Mediterranean Journal of Hematology and Infectious Diseases

Original Article

Dynamic Hemoglobin Trajectories in Renal Anemia and Their Association with Frailty Progression and Cardiovascular Events in Non-Dialysis Chronic Kidney Disease

Lei-Ran[#,1,2], Zhen-Zhen Hao[#,1,2], Ya-Pu Zhang[#,1,2], Jian-Dong Li[1,2], Shan-Shan Guo[1,2] and Li Guo[1,2].

[1] Department of Nephrology, Affiliated Hospital of Hebei University, Baoding, Hebei 071000, China.
[2] Key Laboratory of Bone Metabolism and Physiology in Chronic Kidney Disease of Hebei Province, Baoding, Hebei 071000, China.
[#] These authors contributed equally to this work.

Competing interests: The authors declare no competing interest.

Abstract. ***Background:*** **In non-dialysis chronic kidney disease (ND-CKD), anemia, frailty, and cardiovascular (CV) complications intersect, yet the prognostic relevance of within-patient hemoglobin (Hb) change over time remains unclear. We tested whether distinct 12-month Hb trajectory patterns are associated with frailty worsening and CV events.**
Methods**: Adults with stage 3–5 ND-CKD and renal anemia (men <13 g/dL; women <12 g/dL) were enrolled at a single center (June–December 2023) and followed monthly for 12 months. Hb was measured monthly. Latent-class mixed models were used to derive stable, declining, and fluctuating Hb trajectories from all available Hb measurements during follow-up. Frailty was assessed at baseline, 6 months, and 12 months. Frailty worsening was prespecified as a ≥1-point increase in the FRAIL score or new onset of weak grip or slow gait. Associations were evaluated using mixed-effects logistic regression (frailty worsening) and cause-specific Cox models (time-to-first composite CV event), adjusting for key clinical covariates.**
Results**: Follow-up at 12 months was available for 182 of 190 (95.8%) participants. Trajectory allocation was 39% stable, 41% declining (mean slope −0.18 g/dL/month), and 20% fluctuating (higher within-person variability). Frailty worsened in 57% of participants who declined, 45% of participants who fluctuated, and 25% of participants who remained stable. Adjusted odds ratios versus Stable were 2.8 (95% CI 1.6–5.0) for Declining and 1.9 (0.9–4.0) for Fluctuating. Over 185 person-years, 46 composite CV events occurred (24.9/100 person-years), and adjusted hazard ratios were 2.6 (1.4–4.9) for Declining and 1.7 (0.8–3.6) for Fluctuating.**
Conclusion**: A declining 12-month hemoglobin trajectory was associated with increased risk of frailty worsening and cardiovascular events compared with a stable profile.**

Keywords: Hemoglobin trajectory; Renal anemia; Non-dialysis chronic kidney disease; Frailty; Cardiovascular events.

Citation: Ran L., Hao Z.Z., Zhang Y.P., Li J.D., Guo S.S., Guo L. Dynamic hemoglobin trajectories in renal anemia and their association with frailty progression and cardiovascular events in non dialysis chronic kidney disease. Mediterr J Hematol Infect Dis 2026, 18(1): e2026040, HTTPS://DOI.ORG/ http://dx.doi.org/10.4084/MJHID.2026.040

Published: May 01, 2026 **Received: February 02, 2026** **Accepted: April 08, 2026**

Correspondence to: Li Guo. 212 YuHua East Road, LianChi District, Baoding, Hebei 071000, China. E-mail: LiGuo636@163.com

Introduction. Chronic kidney disease (CKD) is a significant global health issue, affecting over 10% of the adult population worldwide. This prevalence is particularly high in low- and middle-income countries, where healthcare resources are often limited.[1,2] CKD is associated with a high cardiovascular mortality rate[3] and is a major contributor to global mortality.[2] Renal anemia is a modifiable yet complex risk factor in CKD, primarily due to inadequate erythropoietin (EPO) production, iron dysregulation, and inflammation.[4] Anemia in CKD is linked to adverse outcomes such as fatigue, increased hospitalization rates, left ventricular hypertrophy (LVH), and higher mortality.[4] Current guidelines, such as those from KDIGO and ERBP, focus on maintaining static hemoglobin (Hb) targets, but there is ongoing debate about the risks and benefits of normalizing Hb levels in patients with CKD.[4] Given the rising prevalence and the severe outcomes associated with CKD, there is a pressing need for improved prevention, detection, and treatment strategies to mitigate its global impact.[1,5]

