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Joint cardiovascular-kidney-metabolic stage-transition and depressive symptom trajectories and all-cause mortality in middle-aged and older Chinese adults: CHARLS 2011–2018

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Abstract

Background

Depressive symptoms are linked to every component of cardiovascular-kidney-metabolic (CKM) syndrome, yet existing CKM–depression research reads CKM stage once, at baseline, as if it were fixed. Whether longitudinal CKM stage transitions and depressive symptom trajectories jointly carry prognostic information is unknown.

Methods

Using four waves (2011–2018) of the China Health and Retirement Longitudinal Study (n = 14,003), we derived four CKM stage-transition trajectories anchored to the 2011 and 2015 waves and three depressive symptom trajectories (k-means clustering of Center for Epidemiologic Studies Depression Scale scores), and examined their joint association with all-cause mortality in Cox models. We then contrasted the trajectory-based exposure with a static binary CKM classification and developed a LASSO prediction model with geographic external validation.

Results

Between the anchor waves, 12.9% of participants progressed to a higher CKM stage and 5.8% regressed. The double-hit phenotype (Persistent Advanced CKM plus High depressive symptoms) carried a hazard ratio (HR) of 1.61 (95% CI 1.27–2.03) versus Persistent Early plus Low-Stable. CKM trajectory and depressive symptom trajectory each independently predicted mortality, whereas the static binary exposure returned a null association (HR 1.09, 95% CI 0.96–1.23). Depressive symptoms were associated with higher mortality primarily within metabolically burdened trajectories. The LASSO model achieved an area under the receiver operating characteristic curve of 0.812 internally and 0.798 in external validation.

Conclusions

Longitudinal CKM transitions and depressive symptom trajectories jointly stratify mortality risk in middle-aged and older Chinese adults. Depressive symptoms act as a trajectory-dependent amplifier rather than a uniform hazard, and collapsing CKM into a static classification obliterates the prognostic signal.

Background

In 2023 the American Heart Association (AHA) folded metabolic risk factors, chronic kidney disease (CKD) and cardiovascular disease (CVD) into a single staged construct — cardiovascular-kidney-

metabolic (CKM) syndrome, Stages 0–4 [1]. The staging is not cosmetic. Nearly 90% of US adults already meet criteria for Stage 1 or higher, and progression to advanced stages confers substantial excess mortality [2, 3].

Depressive symptoms interact with every element of this axis. Obesity, diabetes, CKD and CVD each raise depressive symptom burden, and depression in turn worsens cardiometabolic prognosis [4, 5]. In NHANES, advanced CKM stages tracked higher depression prevalence, and among participants who were depressed, advanced CKM carried a 94% increase in all-cause mortality [6]. Machine-learning models have since been developed to predict depression within CKM populations [7].

One limitation runs through all of this work: CKM stage is measured once and treated as a fixed attribute. It is not one. Stage transitions have now been characterised — in two Korean nationwide cohorts [8, 9] and, through a multi-state framework, in CHARLS itself [10] — but always as a single-dimension exposure. No study has jointly modelled longitudinal CKM stage transitions and depressive symptom trajectories as dual longitudinal exposures in relation to all-cause mortality, and none has quantified what prognostic information is lost when within-person CKM evolution is collapsed into a static classification. Whether the prognostic weight of depressive symptoms is uniform across CKM trajectories, or concentrates where metabolic burden accumulates, is equally unknown.

We addressed these questions using four waves (2011–2018) of the China Health and Retirement Longitudinal Study (CHARLS). Our objectives were fourfold: to characterise longitudinal CKM stage-transition patterns; to analyse CKM trajectories and depressive symptom trajectories jointly in relation to all-cause mortality; to test effect modification across demographic and clinical subgroups; and to develop and externally validate an interpretable prediction model incorporating these longitudinal phenotypes.

Methods

Study design and population

We used data from CHARLS, a nationally representative cohort of community-dwelling Chinese adults aged 45 years and older and their spouses, interviewed in person with standardised questionnaires. The 2011 baseline survey enrolled 17,708 participants from 10,257 households across 450 communities in 150 counties of 28 provinces through multistage stratified probability sampling, with refreshment samples aged 39–45 years added in later waves; five waves (2011, 2013, 2015, 2018 and 2020) have been completed to date. The design and sampling procedures are detailed elsewhere [11].

From 25,583 participants across the 2011, 2013, 2015 and 2018 waves, we excluded those younger than 45 years, those with fewer than two waves of participation or incomplete CKM staging or Center for Epidemiologic Studies Depression Scale (CES-D) data (N = 4,941), those lacking CKM staging at both the 2011 and 2015 anchor waves (N = 6,068) and those with insufficient longitudinal CES-D data for trajectory grouping (N = 571). The analytical sample comprised 14,003 participants (Fig. 1).

CKM syndrome staging

CKM syndrome was staged according to the 2023 AHA definition, adapted to the variables available in CHARLS. Stage 0 denotes no CKM risk factors; Stage 1, excess adiposity (body mass index [BMI] ≥ 25 kg/m² or abdominal obesity by Chinese-specific cut-offs) or prediabetes (glycated haemoglobin [HbA1c] 5.7–6.4%); Stage 2, hypertension (self-reported diagnosis or measured blood pressure ≥ 140/90 mmHg), diabetes (self-reported diagnosis or HbA1c ≥ 6.5%) or dyslipidaemia; Stage 3, self-reported CKD; and Stage 4, clinical cardiovascular disease (self-reported heart disease or stroke). Participants meeting multiple criteria were assigned the highest stage (4 > 3>2 > 1>0). HbA1c was assayed only in 2011 and 2015; at the 2013 wave, Stage 1 therefore rested on adiposity criteria and Stage 2 diabetes on self-report. Because this reduced definition is not equivalent to the full one, wave-to-wave transitions involving 2013 (Supplementary Fig. S1) are reported descriptively, and all trajectory analyses were anchored to 2011 and 2015, where staging followed the same full definition.

CKM trajectory types

From the 2011 and 2015 stages we derived four trajectory types: Persistent Early (stage ≤ 1 at both waves), Progression (net worsening), Regression (net improvement) and Persistent Advanced (stage ≥ 2 at both waves). We summarised each participant's course as the net transition between the two anchor waves rather than fitting a multi-state transition-intensity model: equivalent full staging exists only at these two waves, and a person-level transition phenotype matches this measurement structure.

