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Prognostic value of total body muscle-fat ratio in patients with kidney stone disease: A US population-based study

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ABSTRACT

Purpose: To examine the relationship between the muscle-fat ratio (MFR) and kidney stone disease (KSD) in the adult population of the United States between 2011 and 2018, and whether it can be used as a predictor of KSD prognosis.

Materials and methods: We conducted a cross-sectional study analysing 9326 patients from the National Health and Nutrition Examination Survey (NHANES) from 2011 to 2018. We analyzed all participants by sex, age, race, level of education, marital status, household income-to-poverty ratio, hypertension, diabetes, vigorous physical activity, moderate physical activity, blood urea nitrogen, creatinine, uric acid, cotinine, and MFR. Dose-response curves with a restricted cubic spline function, univariate and multifactorial logistic regression were used for the analysis of the correlation between MFR and KSD. Finally, we created predictive models based on age, race, hypertension, diabetes mellitus, cotinine and MFR. The prediction model was evaluated using calibration curves, receiver operating characteristic curves and clinical decision curves from the training and test sets.

Results: Of the 9326 participants, 8582 (92%) self-reported that they did not have KSD and 744 (8%) self-reported that they had KSD. Univariate and multifactorial logistic regression showed that MFR was negatively associated with the prevalence of KSD (odds ratio [OR]: 0.770, 95% CI: 0.703–0.843; OR: 0.815, 95% CI: 0.738–0.897). Similarly, the risk of developing KSD decreased with increasing MFR as shown by the dose curves in the restricted cubic bar graphs. Furthermore, there is some accuracy (AUC = 0.652) and clinical applicability to the model we constructed based on the results of multifactorial logistic regression.

Conclusion: The MFR is protective factor against the developing KSD in adults in the USA.

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1. Introduction

Kidney stone disease (KSD) is one of the most common urological diseases, and its incidence is increasing worldwide every year [1]. The etiology of KSD involves the abnormal accumulation of crystalline material in the calyces of the kidney, renal pelvis, and junction of the renal pelvis and ureter [2]. Furthermore, its increasing prevalence heavily burdens society and healthcare systems and causes serious complications such as hematuria and infection, which can lead to hydronephrosis and even renal failure [3]. Therefore, it is important to study the risk factors for KSD and implement preventive measures. Age, obesity, and metabolic syndrome [4,5], are among the known risk factors.

Sarcopenia is the loss of skeletal muscle function and mass [6], which increases the risk of falls, impaired physical function and death [7]. Sarcopenia can also increase the risk of chronic obstructive pulmonary disease (COPD) and chronic kidney disease (CKD) [8]. However, with societal development and changes in dietary habits, obesity has become a disease that seriously impacts physical health [9]. Notably, obesity is associated with an increased risk of KSD [10], and previous studies have mainly used body mass index (BMI) and waist circumference to assess the severity of obesity. However, BMI and waist circumference do not distinguish between the relative amounts of muscle and fat in the body; therefore, a new index needs to be introduced to more comprehensively analyze the effect of fat and muscle on the prevalence of KSD. It has been suggested that the muscle-to-fat ratio (MFR) is a biomarker for chronic kidney disease [11]; however, whether MFR is associated with KSD and can be used as a predictor of KSD is unclear.

To the best of our knowledge, the relationship between total body muscle mass divided by total body fat mass (tMFR) and the prevalence of KSD based on dual-energy X-ray bone densitometry (DXA) has not been previously examined. Therefore, in this study, we used data from the National Health and Nutrition Examination Survey (NHANES) database to assess the association between the tMFR and KSD development. We also examined whether the tMFR could be used as a predictor of KSD prognosis.

2. Materials and methods

2.1. Data source and study population

The National Center for Health Statistics (NCHS) is part of the Centers for Disease Control and Prevention (CDC), which provides vital health statistics for the nation. The NHANES is one of its many programs. The NHANES focuses on different groups and health outcomes and started in the early 1960s and includes demographic, socioeconomic, nutritional, and health issues. In addition to screening components and laboratory tests, screening components include medical, dental, and physiological measurements. Notably, the NHANES provides medical outcome reports to all participants. All publicly available data were obtained with informed consent and ethical approval from the participants. All information collected was strictly confidential and privacy protected by law.

