, 2, and 3 adjusting for the same variables as those mentioned above, to clarify the association between the ratio of serum albumin to globulin and risk of all-cause mortality, with hazard ratios (HRs) and their corresponding 95% CIs being presented.

Subgroup analysis

To identify the potential effect modifiers for the relationship between ratio of serum albumin to globulin, the risk of kidney stones, and the risk of all-cause mortality, we employed several subgroup analyses stratified by age (<60 *vs.* ≥60 years), sex (male *vs.* female), BMI (<28 *vs.* ≥28 kg/m^2), hypertension (yes *vs.* no), diabetes (yes *vs.* no), congestive heart failure (yes *vs.* no), coronary heart disease (yes *vs.* no), malignancy (yes *vs.* no), and eGFR (<60 *vs.* ≥60 mL/min/1.73 m^2). An interaction term was added to each logistic/Cox regression model to assess effect modification.

Sensitivity and additional analyses

We conducted several sensitivity analyses to verify the robustness of the results. First, considering that malignancy was an important risk factor for mortality, we reanalyzed the data after excluding participants with malignancy. Second, participants with a follow-up time of less than 1 year were excluded to minimize the potential for reverse causality. As mentioned above, we categorized causes of death based on ICD-10 diagnostic codes into CV mortality, cancer mortality, and non-CV/cancer mortality, and examined the association between the ratio of serum albumin to globulin and specific causes of death in participants with kidney stones.

All statistical analyses were performed using R version 4.1.2. A two-sided P value <0.05 was considered statistically significant.

Results

Baseline characteristics of the study population

We included a total of 31,091 participants from the NHANES database with information on the ratio of serum albumin to globulin (*Figure 1*). Among them, 2,955 (9.5%) had kidney stones. The mean age of the study population was 49.8±17.7 years, with 48.5% being male, and the mean ratio of serum albumin to globulin was 1.48±0.30. The baseline characteristics of participants stratified by kidney stones are presented in *Table 1*. Participants with kidney stones, as compared to those without kidney stones, were older (56.1 *vs.* 49.1 years), had a higher proportion of females (52.3% *vs.* 44.1%), a higher proportion of non-Hispanic Whites ethnicity (54.3% *vs.* 40.0%), and a higher prevalence of comorbidities such as hypertension, diabetes, congestive heart failure, coronary heart disease, and malignancy. The quartile ranges for the ratio of serum albumin to globulin were as follows: Q1, <1.28; Q2, 1.28 to <1.46; Q3, 1.46 to <1.66; and Q4, ≥1.66. The baseline characteristics of participants stratified by ratio of serum albumin to globulin levels are shown in Table S1. Among the 2,955 individuals with kidney stones, as the ratio of serum albumin to globulin levels increased, the BMI gradually decreased, and the prevalence of hypertension, diabetes, congestive heart failure, and the levels of TG, UA, HbA1c, and WBC (*Table 2*) also decreased. The baseline characteristics of the participants with kidney stones stratified by survival status are shown in Table S2.

Association between the ratio of serum albumin to globulin and risk of kidney stones

The RCS curve indicated a negative linear relationship between the ratio of serum albumin to globulin and the risk of kidney stones (P for nonlinearity =0.67; *Figure 2A*). Multivariable logistic models indicated that a higher ratio of serum albumin to globulin levels was associated with a lower risk of kidney stones (*Table 3*). In Model 1, after adjustments were made for sex, age, and race and ethnicity, each SD increase in the ratio of serum albumin to globulin (SD =0.30) was associated with a 12% reduction in kidney stone risk [adjusted OR (aOR) =0.88; 95% CI: 0.84–0.92]. This association remained significant in Model 2, which further adjusted for additional comorbidities (aOR =0.90; 95% CI: 0.87–0.94). In the fully adjusted Model 3, the association was slightly attenuated (aOR =0.94; 95% CI: 0.90–0.98). Compared to that in the Q1 group, the risk of kidney stones was lower in the Q2, Q3, and Q4 groups (P for trend =0.03), with the lowest risk observed in the Q4 group (aOR =0.87; 95% CI: 0.77–0.98).

