Review

Prediction Models for Frailty in People Living with HIV: Systematic Review

Meilian Xie[1,2*], PhD; Yeye Hu[2*], BSN; Junjia Yuan[1], BSN; Zhiyun Zhang[2], MSc

[1]Capital Center for Children's Health, Capital Medical University, Capital Institute of Pediatrics, Beijing, China
[2]Beijing Ditan Hospital, Capital Medical University, Beijing, China
*these authors contributed equally

Corresponding Author:

Zhiyun Zhang, MSc
Beijing Ditan Hospital, Capital Medical University
No. 8 Jingshun East Street
Beijing, Beijing 100015
China
Phone: 86 13699286867
Email: zzy1968chn@163.com

Abstract

Background: Frailty is increasingly prevalent among people living with HIV, who experience earlier onset and a higher burden of frailty than the general population. Prediction models that identify people living with HIV at risk of future frailty could enable timely, targeted intervention. However, the evidence on prediction models developed specifically for frailty in people living with HIV has not yet been systematically evaluated.

Objective: This review aims to systematically identify and critically appraise multivariable prediction models for the future occurrence of frailty in people living with HIV and to assess and summarize their methodological quality and predictive performance.

Methods: We searched PubMed, Web of Science, Scopus, Cochrane Library, ProQuest, and Chinese databases (SinoMed, CNKI, Wanfang, VIP) from inception to July 24, 2026. Studies that developed or validated any multivariable statistical or machine-learning prediction model for frailty in people living with HIV were eligible. Title and abstract screening, full-text evaluation, data extraction (Checklist for Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modeling Studies [CHARMS]), and risk-of-bias and applicability assessment (Prediction Model Risk of Bias Assessment Tool [PROBAST]) were conducted independently in duplicate.

Results: The search identified 2523 records (initial search: 2205; updated search: 318); 137 full-text articles were assessed for eligibility, and only 1 study met all inclusion criteria. Frail RISC-HIV (Frailty Risk in the Short-Term for Care of People with HIV) was developed in the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort (n=4680; training n=3170; validation n=1510) using Bayesian model averaging and LASSO (least absolute shrinkage and selection operator) regression combined with Cox proportional-hazards models to predict incident frailty within 2 years. The model comprised 8 predictors (baseline frailty score, depressive symptomatology [Patient Health Questionnaire-7], prescribed antidepressants, current illicit opioid use, current marijuana use, current antiretroviral therapy, age, and sex) and achieved acceptable discrimination in the validation set (Harrell C=0.76, 95% CI 0.73-0.79), with a sensitivity of 80% and specificity of 61% at a 5% risk threshold; calibration under-predicted the observed risk (predicted 7.9% vs observed 14.7% in the validation set). PROBAST assessment rated the study at high overall risk of bias, driven primarily by the analysis domain. To our knowledge, no external validation of the model was identified, and TRIPOD (Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis) reporting was incomplete. Quantitative synthesis was not feasible.

Conclusions: The evidence base for frailty prediction in people living with HIV currently comprises a single, internally validated model that has not yet been externally validated. This critical evidence gap underscores an urgent need for further model development and rigorous external validation in diverse settings, with standardized frailty definitions and reporting in accordance with TRIPOD.

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Keywords: HIV; frailty; prediction model; systematic review; risk score

Introduction

With the widespread availability of antiretroviral therapy (ART), HIV infection has evolved from a fatal illness into a manageable chronic condition, and the life expectancy of people living with HIV has increased substantially [1,2]. The Joint United Nations Program on HIV and AIDS (UNAIDS) estimated that 40.8 million people living with HIV globally in 2024 [3]. As this population ages, the proportion of people living with HIV aged 50 years and older is projected to increase from 28% in 2010 to 73% by 2030 [4]. Clinicians and public health practitioners are therefore increasingly confronted not only with viral load management but also with the prevention and treatment of age-related comorbidities and geriatric syndromes among people living with HIV [5].

Frailty—a state of heightened vulnerability to stressors resulting from reduced physiological reserves—is among the most clinically relevant of these geriatric syndromes [6]. The 2 dominant conceptual frameworks are the frailty phenotype (FP), which defines frailty as the presence of 3 or more of 5 criteria (unintentional weight loss, exhaustion, weakness, slowness, and low physical activity) [7], and the frailty index (FI), which quantifies frailty as the accumulation of health deficits [8]. As a prognostic marker, frailty predicts a range of adverse outcomes, including falls, hospitalization, disability, and death [9,10]. Among people living with HIV, the burden is disproportionately high: a systematic review and meta-analysis reported pooled prevalences of frailty and prefrailty of 10.9% and 47.2%, respectively [11], and frailty has been shown to occur at younger ages and with greater severity in people living with HIV than in demographically matched HIV-negative peers [12,13]. These observations reflect persistent immune activation, chronic inflammation, accelerated immunosenescence, and ART-related metabolic disturbances [14].