This study conducted a cross-sectional analysis of publicly available NHANES data from 2011 to 2018 was used in this study. A total of 39,156 participants were surveyed between 2011 and 2018. The exclusion criteria were as follows: (1) participants who did not know if they had a history of kidney stones, n = 16,587; (2) participants who did not know their education level, marital status, and household income-to-poverty ratio, n = 2386; (3) participants who had missing DXA data for total body muscle and total body fat, n = 10205; (4) participants who had missing data on hypertension, diabetes, activity status, blood urea nitrogen, uric acid, and cotinine, n = 652. Based on the exclusion criteria, the final number of participants was 9326.

2.2. The definition of tMFR

The tMFR was calculated as tMFR = total muscle mass/total body fat mass. The main focus of this study was the relationship between tMFR and the prevalence of KSD and whether tMFR predicts the prevalence of KSD. In the NHANES, total muscle mass and total body fat mass were obtained using DXA measurements. Whole-body scans were performed using the Hologic Discovery Model A densitometer (Hologic Inc., Bedford, Massachusetts, USA). The software used was Apex 3.2. The reasons for exclusion from DXA were as follows: ①Pregnancy (positive urine pregnancy test and/or self-report at the time of DXA); ②Self-reported history of radiographic contrast (barium) use in the past 7 days; ③Self-reported weight over 450 pounds or height over 6′5" (DXA table limitation).

2.3. Assessment of KSD

The outcome variable in this study was the KSD, which was determined using data from the NHANES Health and Nutrition Examination Survey. Participants answered the following question: "Have you ever had kidney stones?". We divided the participants into KSD and non-KSD groups.

2.4. Other covariates

Furthermore, we included the following factors in this study: sex (male, female), age, race (non-Hispanic white, non-Hispanic black, Mexican American, other Hispanic, and others), educational attainment (less than 9th grade, 9th–11th grade, high school graduate/GED or equivalent, college or AA degree, and college graduate or higher), marital status (married, widowed, divorced, separated, never married, and living with partner), hypertension, diabetes, vigorous leisure time activity, moderate leisure time activity, blood urea nitrogen, creatinine, uric acid, and cotinine levels. Moreover, hypertension and diabetes were self-reported based on

a professional diagnosis. Cotinine level is a measure of the prevalence and extent of tobacco use; notably, cotinine is a type of nicotine, and its concentration in the blood can be used as a marker of active smoking and an indicator of exposure to secondhand smoke.

2.5. Statistical analysis

The NHANES typically uses weighted sampling to interpret the study design. This study used the mean ± standard deviation (SD) to denote continuous variables that followed a normal distribution. The median (upper and lower quartiles) was used to denote non-normally distributed continuous variables. We also used a weighted *t*-test to analyze continuous variables and a chi-square test to analyze categorical variables and determine their statistical differences. Univariate and multifactorial logistic regression analyses were used to assess the prevalence of KSD and analyze the differences. In addition, we used the R package 'forester' to visualize the odds ratio (OR) and 95% confidence interval (CI). We used a restricted cubic spline function to illustrate the dose-response relationship between the continuous variables tMFR and KSD. Statistical analyses were performed using SPSS (version 24.0) and R (version 4.1.3) software, and all graphs were drawn using R (version 4.1.3) and Adobe Illustrator (version 26.0) software. Statistical significance was set at $p < 0.05$ (two-tailed) were considered statistically significant.

The results of the multifactorial logistic regression provided the basis for the construction and validation of the nonogram, which was constructed in this study using the R package 'rms.' Calibration curves were used to assess the performance and accuracy of the nonograms. Receiver operating characteristic (ROC) curves and decision curve analysis (DCA) were used to evaluate the predictive

Table 1
Baseline characteristics of NHANES participants between 2011 and 2018 (n = 9326).[a]