Dynamic Hb monitoring is increasingly recognized as a crucial factor in capturing disease activity, treatment response, and prognostic risk. This approach is supported by evidence from various fields where latent class trajectory modeling has been applied to identify distinct patterns of disease progression and associated risks. For instance, in type 2 diabetes, different HbA1c trajectories have been linked to varying risks of complications.[6] Despite its potential, this modeling approach is underutilized in the management of CKD anemia. Frailty, a parallel and understudied outcome in CKD, shares biological pathways with anemia and is associated with adverse outcomes like falls and hospitalizations.[7,8] The integration of dynamic assessments of anemia and frailty is crucial, as both contribute to cardiovascular risk, with anemia-related hemodynamic stress and frailty acting as independent cardiovascular risk enhancers.[9] The need for an integrated assessment of anemia dynamics, frailty changes, and cardiovascular events is underscored by the potential to improve prognostic accuracy and patient stratification, as demonstrated in other diseases through dynamic modeling.[10,11] These approaches, such as dynamic phenotype modeling and trajectory alignment, have shown promise for enhancing understanding of disease progression and improving clinical outcomes by capturing the temporal dynamics of disease states.[12] Therefore, adopting similar methodologies in CKD could provide significant clinical benefits, offering a more comprehensive and personalized approach to patient care.

The existing literature highlights a significant knowledge gap regarding the simultaneous examination of longitudinal Hb trajectories, frailty progression, and incident cardiovascular events in patients with stage 3–5 non-dialysis-dependent CKD (ND-CKD). Most studies have primarily focused on single baseline Hb measurements, neglecting the dynamic nature of Hb levels over time and the impact of frailty on clinical outcomes.[13-15] For instance, the CKD-REIN cohort study identified five distinct Hb trajectory profiles, revealing that while two-thirds of patients maintained stable Hb levels, the remaining third exhibited declining trajectories associated with increased risks of major adverse cardiovascular events.[15] Furthermore, frailty, prevalent in advanced CKD, has been linked to adverse outcomes, yet longitudinal studies exploring its progression in this population remain scarce.[16] This underscores the need for comprehensive research that integrates these factors to better understand their interrelationships and implications for patient management in CKD.[17]

The present study sought to delineate 12-month Hb trajectories in adults with stage 3–5 ND-CKD and to evaluate whether these longitudinal patterns are associated with two clinically salient outcomes: frailty worsening and a composite of major cardiovascular events. We hypothesized that a persistently declining Hb pattern, relative to a stable pattern, would be associated with greater frailty worsening and higher risk of cardiovascular events.

Methods

Study design and setting. We conducted a prospective, single-center cohort study at Affiliated Hospital of Hebei University from June 2023 to December 2023. Each participant was followed for 12 months or until death, kidney replacement therapy initiation, or withdrawal of consent, whichever occurred first. The local Institutional Review Board approved the study, and all participants gave written informed consent.

Participants. Adults ≥18 years were eligible if they met all of the following at screening: (1) estimated glomerular filtration rate (eGFR, CKD-EPI 2021)<60 mL/min/1.73 m², classifying as CKD stage3a–5 and not receiving dialysis or having a functioning kidney transplant; (2) renal anemia defined by Hb<13 g/dL for men or <12 g/dL for women on two occasions ≥7 days apart; and (3) ability to attend monthly study visits. Exclusion criteria were: active malignancy, pregnancy or lactation, acute bleeding episode in the preceding 3 months, planned dialysis or transplantation within 3 months, acute kidney injury, or participation in another interventional trial likely to affect Hb concentration.

Data collection and variable definitions. At baseline, we recorded demographics, CKD stage, comorbidities (Charlson index), medication use (including erythropoiesis-stimulating agents [ESAs], hypoxia-inducible factor prolyl-hydroxylase inhibitors [HIF-PHIs], ACE inhibitors/ARBs, and SGLT2

inhibitors), blood pressure, body-mass index (BMI), and laboratory tests (Hb, ferritin, transferrin saturation [TSAT], C-reactive protein [CRP], serum albumin, serum creatinine). Hb was measured monthly using a Sysmex XN-1000 hematology analyzer. All other blood tests were repeated every 3 months or when clinically indicated. Medication exposure variables used in adjusted models reflected baseline ESA/HIF-PHI use. Protocolized time-updated dose-escalation data were unavailable, so whether treatment intensification preceded or followed the Hb decline could not be reliably determined.

Frailty was assessed at baseline, 6 months and 12 months using: (i) the 5-item FRAIL scale (Fatigue, Resistance, Ambulation, Illnesses, Loss of weight; score 0–5) and (ii) objective performance measures: hand-grip strength (Jamar dynamometer, average of three tests; <26 kg men or <18 kg women considered weak) and 4-metre gait speed (slow <0.8 m/s). Frailty worsening was predefined as a ≥1-point increase in the FRAIL score or new onset of either weak grip or slow gait. Because frailty was reassessed only at these prespecified visits, short-term fluctuations between visits were not captured.

Cardiovascular events comprised a prespecified composite of (a) non-fatal myocardial infarction, (b) non-fatal stroke or transient ischemic attack, (c) hospitalization for new-onset or acutely decompensated heart failure, (d) sustained ventricular arrhythmia or atrial fibrillation/flutter requiring hospital care, and (e) cardiovascular death. Two blinded cardiologists adjudicated all suspected events, with disagreements resolved by a third reviewer.