Association between the ratio of serum albumin to globulin and risk of all-cause mortality in participants with kidney stones

The RCS curve revealed a nonlinear L-shaped relationship between the ratio of serum albumin to globulin and all-cause mortality in the population with kidney stones (*Figure 2B*). As the ratio of serum albumin to globulin increased, the risk of all-cause mortality progressively decreased, but this reduction plateaued when the ratio of serum albumin to globulin exceeded 1.5. The KM curve demonstrated that the cumulative risk of all-cause mortality was highest in the Q1 group (*Figure 3*). During a median follow-up of 6.2 years, the number of deaths from any cause sorted by quartiles of ratio of serum albumin to globulin were as follows: 132 (17.9%) in Q1, 93 (12.6%) in Q2, 91 (12.3%) in Q3, and 71 (10.0%) in Q4. The multivariable Cox model showed a significantly lower risk of all-cause mortality in the Q2, Q3, and Q4 groups as compared to the Q1 group [Q2: adjusted HR (aHR) =0.84, 95% CI: 0.63–1.11; Q3: aHR =0.65, 95% CI: 0.48–0.86; Q4: aHR =0.63, 95% CI: 0.46–0.86; P for trend =0.04; *Table 4*]. When Q2 and Q3 were combined, the results remained consistent (Q2–3: aHR =0.73, 95% CI: 0.58–0.94; Q4: aHR =0.63, 95% CI: 0.46–0.87; P for trend =0.002; *Table 4*).

The threshold analysis consistently found that, for each increase in SD (SD =0.30) for the ratio of serum albumin to globulin, there was a 36% decrease in all-cause mortality (aHR =0.64; 95% CI: 0.51–0.80; *Table 4*) in participants with ratio of serum albumin to globulin <1.5, whereas a similar relationship was not observed in participants with a ratio ≥1.5 (aHR =0.99; 95% CI: 0.75–1.30; *Table 4*).

Subgroup analysis

Subgroup analyses indicated a consistent association between the ratio of serum albumin to globulin and risk of kidney stones (*Figure 4*). None of the variables, including age, sex, BMI, hypertension, diabetes, congestive heart failure, coronary heart disease, malignancy, or eGFR, significantly modified the association between the ratio of serum albumin to globulin and kidney stones (all P values for interaction >0.05). The relationship between the ratio of serum albumin to globulin and risk of all-cause death in

Table 1 Baseline characteristics of participants stratified by presence of kidney stones

