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SYSTEMATIC REVIEW

Frailty risk prediction models in maintenance hemodialysis patients: a systematic review and meta-analysis of studies from China

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ABSTRACT

Objectives: To systematically evaluate and meta-analyze the performance, validity, and influencing factors of frailty risk prediction models specifically developed for patients undergoing maintenance hemodialysis in China.

Methods: China National Knowledge Infrastructure, Wanfang Database, China Science and Technology Journal Database, SinoMed, PubMed, Web of Science, Cochrane Library, CINAHL and Embase were searched from inception to October 10, 2024. Two independent reviewers conducted literature screening, data extraction, and risk of bias assessment using the Prediction Model Risk of Bias Assessment Tool (PROBAST). Meta-analysis was performed to pool the incidence rates and identify independent predictors.

Results: Fourteen studies incorporating 16 distinct frailty risk prediction models were included. The predictive accuracy, measured by the area under the receiver operating characteristic curve (AUC), ranged from 0.819 to 0.998. Seven studies performed internal validation, one study executed external validation, and one study conducted both internal and external validation. All studies exhibited a high overall risk of bias. Pooled incidence of frailty among maintenance hemodialysis patients was 32.2% (95% CI: 26.9%–37.6%). Significant predictors of frailty included advanced age, hypoalbuminemia, poor nutritional status, female sex, comorbid conditions, and depression ($p < 0.05$).

Conclusions: The pooled incidence of frailty among maintenance hemodialysis patients was notably high at 32.2%, with advanced age, hypoalbuminemia, poor nutritional status, female sex, comorbid conditions, and depression emerging as significant predictors. Existing frailty prediction models for maintenance hemodialysis patients demonstrated robust predictive capacity but exhibited substantial methodological limitations, high bias and limited external validation. Future research should prioritize multicenter, large sample, validation studies to enhance applicability and reliability.

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1. Introduction

Kidney disease is now the seventh leading risk factor for mortality worldwide and the prevalence is increasing [1]. The Global Burden of Disease Survey shows that from 1990 to 2016, the incidence and prevalence of chronic kidney disease have increased by nearly 90%, and mortality due to it has increased by nearly 100% [2]. Chronic kidney disease (CKD) is a chronic disease characterized by persistent abnormalities in the structure or function of the kidneys for more than three months due to various reasons, and is typically classified into five stages according to glomerular filtration rate [3]. Most patients with CKD will progress to end-stage renal disease (ESRD) [4]. Maintenance hemodialysis (MHD) is the mainstay of treatment for patients with end-stage renal disease and accounts for 90% of all dialysis globally [5]. It primarily utilizes artificial devices to replace the kidney's blood filtration function, aiming to remove excess water, electrolytes, and toxins from the body [6]. Long-term hemodialysis patients are prone to a range of complications, with frailty being one of the most common [7]. Frailty is a nonspecific condition resulting from a decline in physiological reserves, leading to increased vulnerability and diminished capacity to cope with stress [8]. The prevalence of frailty in maintenance hemodialysis patients is relatively high. A meta-analysis revealed that the global prevalence of frailty in maintenance hemodialysis patients is 34.3% [9], while another study found the prevalence of frailty in maintenance hemodialysis patients in China to be 37.4% [10]. Frailty is closely associated with various

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adverse outcomes in maintenance hemodialysis patients, including hospitalization, infections, and mortality [11]. McAdams et al. [12] found that maintenance hemodialysis patients who developed frailty had a 2.6-fold increased risk of death and a 1.4-fold increase in the number of hospitalizations compared to the non-frailty group.

Consequently, early identification of frailty and the implementation of targeted interventions are particularly important for maintenance hemodialysis patients. Risk prediction models, which have long been widely used in clinical practice, are statistical models that predict the probability that an individual will suffer from a certain disease or clinical outcome through a set of characteristics, helping physicians and patients make scientific and accurate clinical decisions [13]. For example, the Framingham Risk Score (FRS) is used to predict the risk of cardiovascular disease in asymptomatic patients over the next 10 years. It has become a widely recognized tool for predicting an individual's future coronary heart disease events and for guiding preventive management decisions [14]. In recent years, several risk prediction models for frailty in maintenance hemodialysis patients have been developed, but their performance and practical value remain unclear.Due to significant differences in the healthcare system between China and other countries, coupled with China being the largest developing country and having the highest number of individuals with chronic kidney disease worldwide [15], research on frailty in maintenance hemodialysis patients is of great significance and offers valuable insights. Therefore, this study aims to conduct a systematic review of existing frailty risk prediction models for maintenance hemodialysis patients in China, providing references for healthcare professionals to develop better risk prediction models and offering evidence-based support for the formulation of intervention strategies.

2. Methods

This study was performed according to the Preferred Reporting items for Systematic Reviews and Meta-Analyses (PRSMA 2020) statement [16]. The study protocol was registered on PROSPERO (registration number: CRD42022370287). The key items in constructing a systematic review of prediction models are based on the PICOS system recommended by prognosis studies in Cochrane [17]. The key items of our systematic review are described below:

P(Population): patients with maintenance hemodialysis. I(Intervention model): Risk prediction models for frailty in patients with maintenance hemodialysis that were developed and published. C(Comparator): No competing model. O(Outcome): The outcome focused on frailty occurrence in maintenance hemodialysis patients.T(Timing): The outcome was predicted during or between hemodialysis sessions. S(Setting): The intended use of the risk prediction model is to help healthcare professionals personalize the prediction of frailty occurrence in maintenance hemodialysis patients, enabling early implementation of preventive measure.