Sample-size justification. Using Schoenfeld's formula for time-to-event analyses, we assumed three trajectory classes with 40% of patients in the "Declining" class, a 12-month composite CV-event rate of 25%, and a clinically meaningful hazard ratio (HR) of 2.5 versus the "Stable" class. With $\alpha = 0.05$ (two-sided) and 80% power, 39 events were required, translating to 156 patients; inflating by 15% for attrition yielded a target enrolment of 190. This sample provided>80% power to detect a 30-percentage-point difference in frailty-worsening risk (30% vs 60%).

Statistical analysis. Continuous variables are reported as mean ± standard deviation (SD) or median (interquartile range, IQR), and categorical variables are reported as counts (%). Baseline differences across trajectory classes were evaluated with ANOVA or Kruskal–Wallis tests (continuous) and $\chi 2$ tests (categorical).

Hemoglobin trajectories were derived using latent-class mixed models based on all available monthly Hb measurements during follow-up. Competing 2- to 5-class models were compared using BIC, AIC, entropy, mean posterior class-membership probabilities, minimum class size, and clinical interpretability. Because class membership is estimated from repeated Hb measurements collected during follow-up, the trajectory classes are interpreted as summaries of longitudinal Hb patterns observed during the study period.

Frailty worsening was evaluated at 6 months and 12 months relative to baseline, yielding up to two repeated binary outcomes per participant. Mixed-effects logistic regression was used with a random intercept for participant and fixed effects for trajectory class and prespecified covariates: age, sex, baseline eGFR, diabetes status, CRP, ferritin, TSAT, baseline ESA/HIF-PHI exposure, and ACE inhibitor/ARB use.

The time to first composite CV event was examined using cause-specific Cox proportional-hazards models. Non-CV death and kidney replacement therapy (KRT) initiation were treated as censoring events in cause-specific analyses. Proportional-hazards assumptions were checked with Schoenfeld residuals.

Sensitivity analyses included: (1) a joint longitudinal–time-to-event model linking longitudinal Hb and time to CV event; (2) Fine–Gray subdistribution hazards treating non-CV death or KRT initiation as competing events; (3) multiple imputation by chained equations (20 datasets) for missing covariates; (4) exclusion of participants with baseline ferritin >800 ng/mL; and (5) stratified analyses by CKD stage (3 vs 4–5).

Exploratory analyses examined whether frailty worsening might lie on the pathway between Hb trajectory and CV events; given the discrete timing of frailty assessments and the possibility that CV events could occur before frailty reassessment, these analyses were considered hypothesis-generating and are presented in the Supplement. All tests were two-sided with significance set at $p < 0.05$. Effect estimates are reported as odds ratios (OR) or hazard ratios (HR) with 95% confidence intervals (CI). Analyses were performed in Rv4.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Study population. We screened 247 adults with stage 3–5 ND-CKD, enrolled 190 who met eligibility criteria, and had 12-month follow-up assessments available for 182 (95.8%) (**Figure 1**). Two participants died, four initiated kidney replacement therapy, and two withdrew consent before the 12-month visit. The cohort's mean ± SD age was 63 ± 12 years, 44% were women, and 58% had CKD stage 4–5. Baseline characteristics were broadly similar across hemoglobin-trajectory classes, although baseline use of erythropoiesis-stimulating agents or HIF-prolyl-hydroxylase inhibitors was higher in the Declining group (59%) than in the Stable (43%) or Fluctuating (53%) groups (**Table 1**).

Table 1. Baseline Characteristics by Hemoglobin-Trajectory Class.

Age, y (mean ± SD)	61 ± 11	65 ± 13	62 ± 12	0.10
Women, n (%)	30 (41)	36 (46)	18 (47)	0.72
CKDstage 4-5, n (%)	38 (51)	50 (64)	22 (58)	0.12
Diabetes, n (%)	36 (49)	46 (59)	20 (53)	0.41
Baseline Hb, g/dL	10.6 ± 1.1	10.2 ± 1.3	10.3 ± 1.2	0.08
Ferritin, ng/mL (median[IQR])	150 [85–300]	170 [95–350]	180 [100–340]	0.34
TSAT, % (median[IQR])	23 [18–31]	21 [16–29]	22 [17–29]	0.65
Baseline ESA/HIF-PH use, n (%)	32 (43)	46 (59)	20 (53)	0.03

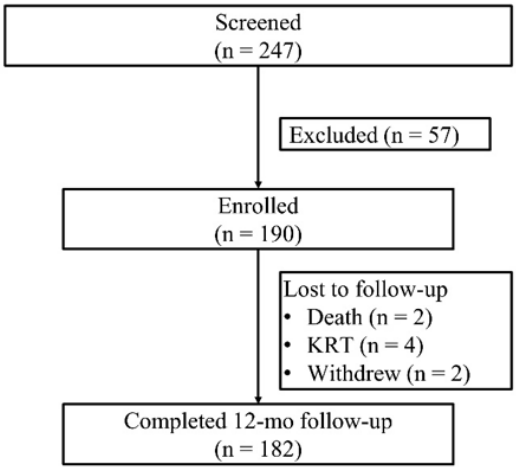

Figure 1. Study enrolment and follow-up. The diagram showed the flow of participants from screening of 247 adults with stage 3–5 non-dialysis chronic kidney disease (ND-CKD), exclusion of 57, enrollment of 190 eligible participants, allocation into three hemoglobin-trajectory classes, and 12-month status (182 completed follow-up; 2 deaths, 4 kidney replacement therapy initiations, and 2 withdrawals).