Depressive symptom assessment and trajectories

Depressive symptoms were assessed with the 10-item CES-D, which asks how many days during the previous week each symptom was experienced (0, rarely or < 1 day; 1, 1–2 days; 2, 3–4 days; 3, 5–7 days; total range 0–30, higher scores indicating greater severity). A cut-off of 10 has shown reasonable sensitivity and specificity among Chinese older adults (Supplementary Methods) [12].

For each participant we computed two longitudinal CES-D features — the mean score and the change from baseline to the final assessment — and clustered the standardised features with k-means (nstart = 25). Three trajectories resulted, supported by the elbow method, the variance-explained criterion and silhouette analysis (maximal silhouette 0.404); we labelled them Low-Stable, Moderate (improving) and High (worsening).

Outcome

Outcome

The outcome was all-cause mortality through 2018, ascertained via CHARLS exit interviews and next-of-kin reports. Follow-up ran from the 2011 baseline for a median of 7.0 years, yielding 92,136 person-years

and 1,105 deaths (incidence 12.0 per 1,000 person-years).

Statistical analysis

Cox proportional-hazards models estimated hazard ratios (HRs) for the 12 joint exposure groups (four CKM trajectories by three depressive symptom trajectories), with Persistent Early plus Low-Stable as reference, adjusted for age, sex, education, marital status and urbanicity. The multiplicative CKM-by-depression interaction was evaluated with a likelihood-ratio test, and additive models without the interaction term estimated the main effect of each dimension. Sensitivity analyses excluded participants with baseline cardiovascular disease (Stage 4), excluded deaths within the first two years, stratified by age (< 65 vs ≥ 65 years) and sex, and restricted follow-up to 2011–2015. Subgroup analyses of the double-hit phenotype covered age, sex, urbanicity, baseline CKM severity and baseline depression strata, with interaction p-values reported. Restricted cubic splines with four knots assessed nonlinearity for CKM stage, CES-D score and age. Survival was visualised with Kaplan–Meier curves and compared by log-rank tests, including curves stratified by depressive symptom trajectory within each CKM trajectory. For prediction of 7-year mortality we compared LASSO regression, Random Forest and XGBoost, training on 14 provinces (70% internal split) and validating externally in 14 geographically distinct provinces. Discrimination was quantified by the area under the receiver operating characteristic curve (AUC) with 95% confidence intervals; standardised LASSO coefficients were examined for interpretability and their stability assessed across cohorts. Analyses were performed in R version 4.5.1.

Results

Cohort characteristics

The 14,003 participants (mean age 56.5 ± 9.5 years; 47.1% male; mean BMI 23.6 ± 3.9 kg/m²) accrued 1,105 deaths (7.9%) over a median follow-up of 7.0 years — an incidence of 12.0 per 1,000 person-years (Fig. 1; Table 1). Mean baseline CES-D score was 8.4 ± 6.3, and 37.0% screened positive (CES-D ≥ 10). The CKM trajectory distribution was: Persistent Early 5,470 (39.1%), Regression 809 (5.8%), Progression 1,808 (12.9%) and Persistent Advanced 5,916 (42.2%) (Fig. 1; Supplementary Table S1). Depressive symptom trajectories split into Low-Stable 7,054 (50.4%), Moderate 3,308 (23.6%) and High 3,641 (26.0%) (Supplementary Fig. S2). Baseline characteristics differed across CKM trajectories (all $p < 0.001$), the Persistent Advanced group carrying the highest burden of hypertension (51.5%), diabetes (15.1%), heart disease (27.1%) and stroke (4.3%) (Table 1).

Table 1
Baseline characteristics by CKM trajectory

Level	Persistent Early	Regression	Progression	Persistent Advanced	p-value
N	5470	809	1808	5916	
Age Baseline (mean (SD))	53.98 (8.80)	58.53 (10.66)	57.17 (9.31)	58.33 (9.43)	< 0.001
Sex (%)					< 0.001
Female	2793 (51.1)	415 (51.4)	914 (50.6)	3271 (55.3)	
Male	2670 (48.9)	392 (48.6)	893 (49.4)	2642 (44.7)	
Education (%)					< 0.001
No formal/Primary	2172 (43.4)	392 (49.1)	756 (46.2)	2603 (46.4)	
Junior high	2270 (45.3)	339 (42.5)	737 (45.0)	2381 (42.4)	
Senior high+	567 (11.3)	67 (8.4)	144 (8.8)	630 (11.2)	
Married (%)					< 0.001
Married	4744 (86.7)	642 (79.4)	1516 (83.8)	4893 (82.7)	
Other	726 (13.3)	167 (20.6)	292 (16.2)	1023 (17.3)	
Region (%)					< 0.001
Rural	3686 (67.4)	514 (63.5)	1200 (66.4)	3595 (60.8)	
Urban	1784 (32.6)	295 (36.5)	608 (33.6)	2321 (39.2)	
BMI (mean (SD))	22.62 (3.48)	23.36 (3.86)	23.42 (3.50)	24.46 (4.11)	< 0.001
Hypertension (%)					< 0.001
No	4976 (100.0)	780 (98.7)	1492 (91.1)	2727 (48.5)	
Yes	0 (0.0)	10 (1.3)	145 (8.9)	2899 (51.5)	
Diabetes (%)					< 0.001

CKM, cardiovascular-kidney-metabolic; BMI, body mass index; CES-D, Center for Epidemiologic Studies Depression Scale. Percentages were calculated among participants with non-missing data for each variable.

Level	Persistent Early	Regression	Progression	Persistent Advanced	p-value
No	5012 (100.0)	761 (95.1)	1599 (97.3)	4795 (84.9)	
Yes	0 (0.0)	39 (4.9)	44 (2.7)	850 (15.1)	
Heart Disease (%)					< 0.001
No	4981 (100.0)	793 (99.7)	1634 (100.0)	4094 (72.9)	
Yes	0 (0.0)	2 (0.3)	0 (0.0)	1521 (27.1)	
Stroke (%)					< 0.001
No	5000 (100.0)	799 (100.0)	1643 (100.0)	5383 (95.7)	
Yes	0 (0.0)	0 (0.0)	0 (0.0)	243 (4.3)	
Obesity BMI25 (%)					< 0.001
No	4124 (82.3)	562 (70.2)	1240 (75.5)	3613 (64.0)	
Yes	888 (17.7)	238 (29.8)	403 (24.5)	2032 (36.0)	
Abdominal Obesity (%)					< 0.001
No	3019 (71.8)	449 (57.6)	749 (56.7)	2281 (46.6)	
Yes	1183 (28.2)	331 (42.4)	572 (43.3)	2610 (53.4)	
Baseline CKM stage, 2011 (%)					< 0.001
0	3837 (70.1)	5 (0.6)	912 (50.4)	16 (0.3)	
1	1587 (29.0)	2 (0.2)	566 (31.3)	5 (0.1)	
2	46 (0.8)	797 (98.5)	309 (17.1)	3547 (60.0)	
3	0 (0.0)	3 (0.4)	20 (1.1)	624 (10.5)	
4	0 (0.0)	2 (0.2)	1 (0.1)	1724 (29.1)	
Total CES-D (mean (SD))	7.86 (6.04)	7.45 (5.98)	8.28 (6.13)	9.13 (6.61)	< 0.001
Depression (%)					< 0.001