Characteristic	Overall	None kidney stone	Kidney stone	P value
N	9326	8582 (92%)	744 (8%)	
Sex				0.503
Male	4610 (49.4)	4251 (49.5)	359 (48.3)	
Female	4716 (50.6)	4331 (50.5)	385 (51.7)	
Age	39.00 [29.00, 49.00]	39.00 [29.00, 49.00]	43.00 [34.75, 52.00]	<0.001
Race (%)				<0.001
Mexican American	1363 (14.6)	1259 (14.7)	104 (14.0)	
Other Hispanic	947 (10.2)	856 (10.0)	91 (12.2)	
Non-Hispanic white	3393 (36.4)	3036 (35.4)	357 (48.0)	
Non-Hispanic black	1860 (19.9)	1765 (20.6)	95 (12.8)	
Other race	1763 (18.9)	1666 (19.4)	97 (13.0)	
Education level (%)				<0.001
Less than 9th grade	537 (5.8)	500 (5.8)	37 (5.0)	
9-11th grade (Includes 12th grade with no diploma)	1055 (11.3)	959 (11.2)	96 (12.9)	
High school graduate/GED or equivalent	2034 (21.8)	1880 (21.9)	154 (20.7)	
Some college or AA degree	3106 (33.3)	2814 (32.8)	292 (39.2)	
College graduate or above	2594 (27.8)	2429 (28.3)	165 (22.2)	
Marital status (%)				<0.001
Married	4567 (49.0)	4173 (48.6)	394 (53.0)	
Widowed	135 (1.4)	124 (1.4)	11 (1.5)	
Divorced	856 (9.2)	764 (8.9)	92 (12.4)	
Separated	333 (3.6)	296 (3.4)	37 (5.0)	
Never married	2397 (25.7)	2263 (26.4)	134 (18.0)	
Living with partner	1038 (11.1)	962 (11.2)	76 (10.2)	
Ratio of family income to poverty (mean (SD))	2.53 (1.66)	2.53 (1.66)	2.50 (1.64)	0.622
Hypertension (%)				<0.001
Yes	2141 (23.0)	1874 (21.8)	267 (35.9)	
No	7185 (77.0)	6708 (78.2)	477 (64.1)	
Diabetes (%)				<0.001
Yes	712 (7.6)	603 (7.0)	109 (14.7)	
No	8614 (92.4)	7979 (93.0)	635 (85.3)	
Vigorous recreational activity (%)				<0.001
Yes	2935 (31.5)	2753 (32.1)	182 (24.5)	
No	6391 (68.5)	5829 (67.9)	562 (75.5)	
Moderate recreational activity (%)				
Yes	4235 (45.4)	3931 (45.8)	304 (40.9)	0.010
No	5091 (54.6)	4651 (54.2)	440 (59.1)	
Blood urea nitrogen, mg/dL	12.54 (4.51)	12.50 (4.41)	13.10 (5.43)	<0.001
Blood creatinine, mg/dL	0.85 (0.38)	0.85 (0.36)	0.89 (0.59)	0.018
Uric acid, mg/dL	5.32 (1.39)	5.32 (1.39)	5.35 (1.40)	0.639
Cotinine, ng/mL	0.04 [0.01, 30.87]	0.04 [0.01, 25.50]	0.06 [0.01, 114.00]	0.003
tMFR	1.97 [1.44, 2.64]	1.99 [1.45, 2.67]	1.80 [1.35, 2.39]	<0.001

Abbreviations.
tMFR, the ratio of total body muscle to total body fat.
[a] For categorical variables, P values were analyzed by chi-square tests. For continuous variables, the *t*-test for slope was used in generalized linear models.

performance of the nomogram.

3. Results

3.1. Participant characteristics

This study included 9326 participants who met the NHANES database criteria between 2011 and 2018. The baseline clinical characteristics of all patients are shown in Table 1, with 8582 (92%) self-reported as patients without KSD and 744 (8%) as patients with KSD. We then assessed the clinical characteristics of all participants using chi-square tests, including sex ($P = 0.503$), age ($P < 0.001$), race ($P < 0.001$), educational level ($P < 0.001$), marital status ($P < 0.001$), household income/poverty ratio ($P = 0.622$), and hypertension ($P < 0.001$), diabetes mellitus ($P < 0.001$), vigorous physical activity ($P < 0.001$), moderate physical activity ($P = 0.010$), blood urea nitrogen ($P < 0.001$), creatinine ($P = 0.018$), uric acid ($P = 0.639$), cotinine ($P = 0.003$), and tMFR ($P < 0.001$). In addition, we conducted covariance analyses on all confounding variables and found no covariance between the confounders (Table S1).

