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Original Research

Declining kidney function and frailty progression: a 7-year cohort study of Chinese middle-aged and older adults

Fan Zhang, Yan Bai, Liuyan Huang, Yifei Zhong *

Department of Nephrology, Longhua Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai, China

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ABSTRACT

Background: This study aimed to investigate the association between baseline kidney function and frailty trajectories in middle-aged and older adults.

Methods: Data were derived from the China Health and Retirement Longitudinal Study (2011–2018), including 5364 participants aged ≥45 years at baseline with up to four assessment waves over approximately 7 years. Kidney function was evaluated using estimated glomerular filtration rate based on serum creatinine and cystatin C ($eGFR_{scr\text{-}cysc}$) and categorized as normal (≥90), mildly reduced (60–89) and moderately-to-severely reduced (<60 ml/min/1.73m^2). Frailty was assessed using a 30-item frailty index (0–100 scale). Linear mixed-effects models with random intercepts were used to examine the effects of baseline kidney function and its interaction with time on frailty index trajectories.

Results: At baseline, the mean frailty index was higher in participants with mildly (β=2.28, 95% CI: 1.63–2.94) and moderately-to-severely (β=3.70, 95% CI: 2.41–4.99) reduced kidney function compared to normal kidney function, where β represents the adjusted difference in frailty index relative to the reference group. Frailty index increased over time in all groups; in participants with normal kidney function, it rose by 0.83 points per year (95% CI: 0.77–0.90). The annual increase was 0.26 points greater (95% CI: 0.18–0.35) in the mildly reduced and 0.70 points greater (95% CI: 0.54–0.87) in the moderately-to-severely reduced group. Over approximately 7 years, predicted mean frailty index increased from 15.1 to 20.9, 17.4 to 25.0, and 18.8 to 29.5 in the normal, mildly reduced and moderately-to-severely reduced groups, respectively.

Conclusions: Middle-aged and older adults with lower kidney function exhibited higher frailty index levels at baseline and faster frailty progression over time.

1. Introduction

Frailty is a multidimensional geriatric syndrome characterized by decreased physiological reserve and increased vulnerability to stressors, resulting in a higher risk of adverse health outcomes [1]. The prevalence of frailty increases substantially with age, affecting up to 25% of persons over age 80 [2]. Its dynamic and progressive nature, often conceptualized as a trajectory rather than a static state, underscores the importance of longitudinal research in understanding its determinants and consequences [3,4].

Chronic kidney disease (CKD)-a progressive loss of kidney function-affects approximately 10% of the adult population worldwide, with even higher rates in older populations [5–7]. Declining kidney function is associated with multiple physiological disruptions, including metabolic imbalance, inflammation, and accumulation of toxins, all of which may contribute to the pathogenesis of frailty [8]. Moreover, CKD has been identified as a powerful predictor of subsequent frailty and functional decline in older adults [9,10]. Although observational studies have demonstrated associations between reduced kidney function and frailty, there is limited longitudinal evidence on how baseline kidney function predicts frailty trajectories, [11–13] especially among middle-aged and older adults. In addition, existing studies mostly use traditional linear regression models, which fail to fully consider individual heterogeneity and dynamic characteristics of temporal changes.

Building on data from the China Health and Retirement Longitudinal Study (CHARLS), this study aimed to examine the association between baseline kidney function and longitudinal frailty index trajectories over 7 years among Chinese middle-aged and older adults.

* Corresponding author at: Department of Nephrology, Longhua Hospital, Shanghai University of Traditional Chinese Medicine, South Wanping Road NO. 725, Shanghai, China.

E-mail address: sh_zhongyifei@shutcm.edu.cn (Y. Zhong).

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2. Methods

2.1. Study population

This study utilized data from the CHARLS collected between 2011 and 2018, [14] in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines (**Table S1**) [15]. CHARLS is a nationally representative longitudinal survey of Chinese residents aged 45 years and older, using a multistage, stratified probability sampling design covering 28 provinces. Baseline data were collected in 2011, with follow-up waves in 2013, 2015, and 2018. Data collection included structured face-to-face interviews, physical examinations, and blood sample assays conducted by trained personnel following standardized protocols.