2.1. Search strategy

The databases systematically searched included China National Knowledge Infrastructure (CNKI), Wanfang Database, China Science and Technology Journal Database (VIP), SinoMed, PubMed, Web of Science, The Cochrane Library, Cumulative Index to Nursing and Allied Health Literature (CINAHL) and Embase, which were searched from the inception of the databases until October 10, 2024.A combination of subject terms and free terms was used for the search, with the following keywords: 'Renal Dialysis', 'Kidneys, Artificial', 'Hemodiafiltration', 'Renal Replacement Therapy', 'Kidney Failure, Chronic', 'Continuous Renal Replacement Therapy', 'Dialysis', 'Dialysis, Renal', 'Dialysis, Extracorporeal', 'Extracorporeal Dialysis', 'blood dialysis', 'MHD', 'hemodialysis', 'end stage renal disease', 'maintenance hemodialysis'; 'Frailty', 'Asthenia', 'Frail Elderly', 'frailty syndrome', 'hyposthenia', 'debility', 'frailness', 'weakness'; 'Risk Assessment' 'Risk Factors', 'Nomograms', 'risk prediction model', 'risk prediction', 'risk score', 'prediction model', 'machine Learning'. The search strategy is shown in Supplementary Table 1.

2.2. Inclusion and exclusion criteria

The inclusion criteria for studies were: (1) Studies involving patients with maintenance hemodialysis; (2) The study focuses on the development and/or validation of frailty risk prediction models for maintenance hemodialysis patients; (3) The study type includes observational studies (cross-sectional studies, cohort studies, case-control studies).

The exclusion criteria were: (1) Reviews, conferences, case reports; (2) Duplicate publications; (3) Full text not accessible; (4) Incomplete data extraction; (5) Models with fewer than two predictors.

2.3. Study selection and data extraction

Two researchers independently managed the literature using EndNote and removed duplicate entries. Then, based on the predefined inclusion and exclusion criteria, the titles, abstracts, and full texts were screened. After literature screening, a standardized form was used to extract relevant data based on the Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modeling Studies checklists (CHARMS) [18]. In case of disagreements regarding study selection, a discussion involving three authors was held to reach a consensus. The extracted data primarily includes: first author, year of publication, study design, sample size, number of outcome events, outcome measurement tools, variable screening methods, treatment of continuous variables, AUC, calibration methods, specificity, sensitivity, accuracy, model presentation methods, et.

2.4. Quality assessment

Two researchers independently assessed the risk of bias and applicability of the literature using the Prediction Model Risk

Of Bias Assessment Tool (PROBAST) [19]. The risk of bias assessment includes four domains: study population, predictors, outcomes, and statistical analysis. Each domain is rated as 'low risk', 'high risk', or 'unclear'. There are 20 questions, each evaluated with 'yes' or 'probably yes', 'no' or 'probably no', and 'unclear'. When the risk of bias in all domains is low, the overall risk of bias for the study is considered low. If any domain has a high risk of bias, the overall risk of bias is considered high. If the risk of bias in one domain is 'unclear' while the other domains have low risks of bias, the overall risk of bias is classified as 'unclear'. The applicability assessment includes three domains: study population, predictors, and outcomes. The evaluation process is similar to the risk of bias assessment method. If there is any disagreement in the quality assessment, the issue will be discussed with a third researcher for resolution.

2.5. Statistical analysis

Meta-analysis of the incidence and predictors of frailty in maintenance hemodialysis patients using stata18.0 software. The effect size for incidence is expressed as rate with 95% confidence intervals (CI) while the effect size for predictive factors is expressed as odds ratios (ORs) with 95% confidence intervals (CIs). The I^2 index provides a measure of heterogeneity, with values of 25%, 50%, and 75% indicating low, moderate, and high heterogeneity, respectively [20]. If $I^2 < 50\%$ and $p > 0.1$, the heterogeneity was not significant and the studies were combined using a fixed-effects model; if $I^2 \geq 50\%$ or $p \leq 0.1$, the heterogeneity among studies was significant, in which case sensitivity analysis was performed. If the heterogeneity still existed after excluding the literature one by one, the random effects model was used to combine the studies. Egger's test was used to identify publication bias [21]. The subgroup analysis explored the sources of heterogeneity. The results were considered statistically significant at $p < 0.05$.

3. Results

3.1. Study selection

Figure 1 shows the literature screening process and results. In this study, a total of 2,685 related studies were retrieved through a preliminary database search, and 390 duplicates were excluded. Then, after reviewing the titles and abstracts,