A three-class latent-class linear mixed-effects model best described the 2,073 hemoglobin observations (mean 10.9 Hb measurements per participant), yielding a Stable class of 74 participants (39%) with an almost flat monthly slope (+0.05 g/dL), a Declining class of 78 participants (41%) exhibiting a mean decrease of −0.18 g/dL per month, and a Fluctuating class of 38 participants (20%) whose linear course had a within-person coefficient of variation exceeding 12%. Model fit statistics were optimal at a Bayesian Information Criterion of 4,015 and entropy of 0.83, and 86% of individuals had posterior class-membership probabilities ≥0.90 (**Table 2** and **Figure 2**). The four-class model had a higher BIC (4,028), lower entropy (0.79), and less clinically interpretable class sizes, supporting retention of the three-class solution.

During follow-up, frailty worsened in 25% of Stable, 57% of Declining, and 45% of Fluctuating participants ($p < 0.001$). In a mixed-effects logistic regression

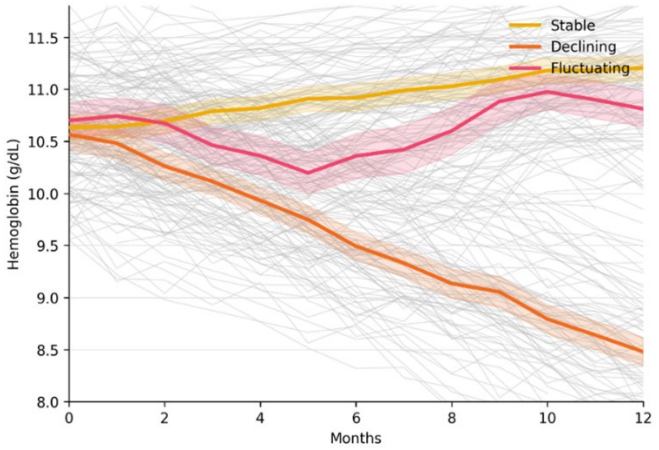

Figure 2. Twelve-month hemoglobin (Hb) trajectories derived from latent-class mixed modelling. Thin gray lines represent individual monthly Hb measurements (2,073 observations from 190 participants), and the superimposed bold lines represent the model-estimated mean trajectory for each latent class: Stable (n = 74; near-flat slope +0.05 g/dL/month), Declining (n = 78; mean slope −0.18 g/dL/month) and Fluctuating (n = 38; higher within-person variability). Shaded band denote 95% confidence intervals around each class-specific mean.

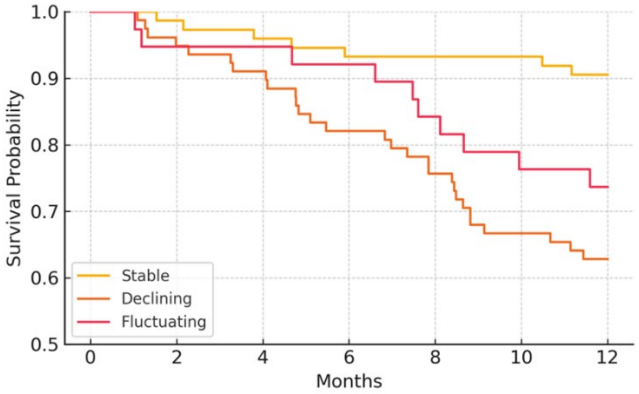

Figure 3. Kaplan–Meier curves for time to first composite cardiovascular event according to hemoglobin (Hb)-trajectory class. Step curves show the event-free probability over 12 months for the Stable, Declining, and Fluctuating classes. The composite endpoint comprised non-fatal myocardial infarction, non-fatal stroke or transient ischemic attack, hospitalization for new-onset or acutely decompensated heart failure, sustained ventricular arrhythmia or atrial fibrillation/flutter requiring hospital care, or cardiovascular death.

Table 2. Latent-Class Model Fit Indices.

2 classes	4 120	4 080	0.77	0.88
3 classes (chosen)	4 015	3 960	0.83	0.90
4 classes	4 028	3 965	0.79	0.87
5 classes	4 045	3 970	0.76	0.85

Table 3. Association Between Hb Trajectory and Frailty Worsening.

Declining	3.9 (2.2 – 6.9)	<0.001	2.8 (1.6 – 5.0)	0.001
Fluctuating	2.3 (1.1 – 4.8)	0.03	1.9 (0.9 – 4.0)	0.08

Table 4. Association Between Hb Trajectory and Composite Cardiovascular Events.