Participants were adults aged 45 years and above from the 2011 baseline survey. Exclusion criteria were: (1) missing baseline kidney function data; (2) missing variables for the frailty index; and (3) loss to follow-up or incomplete baseline covariate data during the study period (Fig. 1). Ultimately, 5364 participants were included, each with four follow-up assessments over a 7-year period. The CHARLS protocol was approved by the Peking University Institutional Review Board (IRB00001052-11015), and written informed consent was obtained from all participants.

2.2. Kidney function assessment

Kidney function was evaluated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation incorporating both serum creatinine and cystatin C ($eGFR_{scr\text{-}cysc}$) as the primary exposure variable [16]. Based on clinical guidelines, participants were classified into three groups: normal kidney function ($eGFR_{scr\text{-}cysc} \geq 90$ ml/min/1.73 m^2), mildly reduced kidney function ($eGFR_{scr\text{-}cysc}$ 60–89 ml/min/1.73 m^2), and moderately-to-severely reduced kidney function ($eGFR_{scr\text{-}cysc} < 60$ ml/min/1.73 m^2) [17].

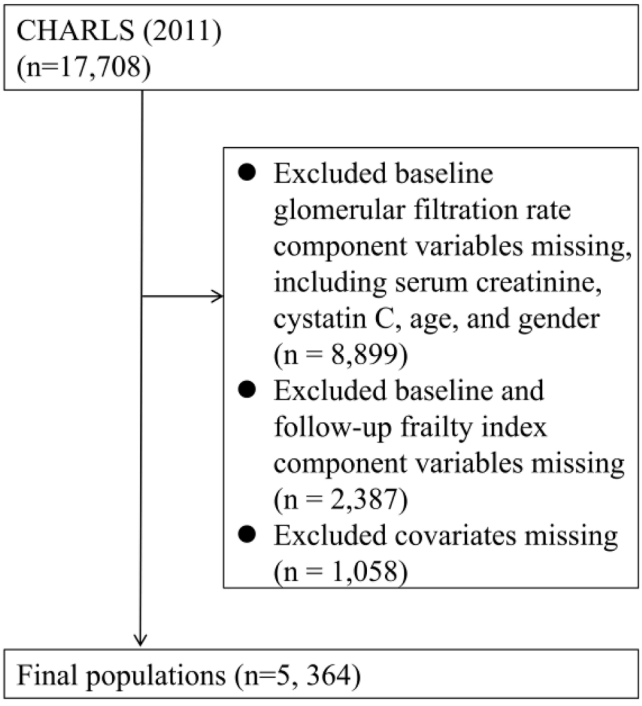

Fig. 1. Participants screening flowchart.

2.3. Frailty assessment

Frailty was assessed using the frailty index, which was constructed following the standard deficit accumulation approach proposed by Rockwood and colleagues. Selected variables met established criteria: they were associated with health status, increased with age, did not saturate too early, and covered multiple physiological systems [18]. Following established literature, [19] thirty available items-including various chronic diseases, self-reported health status, functional limitations, depression, and cognitive function-were selected for frailty index calculation (**Table S2**). Participants with missing data in any of these items were excluded from the frailty index analysis. All variables were derived from standardized CHARLS questionnaires, physical measurements, and laboratory tests, and coded according to predefined criteria. This approach has been widely validated in diverse populations, including CHARLS [12,20].

The frailty index was calculated as the sum of present deficits divided by 30 and multiplied by 100 for ease of interpretation, yielding a continuous variable ranging from 0 to 100, with higher values indicating greater frailty severity. Participants can be categorized into non-frail (frailty index $\leq$ 25) and frail (frailty index $>$ 25), [21,22] based on established frailty index thresholds.

2.4. Covariates

To control for confounding factors, the following covariates were included: [23] (1) demographic characteristics: age, sex, marital status (married/other), and educational attainment (primary school or below/middle school/college or above); (2) lifestyle factors: smoking status (never/former/current) and alcohol consumption (never/former/current); (3) health status: body mass index and chronic diseases (such as hypertension, diabetes, and cardiovascular disease). Diabetes was defined as the use of antidiabetic medications, a fasting blood glucose level $\geq$126 mg/dl, or a non-fasting blood glucose level $\geq$200 mg/dL [24]. Hypertension was defined as a systolic blood pressure $\geq$140 mmHg, diastolic blood pressure $\geq$90 mmHg, or the use of antihypertensive medications [25]. Certified technicians measured blood pressure three times using a validated automated device (OMRON HEM-907 XL) after participants had rested in the seated position for 5 min, and the average value was calculated. CVD was defined as self-reported stroke or heart disease [26]; (4) biochemical indicators: blood urea nitrogen, C-reactive protein, total cholesterol, high-density and low-density lipoprotein cholesterol, triglycerides, serum uric acid, and hemoglobin.