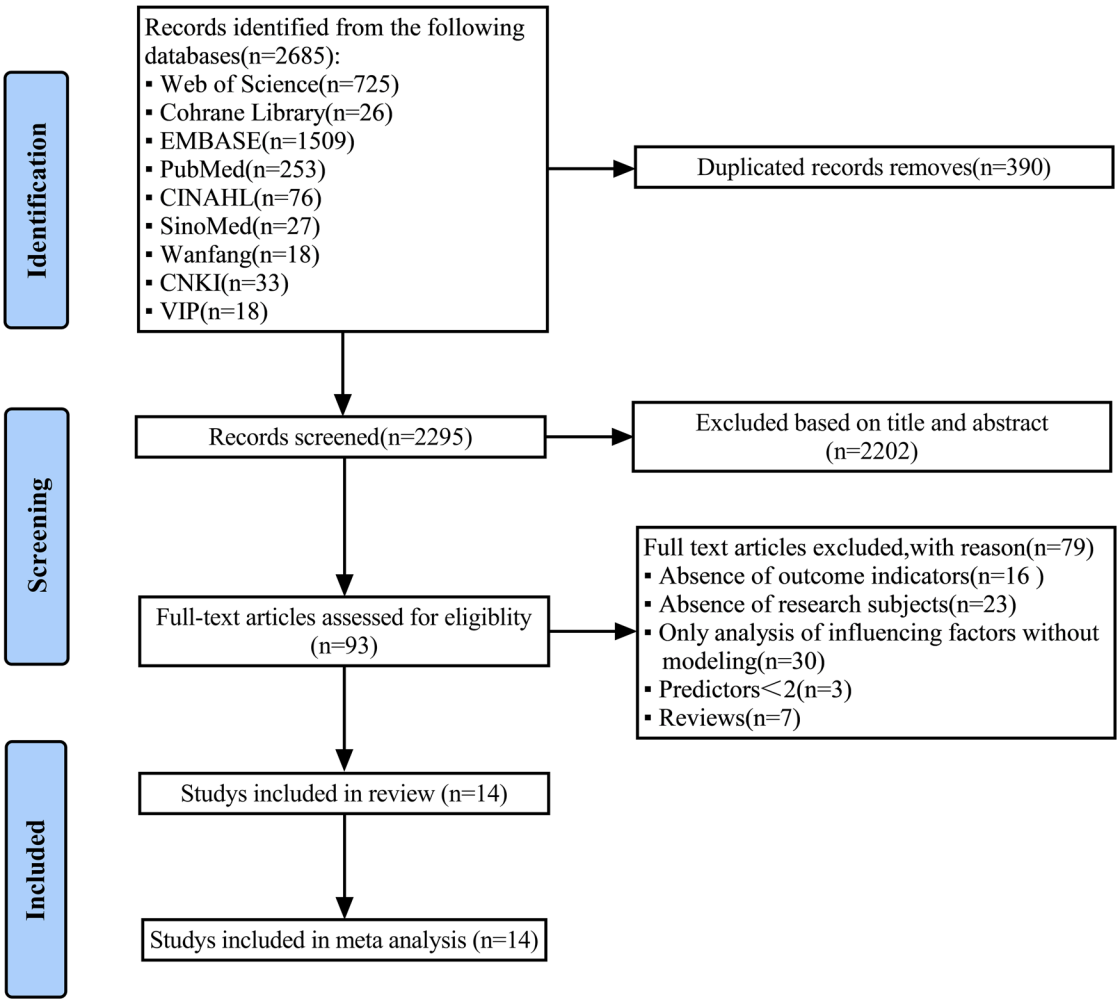

Figure 1. Flowchart of literature search and selection.

Table 1. Basic characteristics of included studies.

Author, year	Country	Data source	Participants	Study design	Model type	Frailty case/ sample size (%)	Outcome indicators
Jiang 2022 [29]	China	Two general hospitals in Zhejiang Province	MHD	Cross-sectional study	E+V_2	177/420(42.14%)	Frailty phenotype
Li 2022 [31]	China	Blood Purification Center, Beijing Aerospace Center Hospital	MHD	Cross-sectional study	E	25/145(17.2%)	FRAIL scale
Zhang 2023 [23]	China	A general hospital in Hebei Province	MHD	Retrospective study	E	80/384(20.8%)	FRAIL scale
Jiang 2023 [24]	China	A general hospital in Dalian	MHD	Cross-sectional study	E	65/260(25.0%)	FRAIL scale
Yang 2023 [26]	China	Blood Purification Center, Lu'An People's Hospital	MHD	Cross-sectional study	E+V_1	85/222/(38.3%)	FRAIL scale
Zhuang 2023 [28]	China	Hemodialysis center in a hospital in Zhejiang Province	MHD	Retrospective study	E+V_1	170/314(54.14%)	FRAIL scale
Ying 2023 [30]	China	A general hospital in Zhejiang Province	MHD	Cross-sectional study	E+V_1	226/876(25.8%)	Frailty phenotype
Chen 2023 [33]	China	Blood purification centers in two general hospitals in Nanchong City	MHD	Cross-sectional study	E+$V_{1,2}$	122/424(28.77%)	FRAIL scale
Wang 2024 [22]	China	Blood purification centers in two general hospitals in Hangzhou City	MHD	Cross-sectional study	E+V_1	205/485/(42.27%)	Frailty phenotype
Xu 2024 [25]	China	Department of Nephrology, Ma'an Shan People's Hospital	MHD	Cross-sectional study	E	54/210(25.71%)	FRAIL scale
Qing 2024 [27]	China	Department of Nephrology, De Yang People's Hospital	MHD	Cross-sectional study	E+V_1	62/260(23.85%)	Frailty phenotype
Xiao 2024 [32]	China	Blood Purification Center, Weifang Yi du Central Hospital	MHD	Retrospective study	E+V_1	87/200(43.5%)	Frailty phenotype
Ma 2024 [34]	China	A general hospital in Shanxi Province	MHD	Cross-sectional study	E	101/247(40.9%)	FRAIL scale
Liu 2024 [35]	China	Blood purification centers in two general hospitals in Anhui Province	MHD	Cross-sectional study	E+V_1	115/479(24.0%)	FRAIL scale

E, Model development; E+V_1, Model development + internal validation; E+$V_{1,2}$, Model development + internal validation + external validation.