Declining	29 / 78	2.9 (1.6 – 5.3)	<0.001	2.6 (1.4 – 4.9)	0.003
Fluctuating	10 / 38	1.9 (0.9 – 4.0)	0.09	1.7 (0.8 – 3.6)	0.17

adjusted for demographic, renal, inflammatory and treatment covariates, the Declining trajectory was associated with nearly threefold higher odds of frailty deterioration compared with the Stable trajectory (adjusted odds ratio [aOR] 2.8, 95% CI 1.6–5.0), whereas the Fluctuating trajectory showed an elevated but non-significant odds ratio of 1.9 (95% CI 0.9–4.0) (**Table 3**).

Over 185 person-years (median follow-up 364 days), 46 composite cardiovascular events occurred—29 in the Declining, 10 in the Fluctuating, and 7 in the Stable class—yielding an incidence of 24.9 per 100 person-years and clearly separated Kaplan–Meier estimates of time-to-first composite CV events (**Figure 3**). After multivariable adjustment, the Declining trajectory conferred a 2.6-fold higher hazard of cardiovascular events relative to the Stable trajectory (adjusted hazard ratio [aHR] 2.6, 95% CI 1.4–4.9; $p = 0.003$), whereas the Fluctuating trajectory carried a non-significant 70 % increase (aHR 1.7, 95% CI 0.8–3.6; $p = 0.17$) (**Table 4**); proportional-hazards assumptions were satisfied.

Discussion. This prospective cohort study examined whether distinct 12-month Hb trajectory patterns are associated with frailty worsening and cardiovascular outcomes in adults with stage 3–5 ND-CKD and renal anemia. Using latent-class mixed modeling, we identified three patterns—Stable, Declining, and Fluctuating. The Declining group was independently associated with substantially higher odds of frailty worsening and more than doubled hazard of composite CV events compared with the Stable class, whereas the Fluctuating class showed intermediate, non-significant associations. These longitudinal Hb trajectories should be interpreted as prognostic pattern markers rather than proven mediators of frailty progression or cardiovascular injury.

Recent work in oncology and cardiology has already illustrated that the direction and velocity of hemoglobin change can matter more than its absolute value at a single visit: in non-small-cell lung cancer and colorectal cancer a post-diagnosis shift of $|\Delta Hb| > 2.6$ g/dL heralds poorer survival,[18] while in heart-failure with reduced ejection fraction declining Hb portends higher rehospitalization and death.[19] In nephrology, however, most observational or interventional studies, including the landmark CREATE, TREAT, and PIVOTAL trials, categorized anemia exposure by a baseline or target Hb threshold and therefore could not capture within-patient trends.[20-22] Our identification of three 12-month Hb trajectories (Stable, Declining, Fluctuating) suggests that a persistently declining profile was associated with a substantially higher probability of frailty worsening and an increased risk of cardiovascular events compared with a stable trajectory, consistent with recent CKD trajectory analyses.[15] Notably, the 57% frailty-worsening rate observed in the Declining group suggests that progressive anemia may identify a particularly vulnerable subgroup within ND-CKD.

The association between a declining Hb pattern and CV events is likely multifactorial. The observed pattern may reflect a combination of worsening underlying disease, inflammation, iron-restricted erythropoiesis, and treatment hyporesponsiveness rather than a direct causal effect of Hb decline itself. Anemia amplifies myocardial workload, while activation of hypoxia-inducible factors drives both renal fibrosis and cardiomyocyte hypertrophy.[23-25] Concurrent inflammation and iron dysregulation accelerate muscle catabolism and sarcopenia, which may help explain why declining Hb co-occurred with frailty worsening.[24,26] Because baseline ESA/HIF-PHI use was more frequent in the Declining group and time-updated dose-escalation data were not modeled, confounding by indication remains possible. The continued Hb fall despite greater treatment exposure is also compatible with ESA/HIF-PHI

hyporesponsiveness, suboptimal titration, or treatment resistance.[27] By contrast, the Fluctuating group showed no significant excess CV risk, a pattern that may reflect reversible Hb dips during intercurrent illness or preserved physiological reserve.[28] This heterogeneity highlights the need to interpret episodic anemia in its clinical context.

Besides hemodynamic overload, oxidative stress, and endothelial dysfunction, frailty may also contribute to the association between a declining Hb trajectory and CV events.[29,30] Clinically, these data support that trajectory-based risk stratification may complement conventional anemia assessment.[31,32,33] Hb trajectories should be viewed as risk markers that may identify patients who merit closer evaluation of reversible causes of anemia, frailty, and cardiovascular vulnerability within existing guideline-based care.[31,32,33] This approach is best considered an adjunct to, not a replacement for, conventional anemia assessment and individualized clinical judgment.[31,32] More frequent hemoglobin monitoring could help detect an emerging decline in routine care, but whether intervening guided by the trajectory pattern improves outcomes remains unproven.[31,33] Any treatment modification should continue to follow established anemia guidelines and the broader clinical context rather than the trajectory pattern alone.[31,32,33]