Variables	Overall (n=31,091)	Kidney stones		P value
		No (n=28,136)	Yes (n=2,955)	
Ratio of serum albumin to globulin	1.48±0.30	1.48±0.30	1.47±0.29	0.09
Age (years)	49.8±17.7	49.1±17.7	56.1±16.2	<0.001
Male	16,023 (51.5)	14,719 (52.3)	1,304 (44.1)	<0.001
BMI (kg/m^2)	29.3±7.0	29.1±7.0	30.5±7.0	<0.001
Ethnicity				<0.001
Mexican American	4,747 (15.3)	4,359 (15.5)	388 (13.1)	
Other Hispanic	3,281 (10.6)	2,953 (10.5)	328 (11.1)	
Non-Hispanic White	12,849 (41.3)	11,245 (40.0)	1,604 (54.3)	
Non-Hispanic Black	6,403 (20.6)	6,025 (21.4)	378 (12.8)	
Other race	3,811 (12.3)	3,554 (12.6)	257 (8.7)	
Education				0.64
Less than high school	7,675 (24.7)	6,925 (24.6)	750 (25.4)	
High school grade or equivalent	7,076 (22.8)	6,405 (22.8)	671 (22.7)	
Some college or above	16,340 (52.6)	14,806 (52.6)	1,534 (51.9)	
SBP (mmHg)	124.2±18.3	124.0±18.3	126.9±18.7	<0.001
DBP (mmHg)	70.2±12.6	70.2±12.6	70.6±12.9	0.11
Hypertension	11,276 (36.3)	9,776 (34.7)	1,500 (50.8)	<0.001
Diabetes	4,121 (13.3)	3,451 (12.3)	670 (22.7)	<0.001
Congestive heart failure	1,025 (3.3)	835 (3.0)	190 (6.4)	<0.001
Coronary heart disease	1,276 (4.1)	1,035 (3.7)	241 (8.2)	<0.001
Malignancy	2,932 (9.4)	2,485 (8.8)	447 (15.1)	<0.001
TG (mmol/L)	1.4 (0.9, 2.1)	1.4 (0.9, 2.1)	1.5 (1.0, 2.3)	<0.001
TC (mmol/L)	4.9 (4.2, 5.6)	4.9 (4.2, 5.6)	4.9 (4.2, 5.6)	0.007
HDL-C (mmol/L)	1.3 (1.1, 1.6)	1.3 (1.1, 1.6)	1.2 (1.0, 1.5)	<0.001
BUN (mmol/L)	4.6 (3.6, 5.7)	4.6 (3.6, 5.7)	5.0 (3.9, 6.4)	<0.001
UA (mg/dL)	5.5±1.5	5.4±1.5	5.6±1.5	<0.001
HbA1c (%)	5.8±1.1	5.8±1.1	6.0±1.2	<0.001
WBC (×10^9/L)	6.9 (5.7, 8.4)	6.9 (5.7, 8.4)	7.1 (5.9, 8.5)	<0.001
MCHC (g/L)	33.9±1.1	33.9±1.1	33.9±1.1	0.12
eGFR (mL/min/1.73 m^2)	97.3 (80.4, 111.5)	98.1 (81.2, 112.0)	90.7 (73.3, 105.5)	<0.001
Albumin (g/L)	42.2±3.5	42.3±3.5	41.7±3.4	<0.001
Globulin (g/L)	29.4±4.6	29.4±4.6	29.2±4.6	0.051
ALT (U/L)	20.0 (16.0, 28.0)	20.0 (16.0, 28.0)	21.0 (16.0, 28.0)	0.003
AST (U/L)	23.0 (19.0, 27.0)	23.0 (19.0, 27.0)	23.0 (19.0, 28.0)	0.11
GGT (U/L)	20.0 (14.0, 31.0)	20.0 (14.0, 30.0)	21.0 (15.0, 33.0)	<0.001

Data are presented as mean ± SD, n (%), or median (25th percentile, 75th percentile). ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; GGT, gamma-glutamyltransferase; HbA1c, glycated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; MCHC, mean cell hemoglobin concentration; SBP, systolic blood pressure; SD, standard deviation; TC, total cholesterol; TG, triglyceride; UA, uric acid; WBC, white blood cell count.

Table 2 Baseline characteristics of participants with kidney stones stratified by the ratio of serum albumin to globulin