2,202 unrelated articles were excluded. The remaining 93 articles were read in full, and 79 were excluded. Among them, sixteen studies had outcome measures that did not align; thirteen studies had mismatched study populations; thirty studies only analyzed influencing factors without modeling; two studies had fewer than two predictors; and seven were reviews. Ultimately, fourteen studies with sixteen models were included in this review [22–35].

3.2. Study characteristics

Table 1 summarizes the basic characteristics of the included studies. Fourteen studies were published between 2022 and 2024. Of these, thirteen were published in Chinese [22–34], and one was published in English [35]. Among the studies, eleven studies were cross-sectional studies [22,24–27, 29–31,33–35], while three were retrospective studies [23,28,32]. In terms of study design, ten studies were single-center studies [23–28,30–32,34], and four were multi-center studies [22,29, 33,35]. The sample size of the included studies ranged from 145 to 876 cases, with the number of outcome events ranging from 25 to 226, and the prevalence ranging from 17.2% to 54.14%. Regarding the measurement of frailty as the outcome, five studies employed the Fried frailty phenotype [22,27, 29,30,32], while nine studies used the FRAIL scale for measurement [23–26,28, 31,33–35].

Table 2 presents the construction of risk prediction models for frailty in patients with maintenance hemodialysis. A total of sixteen frailty risk prediction models for maintenance hemodialysis patients were developed across fourteen studies. In terms of modeling methods, thirteen studies used only logistic regression models [23–35], while one study employed logistic regression, decision tree algorithm (CART), and random forest methods to develop separate models [22]. Regarding variable selection, all studies performed variable selection based on univariate analysis. For handling continuous variables, eight studies did not apply any transformations [23,25–28, 31,32,34], whereas six studies either partially or fully converted continuous variables into categorical variables [22,24, 29,30, 33,35]. In terms of missing data handling, two studies [33,35] reported the exact amount of missing data and used deletion methods for handling, while the remaining studies did not explicitly address whether data was missing. The predictors most frequently reported in the models (three or more times) included: age, albumin, nutritional status, gender, comorbidities, activities of daily living, and depression

Table 3 summarizes the performance and presentation methods of the prediction models. Model performance was primarily evaluated using the area under the receiver operating characteristic curve (AUC) to assess discriminatory ability. Eleven studies reported the AUC during model development, with values ranging from 0.819 to 0.998 [22–24,27–30]. Six studies reported the AUC for internal validation, ranging from 0.828 to 0.957 [22,26, 30,32, 33,35], while two studies reported the AUC for external validation, with values of 0.865

Table 2. The construction of risk prediction models for frailty in patients with maintenance hemodialysis.

Author, year	Model development method	Variable selection	Continuous variable processing method	Sample size (D/I/E)	Missing data		Final predictors
					Number	Handling method	
Jiang 2022 [29]	Logistic regression model	Perform univariate analysis followed by multivariate analysis.	Categorical variables	320/–/100	–	–	Age, Combined cerebrovascular conditions, Combined heart disease, Physical exercise, Social support
Li 2022 [31]	Logistic regression model	Perform univariate analysis followed by multivariate analysis.	Continuous variable	145/–/–	–	–	Gender, Residency Style, Nutritional status, Hemoglobin, CCI, Self-care ability
Zhang 2023 [23]	Logistic regression model	Perform univariate analysis followed by multivariate analysis.	Continuous variable	384/–/–	–	–	Age, MIS, ALB, SMI
Jiang 2023 [24]	Logistic regression model	Perform univariate analysis followed by multivariate analysis.	Categorical variables	260/–/–	–	–	Gender, Self-assessed health status, Exercise situation, Combined peripheral cardiovascular disease, NRS-2002, Resilience, Depression.
Yang 2023 [26]	Logistic regression model	Perform univariate analysis followed by multivariate analysis.	Continuous variable	222/–/–	–	–	Age, Number of dialysis complications, Nighttime sleep duration, ALB, Physical exercise.
Zhuang 2023 [28]	Logistic regression model	Perform univariate analysis followed by multivariate analysis.	Continuous variable	220/94/–	–	–	Age, CCI, Sarcopenia, ALB, NRS-2002, Grip
Ying 2023 [30]	Logistic regression model	Perform univariate analysis followed by multivariate analysis.	Categorical variables	491/385/–	–	–	Activities of daily living, Age, History of stroke, ALB, C-reactive protein, Serum creatinine
Chen 2023 [33]	Logistic regression model	Perform univariate analysis followed by multivariate analysis.	Categorical variables	297/–/127	13	delete	Age, Depression, Sleep quality, Self-care ability, Dialysis age, Comorbidity index, Complications
Wang 2024 [22]	1.Logistic regression model 2.Decision tree 3.Random forest	Univariate analysis	Categorical variables	341/144/–	–	–	1.Age, Gender, Daily exercise, ALB, SSRS, ADL, NRS-2002 2.CCI, Depression, NRS-2002, Age, Gender, SSRS 3.CCI, Age, NRS-2002, Gender, Depression, Daily exercise, Smoke
Xu 2024 [25]	Logistic regression model	Perform univariate analysis followed by multivariate analysis.	Continuous variable	210/–/–	–	–	Age, Dialysis duration, Exercise situation, SPBB, ALB
Qing 2024 [27]	Logistic regression model	Perform univariate analysis followed by multivariate analysis.	Continuous variable	260/–/–	–	–	Sedentary behavior, TUG, FTSST, SARC-F
Xiao 2024 [32]	Logistic regression model	Perform univariate analysis followed by multivariate analysis.	Continuous variable	140/60/–	–	–	Age, Activity level, Depression, Comorbidity
Ma 2024 [34]	Logistic regression model	Perform univariate analysis followed by multivariate analysis.	Continuous variable	247/–/–	–	–	Age, Dialysis age, ALB, C-reactive protein, Kt/V、BUN/Cr
Liu 2024 [35]	Logistic regression model	Perform univariate analysis followed by multivariate analysis.	Categorical variables	479/–/–	21	delete	Malnutrition, Sarcopenia, Gender, Feel tired after dialysis, ALB