Several limitations should be noted for this study. The single-center setting may limit generalizability. The modest sample and event counts limit statistical power for subgroup or interaction testing. Residual confounding is possible because we lacked repeated high-sensitivity inflammatory markers, detailed dietary data, objective measures of physical activity, and protocolized time-updated anemia-treatment dosing. Trajectory assignment, although supported by high entropy values, remains vulnerable to misclassification, and frailty was assessed only at baseline, 6, and 12 months, potentially missing short-term fluctuations. In addition, some CV events may have preceded the next frailty reassessment, limiting temporal sequencing. Because trajectory assignment used Hb information accrued during follow-up, the CV analyses should be interpreted as associations with the longitudinal Hb pattern rather than as time-zero causal estimates. Future research should therefore focus on multicenter validation in larger, ethnically diverse cohorts with extended follow-up to capture kidney-replacement outcomes, on pragmatic randomized trials that test whether trajectory-guided anemia management or frailty-targeted interventions improve hard clinical endpoints, and on mechanistic studies that unravel the roles of iron metabolism, erythropoietin resistance, and skeletal-muscle bioenergetics in progressive anemia.

In summary, with this observational cohort, the shape of a patient's hemoglobin curve may provide additional prognostic information beyond a single reading: a persistently declining trajectory was associated with higher observed rates of frailty worsening and cardiovascular events in adults with stage 3-5 ND-CKD. Dynamic trajectory-based assessment may help risk recognition, but interventional studies are needed before trajectory patterns are used to guide treatment decisions.

Founding. Hebei Province Medical Applicable Technology Tracking Project (Grant No. GZ2024096); Baoding Science and Technology Program Project (Grant No. 2041ZF160).

Ethics approval and consent to participate. The protocol conformed to the Declaration of Helsinki. The Institutional Review Board of Affiliated Hospital of Hebei University approved the study, and all participants gave written informed consent.

Data availability statement. Data sets generated during the current study are available from the corresponding author on reasonable request.

Author Contribution Statement. The authors confirm contribution to the paper as follows: study conception and design: L G; data collection: L-R, Z-Z H, Y-P Z, J-D L, S-S G; analysis and interpretation of results: L-R, Z-Z H, Y-P Z, J-D L, S-S G; draft manuscript preparation: L-R, Z-Z H, Y-P Z, J-D L, S-S G, L G. All authors reviewed the results and approved the final version of the manuscript.

References:

1. Kovesdy, C. P. (2022). Epidemiology of chronic kidney disease: an update 2022. Kidney International Supplements, 12 1(1), 7–11. https://doi.org/10.1016/j.kisu.2021.11.003
2. Bello, A. K., Okpechi, I. G., Levin, A., & Johnson, D. W. (2024). Variations in kidney care management and access: regional assessments of the 2023 International Society of Nephrology Global Kidney Health Atlas (ISN-GKHA). Kidney International Supplements, 13(1), 1–5. https://doi.org/10.1016/j.kisu.2023.12.001
3. Sarnak, M. J., Levey, A. S., Schoolwerth, A. C., Coresh, J., Culleton, B. F., Hamm, L. L., McCullough, P. A., Kasiske, B. L., Kelepouris, E., Klag, M. J., Parfrey, P. S., Pfeffer, M. A., Raij, L., Spinosa, D. J., & Wilson, P. W. F. (2003). Kidney Disease as a Risk Factor for Development of Cardiovascular Disease: A Statement From the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Hypertension, 42(5), 1050–1065. https://doi.org/10.1161/01.HYP.0000102971.85504.7C
4. Raza, I. I., Younus, S., Azhar, H., Fatima, H., Anwar, Z., Farah, A. A., & Rangwala, H. S. (2024). Transforming the management of chronic kidney disease-associated anemia using daprodustat. Annals of medicine and surgery (2012), 86(7), 3824–3826. https://doi.org/10.1097/MS9.0000000000002207
5. Mills, K. T., Xu, Y., Zhang, W., Bundy, J. D., Chen, C. S., Kelly, T. N., Chen, J., & He, J. (2015). A systematic analysis of