Variables	Overall (n=2,955)	Quartiles for the ratio of serum albumin to globulin			P value
		Q1 (n=739)	Q2–Q3 (n=1,477)	Q4 (n=739)	
Ratio of serum albumin to globulin	1.47±0.29	1.12±0.13	1.46±0.11	1.84±0.19	<0.001
Age (years)	56.1±16.2	57.7±15.8	55.7±16.2	55.0±16.6	0.003
Male	1,651 (55.9)	336 (45.5)	827 (56.0)	488 (66.0)	<0.001
BMI (kg/m^2)	30.5±7.0	33.9±8.1	30.3±6.6	28.5±5.7	<0.001
Ethnicity					<0.001
Mexican American	388 (13.1)	126 (17.1)	184 (12.5)	78 (10.6)	
Other Hispanic	328 (11.1)	95 (12.9)	171 (11.6)	62 (8.4)	
Non-Hispanic White	1,604 (54.3)	283 (38.3)	817 (55.3)	504 (68.2)	
Non-Hispanic Black	378 (12.8)	161 (21.8)	174 (11.8)	43 (5.8)	
Other race	257 (8.7)	74 (10.0)	131 (8.9)	52 (7.0)	
Education					<0.001
Less than high school	750 (25.4)	249 (33.7)	360 (24.4)	141 (19.1)	
High school grade or equivalent	671 (22.7)	157 (21.2)	338 (22.9)	176 (23.8)	
Some college or above	1,534 (51.9)	333 (45.1)	779 (52.7)	422 (57.1)	
SBP (mmHg)	126.9±18.7	129.7±19.8	126.5±18.5	125.1±17.8	<0.001
DBP (mmHg)	70.6±12.9	70.9±14.1	70.6±12.6	70.3±12.1	0.73
Hypertension	1,500 (50.8)	435 (58.9)	750 (50.8)	315 (42.6)	<0.001
Diabetes	670 (22.7)	228 (30.9)	328 (22.2)	114 (15.4)	<0.001
Congestive heart failure	190 (6.4)	84 (11.4)	77 (5.2)	29 (3.9)	<0.001
Coronary heart disease	241 (8.2)	73 (9.9)	100 (6.8)	68 (9.2)	0.02
Malignancy	447 (15.1)	116 (15.7)	203 (13.7)	128 (17.3)	0.08
TG (mmol/L)	1.5 (1.0, 2.3)	1.5 (1.0, 2.2)	1.6 (1.1, 2.3)	1.51 (1.0, 2.4)	0.40
TC (mmol/L)	4.9 (4.2, 5.6)	4.8 (4.1, 5.6)	4.9 (4.2, 5.6)	4.9 (4.2, 5.6)	0.49
HDL-C (mmol/L)	1.2 (1.0, 1.5)	1.2 (1.0, 1.5)	1.2 (1.0, 1.5)	1.2 (1.0, 1.6)	0.14
BUN (mmol/L)	5.0 (3.9, 6.4)	5.0 (3.9, 6.8)	5.0 (3.9, 6.4)	5.0 (3.9, 6.3)	0.72
UA (mg/dL)	5.6±1.5	5.8±1.7	5.7±1.5	5.5±1.4	0.004
HbA1c (%)	6.0±1.2	6.4±1.5	6.0±1.1	5.7±0.9	<0.001
WBC (×10^9/L)	7.1 (5.9, 8.5)	7.5 (6.1, 9.2)	7.1 (5.9, 8.5)	6.7 (5.7, 7.9)	<0.001
MCHC (g/L)	33.9±1.1	33.6±1.2	33.9±1.0	34.1±1.0	<0.001
eGFR (mL/min/1.73 m^2)	90.7 (73.3, 105.5)	88.5 (66.0, 105.8)	90.7 (74.6, 106.4)	92.36 (76.0, 104.3)	0.002
Albumin (g/L)	41.7±3.4	38.6±3.2	42.0±2.6	44.4±2.5	<0.001
Globulin (g/L)	29.2±4.6	34.9±3.8	28.8±2.3	24.2±2.1	<0.001
ALT (U/L)	21.0 (16.0, 28.0)	19.0 (14.0, 27.0)	21.0 (17.0, 29.0)	22.0 (17.0, 30.0)	<0.001
AST (U/L)	23.0 (19.0, 28.0)	22.0 (18.0, 28.0)	23.0 (19.0, 28.0)	23.0 (20.0, 28.0)	<0.001
GGT (U/L)	21.0 (15.0, 33.0)	24.0 (16.0, 39.0)	21.0 (15.0, 32.0)	20.0 (15.0, 29.0)	<0.001

Data are presented as mean ± SD, n (%), or median (25th percentile, 75th percentile). ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; GGT, gamma-glutamyltransferase; HbA1c, glycated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; MCHC, mean cell hemoglobin concentration; SBP, systolic blood pressure; SD, standard deviation; TC, total cholesterol; TG, triglyceride; UA, uric acid; WBC, white blood cell count.