A clinical prediction model is a statistical tool that combines multiple predictors to estimate an individual's risk of having a condition (diagnostic model) or of developing it in the future (prognostic model) [15]. Prognostic models for frailty could support the proactive identification of people living with HIV at highest risk, enabling early interventions to prevent or delay the progression of frailty. Numerous frailty prediction models exist in general geriatric medicine; however, applying standardized FP- or FI-based instruments directly to people living with HIV poses significant challenges because these instruments typically do not incorporate HIV-specific drivers of risk, such as nadir CD4 cell count, viral load, chronic immune activation, ART regimens, and common coinfections [16]. The comorbidity spectrum, patterns of functional decline, and psychosocial stressors among people living with HIV also differ from those of the general older population [16], collectively suggesting that general-population models may lack direct transferability to people living with HIV.

Although a growing body of research has developed frailty assessment or screening tools for HIV care [17,18], a comprehensive, systematic evaluation of the methodological rigor, predictive performance, and clinical applicability of models designed to predict future frailty in people living with HIV has been notably lacking. Whether generic frailty prediction models retain clinically useful performance in people living with HIV, or whether HIV-specific models are required, remains uncertain and warrants direct comparison. To address this gap, we published a protocol for a systematic review of prognostic models for frailty in people living with HIV and registered the review with PROSPERO (CRD420261332573) [19]. The objectives of this systematic review were to (1) identify all multivariable prediction models developed or validated to predict future frailty in people living with HIV, (2) summarize and compare their predictive performance, and (3) critically appraise their methodological quality, risk of bias, and applicability using recommended tools.

Methods

Protocol and Registration

This review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [20,21]. The protocol was developed following the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses–Protocols) checklist [22], registered with PROSPERO (CRD420261332573) in June 2025, and published in *JMIR Research Protocols* [19]. The review question was framed according to the CHARMS (Checklist for Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modeling Studies) guidance for prediction models [23]. After registration, two deviations from the protocol occurred: (1) the preliminary screening identified 5 potentially eligible studies, but strict reapplication of the prespecified eligibility criteria during full-text evaluation resulted in the exclusion of 4 of them (see the "Study Selection" section), and (2) meta-analysis was not performed because only 1 study was included; a narrative synthesis was conducted instead.

Eligibility Criteria

Eligibility criteria were defined using the PICOS (population, intervention, comparison, outcome, study design) framework and the CHARMS items to frame the review question [23] (Table 1). Studies were included if they (1) developed or validated a multivariable prediction model—whether a statistical model, machine-learning algorithm, or clinical risk score—with or without external validation; (2) enrolled adults (≥18 years) diagnosed with HIV/AIDS according to recognized diagnostic guidelines (eg, the Chinese guidelines for the diagnosis and treatment of HIV infection/ AIDS 2024 edition, WHO consolidated guidelines, US CDC laboratory testing guidance, European AIDS Clinical Society guidelines version 12, or UK testing guidelines) [24];

and (3) reported a primary outcome reflecting the future occurrence of frailty, with frailty defined using established multidimensional instruments (eg, FP, FI, Clinical Frailty Scale, Edmonton Frail Scale, FRAIL scale, or other validated frailty measures), regardless of the terminology used (eg, prediction model, risk score, prediction index, clinical prediction rule). Studies were excluded if they (1) evaluated the predictive value of more than 1 variable without reporting subgroups or evaluation outcomes; (2) were cross-sectional studies, because such designs do not assess future risk; (3) were nonprimary research (literature reviews, systematic reviews, meta-analyses, protocols, theses, editorials, comments, or letters); or (4) were unavailable in full text. No restrictions were applied regarding year or language. When multiple studies reported results from the same cohort for a given outcome, the study with the largest patient population was selected; if sample sizes were equal, the most recent publication was used.

Table 1. Eligibility criteria for study inclusion based on the PICOS (population, intervention, comparison, outcome, study design) framework and CHARMS (Checklist for Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modeling Studies) key items.