worldwide population-based data on the global burden of chronic kidney disease in 2010. Kidney International, 88(5), 950–957. https://doi.org/10.1038/ki.2015.230
6. Handley D, Gillett AC, Bala R, Tyrrell J, Lewis CM. Latent class growth mixture modeling of HbA1C trajectories identifies individuals at high risk of developing complications of type 2 diabetes mellitus in the UK Biobank. BMJ Open Diabetes Research & Care. 2025;13(5):e004826. https://doi.org/10.1136/bmjdrc-2024-004826
7. Chowdhury, R., Peel, N. M., Krosch, M., & Hubbard, R. E. (2017). Frailty and chronic kidney disease: A systematic review. Archives of gerontology and geriatrics, 68, 135–142. https://doi.org/10.1016/j.archger.2016.10.007
8. Afilalo, J., Karunananthan, S., Eisenberg, M. J., Alexander, K. P., & Bergman, H. (2009). Role of frailty in patients with cardiovascular disease. The American journal of cardiology, 103(11), 1616–1621. https://doi.org/10.1016/j.amjcard.2009.01.375
9. James, K., Jamil, Y., Kumar, M., Kwak, M. J., Nanna, M. G., Qazi, S., Troy, A. L., Butt, J. H., Damluji, A. A., Forman, D. E., & Orkaby, A. R. (2024). Frailty and Cardiovascular Health. Journal of the American Heart Association, 13(15), e031736. https://doi.org/10.1161/JAHA.123.031736
10. 10.Proust-Lima, C., & Taylor, J. M. (2009). Development and validation of a dynamic prognostic tool for prostate cancer recurrence using repeated measures of posttreatment PSA: a joint modeling approach.Biostatistics (Oxford, England),10(3), 535–549. https://doi.org/10.1093/biostatistics/kxp009
11. Spohr P, Froehlich RC, Scharf S, Rommerskirchen A, Bobak J, Schweier S, Jaeger P, Kobbe G, Dietrich S, Dilthey AT, Henrich B, Pfeffer KT, Haas R, Klau GW. Dynamic Prediction of Mortality Risk Following Allogeneic Hematopoietic Stem Cell Transplantation. Machine Learning: Health. 2025;1(1). https://doi.org/10.1088/3049-477X/adf74e
12. Paik, H., & Kim, J. (2021). Condensed trajectory of the temporal correlation of diseases and mortality extracted from over 300,000 patients in hospitals. PLOS ONE, 16(10). https://doi.org/10.1371/JOURNAL.PONE.0257894
13. Prezelin-Reydit, M., Combe, C., Massy, Z. A., Lange, C., Stengel, B., Alencar de Pinho, N., Harambat, J., & Leffondré, K. (2023). #3381 profiles of hemoglobin trajectory in ckd patients and associated risks of major adverse cardiovascular events: the ckd-rein cohort study. Nephrology Dialysis Transplantation, 38(Supplement_1). https://doi.org/10.1093/ndt/gfad063a_3381
14. Kuragano, T., Okami, S., Tanaka, S., Uenaka, H., Kimura, T., Ishida, Y., James, G., & Hayasaki, T. (2023). #2560 hemoglobin variability and adverse clinical events in patients with non-dialysis-dependent chronic kidney disease and anemia in continuous care. Nephrology Dialysis Transplantation, 38(Supplement_1). https://doi.org/10.1093/ndt/gfad063a_2560
15. Le Gall, L., Harambat, J., Combe, C., Philipps, V., Proust-Lima, C., Dussartre, M., Drüeke, T., Choukroun, G., Fouque, D., Frimat, L., Jacquelinet, C., Laville, M., Liabeuf, S., Pecoits-Filho, R., Massy, Z. A., Stengel, B., Alencar de Pinho, N., Leffondré, K., Prezelin-Reydit, M., & CKD-REIN study group (2024). Haemoglobin trajectories in chronic kidney disease and risk of major adverse cardiovascular events. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association, 39(4), 669–682. https://doi.org/10.1093/ndt/gfad235
16. Walker, S. R., Brar, R., Eng, F., Komenda, P., Rigatto, C., Prasad, B., Bohm, C., Storsley, L., & Tangri, N. (2015). Frailty and physical function in chronic kidney disease: the CanFIT study. Canadian Journal of Kidney Health and Disease, 2(1), 32. https://doi.org/10.1186/S40697-015-0067-4
17. Le Gall, L., Harambat, J., Combe, C., Alencar de Pinho, N., Stengel, B., Lange, C., Leffondré, K., & Prezelin-Reydit, M. (2024). Anaemia in CKD and cardiovascular risk; all cut from the same cloth? Nephrology Dialysis Transplantation, 39(Suppl. 1), gfae069–0670–1122. https://doi.org/10.1093/ndt/gfae069.670
18. Wan, S., Lai, Y., Myers, R. E., Li, B., Palazzo, J. P., Burkart, A. L., Chen, G., Xing, J., & Yang, H. (2013). Post-diagnosis hemoglobin change associates with overall survival of multiple malignancies – results from a 14-year hospital-based cohort of lung, breast, colorectal, and liver cancers. BMC Cancer, 13(1), 340. https://doi.org/10.1186/1471-2407-13-340