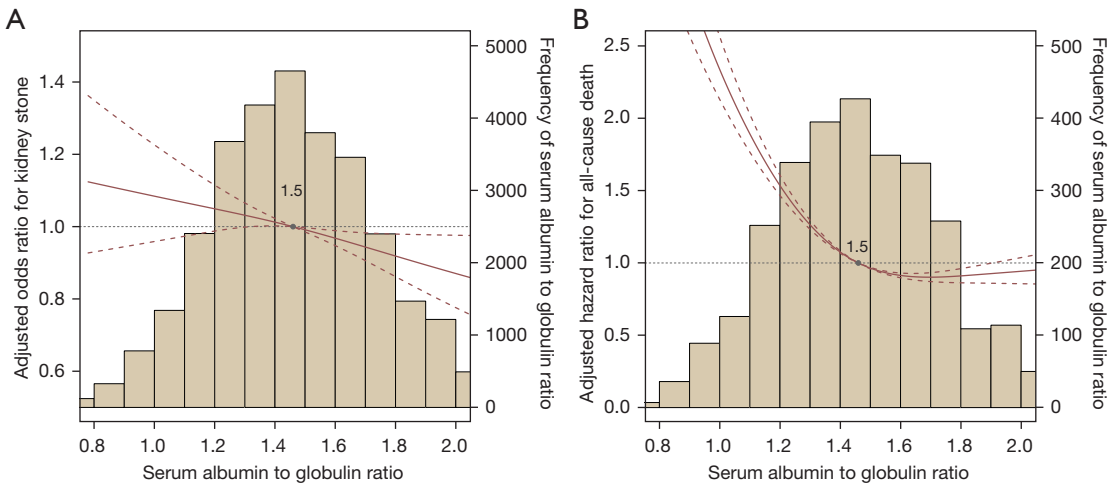

Figure 2 Association of the ratio of serum albumin to globulin with (A) the risk of kidney stones and (B) risk of all-cause mortality in participants with kidney stones. The model was adjusted for sex, age, race and ethnicity, education, SBP, hypertension, diabetes, congestive heart failure, coronary heart disease, malignancy, BMI, TC, TG, BUN, UA, HbA1c, WBC, eGFR, MCHC, AST, and GGT. AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; GGT, gamma-glutamyltransferase; HbA1c, glycated hemoglobin A1c; MCHC, mean cell hemoglobin concentration; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; UA, uric acid; WBC, white blood cell count.

Table 3 The association between the ratio of serum albumin to globulin and the risk of kidney stones

Ratio of serum albumin to globulin	Total, n	No. of events (%)	Model 1		Model 2		Model 3	
			OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Quartile								
Q1 (<1.28)	7,773	770 (9.9)	Ref.		Ref.		Ref.	
Q2 (1.28 to <1.46)	7,773	723 (9.3)	0.85 (0.76, 0.94)	0.003	0.88 (0.79, 0.98)	0.02	0.92 (0.82, 1.03)	0.14
Q3 (1.46 to <1.66)	7,772	733 (9.4)	0.81 (0.72, 0.90)	<0.001	0.86 (0.77, 0.96)	0.008	0.92 (0.82, 1.03)	0.17
Q4 (≥1.66)	7,773	729 (9.4)	0.74 (0.66, 0.83)	<0.001	0.79 (0.71, 0.89)	<0.001	0.87 (0.77, 0.98)	0.03
P for trend				<0.001		<0.001		0.04
Continuous (SD =0.30)								
Per SD increasement	31,091	2,955 (9.5)	0.88 (0.84, 0.92)	<0.001	0.90 (0.87, 0.94)	<0.001	0.94 (0.90, 0.98)	0.003

Model 1: adjustments for sex, age, and race and ethnicity. Model 2: Model 1 + further adjustments for education, SBP, hypertension, diabetes, congestive heart failure, coronary heart disease, and malignancy. Model 3 (full model): Model 2 + further adjustments for BMI, TC, TG, BUN, UA, HbA1c, WBC, eGFR, MCHC, AST, and GGT. AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; CI, confidence interval; eGFR, estimated glomerular filtration rate; GGT, gamma-glutamyltransferase; HbA1c, glycated hemoglobin A1c; MCHC, mean cell hemoglobin concentration; OR, odds ratio; Q, quartile; ref., reference; SBP, systolic blood pressure; SD, standard deviation; TC, total cholesterol; TG, triglyceride; UA, uric acid; WBC, white blood cell count.

different subgroups were presented in Figure S1.