2.5. Statistical analysis

Continuous variables were described as mean±standard deviation; categorical variables as frequency and percentage. Group comparisons used one-way ANOVA or the chi-squared test as appropriate. A linear mixed-effects model was constructed with frailty index as the dependent variable. Time was coded as years since baseline (year = 0 for 2011, 2 for 2013, 4 for 2015, and 7 for 2018). We fitted linear mixed-effects models with a random intercept at the individual level using restricted maximum likelihood (REML), including fixed effects for time (year), baseline eGFR group, and their interaction (eGFR group $\times$ year). Covariates were included to adjust for confounding. Variable significance was assessed using the Wald test, with significance set at $P < 0.05$. The margins command estimated the marginal effects of $eGFR_{scr\text{-}cysc}$ groups on frailty index during follow-up, and frailty index trajectories were plotted. The intraclass correlation coefficient was calculated to quantify the proportion of total variance in frailty index attributable to differences between individuals. For robustness, analyses were repeated after excluding individuals with baseline frailty (frailty index $\geq$ 25) [21]. All analyses were performed with Stata 16.0.

3. Results

A total of 5364 middle-aged and older adults were included in the analysis. $eGFR_{scr\text{-}cysc}$ levels declined significantly with increasing age ($P < 0.001$), with the moderate-to-severe kidney impairment group having the highest mean age (70.5 ± 8.8 years) (Table 1). The proportion of females was highest in the normal kidney function group (59.5%), while males predominated in the moderate-to-severe impairment group (50.9%). Prevalence of hypertension, cardiovascular disease, and frailty index were significantly higher in the moderate-to-severe impairment group ($P < 0.001$). Additionally, serum uric acid, cystatin C, and C-reactive protein levels were significantly elevated, whereas hemoglobin levels were lower in the lower $eGFR_{scr\text{-}cysc}$ groups ($P < 0.001$).

The linear mixed-effects model demonstrated good fit (log restricted-likelihood = −79,633.8; $P < 0.001$). Estimated parameters for frailty index trajectories according to baseline $eGFR_{scr\text{-}cysc}$ groups are presented in Table 2. At baseline, the predicted mean frailty index in the normal kidney function group was 15.07 (95% CI: 14.58–15.56). Participants with mildly reduced kidney function had a 2.28-point higher baseline frailty index (95% CI: 1.63–2.94), and those with moderately-to-severely reduced kidney function had a 3.70-point higher baseline frailty index (95% CI: 2.41–4.99), compared with the normal group.

Over time, frailty index increased significantly in all kidney function groups. Among participants with normal kidney function, frailty index increased by an average of 0.83 points per year (95% CI: 0.77–0.90). Compared with this group, the annual increase in frailty index was 0.26 points greater (95% CI: 0.18–0.35) in the mildly reduced kidney function group and 0.70 points greater (95% CI: 0.54–0.87) in the moderately-to-severely reduced group. Based on model predictions, the mean frailty index increased from 15.1 to 20.9 over 7 years in the normal kidney function group, from 17.4 to 25.0 in the mildly reduced group, and from 18.8 to 29.5 in the moderately-to-severely reduced group (Fig. 2 and **Table S3**).

Random-effects estimates indicated substantial between-individual heterogeneity in baseline frailty index (random intercept variance = 98.90, 95% CI: 94.67–103.32). The intraclass correlation coefficient was 0.62 (95% CI: 0.61–0.63), suggesting that 62% of the total variance in frailty index was attributable to differences between individuals rather than within-individual change over time.