D, Model development; I, Internal validation; E, External validation; CCI, Charlson Comorbidity Index; MIS, Malnutrition-Inflammation Score; ALB, Albumin; SMI, Skeletal Muscle Mass Index; SSRS, Social Support Assessment Scale; ADL, Activities of Daily Living ADL;SPBB, Simple Physical Performance Test; TUG, Time up and go; FTSST, five times sit-to-stand test; SARC-F, Sarcopenia -Five Scale; BUN/Cr, BUN/Creatinine; kt/V, Urea Clearance Index; "–", not reported.

Table 3. The performance and presentation of risk prediction models for frailty in patients with maintenance hemodialysis.

	Model performance			Validation method		
Author, year	AUC (D/I/E)	Calibration method	A/B/C (%)	Internal validation	External validation	Model presentation
Jiang 2022 [29]	0.893/–/0.865	H-L test	90.4/77.2/–	–	Geographical validation	Regression equation, Nomogram model
Li 2022 [31]	0.94/–/–	H-L test	86/86.4/–	–	–	Regression equation
Zhang 2023 [23]	0.927/–/–	–	85.2/87.5/–	–	–	Formula of risk score obtained by partial regression coefficient of each factor
Jiang 2023 [24]	0.928/–/–	H-L test	86.2/87.7/–	–	–	Regression equation
Yang 2023 [26]	–/0.829/–	Calibration curve, H-L test	–	Bootstrap	–	Nomogram model
Zhuang 2023 [28]	0.875/–/–	H-L test	83.2/86.7/–	Split sample internal validation	–	Regression equation
Ying 2023 [30]	0.955/0.914/	H-L test, Calibration curve	87.7/89.7/–	Temporal validation	–	Regression equation, Nomogram model
Chen 2023 [33]	–/0.939/0.904	Calibration curve, H-L test	0.862/0.885/–	Bootstrap	Geographical validation	Regression equation, Nomogram model
Wang 2024 [22]	Model 1: 0.971/0.957/– Model 2: 0.954/0.87/– Model 3: 0.998/0.934/–	–	96.84/85.43/91.79 92.11/90.73/91.5 96.91/99.32/97.95	Split sample internal validation	–	Formula of risk score obtained by partial regression coefficient of each factor
Xu 2024 [25]	–	Calibration curve,	–	–	–	Nomogram model
Qing 2024 [27]	0.819/–/–	Calibration curve	77.8/74.3/–	Bootstrap	–	Nomogram model、Regression equation
Xiao 2024 [32]	0.88/0.828/–	Calibration curve	81.7/82.5/–	Split sample internal validation	–	Nomogram model
Ma 2024 [34]	0.929/–/–	–	82.9/90.1/–	–	–	Formula of risk score obtained by partial regression coefficient of each factor
Liu 2024 [35]	0.905/0.901/–	Calibration curve, H-L test	90.1/79.1/–	Split sample internal validation	–	Nomogram model

AUC, Area under the curve; D, Model development; I, Internal validation; E, External validation; A, Specificity; B, Sensitivity; C, Accuracy; H-L test, Hosmer-Leme show text; "–", not reported.

and 0.904, respectively [29,33]. All reported AUC values for the models were greater than 0.8. The specificity ranged from 77.8% to 96.91%, and the sensitivity ranged from 74.3% to 99.32%. Model calibration was primarily assessed using the Hosmer-Lemeshow test, calibration curves, and decision analysis curves. Six studies reported calibration curves [25–27,32, 33,35], eight studies reported the Hosmer-Lemeshow test [24,26, 28–31,33,35], six studies reported clinical decision curves [26,27, 30,32, 33,35]. Three studies did not provide any of these assessments [22,23,34]. Regarding model validation, seven studies performed internal validation [22,26–28, 30,32,35], one study conducted external validation [29], and one study combined both internal and external validation methods [33]. In terms of model presentation, the majority of studies used either nomograms or regression equations. Four studies presented both nomograms and regression equations [27,29, 30,33], four studies used nomograms [25,26, 32,35], three studies used regression equations [24,28,31], and three studies provided the regression coefficients for each predictor [22,23,34].

3.3. Results of quality assessment

Table 4 summarizes the risk of bias and applicability of the included studies. All the included studies were assessed as having a high risk of bias. In the domain of study participants, three studies were assessed as having a high risk of bias [23,28,32], as these retrospective studies relied on existing case data, which may be subject to recall and selection biases. In the domain of predictors, five studies were assessed as having an unclear risk of bias [22,23, 28,32,35]. This was due to the following reasons: three studies were retrospective [23,28,32], making it unclear whether the measurement of predictors was influenced by outcomes that had already occurred; and two studies did not specify whether the definition and measurement of predictors were consistent across different centers during multicenter data collection [22,35]. In the domain of outcomes, three studies were assessed as having an unclear risk of bias [23,28,32] as they did not clearly explain whether the determination of outcomes was associated with the predictors.