CKM, cardiovascular-kidney-metabolic; BMI, body mass index; CES-D, Center for Epidemiologic Studies Depression Scale. Percentages were calculated among participants with non-missing data for each variable.

Level	Persistent Early	Regression	Progression	Persistent Advanced	p-value
No	3664 (67.0)	557 (68.9)	1152 (63.7)	3449 (58.3)	
Yes	1806 (33.0)	252 (31.1)	656 (36.3)	2467 (41.7)	
Survival time (mean (SD))	6.60 (1.07)	6.44 (1.28)	6.61 (1.07)	6.57 (1.13)	< 0.001
Event (%)					< 0.001
No	5206 (95.2)	720 (89.0)	1632 (90.3)	5340 (90.3)	
Yes	264 (4.8)	89 (11.0)	176 (9.7)	576 (9.7)	

CKM, cardiovascular-kidney-metabolic; BMI, body mass index; CES-D, Center for Epidemiologic Studies Depression Scale. Percentages were calculated among participants with non-missing data for each variable.

CKM stage transitions

Roughly one-quarter to one-third of participants changed CKM stage between consecutive waves. These wave-to-wave estimates include transitions involving the 2013 wave, staged under the reduced definition, and should be read as descriptive (Supplementary Fig. S1). Between the 2011 and 2015 anchor waves — where staging followed the same full definition — 1,808 participants (12.9%) showed net progression and 809 (5.8%) net regression, while the remainder stayed within their baseline early-stage (Stages 0–1) or advanced-stage (Stages 2–4) categories (Fig. 1).

Joint association with mortality

In fully adjusted models (Fig. 2), the double-hit phenotype — Persistent Advanced CKM plus High depressive symptoms — carried an HR of 1.61 (95% CI 1.27–2.03, $p < 0.001$) against Persistent Early plus Low-Stable. The largest point estimates appeared where Regression met depressive symptoms: HR 1.82 (95% CI 1.14–2.89) with the Moderate trajectory and 1.74 (95% CI 1.16–2.62) with the High trajectory. Participant flow across trajectory, depression and outcome strata is shown in Supplementary Fig. S9. The multiplicative interaction between the two trajectory dimensions was not significant (likelihood-ratio test $p = 0.52$ in the main model; $p = 0.75$ fully adjusted): the dimensions combine additively on the multiplicative scale, without supra-multiplicative synergy (Supplementary Table S3).

Independent effects and the value of longitudinal staging

In the additive model (Supplementary Fig. S4), CKM trajectory independently predicted mortality (reference Persistent Early): Progression HR 1.34 (95% CI 1.10–1.63, $p = 0.004$), Persistent Advanced HR 1.30 (95% CI 1.11–1.51, $p < 0.001$) and Regression HR 1.35 (95% CI 1.05–1.72, $p = 0.018$). Depressive symptoms predicted mortality independently as well (High vs Low-Stable HR 1.19, 95% CI 1.02–1.38, $p = 0.025$).

We then pitted this trajectory parameterisation against the conventional alternative — a static binary CKM exposure (Low vs High, based on each participant's mean stage over 2011–2015 with threshold 1.5), fitted in the same participants with the same covariates (Supplementary Table S4). The trajectory model returned robust, significant hazards for all three non-reference groups; the static exposure returned HR 1.09 (95% CI 0.96–1.23, p = 0.18), a null result capturing less than a third of the excess risk recovered by trajectory modelling. Collapsing a dynamic four-state process into one binary attribute obliterated the mortality signal.

Effect modification

Stratified Kaplan–Meier analysis (Fig. 3; Supplementary Fig. S5) suggested that depressive symptoms tracked higher mortality only within metabolically burdened trajectories: log-rank p = 0.039 for Regression and p = 0.057 for Persistent Advanced, against p = 0.68 for Persistent Early. Subgroup analysis of the double-hit phenotype (Supplementary Fig. S6; Supplementary Table S5) revealed a strong interaction with baseline depression (p = 0.0003): HR 5.84 (95% CI 2.37–14.4) among participants depressed at baseline, versus 1.24 (95% CI 0.94–1.65) among those not depressed. Effects were stronger in women (HR 2.00) and urban residents (HR 2.01).

Sensitivity and nonlinear analyses

Estimates held across all sensitivity analyses (Supplementary Table S6). Restricted cubic splines (Supplementary Fig. S7) confirmed a linear dose–response with mortality for both CKM stage (P-nonlinear = 0.72) and CES-D score (P-nonlinear = 0.86): any stage progression appears to contribute proportionally to risk, with no threshold.

Prediction model: development, external validation and interpretability

Of the three candidate algorithms, LASSO regression achieved the best discrimination and was selected as the primary model (Supplementary Fig. S8). On the internal hold-out set (N = 1,697; 78 deaths) the AUC was 0.812 (95% CI 0.765–0.858); on the geographically independent external cohort (14 provinces; N = 8,147; 365 deaths) it was 0.798 (95% CI 0.776–0.821) — a drop of only 0.014, indicating minimal overfitting and good transportability. LASSO outperformed XGBoost and Random Forest in both settings (Supplementary Table S7).

At the Youden-index optimal threshold (~ 0.05) the model showed balanced, clinically usable performance (Supplementary Table S8): sensitivity 0.69, specificity 0.78, negative predictive value 0.982 in both cohorts, overall accuracy 0.78 and a Brier score of 0.040. Positive predictive value was modest (0.13), a consequence of the 8% event rate rather than poor discrimination. Calibration curves agreed closely with observed probabilities across risk deciles in both cohorts, decision-curve analysis showed positive net benefit over the clinically relevant threshold range (~ 0.02–0.20), and precision–recall curves confirmed stable performance under class imbalance (Fig. 5).