4. Discussion

In this large, nationally representative longitudinal cohort of middle-aged and older Chinese adults, we found that baseline kidney function was significantly associated with frailty trajectories over a 7-year follow-up. Participants with moderate-to-severe declines in kidney function exhibited the greatest increase in frailty index over time: even mild declines in baseline kidney function were associated with accelerated frailty progression compared to those with normal kidney function. Notably, these associations persisted after adjustment for an extensive range of demographic, lifestyle, clinical, and biochemical confounders, supporting an independent role of renal dysfunction in the development and worsening of frailty.

Our findings are consistent with and extend prior longitudinal research addressing the bidirectional relationship between kidney function and frailty [27,28]. For example, the Seattle Kidney Study demonstrated an independent association between lower kidney function and greater risk of frailty in clinic-based older adults [28]. Our study expands this literature by presenting data from a socio-demographically distinct Chinese population and by characterizing frailty as a dynamic trajectory rather than a static binary outcome. This approach aligns with recent perspectives that emphasize frailty as a continuum that evolves over time in response to cumulative physiological deficits [29]. In addition, previous studies have suggested that the frailty index typically increases at a rate of approximately 0.02–0.03 per year in older adults [30]. Our findings are broadly consistent with

Table 1
Baseline characteristics of included participants by $eGFR_{scr\text{-}cysc}$ category.

Characteristic	$eGFR_{scr\text{-}cysc}$, ml/min/1.73m^2				*P*-value
	All, *N* = 5,364[1]	≥90, *N* = 2,206[1]	[60, 90), *N* = 2,787[1]	<60, *N* = 371[1]	
Age, years	59.3 ± 9.6	54.0 ± 7.5	62.0 ± 8.7	70.5 ± 8.8	<0.001[2]
Gender					<0.001[3]
Male	2381 (44.4%)	893 (40.5%)	1299 (46.6%)	189 (50.9%)	
Female	2983 (55.6%)	1313 (59.5%)	1488 (53.4%)	182 (49.1%)	
Education					
Less than middle school education	4902 (91.4%)	1979 (89.7%)	2570 (92.2%)	353 (95.1%)	
High school	418 (7.8%)	204 (9.2%)	199 (7.1%)	15 (4.0%)	
Higher education	44 (0.8%)	23 (1.0%)	18 (0.6%)	3 (0.8%)	
Marriage					<0.001[3]
Marriage	4735 (88.3%)	2062 (93.5%)	2389 (85.7%)	284 (76.5%)	
Other	629 (11.7%)	144 (6.5%)	398 (14.3%)	87 (23.5%)	
Smoking					<0.001[3]
Never smoker	3371 (62.8%)	1483 (67.2%)	1680 (60.3%)	208 (56.1%)	
Past smoker	427 (8.0%)	145 (6.6%)	243 (8.7%)	39 (10.5%)	
Current smoker	1566 (29.2%)	578 (26.2%)	864 (31.0%)	124 (33.4%)	
Drinking					<0.001[3]
Never drinker	3335 (62.2%)	1365 (61.9%)	1740 (62.4%)	230 (62.0%)	
Past drinker	451 (8.4%)	151 (6.8%)	245 (8.8%)	55 (14.8%)	
Current drinker	1578 (29.4%)	690 (31.3%)	802 (28.8%)	86 (23.2%)	
Body mass index, kg/m^2	24.2 ± 4.5	23.9 ± 3.7	24.5 ± 4.8	23.1 ± 4.4	<0.001[2]
Hypertension					<0.001[3]
None	2813 (52.4%)	1335 (60.5%)	1353 (48.5%)	125 (33.7%)	
Yes	2551 (47.6%)	871 (39.5%)	1434 (51.5%)	246 (66.3%)	
Diabetes					0.111[3]
None	4600 (85.8%)	1882 (85.3%)	2411 (86.5%)	307 (82.7%)	
Yes	764 (14.2%)	324 (14.7%)	376 (13.5%)	64 (17.3%)	
Cardiovascular disease					<0.001[3]
None	4640 (86.5%)	1971 (89.3%)	2364 (84.8%)	305 (82.2%)	
Yes	724 (13.5%)	235 (10.7%)	423 (15.2%)	66 (17.8%)	
Urea nitrogen, mg/dl	15.7 ± 4.4	14.7 ± 4.0	16.0 ± 4.3	19.6 ± 5.2	<0.001[2]
Serum creatinine, mg/dl	0.8 ± 0.2	0.7 ± 0.1	0.8 ± 0.2	1.1 ± 0.3	<0.001[2]
Total cholesterol, mg/dl	193.9 ± 38.7	193.3 ± 40.0	194.1 ± 37.5	195.3 ± 39.7	0.573[2]
Triglyceride, mg/dl	130.3 ± 92.0	137.6 ± 102.3	124.7 ± 83.9	129.0 ± 82.1	<0.001[2]
HDL, mg/dl	51.3 ± 15.1	50.4 ± 14.9	51.9 ± 15.2	51.7 ± 14.8	0.002[2]
LDL, mg/dl	117.1 ± 35.2	115.0 ± 34.9	118.5 ± 35.1	118.7 ± 37.0	0.002[2]
CRP, mg/l	2.4 ± 6.0	2.0 ± 4.6	2.6 ± 6.9	3.2 ± 6.1	<0.001[2]
Serum urea acid, mg/dl	4.4 ± 1.2	4.0 ± 1.1	4.6 ± 1.2	5.5 ± 1.4	<0.001[2]
Hemoglobin, g/dl	14.3 ± 2.2	14.3 ± 2.1	14.4 ± 2.2	13.9 ± 2.2	<0.001[2]