In the domain of analysis, all 14 studies were assessed as having a high risk of bias. It is recommended that each independent variable have at least 20 events per variable (EPV) during model construction to ensure statistical power. During model validation, the sample size should include at least 100 cases to ensure the robustness and reliability of the validation. EPV refers to the ratio of the number of events occurring for the outcome variable to the total number of variables included during the model construction phase [19]. Twelve studies did not meet this standard, which may lead to overfitting [22–28,30–32, 34,35]. Six studies partially or fully converted continuous variables into categorical variables, potentially leading to the loss of important information [22,24, 29,30, 33,35]. Two studies directly excluded missing data, which could introduce bias into the results [33,35]. Additionally, all studies used univariate analysis for variable selection, which may overlook relationships between variables and miss important predictors. Two studies did not report key metrics such as specificity and sensitivity, resulting in incomplete performance evaluations of the models [25,26]. Regarding model validation, five studies only developed models without validation [23–25,31,34], while four studies used simple random splitting for validation, which may lead to an optimistic bias in model performance [22,28, 32,35]. All studies demonstrated good applicability in terms of study participants, predictors, and outcomes.

3.4. Meta-analysis results

The frailty prevalence in maintenance hemodialysis patients across the fourteen included studies was pooled, revealing significant heterogeneity between studies (I^2 = 94.260%, $p < 0.001$). Sensitivity analysis was conducted, and excluding any single study did not result in significant changes in the prevalence, thus a random-effects model was applied. The results of the meta-analysis indicated that the frailty prevalence in maintenance hemodialysis patients was 32.2% (95% CI: 26.9%–37.6%) as shown in Figure 2. Additionally, Egger's test yielded a t-value of 1.44 ($p > 0.05$), suggesting the absence of publication bias. Subgroup analysis was performed based on the frailty measurement methods. The results showed that there was still high heterogeneity when

Table 4. Bias risk and applicability assessment.

	Bias risk				Applicability			Overall	
Author, year	Participants	Predictors	Outcome	Analysis	Participants	Predictors	Outcome	Bias risk	Applicability
Jiang 2022 [29]	+	+	+	−	+	+	+	−	+
Li 2022 [31]	+	+	+	−	+	+	+	−	+
Zhang 2023 [23]	−	?	?	−	+	+	+	−	+
Jiang 2023 [24]	+	+	+	−	+	+	+	−	+
Yang 2023 [26]	+	+	+	−	+	+	+	−	+
Zhuang 2023 [28]	−	?	?	−	+	+	+	−	+
Ying 2023 [30]	+	+	+	−	+	+	+	−	+
Chen 2023 [33]	+	+	+	−	+	+	+	−	+
Wang 2024 [22]	+	?	+	−	+	+	+	−	+
Xu 2024 [25]	+	+	+	−	+	+	+	−	+
Qing 2024 [27]	+	+	+	−	+	+	+	−	+
Xiao 2024 [32]	−	?	?	−	+	+	+	−	+
Ma 2024 [34]	+	+	+	−	+	+	+	−	+
Liu 2024 [35]	+	?	+	−	+	+	+	−	+

"+", Low risk bias/high applicability; "−", High risk bias/Low applicability; "?", Unclear.