PICOS element	Criteria applied in this review
Population	Adults (≥18 years) diagnosed with HIV/AIDS according to recognized diagnostic guidelines
Index prediction model	Multivariable statistical models, machine-learning algorithms, or clinical risk scores developed or validated to predict the future occurrence of frailty, with or without external validation
Comparator	Not applicable (single-index-model review); comparator models described when reported
Outcome to be predicted	Future occurrence of frailty, defined by established multidimensional instruments (frailty phenotype, frailty index, Clinical Frailty Scale, Edmonton Frail Scale, FRAIL scale, or other validated measures)
Timing	Any prediction horizon for the future occurrence of frailty; moment of model use in clinical care
Setting	Any clinical or research setting in which adults with HIV receive care
Study design	Model development or validation studies. Excluded: cross-sectional studies, nonprimary research (reviews, protocols, theses, editorials, letters), studies unavailable in full text

Information Sources and Search Strategy

We searched PubMed, Web of Science, Scopus, Cochrane Library, ProQuest, and 4 Chinese databases (SinoMed, CNKI, Wanfang, and VIP) from database inception to July 20, 2025. The search was updated on July 24, 2026. The search strategy combined three thematic blocks: (1) population terms related to HIV/AIDS; (2) index-model terms related to prediction models, risk scores, and nomograms; and (3) outcome terms related to frailty (Table 2). A model-specific search filter was adapted where appropriate, and reference lists of relevant articles were screened for additional studies. All search strategies are provided in full in Multimedia Appendix 1.

Table 2. Summary of the search strategy used in each database.

Database	Key search concepts	Records identified (initial search, July 20, 2025), n	Records identified (updated search, July 24, 2026), n	Total, n
PubMed	#1 HIV/AIDS terms (MeSH + title/abstract) AND #2 prediction-model terms AND #3 frailty terms	282	44	326
Web of Science	TI/AB HIV/AIDS AND TI/AB prediction-model terms AND TI/AB frailty terms	1643	239	1882
Scopus	TITLE-ABS-KEY HIV/AIDS AND prediction AND frailty	11	1	12
Cochrane Library	MeSH and keyword combinations of HIV/AIDS, prediction-model, and frailty terms	112	11	123
ProQuest (gray literature)	summary (HIV AND frailty AND prediction terms)	157	23	180
SinoMed/CNKI/Wanfang/VIP	Title/keyword combinations of HIV, frailty, and prediction-model terms (Chinese)	0	0	0
Total	—[a]	2205	318	2523

[a]Not applicable

Study Selection

Records identified by the search strategy were imported into EndNote, and duplicates were removed. Two reviewers (YH and MX) independently screened titles and abstracts, followed by full-text evaluation. Disagreements were resolved by discussion or, if necessary, adjudicated by a third reviewer (JY). When published reports contained insufficient information, the corresponding authors were contacted; if the information could not be obtained, the study was recorded as having missing data rather than automatically excluded. The study selection process is summarized in the PRISMA 2020 flow diagram in the Results section.

Data Extraction

Data were extracted independently by 2 reviewers (YH and MX) using a standardized, piloted extraction form based on the CHARMS checklist [23]. Extracted items included: source of data; participant eligibility, recruitment, and description; details of treatment received; study dates;

outcome definition and measurement; candidate predictors and their handling; sample size and events per variable; missing data handling; model development methods (modeling technique, predictor-selection method, shrinkage); model performance (discrimination, calibration, classification); model evaluation (internal/external validation, model updating); and interpretation and discussion of results. Reporting completeness was additionally assessed against the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) statement [25]. Discrepancies between reviewers were resolved by discussion; if consensus could not be reached, a third reviewer (JY) adjudicated.

Risk of Bias and Applicability Assessment

The methodological quality of the included study was assessed using the Prediction Model Risk of Bias Assessment Tool (PROBAST) [26], which comprises 4 domains (participants, predictors, outcome, and analysis) and 20 signaling questions. Each domain was judged as being at low, high, or unclear risk of bias, and its applicability to the review question was rated as low, high, or unclear concern. Two reviewers (YH and MX) independently rated the study, with a target interrater reliability (Cohen kappa) of ≥0.8; disagreements were resolved by consensus or adjudication by a third reviewer (JY).

Data Synthesis

Consistent with the registered protocol, a meta-analysis of discrimination (C statistics) and calibration was planned a priori using random-effects models [27]; however, because only 1 study met the inclusion criteria, quantitative synthesis was not feasible. Instead, a narrative synthesis was conducted following the Synthesis Without Meta-Analysis (SWiM) reporting guidance [28], summarizing the characteristics, predictive performance, and methodological quality of the included study in tabular form. Between-study heterogeneity and subgroup or meta-regression analyses were not applicable.