Standardised LASSO coefficients (Fig. 4) identified age (OR 2.63 per SD), male sex (OR 1.43), CES-D score (OR 1.15) and the High depressive symptom trajectory as the strongest risk factors; persistent early CKM (OR 0.85, reference phenotype) and higher education (OR 0.90) were protective. Both trajectory variables retained non-zero coefficients after shrinkage, so the longitudinal phenotypes contribute predictive information beyond demographics. Coefficients were stable across cohorts: seven features were selected in both the development and external refits, six of them sign-consistent (Supplementary Table S9).

As a non-linear extension, SHAP feature importance from the XGBoost model (Supplementary Fig. S10) confirmed the ranking: age and male sex strongest, followed by CES-D score (third by SHAP), CKM stage and the CKM trajectory states. Trajectory features each retained appreciable SHAP values, indicating that the longitudinal phenotypes carry predictive information beyond demographics even within a non-linear framework.

Discussion

To our knowledge, this is the first study to jointly model longitudinal CKM stage transitions and depressive symptom trajectories as dual longitudinal exposures in relation to all-cause mortality, and the first to do so in a nationally representative Chinese cohort. Four findings stand out. CKM syndrome proved dynamic: between the 2011 and 2015 anchor waves, 12.9% of participants progressed and 5.8% regressed, and these trajectories predicted mortality independently of demographic and socio-economic factors. The signal disappeared entirely when CKM was collapsed into a static binary exposure — a direct demonstration of what static classification throws away. The double-hit phenotype, Persistent Advanced CKM combined with High depressive symptoms, carried a 61% higher mortality risk (HR 1.61, 95% CI 1.27–2.03) than the metabolically healthy and psychologically stable reference. And depressive symptoms did not act uniformly: they amplified risk within the metabolically burdened trajectories — Regression and Persistent Advanced — most sharply among participants already depressed at baseline (HR 5.84, 95% CI 2.37–14.4). A LASSO model built on these longitudinal phenotypes validated externally with little loss of discrimination (AUC 0.798, 95% CI 0.776–0.821) and stable coefficients across geographically distinct cohorts.

These results extend a fast-moving literature, and the position of this study within it deserves precision. Liu et al. established the cross-sectional version of the CKM–depression–mortality triangle in NHANES: advanced stages tracked depression prevalence, and among depressed participants advanced CKM raised mortality by 94% [6]. He et al. carried the same trio into two nationally representative cohorts, CHARLS included, but read the arrow the other way — depression severity predicting subsequent CKM stage and death — with exposure and staging both measured statically [13]. The longitudinal half of our design has Korean precedents: Kim et al. showed that stage increases over one to two years predicted a composite of death and cardiovascular events [8], and Park et al. reported a stepwise mortality gradient by four-year stage change in 2.8 million East Asian adults, improvement included [9]. Both modelled CKM transitions alone. Within CHARLS, Mou et al. characterised bidirectional stage transitions in a multi-state

Markov framework, but asked what physical activity does to transitions rather than what transitions do to survival [10]. Depressive symptom trajectories themselves predict mortality in Chinese older adults [14]. What none of these designs could capture is the joint phenotype: in our data CKM became a significant mortality predictor only when modelled as a four-year trajectory, whereas a static dichotomy returned a null association. Cross-sectional gradients point the same way — mortality rising from Stage 0 through Stage 4 in NHANES [15], CKM stage linked to all-cause and cardiovascular mortality in a Taiwanese cohort [16], and a threshold-free dose–response in the work of Li et al. [17], consistent with our spline results. Static stage-stratified analyses have reported depressive symptoms to be harmful at every CKM stage [18]; our trajectory analysis suggests this apparent uniformity is an artefact of static classification, because the harm concentrates where metabolic burden accumulates. The linear, threshold-free dose–response helps explain why trajectory modelling wins: without a discrete risk boundary, no single cut-point can mark it, whereas trajectory states encode the direction of within-person evolution.

Two interaction analyses were performed, and they answer different questions. The multiplicative interaction between the two trajectory dimensions was non-significant (likelihood-ratio $p = 0.52$ main model; $p = 0.75$ fully adjusted) — the hazard ratios for CKM trajectories were similar across depressive symptom trajectories, an additive combination without supra-multiplicative synergy. The double-hit phenotype, by contrast, showed strong effect modification by baseline depression status ($p = 0.0003$): a markedly amplified hazard among participants already depressed at baseline (HR 5.84 vs 1.24). These results do not conflict. The first test asks whether two trajectory variables interact within the joint model; the second asks whether a specific high-risk phenotype lands differently on a fixed baseline vulnerability. Both can hold at once, and the biology is compatible with that reading: baseline depression may mark a chronically susceptible substrate on which the double-hit phenotype exerts disproportionate harm, even as the two trajectory dimensions combine proportionally across the population. Prigge et al. similarly found that depression and socioeconomic deprivation raised cardiovascular risk through additive and multiplicative pathways whose balance shifted with the indicator chosen [19].

Why depressive symptoms preferentially amplify risk within metabolically burdened trajectories is open to several readings. Chronic psychosocial stress activates the hypothalamic–pituitary–adrenal axis and sympathetic nervous system, producing endothelial dysfunction, arterial inflammation and plaque vulnerability — processes that intensify alongside metabolic dysregulation [20]. Advanced CKM stages supply exactly that environment: chronic metabolic dysregulation, low-grade systemic inflammation and vascular injury may give depressive symptoms a pathophysiological substrate on which they are more likely to convert into clinical events [21]. Depression itself brings dysregulated hypothalamic–pituitary–adrenal activity, altered autonomic tone and poor adherence to therapy, each capable of compounding existing metabolic damage [22]. The clinical implication is practical: depression screening buys the most prognostic information in patients with advanced or progressing CKM stage, rather than applied uniformly — a priority that matters as the cardiorenal-metabolic burden now affects the majority of middle-aged and older adults worldwide [23].

One finding runs against intuition. The Regression phenotypes — participants whose CKM stage improved — showed the highest hazard ratios when paired with depressive symptoms: HR 1.82 (95% CI 1.14–2.89) with the Moderate trajectory and 1.74 (95% CI 1.16–2.62) with the High trajectory, both above the double-hit group. Three explanations, none mutually exclusive, are worth weighing.