3.2. tMFR and KSD

Sex, age, race, educational level, marital status, household income-to-poverty ratio, hypertension, diabetes, vigorous recreational activity, moderate recreational activity, blood urea nitrogen, creatinine, uric acid, cotinine, and tMFR were analyzed in the 9326 participants using univariate logistic regression. From Fig. S1, we know that age (OR:1.029, 95% CI: 1.022–1.036), race (OR:0.877, 95% CI: 0.827–0.929), marital status (OR:0.934, 95% CI: 0.899–0.971), hypertension (OR:2.004, 95% CI: 1.710–2.347), diabetes mellitus (OR:2.271, 95% CI: 1.824–2.829), vigorous leisure activities (OR:0.686, 95% CI: 0.577–0.816), moderate leisure-time activity (OR:0.818; 95% CI:0.702–0.952), blood urea nitrogen (OR:1.026; 95% CI:1.011–1.041), creatinine (OR:1.163, 95% CI:1.017–1.331), cotinine (OR:1.001, 95% CI:1.001–1.002), and tMFR (OR:0.770, 95% CI:0.703–0.843) were strongly associated with the prevalence of KSD. Subsequently, we performed multivariate logistic regression analysis (Fig. 1) using the above indicators, yielding age (OR:1.015, 95% CI:1.007–1.023), race (OR:0.874, 95% CI:0.822–0.929), hypertension (OR:1.509, 95% CI:1.266–1.795), diabetes mellitus (OR:1.513, 95% CI:1.191–1.907), cotinine (OR:1.001, 95% CI:1.001–1.002), and tMFR (OR:0.815, 95% CI:0.738–0.897) were strongly associated with the prevalence of KSD. We also used the dose curve in the restricted cubic bar chart to analyze the dose-response relationship between tMFR and KSD. The association between kidney stone and tMFR with the number of knots between three and seven, the knot was chosen as the lowest value for the Akaike information criterion (AIC). Finally, the restricted cubic spline model was constructed with 3 knots at the 10th, 50th and 90th percentiles of tMFR. Fig. 2 shows that the prevalence of KSD decreased with increasing tMFR.

3.3. Model development and validation

Based on the multifactorial logistic regression analysis results, we randomly selected 50% of the participants for the training set and the remaining 50% for the test set. We constructed a nomogram to predict the prognosis of patients with KSD based on a training set (Fig. S2). To validate the predictive performance of the training set nomogram model, calibration curves were used to assess the accuracy of the nomogram model. Fig. 3A, D shows the calibration of the training and test sets, and the predicted KSD prevalence risk of both is highly consistent with the actual observed results, indicating that the nomogram is well calibrated. Fig. 3B, E shows the ROC results for the training and test sets; the area under the curve (AUC) was 0.647 (0.618–0.675) and 0.652 (0.624–0.680), respectively,

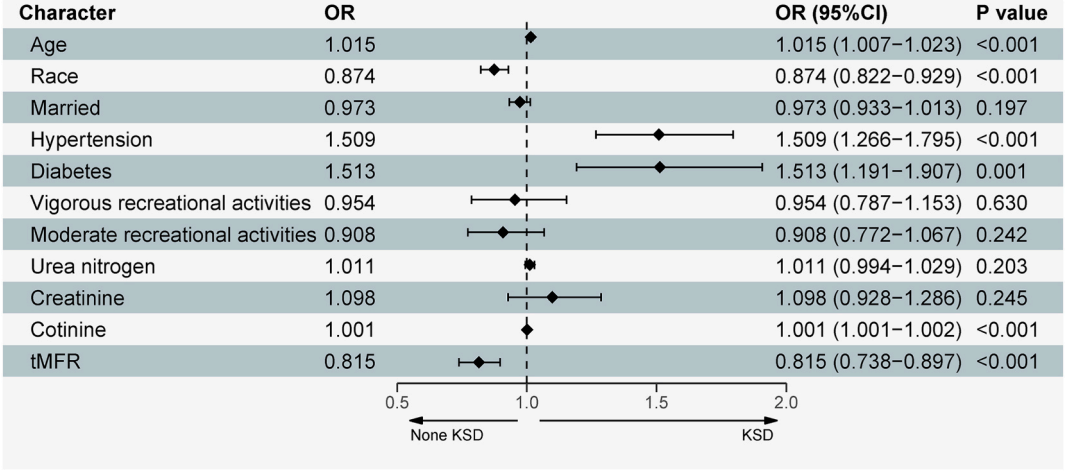

Fig. 1. Results of multivariate logistic regression analysis of age, race, marital status, hypertension, diabetes, vigorous recreational activity, moderate recreational activity, blood urea nitrogen, creatinine, cotinine level and tMFR with prevalence of KSD for all participants.