Ethical Considerations

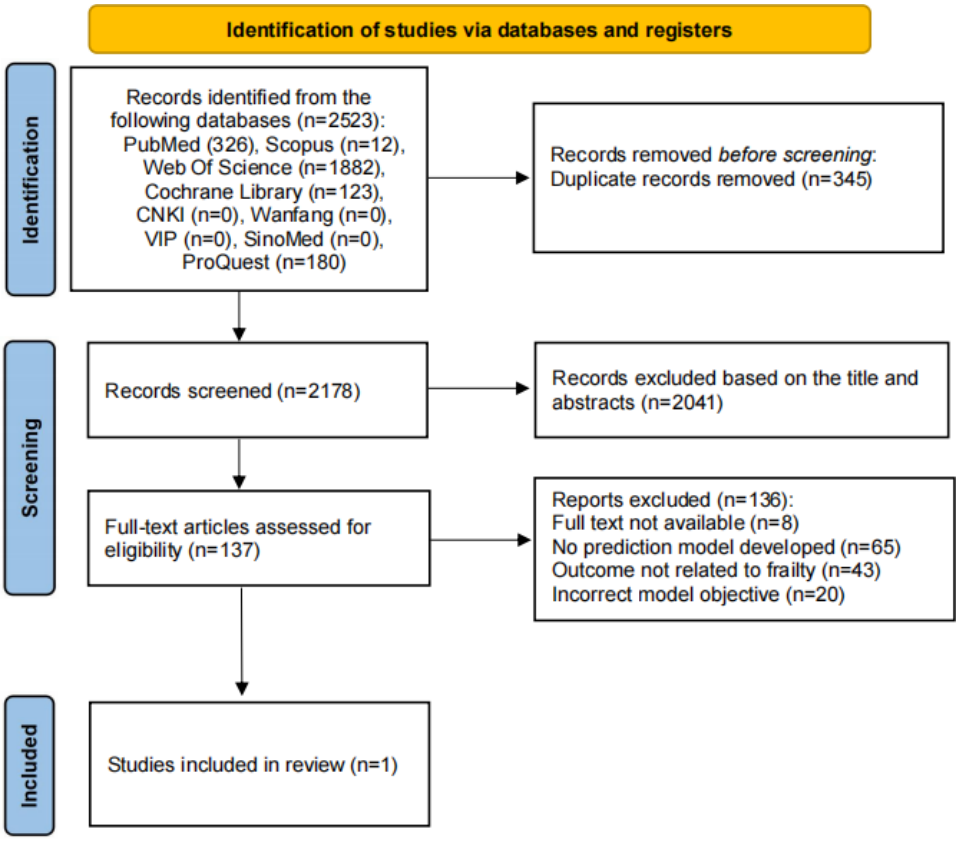
Ethical approval was not required because this study is a systematic review of published literature.

Results

Study Selection

The search identified 2523 records in total (initial search: 2205; updated search: 318). The initial search identified 2205 records (PubMed: 282; Web of Science: 1643; Scopus: 11; Cochrane Library: 112; ProQuest: 157; and none from the 4 Chinese databases). The updated search on July 24, 2026, identified 318 additional records (PubMed: 44; Web of Science: 239; Scopus: 1; Cochrane Library: 11; ProQuest: 23; and none from the 4 Chinese databases). After removal of 345 duplicates, 2178 records were screened by title and abstract, of which 2041 were excluded. The remaining 137 full-text articles were assessed for eligibility, and 136 were excluded for the following reasons: full text unavailable (n=8); no prediction model developed (n=65); outcome not related to frailty (n=43); and incorrect model objective, that is, studies that assessed frailty-related factors or cross-sectional correlates of current frailty status without developing or validating a multivariable model for the future occurrence of frailty (n=20). Ultimately, 1 study met all inclusion criteria (Figure 1). Following the published protocol [19], 5 studies were initially identified. However, full-text evaluation against predefined criteria—specifically the exclusion of cross-sectional designs and studies not predicting future frailty—led to the exclusion of 4 studies and left only 1 study that met all inclusion criteria. Excluded articles with reasons are detailed in Multimedia Appendix 2.

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 flow diagram of the study selection process.



Characteristics of the Included Study

The single eligible study was the development and internal validation of Frail RISC-HIV (Frailty Risk in the Short-Term for Care of People with HIV) by Ruderman et al [18], published in *AIDS* in 2023. The study was conducted within the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS), a multicenter prospective clinical cohort of people living with HIV receiving care at 7 US academic HIV clinics (study period 2011-2021) [29]. The analytic cohort comprised 4680 nonfrail people living with HIV (training set: n=3170; validation set: n=1510). The validation set consisted of people living with HIV from the entire site, which was withheld during development to ensure independence of subpopulations (a split-site internal validation design). Detailed characteristics extracted according to the CHARMS domains are presented in Table 3.