Sensitivity and additional analyses

The results of several sensitivity analyses indicated that a lower ratio of serum albumin to globulin was associated with a higher risk of all-cause mortality, which remained consistent with the original findings (Table S3). The results of additional analyses were presented in Table S4. Our results did not find a significant association between

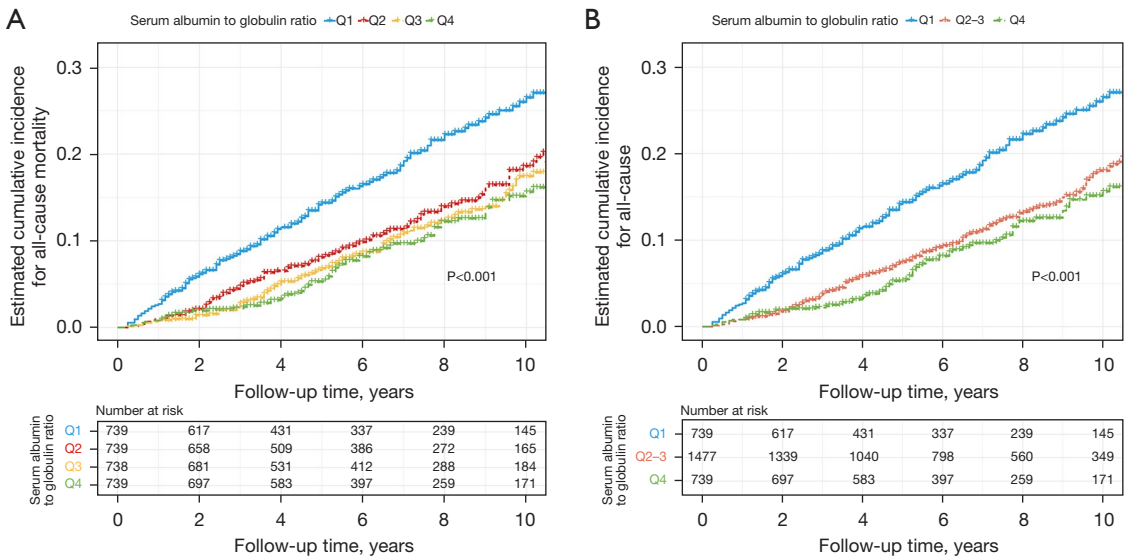

Figure 3 Estimated cumulative incidence of all-cause mortality stratified by (A) the quartiles of the ratio of serum albumin to globulin and by (B) the categories of the ratio of serum albumin to globulin. Q, quartile.

Table 4 The association between the ratio of serum albumin to globulin and the risk for all-cause mortality in participants with kidney stones

Ratio of serum albumin to globulin	Total, n	No. of events (%)	Model 1		Model 2		Model 3	
			HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Quartile								
Q1 (<1.28)	739	132 (17.9)	Ref.		Ref.		Ref.	
Q2 (1.28 to <1.46)	738	93 (12.6)	0.65 (0.50, 0.85)	0.002	0.74 (0.56, 0.97)	0.03	0.84 (0.63, 1.11)	0.21
Q3 (1.46 to <1.66)	739	91 (12.3)	0.52 (0.40, 0.69)	<0.001	0.55 (0.41, 0.72)	<0.001	0.65 (0.48, 0.86)	0.003
Q4 (≥1.66)	739	74 (10.0)	0.44 (0.33, 0.60)	<0.001	0.53 (0.39, 0.71)	<0.001	0.63 (0.46, 0.86)	0.004
P for trend				<0.001		<0.001		0.04
Category								
Q1 (<1.28)	739	132 (17.9)	Ref.		Ref.		Ref.	
Q2–Q3 (1.28 to <1.66)	1,477	184 (12.5)	0.58 (0.46, 0.73)	<0.001	0.63 (0.50, 0.79)	<0.001	0.73 (0.58, 0.94)	0.01
Q4 (≥1.66)	739	74 (10.0)	0.45 (0.33, 0.60)	<0.001	0.53 (0.39, 0.71)	<0.001	0.63 (0.46, 0.87)	0.004
P for trend				<0.001		<0.001		0.002
Continuous per SD increase (SD =0.30)								
<1.5	1,613	244 (15.1)	0.49 (0.40, 0.61)	<0.001	0.56 (0.45, 0.69)	<0.001	0.64 (0.51, 0.80)	<0.001
≥1.5	1,342	146 (10.9)	0.93 (0.71, 1.23)	0.62	0.98 (0.75, 1.29)	0.90	0.99 (0.75, 1.30)	0.94