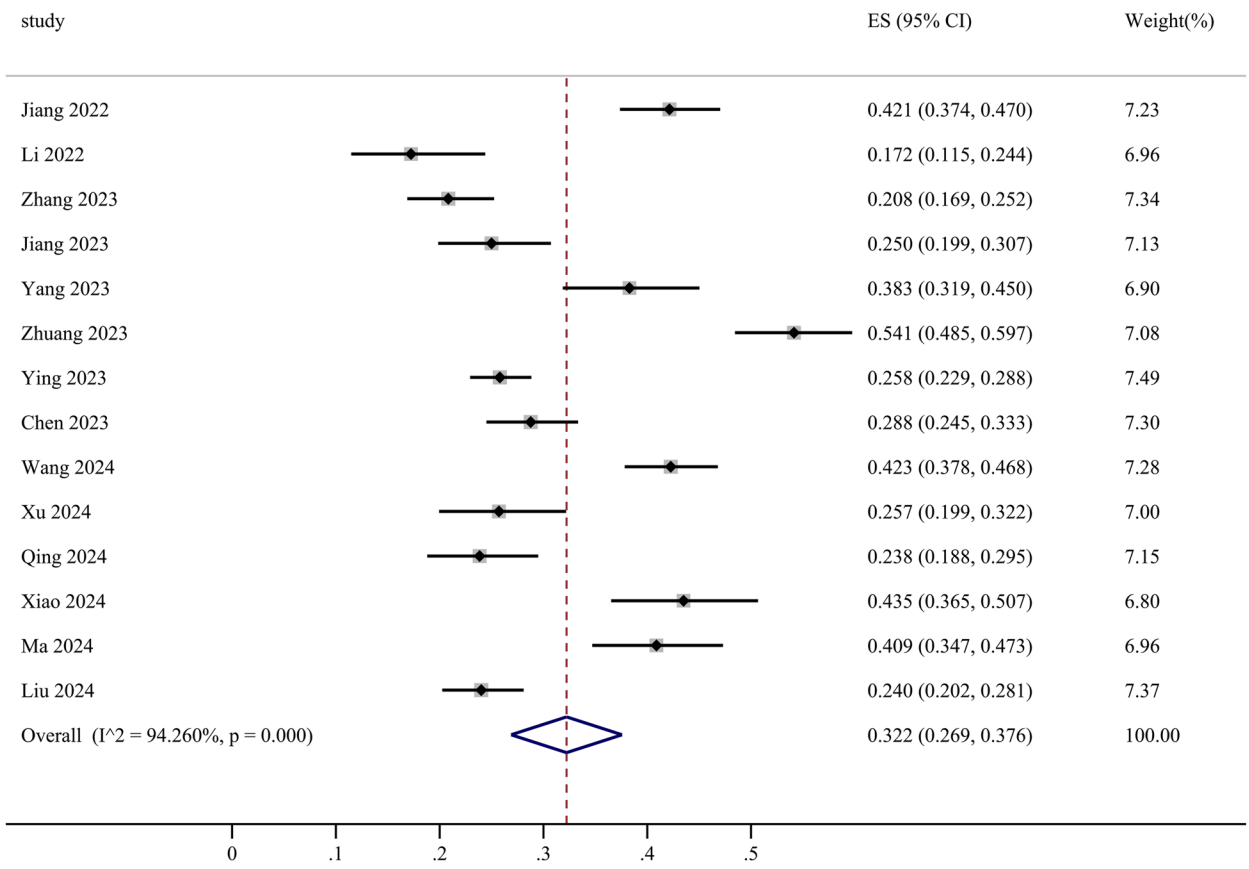

Figure 2. Forest plot of prevalence of frailty in patients with maintenance hemodialysis.

Table 5. Meta-analysis results of influencing factors of frailty in maintenance hemodialysis patients.

Predictors	Number of studies included	Heterogeneity test		Model Selection	Confluence effect size			
		I^2(%)	*p* value		OR	95%CI	Z value	*p* value
Age [22,23,25,26, 28,30,32–34]	9	92.3	<0.001	Random effects model	1.109	1.043–1.179	3.28	0.001
Albumin [22,23,25,26, 28,30, 34,35]	8	83.2	0.024	Random effects model	0.833	0.725–0.958	2.57	0.010
Nutritional status [22,24, 28,31,35]	5	92.2	<0.001	Random effects model	3.880	1.027–14.665	2.00	0.046
CCI [22,28, 31,33]	4	8.9	0.349	Fixed effects model	1.701	1.468–1.972	7.05	<0.001
Biologic sex [22,24, 31,35]	4	71.8	0.014	Random effects model	4.657	1.980–10.955	3.52	<0.001
Depression [24,32,33]	3	61.9	0.072	Random effects model	1.263	1.043–1.529	2.39	0.017
ADL [22,30, 31,33]	4	97.2	<0.001	Random effects model	2.482	0.727–8.472	1.45	0.147

frailty was measured using the frailty phenotype (I^2 = 94.741%, $p < 0.001$) or the FRAIL scale (I^2 = 94.367%, $p < 0.001$), indicating that the measurement method is not the source of the heterogeneity (Supplementary Figure 1).

Next, the predictors that appeared three or more times in the models were pooled for effect size analysis. Wang et al. [22]conducted a study that explored multiple model-building methods based on the same sample. Since all other studies used logistic regression models, only the effect sizes from models built using logistic regression were included in this analysis.Taking age as an example of a predictor, due to significant heterogeneity, a random effects model was used for the meta-analysis. The results are shown in Figure 3. Ultimately, the analysis indicated that age, albumin, nutritional status, sex, comorbidities, and depression are independent influencing factors for frailty in maintenance hemodialysis patients ($p < 0.05$). The results were summarized in Table 5.

4. Discussion

This study reviews the existing frailty models for maintenance hemodialysis patients in China, aiming to evaluate the overall performance of these risk prediction models and summarize the predictors of frailty. This will provide evidence-based