Table 3. Characteristics of the included study (Frail RISC-HIV)[a], extracted according to the CHARMS[b] checklist.

CHARMS domain	Extracted details
Source of data	CNICS cohort (Centers for AIDS Research Network of Integrated Clinical Systems); multicenter prospective clinical cohort; 7 US academic HIV clinics; 2011-2021
Participants	4680 nonfrail people living with HIV (training: n=3170; validation: n=1510); aged ≥18 years; ≥2 patient-reported outcome (PRO) assessments; complete baseline candidate-predictor data; frailty measures at all follow-up assessments
Outcome to be predicted	Incident frailty within 2 years, defined as ≥3 of 4 components of a modified self-reported Fried phenotype (fatigue, unintentional weight loss, inactivity, poor mobility); correlated with the original Fried phenotype (ϱ=0.81)
Candidate predictors	~40 variables: demographics (age, sex, race/ethnicity); HIV-related (nadir and current CD4 cell count, viral load, current ART[c] use, ever-prescribed DDI/d4T)[d]; comorbidities (HCV/HBV[e] coinfection, diabetes, dyslipidemia); anthropometric/metabolic (BMI, blood pressure, lipohypertrophy/lipoatrophy, eGFR[f], fibrosis-4); depression (PHQ-7[g] score, antidepressant prescription); substance use (marijuana, cocaine, methamphetamine, illicit opioids, tobacco, alcohol)
Sample size	Training: 3170 participants, 220 events (7%); validation: 1510 participants, 186 events (12%); events per variable adequate for the final model
Missing data	Complete-case analysis; extent and handling of missing data not fully described
Model development	Bayesian Model Averaging (BMA; >45% posterior inclusion probability) and LASSO[h] regression (5-fold cross-validation) for variable selection; Cox proportional-hazards models for effect estimation; age and sex forced into the model; no shrinkage of regression coefficients described

CHARMS domain	Extracted details
Final model (predictors and HRs)[i]	Baseline frailty score HR 2.9 (95% CI 2.4-3.6); current illicit opioid use HR 2.3 (1.3-4.2); female sex HR 1.5 (1.1-2.1); current marijuana use HR 1.4 (1.1-1.9); prescribed antidepressants HR 1.4 (1.1-2.0); age per decade HR 1.1 (0.96-1.2); depressive symptomatology (PHQ-7) HR 1.1 (1.0-1.1); not prescribed ART HR 0.6 (0.3-0.97)
Model performance	Discrimination: Harrell C 0.76 (95% CI 0.73-0.79) in the validation set. Classification: at 5% risk cutoff, sensitivity 80%, specificity 61%; at 10% cutoff, sensitivity 58%, specificity 81%. Calibration: under-prediction in the validation set (predicted 7.9% vs observed 14.7%). Lift plots: 5-fold higher risk in the top 3 deciles
Model evaluation	Internal validation only: split-site design (1 site withheld as the validation set); no external validation; no model updating or recalibration
Results and presentation	Risk score with ROC[j] curves and lift plots; recommended for administration during routine HIV care visits
Interpretation	Authors positioned the score as a simple tool to identify people living with HIV at risk of transitioning to frailty in the short term, supporting early targeted intervention

[a]Frail RISC-HIV: Frailty Risk in the Short-Term for Care of People with HIV.
[b]CHARMS: Checklist for Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modeling Studies
[c]ART: antiretroviral therapy
[d]DDI/d4T: didanosine and stavudine.
[e]HCV/HBV: hepatitis C and hepatitis B.
[f]eGFR: estimated glomerular filtration rate.
[g]PHQ-7: Patient Health Questionnaire-7.
[h]LASSO: least absolute shrinkage and selection operator.
[i]HR: hazard ratio.
[j]ROC: receiver operating characteristic.

Model Development and Predictors

Incident frailty within 2 years was defined using a modified, self-reported Fried phenotype (fatigue, unintentional weight loss, inactivity, and poor mobility; presence of ≥3 components), which has been shown to correlate highly with the original Fried phenotype (ϱ=0.81) [30]. Approximately 40 candidate predictors spanning demographic, HIV-related clinical, comorbidity, depression, and substance-use variables were considered. Bayesian Model Averaging (inclusion threshold >45% posterior probability) and LASSO (least absolute shrinkage and selection operator) regression with 5-fold cross-validation were used for predictor selection, and the final score was estimated using Cox proportional hazards models; age and sex were forced into the model. The final 8-predictor model comprised baseline frailty score, Patient Health Questionnaire-7 depressive symptomatology, prescribed antidepressants, current illicit opioid use, current marijuana use, current use of ART, age, and sex (Table 3). The strongest predictor was the baseline frailty score (hazard ratio (HR) 2.9 per additional component, 95% CI 2.4-3.6), followed by current illicit opioid use (HR 2.3, 95% CI 1.3-4.2).