Metabolic regression may be reactive rather than genuine remission. An acute cardiovascular or cerebrovascular event typically triggers aggressive risk-factor modification — medication intensification, lifestyle intervention, surgery — and the resulting stage reduction can mark recent clinical instability rather than recovered health [24]. The accompanying depressive symptoms may then reflect the psychological toll of a life-threatening event or a direct neuropsychiatric sequela of vascular brain injury [22]. Stage assessments at two anchor waves cannot tell true metabolic recovery from event-driven risk-factor modification; intermediate measurements would be needed.

A second reading is inflammatory. Participants who improve metabolically yet remain depressed may carry high residual inflammatory burden: controlling blood pressure, glycaemia and lipids does not necessarily extinguish the systemic inflammation that drives both vascular disease and depression [25]. Ridker has called this residual inflammatory risk — IL-6 and CRP predict cardiovascular events independently of LDL, blood pressure and glucose control [26]. Depression shows the same dissociation. Roughly a quarter of patients with major depression carry persistently elevated CRP above 3 mg/L, and IL-6 often stays high after metabolic parameters improve [27, 28]; these mediators sustain arterial wall inflammation even after traditional risk factors are managed [29], a pattern reported well beyond the cardiovascular literature [30]. Direct inflammatory measurement in future waves would settle how much of the paradox this explains.

A third is measurement artefact. Blood pressure falls sharply with initial weight loss, but the benefit roughly halves within two years and can reverse even when weight loss is maintained [31]; the neurohormonal changes behind these improvements — reduced sympathetic activity among them — typically fade within six months despite maintained weight [32, 33]. Our staging rests on a limited biomarker panel and self-reported disease history, so transient shifts in easily modifiable parameters could move a participant to a lower stage without any meaningful change in disease burden. If depressive symptoms track long-term biological insults more strongly than short-term fluctuations, apparent metabolic improvement paired with persistent distress could produce a spuriously high hazard ratio. This reading fits the allostatic load framework, in which depressive symptoms index cumulative multisystem wear rather than transient biomarker deviation [34]. Whatever the mechanism, this improvement-with-depression phenotype is a clinically important subgroup that deserves targeted prospective study.

Three design features strengthen these claims. Modelling CKM transitions and depressive symptom trajectories simultaneously moves beyond the cross-sectional exposure definitions that dominate this literature. CHARLS samples Chinese adults aged 45 and older representatively — a point underscored by Zhu et al., who showed that CKM stage distribution varies sharply with social determinants of health, so

a sample spanning the full demographic breadth matters [35]. And the geographic external validation — training in 14 provinces, testing in 14 different provinces — offers stronger evidence of transportability than a random-split validation would [36]. Trajectory groups were derived data-analytically (k-means with multiple validation criteria), reducing subjective classification bias.

Coefficient stability warrants a caveat of its own. LASSO selected seven features in both cohorts, six with consistent direction. The exception — marital status classified as Other, a heterogeneous category of divorced, widowed and never-married participants — shifted from harmful in the development cohort to weakly protective in the external one. Compositional differences across cohorts explain this better than biological instability, since the core predictors (age, sex, CES-D score, education, urban residence and the Persistent Early trajectory) were consistently selected and directionally stable. We caution against overinterpreting the Other category and recommend disaggregating it in future work.

Several limitations qualify these findings. The staging framework was adapted to CHARLS data availability. The survey lacks objective renal measures — estimated glomerular filtration rate and urinary albumin-to-creatinine ratio — so Stage 3 rests on self-reported kidney disease; we could apply neither the Kidney Disease: Improving Global Outcomes risk stratification nor the AHA PREVENT equations, and Stage 3 is probably under-ascertained [37]. Resulting misclassification of subclinical kidney disease into lower stages would bias estimates towards the null. HbA1c was measured only in 2011 and 2015, anchoring trajectory analyses to those waves; the 2013 wave, staged under the reduced definition, contributed only descriptive transitions and CES-D data. Depressive symptoms were measured with the CES-D rather than diagnostic interviews, so our trajectories reflect symptom burden patterns, not clinical major depressive disorder [12] — a distinction that matters because subthreshold symptoms, however prognostic, may differ aetiologically and therapeutically from major depression. Unmeasured confounding by diet, physical activity or medication adherence cannot be excluded, although the extensive covariate adjustment and stable sensitivity results make large residual confounders unlikely.

Conclusions

Longitudinal CKM stage transitions and depressive symptom trajectories jointly stratify all-cause mortality in ways that static classification cannot recover. Depressive symptoms amplify risk selectively — among individuals on metabolically burdened trajectories and among those already depressed at baseline. The externally validated LASSO model packages these longitudinal phenotypes into a parsimonious prediction tool for middle-aged and older Chinese adults. The next question is interventional: whether targeting depression treatment at patients with advanced or progressing CKM stage yields measurable survival benefit.

Abbreviations

AHA, American Heart Association; AUC, area under the receiver operating characteristic curve; BMI, body mass index; CES-D, Center for Epidemiologic Studies Depression Scale; CHARLS, China Health and

Retirement Longitudinal Study; CI, confidence interval; CKD, chronic kidney disease; CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease; HbA1c, glycated haemoglobin; HR, hazard ratio; LASSO, least absolute shrinkage and selection operator; NHANES, National Health and Nutrition Examination Survey; SD, standard deviation; SHAP, SHapley Additive exPlanations.

Declarations

Ethics approval and consent to participate

The CHARLS study protocol was approved by the Biomedical Ethics Review Committee of Peking University (IRB00001052-11015 for the main survey; IRB00001052-11014 for biomarker collection), and all participants provided written informed consent.

Consent for publication

Not applicable.

Availability of data and materials

Data are available from the CHARLS website (http://charls.pku.edu.cn/) upon registration.

Competing interests

The authors declare no competing interests.

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Authors' contributions

Jiayi Sun: Conceptualisation, Writing – review & editing. Zuochen Xue: Investigation, Data curation. Aijuan Cheng: Supervision, Project administration. All authors read and approved the final manuscript.