19. Suenaga, T., Fujino, T., Hashimoto, T., Ishikawa, Y., Shinohara, K., Matsushima, S., Komman, H., Toyosawa, M., Ide, T., Tsutsui, H., Shiose, A., & Kinugawa, S. (2024). Hemoglobin Level Can Predict Heart Failure Hospitalization in Patients with Advanced Heart Failure Awaiting Heart Transplantation without Inotropes or Mechanical Circulatory Support. International Heart Journal, 65(4), 667–675. https://doi.org/10.1536/ihj.24-067
20. Drüeke, T. B., Locatelli, F., Clyne, N., Eckardt, K. U., Macdougall, I. C., Tsakiris, D., Burger, H. U., Scherhag, A., & CREATE Investigators (2006). Normalization of hemoglobin level in patients with chronic kidney disease and anemia. The New England journal of medicine, 355(20), 2071–2084. https://doi.org/10.1056/NEJMoa062276
21. Pfeffer, M. A., Burdmann, E. A., Chen, C. Y., Cooper, M. E., de Zeeuw, D., Eckardt, K. U., Feyzi, J. M., Ivanovich, P., Kewalramani, R., Levey, A. S., Lewis, E. F., McGill, J. B., McMurray, J. J., Parfrey, P., Parving, H. H., Remuzzi, G., Singh, A. K., Solomon, S. D., Toto, R., & TREAT Investigators (2009). A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. The New England journal of medicine, 361(21), 2019–2032. https://doi.org/10.1056/NEJMoa0907845
22. Macdougall, I. C., White, C., Anker, S. D., Bhandari, S., Farrington, K., Kalra, P. A., McMurray, J. J. V., Murray, H., Tomson, C. R. V., Wheeler, D. C., Winearls, C. G., Ford, I., & PIVOTAL Investigators and Committees (2019). Intravenous Iron in Patients Undergoing Maintenance Hemodialysis. The New England journal of medicine, 380(5), 447–458. https://doi.org/10.1056/NEJMoa1810742
23. Taddei, S., Nami, R., Bruno, R. M., Quatrini, I., & Nuti, R. (2011). Hypertension, left ventricular hypertrophy and chronic kidney disease. Heart Failure Reviews, 16(6), 615–620. https://doi.org/10.1007/S10741-010-9197-Z
24. Todorova, G. V., Akisheva, A., & Stoimenova, M.-Y. (2022). Anemia and Left Ventricular Hypertrophy in Chronic Renal Failure. Journal of Biomedical and Clinical Research, 15(2), 151–157. https://doi.org/10.2478/jbcr-2022-0021
25. Liu, J., Wei, Q., Guo, C., Dong, G., Liu, Y., Tang, C., Dong, Z., & Dong, Z. (2017). Hypoxia, HIF, and Associated Signaling Networks in Chronic Kidney Disease. International Journal of Molecular Sciences, 18(5), 950. https://doi.org/10.3390/IJMS18050950
26. Butler, K. G. (2002). Hemoglobin Levels, Cardiovascular Disease, and Left Ventricular Hypertrophy in Patients with Chronic Kidney Disease. Nephrology Nursing Journal, 29(2), 189–192. https://dialnet.unirioja.es/servlet/articulo?codigo=1330742
27. Mase, K., Yamagata, K., Yamamoto, H., Tsuruya, K., Hase, H., Nishi, S., Nangaku, M., Wada, T., Hayashi, T., Uemura, Y., & Hirakata, H. (2023). Predictors of hyporesponsiveness to erythropoiesis-stimulating agents in patients with non-dialysis-dependent chronic kidney disease (RADIANCE-CKD study). American Journal of Nephrology, 54(11-12), 471-478. https://doi.org/10.1159/000534438
28. Habas, E., Sr, Al Adab, A., Arryes, M., Alfitori, G., Farfar, K., Habas, A. M., Akbar, R. A., Rayani, A., Habas, E., & Elzouki, A. (2023). Anemia and Hypoxia Impact on Chronic Kidney Disease Onset and Progression: Review and Updates. Cureus, 15(10), e46737. https://doi.org/10.7759/cureus.46737
29. Volis, I., & Zafrir, B. (2024). Frailty and Cardiovascular Disease: A Bidirectional Association. Cardiology, 149(3), 205–207. https://doi.org/10.1159/000535494
30. Govindarajulu, U. S. & Qadri, M. (2019). Survival and Mediation Analysis with Correlated Frailty. Current Research in Biostatistics, 9(1), 21-30. https://doi.org/10.3844/amjbsp.2019.21.30
31. Locatelli, F., Bárány, P., Covic, A., de Francisco, A. L. M., Del Vecchio, L., Goldsmith, D., Hörl, W. H., London, G. M., Vanholder, R., & Van Biesen, W. (2013). Kidney Disease: Improving Global Outcomes guidelines on anaemia management in chronic kidney disease: a European Renal Best Practice position statement. Nephrology Dialysis Transplantation, 28(6), 1346–1359.

https://doi.org/10.1093/NDT/GFT033
32. Locatelli, F., Aljama, P., Canaud, B., Covic, A., de Francisco, A. L. M., Macdougall, I. C., Wiecek, A., & Vanholder, R. (2010). Target haemoglobin to aim for with erythropoiesis-stimulating agents: a position statement by ERBP following publication of the Trial to Reduce Cardiovascular Events with Aranesp® Therapy (TREAT) Study. Nephrology Dialysis Transplantation, 25(9), 2846–2850. https://doi.org/10.1093/NDT/GFQ336
33. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. (2026). KDIGO 2026 clinical practice guideline for the management of anemia in chronic kidney disease (CKD). Kidney International, 109(1 Suppl), S1-S99. https://doi.org/10.1016/j.kint.2025.06.006