Model Performance

In the training set, 7% (220/3170) of people living with HIV became frail within 2 years, while in the validation set, 12% (186/1510) did. The model showed acceptable discrimination in the validation set (Harrell C=0.76; 95% CI 0.73-0.79). At a 5% predicted-risk cutoff, sensitivity was 80% and specificity was 61%; at 10%, they were 58% and 81%, respectively. Calibration was suboptimal; overall risk was under-predicted in validation (predicted 7.9% vs observed 14.7%), though training-set predictions aligned with observed events (8.6%). Lift plots revealed that most frailty risk was concentrated in the top 3 risk-score deciles (≈5-fold higher than the bottom 7 deciles). The model was formulated as a simple risk score with receiver operating characteristic curves and lift plots for use in routine HIV care. We identified no evidence of external validation in an independent population.

Risk of Bias and Applicability (PROBAST)

The PROBAST assessment is summarized in Table 4. Domains 1-3 (participants, predictors, and outcome) were judged at low risk of bias with low concern regarding applicability; the model was developed in a large, multicenter prospective cohort of people living with HIV using standardized, prospectively measured predictors and a validated outcome definition, consistent with the target population and outcome of this review. However, the baseline frailty score—the strongest predictor—was measured with the same modified Fried instrument used to define the outcome, which, although assessed at baseline and not part of the outcome event, creates partial overlap between a predictor and the outcome construct. Domain 4 (analysis) was judged at high risk of bias for the following reasons: handling of missing data was not described (a complete-case approach appears to have been used); candidate predictors were selected using data-driven methods without a fully pre-specified analysis plan; calibration was reported descriptively (predicted vs observed risk) without standard calibration metrics (eg, calibration slope or intercept); competing risks (eg, death) were not addressed; and model evaluation was limited to split-site internal validation, with no external validation. Overall, the study was judged to be at a high risk of bias, with low concern regarding applicability to the review question.

Table 4. PROBAST[a] risk-of-bias and applicability assessment of the included study (Frail RISC-HIV)[b].

Domain	Risk of bias	Rationale (key signaling questions)
Participants	Low	Large multicenter prospective clinical cohort of people living with HIV; inclusion/exclusion criteria appropriate for the target population; data source suitable for development of a frailty prediction model. Applicability: low concern.
Predictors	Low	Predictors defined and assessed in a standardized manner across sites; predictor data available at the time of intended model use; predictors measured before outcome ascertainment. Applicability: low concern.
Outcome	Low	Outcome (incident frailty within 2 years) defined with a validated instrument applied uniformly; time horizon explicit. Note: the baseline frailty score, a predictor, was measured with the same modified Fried instrument as the outcome, creating partial overlap between predictor and outcome constructs. Applicability: low concern.
Analysis	High	Handling of missing data not described (apparent complete-case analysis); data-driven variable selection without a fully prespecified analysis plan; calibration reported descriptively without standard calibration metrics; competing risks not addressed; evaluation limited to split-site internal validation with no external validation.
Overall	High	Overall high risk of bias driven by the analysis domain; applicability concerns were overall low.

[a]PROBAST: Prediction Model Risk of Bias Assessment Tool.
[b]Frail RISC-HIV: Frailty Risk in the Short-Term for Care of People with HIV.

Reporting Quality (TRIPOD)

Reporting completeness was partial when assessed against the TRIPOD statement. The study clearly reported participant selection, outcome definition, predictor definition, sample size, statistical analysis methods, model development and specification, discrimination with confidence intervals, and interpretation of results. Reporting was incomplete or absent for data-handling procedures, standard calibration metrics, model-updating procedures, study protocol or registration, and the electronic availability of the model.

Synthesis

Quantitative synthesis was not feasible because only 1 study met the inclusion criteria; a pooled estimate of predictive performance could therefore not be generated. In summary, the current body of evidence consists of a single internally validated model (Frail RISC-HIV) with acceptable but unreplicated discrimination, suboptimal calibration, high risk of bias in the analysis domain, and no external validation.