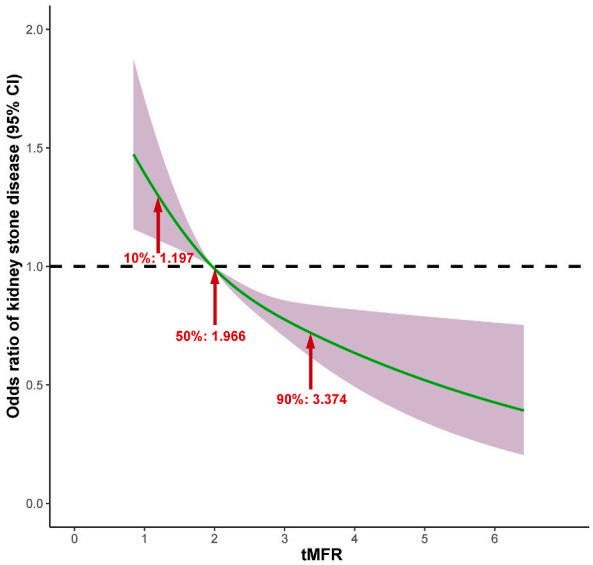

Fig. 2. Dose-response relationship between tMFR and KSD. The restricted cubic spline model was constructed with 3 knots at the 10th, 50th and 90th percentiles of tMFR.

indicating that the nomogram was highly accurate in predicting the prognosis of KSD. The DCA curve can demonstrate the clinical value of the nomogram in predicting the risk of KSD, and Fig. 3C and F shows that it has good clinical decision value.

4. Discussion

The etiology of KSD is still incompletely understood and the recurrence rate is high. Therefore, it is important to study the risk factors and predictors of developing KSD for its treatment and prevention. In this study, we investigated whether tMFR can be used as a tool to predict the prognosis of KSD by analyzing data from a large sample from the NHANES database. The results showed that tMFR was negatively correlated with the risk of KSD; that is, the higher the percentage of body muscle mass, the higher the prevalence of