Model 1: adjustments for sex, age, and race and ethnicity. Model 2: Model 1 + further adjustments for education, SBP, hypertension, diabetes, congestive heart failure, coronary heart disease, and malignancy. Model 3 (full model): Model 2 + further adjustments for BMI, TC, TG, BUN, UA, HbA1c, WBC, eGFR, MCHC, AST, and GGT. AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; CI, confidence interval; eGFR, estimated glomerular filtration rate; GGT, gamma-glutamyltransferase; HbA1c, glycated hemoglobin A1c; HR, hazard ratio; MCHC, mean cell hemoglobin concentration; Q, quartile; ref., reference; SBP, systolic blood pressure; SD, standard deviation; TC, total cholesterol; TG, triglyceride; UA, uric acid; WBC, white blood cell count.

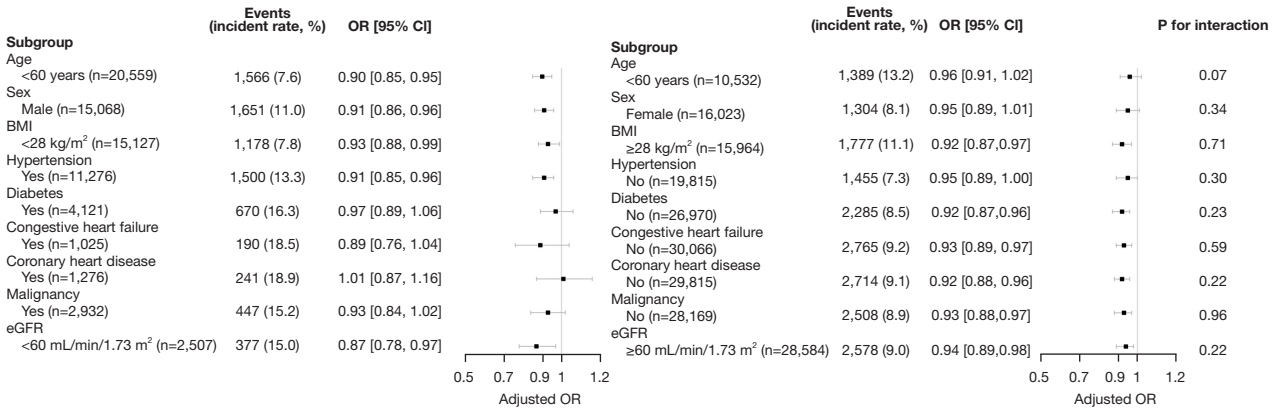

Figure 4 Subgroup analyses for the potential modifiers of the association between ratio of serum albumin to globulin and risk of kidney stones. The model was adjusted for sex, age, race and ethnicity, education, SBP, hypertension, diabetes, congestive heart failure, coronary heart disease, malignancy, BMI, TC, TG, BUN, UA, HbA1c, WBC, eGFR, MCHC, AST, and GGT. AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; CI, confidence interval; eGFR, estimated glomerular filtration rate; GGT, gamma-glutamyltransferase; HbA1c, glycated hemoglobin A1c; MCHC, mean cell hemoglobin concentration; OR, odds ratio; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; UA, uric acid; WBC, white blood cell count.

a higher ratio of serum albumin to globulin and CV and cancer mortality.

Discussion

To the best of our knowledge, this is the first study to examine the association between the ratio of serum albumin to globulin and the risk of kidney stones, as well as the long-term prognosis for individuals with kidney stones. In this nationally representative prospective cohort study, we found that the prevalence of kidney stones in the US population was 9.5% and that as the ratio of serum albumin to globulin increased, the risk of kidney stones decreased. Furthermore, in individuals with kidney stones, we observed an L-shaped nonlinear relationship between the ratio of serum albumin to globulin and long-term all-cause mortality. Compared to the Q1 group, the Q4 group was associated with a 37% lower risk of all-cause mortality. The lowest risk was observed when the ratio of serum albumin to globulin levels remained above 1.5.