(*continued on next page*)

Table 1 (*continued*)

Characteristic	$eGFR_{scr-cysc}$, ml/min/1.73m^2				*P*-value
	All, *N* = 5,364[1]	≥90, *N* = 2,206[1]	[60, 90), *N* = 2,787[1]	<60, *N* = 371[1]	
Cystatin C, mg/l	1.0 ± 0.2	0.8 ± 0.1	1.1 ± 0.1	1.5 ± 0.4	<0.001[2]
$eGFR_{scr-cysc}$, ml/min/1.73m^2	85.8 ± 17.1	101.7 ± 9.1	77.7 ± 8.0	51.3 ± 7.6	<0.001[2]

[1]Data are described as mean ± standard deviation or frequency (%).
[2]Welch Two Sample *t*-test.
[3]Pearson's Chi-squared test.
HDL = high-density lipoprotein; LDL = low-density lipoprotein; CRP = *C* reactive protein; eGFR = estimated glomerular filtration rate.

Table 2
Linear mixed-effects model with time coded as years since baseline.

Parameter	β (95% CI)	Interpretation
Time effect		
Year (eGFR ≥90)	0.83 (0.77–0.90)	Annual increase in frailty index in reference group
Year × eGFR 60–89	0.26 (0.18–0.35)	Additional annual increase vs. eGFR ≥90
Year × eGFR <60	0.70 (0.54–0.87)	Additional annual increase vs. eGFR ≥90
Baseline		
eGFR ≥90	15.07 (14.58–15.56)	Predicted mean frailty index at baseline
eGFR 60–89	17.35 (16.92–17.79)	Predicted mean frailty index at baseline (eGFR ≥90 + 2.28)
eGFR <60	18.77 (17.58–19.97)	Predicted mean frailty index at baseline (eGFR ≥90 + 3.70)

Adjusted for demographic characteristics, lifestyle factors, physical condition and biochemical indicators.
Frailty index values can be directly converted to the conventional 0–1 scale by dividing by 100.

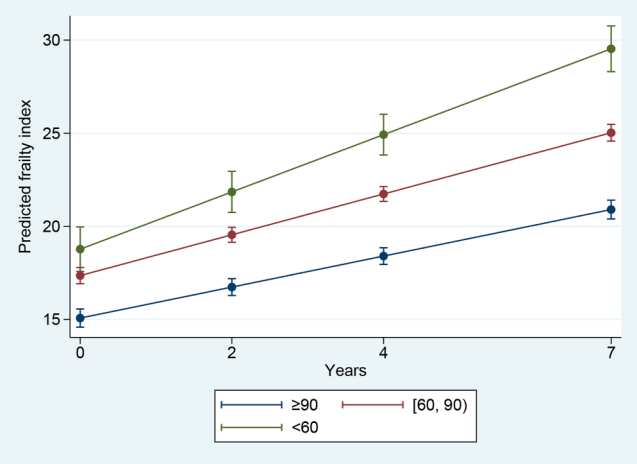

Fig. 2. The impact of baseline kidney function on frailty index trajectories. Adjusted for demographic characteristics, lifestyle factors, physical condition and biochemical indicators. Higher frailty index values indicate greater frailty severity. Time is coded as years since baseline (0, 2, 4 and 7, corresponding to the 2011, 2013, 2015 and 2018 CHARLS waves). *Note:* predicted values refer to model-based marginal estimates derived from the linear mixed-effects model, adjusted for covariates.

this range, while demonstrating that individuals with impaired kidney function experience a significantly accelerated rate of deficit accumulation.