Discussion

Principal Findings

This systematic review, conducted according to a published, PROSPERO-registered protocol, found that the evidence base for predicting future frailty in people living with HIV comprises a single model: the Frail RISC-HIV, developed in the US CNICS cohort [18]. To our knowledge, no other study was identified that developed or validated a multivariable prediction model for incident frailty in people living with HIV, and we found no evidence of external validation for the existing model. This finding is itself the principal result of our review: despite the substantial and growing burden of frailty in the aging HIV population [5,11] and repeated calls to move from characterizing frailty toward prediction and intervention [31], the field remains in its infancy with respect to prognostic modeling.

The single available model demonstrated acceptable internal discrimination (C=0.76) but was rated at high risk of bias overall, driven primarily by methodological limitations in the analysis domain, and its calibration under-predicted the observed frailty risk in the validation set. Moreover, the model has not yet been externally validated, which limits any recommendation for its use in routine clinical practice. Its predictors are predominantly psychosocial and behavioral characteristics such as depression, antidepressant prescription, and substance use, which are clinically sensible and actionable, yet largely do not include the HIV-specific biomarkers (eg, nadir CD4 cell count, viral load, inflammatory markers) that many clinicians associate with frailty risk in people living with HIV [14,16]. Whether the omission of HIV-specific factors reflects true nonpredictiveness in the contemporary treatment era or reflects limitations of the candidate-predictor set remains unknown and warrants investigation.

Comparison With the Wider Literature

Our finding contrasts sharply with the general geriatric literature, in which dozens of frailty prediction and screening models exist and have been the subject of multiple systematic reviews. These generic models, however, have rarely been evaluated in people living with HIV. It does not necessarily follow that they are ineffective in this population; they may still capture shared aging-related mechanisms, such as multisystem physiological decline, comorbidity burden, and functional limitations, and could therefore retain some discriminative ability. However, their performance is likely to be suboptimal, particularly with respect to calibration, because they omit HIV-specific factors such as nadir CD4 cell count, viral load, chronic immune activation, and ART-related metabolic disturbances. To date, generic frailty prediction models have rarely been externally validated in people living with HIV, and we found no evidence of head-to-head comparisons with HIV-specific models. In addition, HIV-specific frailty prediction models themselves remain scarce, which is especially striking given that people living with HIV experience frailty earlier and more frequently than their HIV-negative peers [5,12]. Future studies should therefore both externally validate existing generic models in people living with HIV and develop HIV-specific models, comparing their performance before concluding that HIV-specific tools are universally necessary. The studies excluded from this review illustrate the nature of the gap: the large majority of retrieved articles characterized frailty or examined factors associated with current frailty status,

including cross-sectional analyses of frailty correlates [32,33], frailty instrument construct validation [34], and machine-learning classification of prevalent frailty [35,36], rather than developing or validating models that predict future frailty. To our knowledge, only one other frailty-related tool for older people living with HIV, the FUNCFRAIL score, has been developed, but it was based on cross-sectional data and discriminates prevalent frailty rather than predicting its future occurrence [18]. Within the wider HIV literature, well-established prediction instruments such as the Veterans Aging Cohort Study Index predict mortality and other outcomes rather than frailty itself [37], and predictors of transitions in frailty severity or incidence have been reported in observational analyses [38,39], but neither constitutes a frailty prediction model of the type examined here.

Implications for Research

The critical evidence gap identified by this review has direct implications for future research. First, there is an urgent need for external validation and recalibration of Frail RISC-HIV in independent populations, particularly outside the United States and in low- and middle-income settings, where the HIV burden is greatest and where comorbidity and treatment contexts differ substantially. Such validation should include cohorts of people living with HIV who are confirmed to be nonfrail at baseline (0-2 components of the modified Fried phenotype, ie, not frail or prefrail), because Frail RISC-HIV was developed with 4680 people living with HIV who were not frail at baseline. The baseline frailty score was a continuous count of 0-2 components rather than a diagnosis of frailty (≥3 components); it therefore captured subclinical vulnerability or prefrailty rather than prevalent frailty. Although this score was the strongest predictor, its predictive performance should be confirmed in independently recruited nonfrail populations. Second, new prediction models should be developed that (1) incorporate HIV-specific predictors (eg, nadir and current CD4 cell count, viral load, markers of immune activation and inflammation) alongside established demographic, psychosocial, and behavioral factors; (2) use standardized and consensus, based frailty definitions; (3) are based on adequate sample sizes with sufficient events per variable; and (4) follow prespecified analysis plans with appropriate handling of missing data and competing risks. Third, all future model development and validation studies should adhere to the TRIPOD reporting statement [25], register their analysis plans, and make models electronically available. Finally, investigators should consider whether dynamic data from electronic health records can support the development of flexible, time-updated models that align with routine HIV care workflows.