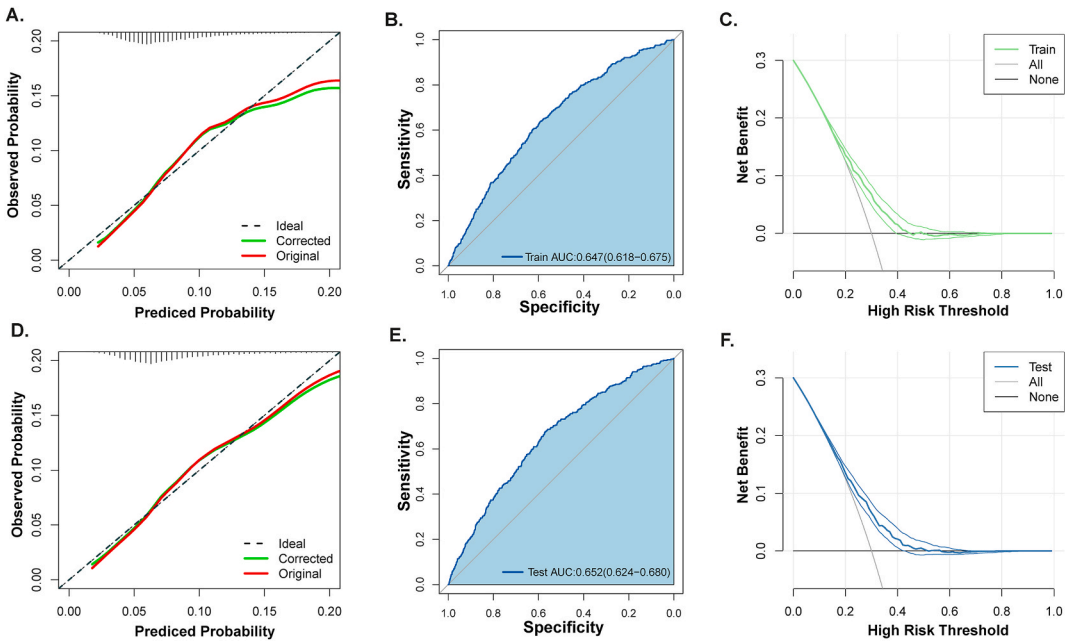

Fig. 3. Evaluation of the model. A. Calibration curve of the model constructed from the training set; B. ROC curve of the model constructed from the training set; C. DCA curve of the model constructed from the training set; D. Calibration curve of the model constructed from the test set; E. ROC curve of the model constructed from the test set; F. DCA curve of the model constructed from the test set.

KSD. The tMFR was also been shown to be a good physical measure for predicting the prognosis of KSD and has some clinical utility.

tMFR has been shown to predict the risk of chronic kidney disease, metabolic syndrome, and insulin resistance [11,12], but it is unclear whether MFR predicts the prognosis of KSD; therefore, we used tMFR to achieve our study objectives. The tMFR is determined by the total body muscle mass and total fat mass. However, Taylor et al. [13], showed that an increase in body fat increases the likelihood of developing KSD. Furthermore, body fat and trunk fat are determinants of uric acid stone risk compared with non-KSD populations [14], and supersaturation of uric acid in the body is indeed one of the mechanisms of KSD pathogenesis.

Muscle mass and function are the primary diagnostic criteria for sarcopenia. Our previous study [15] showed that sarcopenia is strongly associated with the risk of developing kidney stones. Therefore, tMFR could be used as a biomarker for the prognosis of KSD.

A low tMFR may promote kidney stone formation in several ways. According to Taguchi K [16,17] et al., increased crystals and lipids in renal tubules promote the formation of adipocytokines and macrophages, leading to the formation of kidney stones. They also found that fatty acid binding protein 4 (FABP4), a protein involved in lipid metabolism, is a key molecule in kidney stone formation and that knockdown of FABP4 results in a significant increase in kidney stone formation. In addition, obesity may increase the risk of oxalate stones by decreasing oxalate breakdown by intestinal bacterial flora [18] and increasing oxalate absorption by the intestine [19]. Jhee et al. [11] found that a low MFR increased the risk of CKD. In contrast, reduced renal function in patients with CKD leads to impaired glomerular filtration, which disrupts the balance between crystal production and excretion, leading to the development of stones.

This study has several important advantages. To our knowledge, this is the first analysis of tMFR to predict the prognosis of patients with KSD. Second, the NHANES has quality assurance, and the large sample size makes our findings more credible and can be generalized to the entire US adult population. Finally, analyzing body muscle and fat content using DXA may not be the clinical gold standard compared to conventional computed tomography and magnetic resonance imaging. However, it is a convenient, low-level X-ray exposure [20] and an inexpensive screening method for many older adults with activity limitations.

This study had some limitations in addition to its various strengths. First, this was a cross-sectional study; therefore, we could not establish a clear causal relationship between high tMFR and a lower risk of KSD prevalence. Second, some of the data in this study were based on participants' self-reports, and there may have been recall and reporting bias. Third, detailed information on kidney stones, such as stone composition, was not available in the NHANES database. In addition, the study utilized only the NHANES database for internal validation and lacked external validation. Therefore, prospective studies are required to confirm these findings.

5. Conclusion

We found that the tMFR correlated with the risk of KSD in the US population, demonstrating excellent clinical implications as a tool for predicting the risk of developing KSD.

Author contribution statement

Wei Song: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote thepaper.
Huiqing Hu, Jinliang Ni: Contributed, materials, analysis tools or data; Analyzed and interpreted the data.
Haipeng Zhang, Houliang Zhang, Jiahao Lu: Analyzed and interpreted the data; Wrote the paper.
Keyi Wang, Weipu Mao, Bo Peng: Conceived and designed the experiments; Wrote the paper.

Data availability statement

Data associated with this study has been deposited at https://wwwn.cdc.gov/nchs/nhanes/Default.aspx.

Ethical statement

We are accountable for all aspects of this study.

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Declaration of competing 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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e20339.

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