The ratio of serum albumin to globulin reflected the body's nutritional status and its response to inflammation. The relationship between chronic inflammation and kidney stones has been widely studied (20,21). Capolongo *et al.* found that local inflammatory responses induced by NLRP3 inflammasome activation were closely associated with crystal formation (33). This "crystalline disease" might play a critical role in the pathophysiology of kidney stones. Moreover, it has been reported that anti-inflammatory agents such as aspirin, vitamin E, and green tea can decrease urinary oxalate excretion and the formation of calcium oxalate deposits (34-36).

Previous studies have shown that the ratio of serum albumin to globulin is associated with long-term prognosis in certain populations. Wen *et al.* enrolled 8,508 patients with diabetes (11), and the results showed that the quartile of patients with the highest ratio of serum albumin to globulin was associated with lower all-cause mortality (aHR =0.51; 95% CI: 0.42–0.60), lower CV mortality (aHR =0.62; 95% CI: 0.46–0.83), and lower cancer mortality (aHR =0.57; 95% CI: 0.39–0.85). Wang *et al.* also reported that the highest ratio of serum albumin to globulin quartile was correlated with a decreased risk of all-cause mortality at 3-month (aHR =0.58; 95% CI: 0.36–0.94) and 1-year (aHR =0.70; 95% CI: 0.51–0.96) follow-up, among patients with acute ischemic stroke (12). Additionally, in a meta-analysis including 21 studies comprising 18,269 patients with urinary system cancer (13), patients with a low ratio of serum albumin to globulin had a poor overall survival (aHR =1.93; 95% CI: 1.56–2.39) and cancer-specific survival (aHR =2.22; 95% CI: 1.67–2.96). Similar findings have been observed in other malignancies (17-19). Consistent with the findings of previous studies, our study also found that a higher ratio of serum albumin to globulin was associated with a lower risk of all-cause mortality in individuals with kidney stones. However, while there was a

negative relationship between the ratio of serum albumin to globulin and cancer mortality, this association did not reach statistical significance (P for trend =0.06), which might be attributed to the limited sample size. Our study further addressed the lack of data regarding the relationship between the ratio of serum albumin to globulin and long-term prognosis individuals with kidney stones, discovering that the highest quartile of ratio of serum albumin to globulin was associated with a 37% decreased risk of all-cause mortality. Our findings underscore the importance of maintaining a reasonable ratio of serum albumin to globulin in individuals with kidney stones.

This study has several strengths. First, the data were drawn from the NHANES database, which possesses good national representativeness. Moreover, we adjusted for potential confounders in the models as much as possible and conducted several sensitivity analyses, additional analyses, and subgroup analyses to ensure the robustness of our findings. Nonetheless, our study also involves certain limitations. First, due to the temporal ambiguity between precise timing of the ratio of serum albumin to globulin detection and onset of kidney stones, history of kidney stones evacuation, and observational nature of the study, we cannot draw causal inferences between the ratio of serum albumin to globulin, kidney stones, and long-term mortality. Second, since the study population was from the US, and further studies from other regions and countries are needed to validate these findings. Third, other potential confounding factors including unhealthy habits such as urinary retention and different treatment therapies for kidney stones are not available in the NHANES database (37,38), which reduces the comprehensiveness of our conclusions. Fourth, using of questionnaires to assess kidney stone exposure might lead to recall bias, particularly if individuals with clinical symptoms or more severe kidney stones were more likely to report their condition accurately. This could result in an overestimation of the association between the serum albumin to globulin and kidney stones. Finally, due to the absence of information on stones sizes and stones types, we could not further analyze the relationship between the ratio of serum albumin to globulin and long-term mortality in individuals with different kidney stone sizes.

Conclusions

We found that a lower ratio of serum albumin to globulin was associated with an increased risk of kidney stones in the US population. Additionally, for participants with kidney stones, a lower ratio of serum albumin to globulin was associated with a higher risk of all-cause mortality. Our findings suggest that maintaining a relatively high ratio of serum albumin to globulin can help reduce the risk of kidney stones and potentially improve long-term outcomes.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-2025-127/rc

Peer Review File: Available at https://tau.amegroups.com/article/view/10.21037/tau-2025-127/prf

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-2025-127/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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