Implications for Clinical Practice

From a clinical standpoint, our findings counsel caution. While Frail RISC-HIV is simple, brief, and potentially feasible for administration during HIV clinic visits, its use for risk stratification in routine care is premature in the absence of external validation and given its calibration under-prediction. Until such evidence is available, clinicians caring for aging people living with HIV should continue to rely on direct frailty assessment and on addressing the modifiable risk factors consistently associated with frailty, including depression, substance use, and polypharmacy, which were also identified as predictors in the sole available model.

Strengths and Limitations

This review has several strengths. It was conducted according to a peer-reviewed, published protocol and registered prospectively with PROSPERO. The search was comprehensive, covering 10 databases, including gray literature and 4 Chinese databases, with no language or date restrictions, and was updated through July 2026. Screening, data extraction, and quality appraisal were performed independently in duplicate, and methodological evaluation followed the internationally recommended CHARMS and PROBAST frameworks.

Several limitations should be acknowledged. First, the inclusion of a single study precluded quantitative synthesis and limited the generalizability of our conclusions; this scarcity of evidence is, however, itself the key finding of the review. Second, the review did not require prediction models to include HIV-specific health outcomes, such as viral load suppression or opportunistic infections, or HIV-specific biomarkers, such as nadir CD4 cell count and inflammatory markers. This inclusion criterion was intentionally broad to identify all available frailty prediction models for people living with HIV; however, it means that the only included model, Frail RISC-HIV, is predominantly based on psychosocial and behavioral predictors and lacks HIV-specific biomarkers. Had HIV-specific outcomes been required as an inclusion criterion, no eligible study would have been identified. This limitation reflects the current evidence base rather than the review question and highlights the need for future models that incorporate HIV-specific predictors and for comparative studies of frailty measurement between the general population and people living with HIV. Third, despite the comprehensive search, it remains possible that eligible models were published in nonindexed journals or non-English sources and were missed, although no language restrictions were applied. Fourth, the validity of our appraisal is constrained by the completeness of reporting in the primary study; for example, several PROBAST signaling items could not be fully judged, and the corresponding authors were not contacted during this review. Finally, because only published information was assessed, unpublished or in-development models are not captured.

Conclusions

This systematic review identified a single prediction model for the future occurrence of frailty in people living with HIV, Frail RISC-HIV, which demonstrated acceptable internal discrimination but was rated at high risk of bias, showed suboptimal calibration, and has not been externally validated. The paucity of prognostic models for frailty in this vulnerable and rapidly aging population represents a critical evidence gap. Coordinated research efforts are urgently needed to develop robust models that incorporate HIV-specific factors,

to externally validate and recalibrate the existing model in diverse settings, and to ensure that future studies are reported in accordance with TRIPOD guidelines. Until such evidence accumulates, model-based risk stratification for frailty in HIV care should be regarded as an emerging, rather than established, clinical tool.

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Data Availability

All data used in this systematic review were derived from published articles and the supplementary materials. The complete search strategies are provided in Multimedia Appendix 1.

Authors' Contributions

Conceptualization: MX, YH, ZZ, and JY
Data curation: YH, MX, ZZ, and JY
Formal analysis: YH and MX
Investigation: YH and MX
Methodology: YH, MX, and ZZ
Project administration: MX and ZZ
Supervision: MX and ZZ
Writing – original draft: MX, YH, JY, and ZZ
Writing – review and editing: MX and ZZ

Conflicts of Interest

None declared.

Multimedia Appendix 1

Complete search strategies for all databases.
[DOCX File (Microsoft Word File), 26 KB-Multimedia Appendix 1]

Multimedia Appendix 2

Full-text articles excluded after detailed evaluation, with reasons.
[DOCX File (Microsoft Word File), 16 KB-Multimedia Appendix 2]

Checklist 1

PRISMA checklist.
[DOCX File (Microsoft Word File), 32 KB-Checklist 1]

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Abbreviations

ART: antiretroviral therapy
CHARMS: Checklist for Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modeling Studies
CNICS: Centers for AIDS Research Network of Integrated Clinical Systems
FI: frailty index
FP: frailty phenotype
Frail RISC-HIV: Frailty Risk in the Short-Term for Care of People with HIV
HR: hazard ratio
LASSO: least absolute shrinkage and selection operator
PICOS: population, intervention, comparison, outcome, study design
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses–Protocols
PROBAST: Prediction Model Risk of Bias Assessment Tool
SWiM: Synthesis Without Meta-Analysis
TRIPOD: Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis
UNAIDS: United Nations Program on HIV and AIDS

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