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Figures

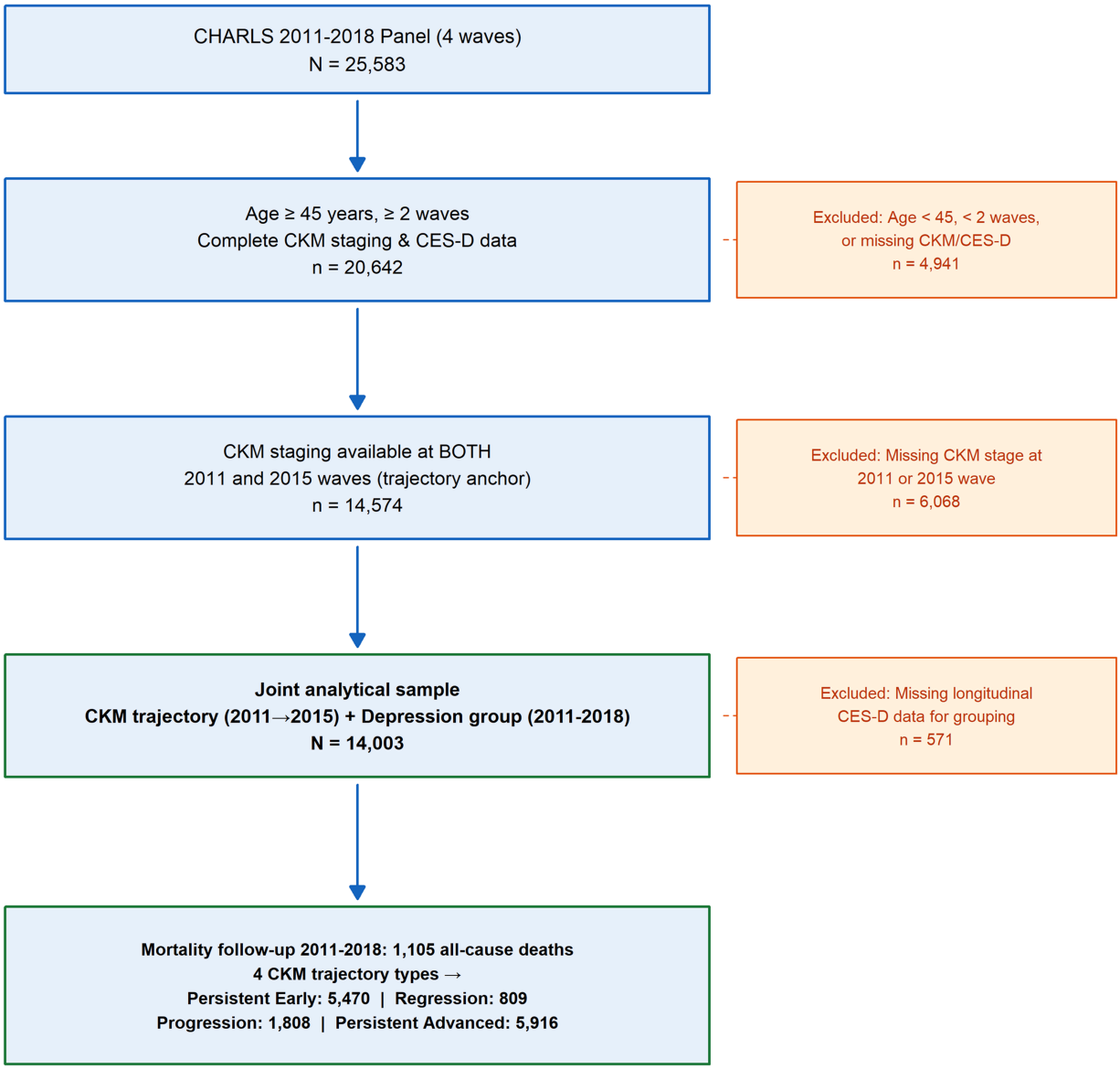


Figure 1

STROBE-style participant flow diagram. Flow of participants from the initial CHARLS pool through the exclusion steps to the analytical sample of 14,003 participants, and their distribution across the four CKM trajectory groups.