Our results additionally highlight the clinical significance of even mild reductions in kidney function on subsequent frailty development. While moderate-to-severe CKD has long been recognized as a health risk, our findings suggest that clinicians should be vigilant regarding frailty risk even among patients with modestly impaired eGFR. Routine assessment of frailty in CKD patients, as recommended by some guidelines, should also extend to individuals with early-stage CKD or age-related mild kidney function decline [31,32]. Early identification of at-risk individuals creates opportunities for timely intervention, potentially including nutrition optimization, physical activity enhancement, and management of comorbidities, to slow or prevent frailty progression [33,34].

The observation that frailty index increased significantly over time in all kidney function groups, but more rapidly among those with lower eGFR, may illustrate shared mechanisms underlying both CKD and frailty: chronic inflammation, oxidative stress, malnutrition, and hormonal dysregulation have all been implicated as mediators [35,36]. Further, our analysis, adjusting for various covariates, indicates that impaired kidney function exerts an additional, independent influence. Random effects analysis suggested meaningful inter-individual heterogeneity in baseline frailty, consistent with the complex interplay between genetics, environment, and life-course exposures in shaping frailty phenotypes [37,38].

This study has several limitations. First, residual confounding from unmeasured variables, such as use of specific medications (e.g., corticosteroids or nephrotoxic drugs), psychosocial factors, or genetic predispositions, may influence both kidney function and frailty trajectories. Second, the frailty index, though validated and widely used, primarily relies on self-reported information and may be subject to reporting bias or measurement errors. Third, the exclusion or underrepresentation of institutionalized individuals and those with end-stage renal disease could limit the generalizability of our findings to these more vulnerable populations. Fourth, the categorization of kidney function and frailty index levels may obscure potential nonlinear or threshold effects, as both parameters are complex and may not be fully captured by broad groupings. Fifth, while we adjusted for a comprehensive range of covariates, there is a potential for reverse causation, as baseline frailty could affect kidney function over time and influence participant attrition in longitudinal follow-up. However, the sensitivity analysis excluding those with frailty baselines obtained the same results.

Future research should focus on several key areas. Interventional trials are needed to determine whether targeted management of kidney function decline-through pharmacologic, nutritional, or exercise-based strategies-can mitigate or slow frailty progression, especially in early-stage CKD. There is also a need for cross-cultural and multi-ethnic studies to assess the generalizability of these associations, as well as for implementation research to develop scalable frailty screening and prevention programs in community and clinical settings. Lastly, exploring the role of social determinants, health policies, and access to care in modifying these relationships could inform broader public health interventions to support healthy aging among CKD populations.

5. Conclusion

In summary, our findings reveal that declining kidney function, even at mild levels, predicts more rapid frailty progression over time among Chinese middle-aged and older adults. These results emphasize the need for early identification and multidimensional management of frailty risk in CKD.

Data availability statement

The data that support the findings of this study are available from the China Health and Retirement Longitudinal Study (CHARLS) (http://charls.pku.edu.cn).

Ethics approval and consent to participate

This is a retrospective study based on CHARLS database. The patient's information has been hidden before the study. There is no need for the patient's informed consent and no ethical conflict. The original CHARLS was approved by the Ethical Review Committee of Peking University (IRB00001052-11015), and all participants signed the informed consent at the time of participation. This research followed the guidance of the Declaration of Helsinki.

Consent for publication

Not applicable.

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Declaration of the use of generative AI and AI-assisted technologies in scientific writing and in figures, images and artwork

During the preparation of this work the authors used ChatGPT in order to optimize language. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

CRediT authorship contribution statement

Fan Zhang: Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation, Conceptualization. **Yan Bai:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Liuyan Huang:** Writing – original draft, Data curation, Conceptualization. **Yifei Zhong:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare no competing interests.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjfa.2026.100151.

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