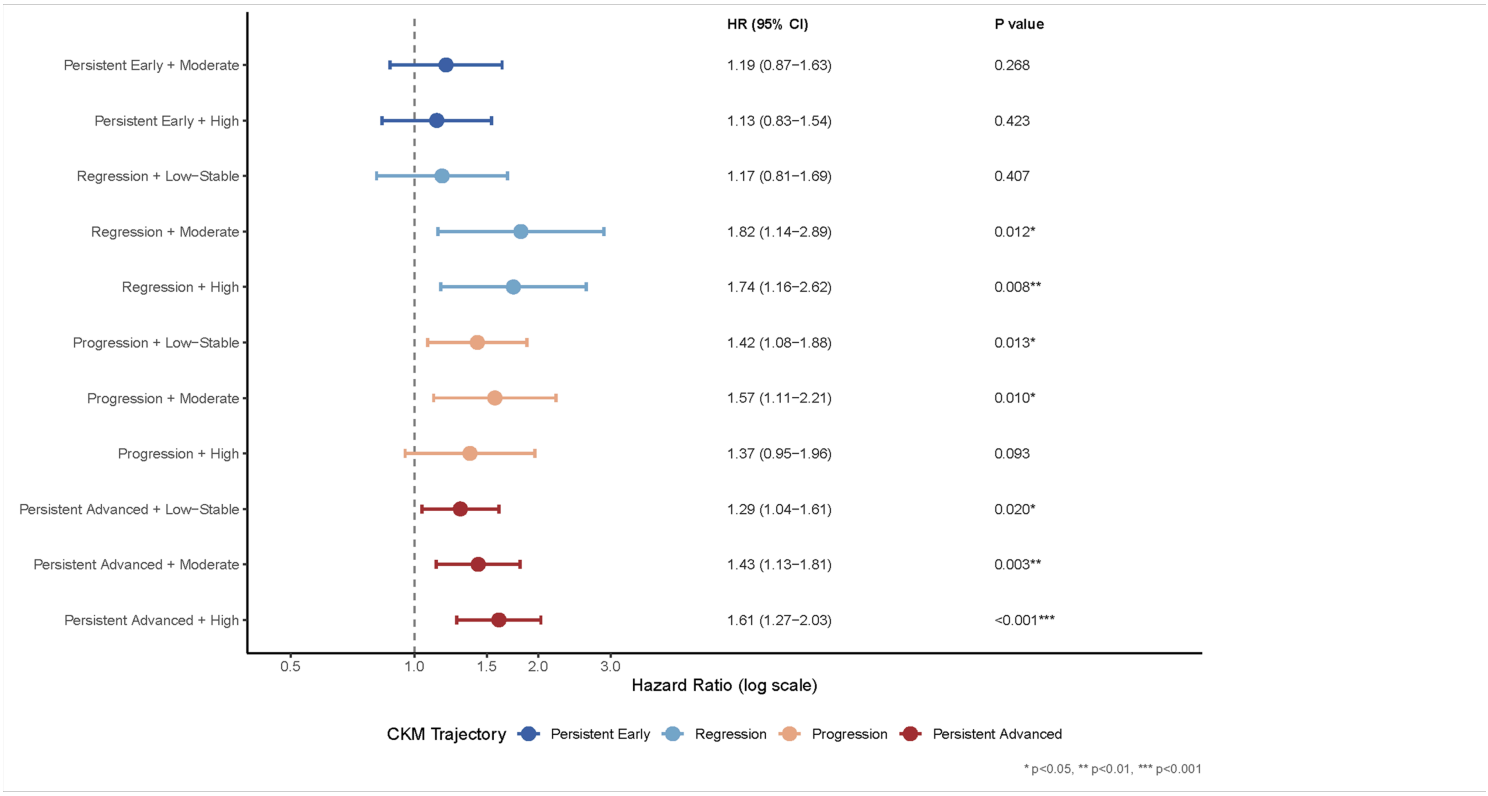


Figure 2

Twelve-group joint forest plot. Fully adjusted hazard ratios (95% confidence intervals) for all-cause mortality across the 12 joint exposure groups defined by CKM trajectory (Persistent Early, Regression, Progression, Persistent Advanced) and depressive symptom trajectory (Low-Stable, Moderate, High), with Persistent Early plus Low-Stable as reference.

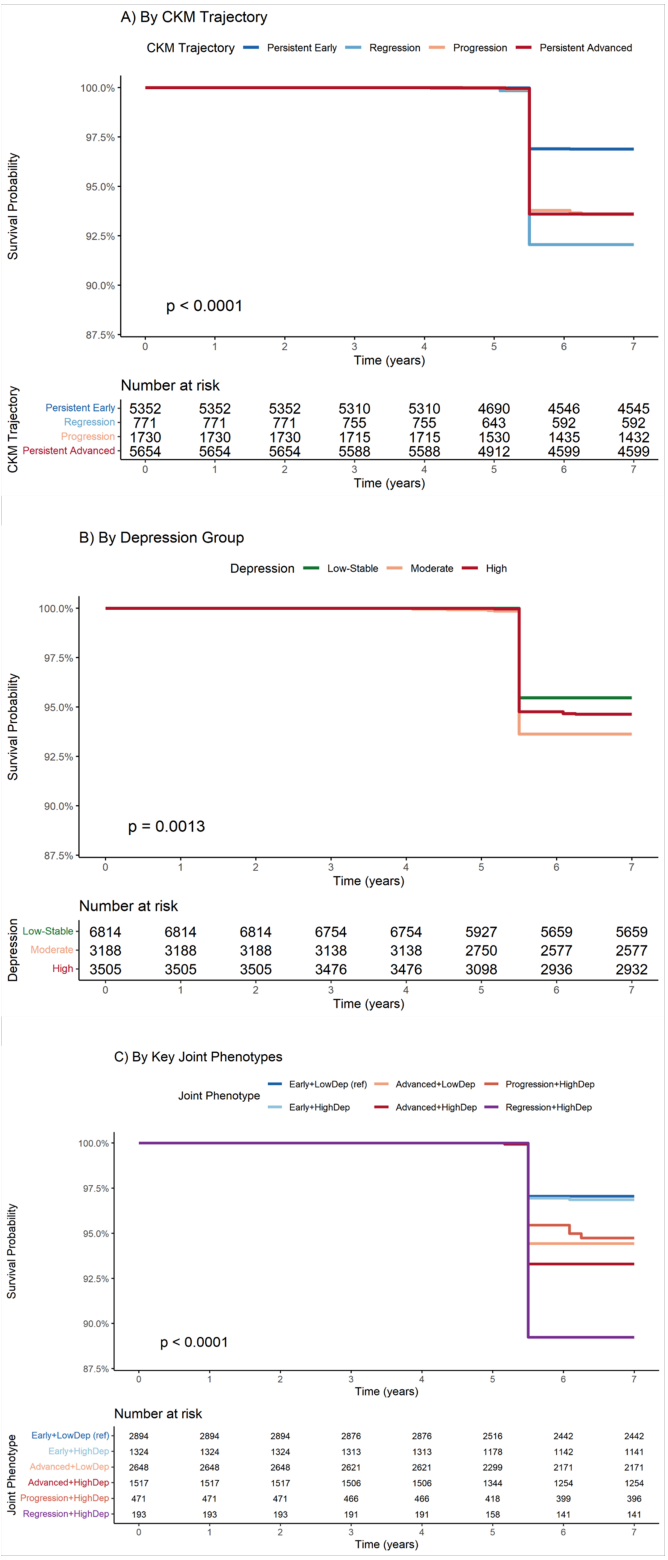


Figure 3

Kaplan–Meier curves for all-cause mortality. (a) Stratified by CKM trajectory; (b) stratified by depressive symptom trajectory; (c) stratified by joint CKM–depression phenotype.

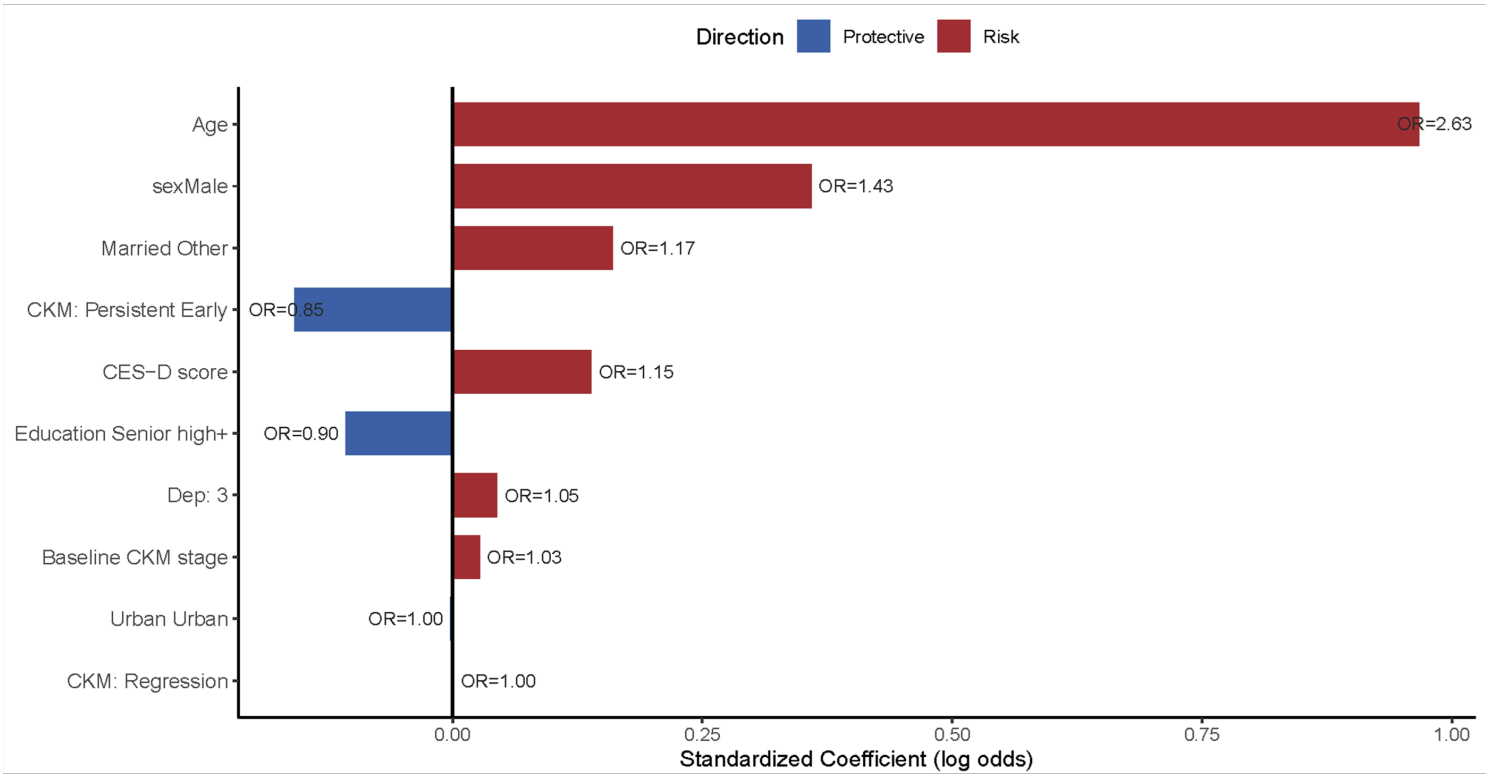


Figure 4

Standardised coefficients from LASSO regression. Standardised coefficients for predictors of all-cause mortality in the development and external validation cohorts.

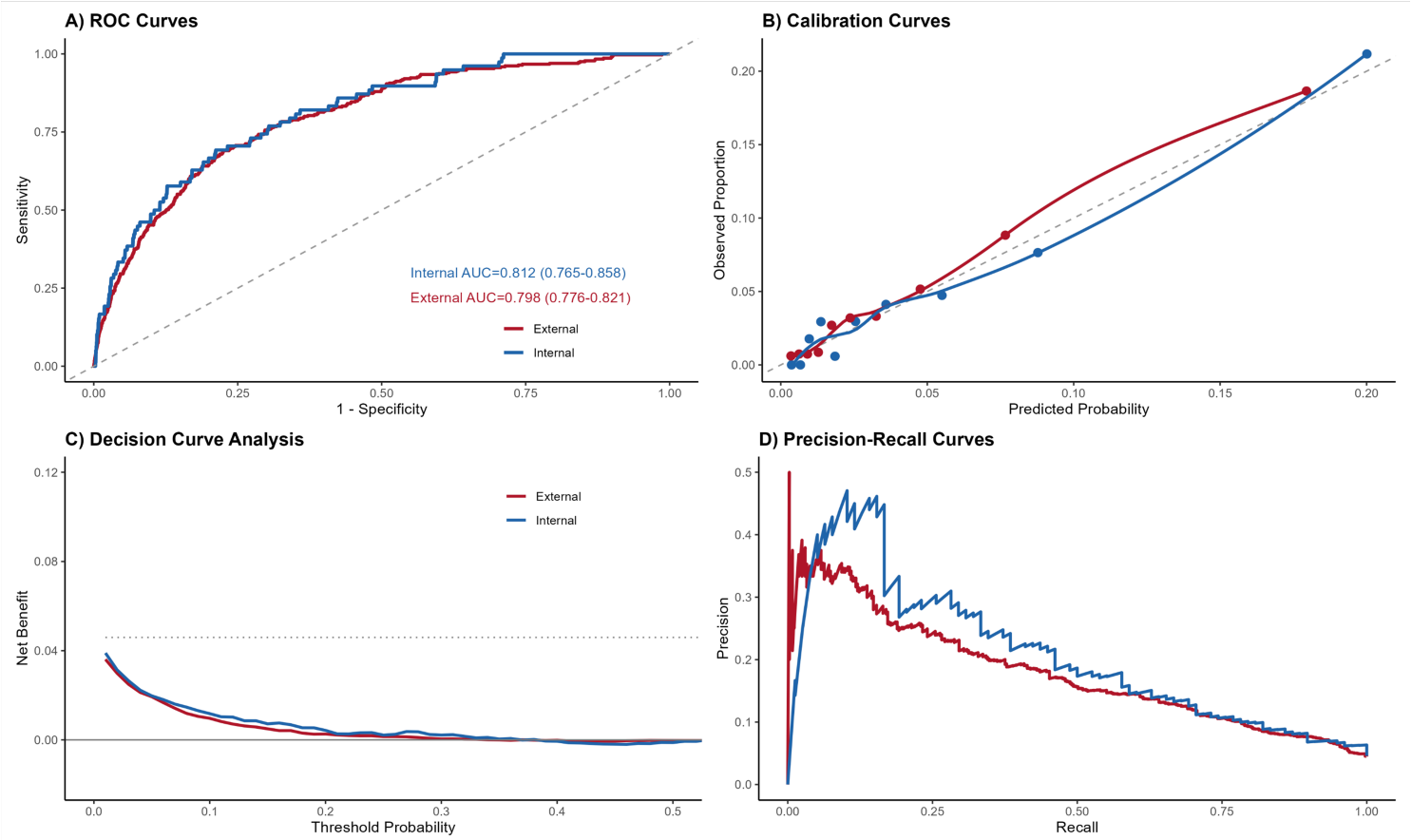


Figure 5

Performance evaluation of the LASSO model. Discrimination (receiver operating characteristic curves), calibration, decision-curve analysis and precision–recall performance in the internal and external validation cohorts.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- STROBEchecklist.docx
- Supplement.docx