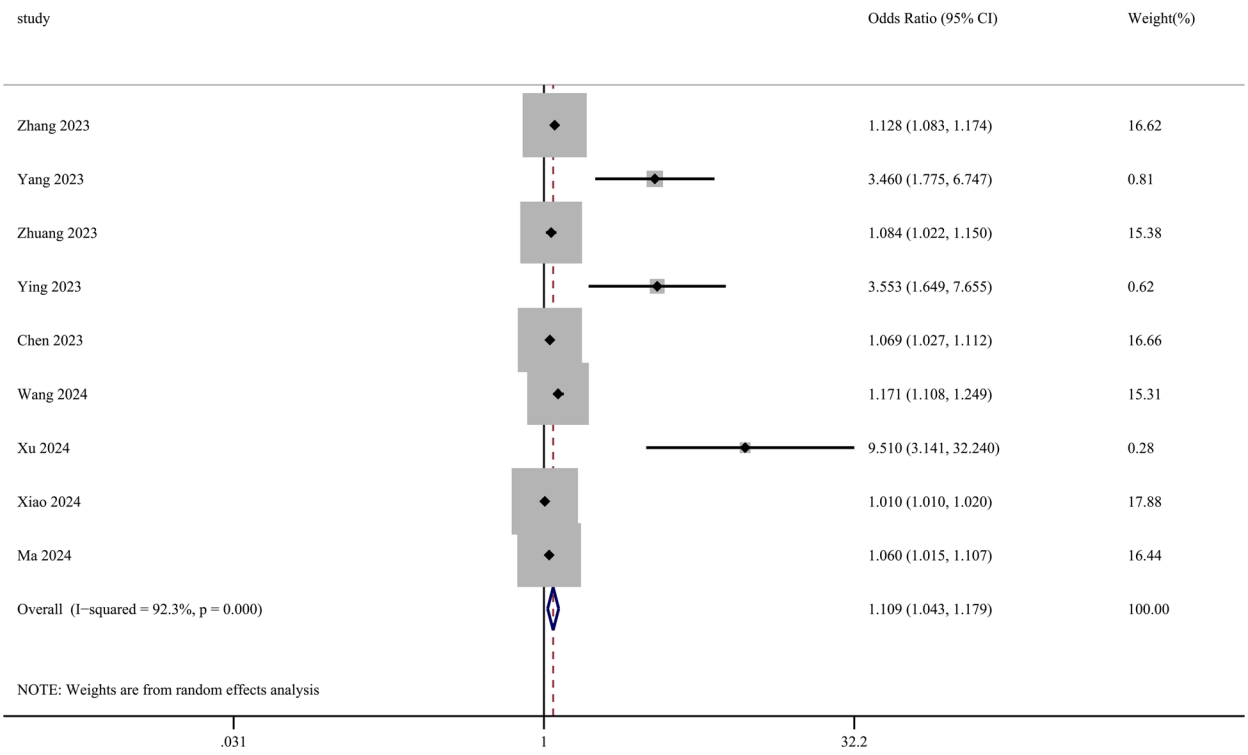

Figure 3. Forest plot of pooled effect size for age.

guidance to help healthcare professionals develop frailty screening tools and interventions for maintenance hemodialysis patients. This study found that the included studies were at high risk of bias, and the predictors of frailty in maintenance hemodialysis patients included: age, albumin, nutritional status, sex, comorbidities, and depression.

4.1. Risk prediction models for frailty in patients with maintenance hemodialysis are still in the exploratory stage

In this study, we included sixteen risk prediction models for analysis, with logistic regression being the primary modeling method. All included studies reported an area under the curve (AUC) greater than 0.8 during model development or validation. Among them, five studies were purely developmental without any validation [23–25,31,34], meaning their feasibility requires further investigation, although they demonstrated high specificity and sensitivity. Only one study did not report any model performance indicators [25], indicating that most models showed good predictive performance. However, all the included studies had a high risk of bias, and further optimization is needed in terms of sample sourcing, data handling, and model construction and validation.

First, sample sourcing. Most of the samples were from single-center studies with small sample sizes. Among them, twelve studies [22–28,30–32, 34,35] had an EPV < 20, and three studies [23,28,32] were retrospective. PROBAST [19] indicates that when the EPV is < 20 during the development of risk prediction models, there is an increased risk of model overfitting, which may lead to an overestimation of model performance in real-world applications. For the sample size of risk prediction models, it is recommended to use 20 EPV, or to apply the sample size calculation method for clinical prediction models proposed by Riley et al. [36], or the sample size calculation formula for binary outcome prediction models. Retrospective studies utilizing existing data and records are not well suited for model construction and may result in recall bias information bias and selection bias, as well as being subject to confounding factors that reduce the applicability of the model in clinical practice. Furthermore, frailty was measured using the frailty phenotype or the FRAIL scale. Although these methods are widely used in clinical practice, there are differences in their measurement content, which may lead to biases in the results. Currently, there is no standardized criterion for the assessment of frailty, among which the frailty index created by Mitnitski et al. [37] has a higher measurement accuracy, but there are more measurement entries and the data are not easy to obtain. Studies have shown that both the frailty phenotype and the FRAIL scale provide reliable and consistent frailty measurements in dialysis populations [38,39]. Therefore, future risk prediction model studies should adopt more accurate frailty diagnostic methods, and multicenter, large-scale prospective studies are needed.

Second, data handling. Six studies [22,24, 29,30, 33,35] partially or completely converted continuous variables into categorical variables. Studies have shown that when continuous variables are converted into two or more categorical variables during the construction of risk prediction models, significant information may be lost, reducing the statistical power of the model and potentially leading to a decline in

model performance [40]. It is recommended that continuous predictors be retained as continuous variables or transformed into ordinal data with clear classification criteria. Regarding the handling of missing values, only two studies [33,35] reported the specific number of missing values and performed deletion. Deleting missing data may introduce bias in the correlation between predictors and outcomes, affecting the quality of data analysis and the accuracy of the model. PROBAST [19] recommends that missing values should not be deleted outright but instead handled using multiple imputation. Multiple imputation can effectively reduce the adverse impact of missing data on model performance, ensuring the reliability of the results. Future risk prediction models should apply appropriate methods for handling continuous variables and missing values based on expert knowledge, aiming to minimize any adverse effects on model performance

Third, model construction and validation. Variable selection was based on univariate analysis in all studies. Although this method is simple and quick, it overlooks the interactions between variables and potential collinearity issues, which may lead to the omission of important variables. This is one of the key reasons contributing to the high risk of bias in the models. It is recommended to use more robust methods, such as forward stepwise selection, backward stepwise selection, or LASSO regression, for variable selection. In model construction, only one study [22] incorporated machine learning, while the remaining studies employed logistic regression, assigning values to predictors based on the regression coefficients to calculate risk. Logistic regression, as a traditional modeling method, is characterized by strong interpretability and robustness with small sample sizes. However, when variables exhibit strong correlations or interactions, its accuracy can decrease, potentially leading to bias or overfitting. Furthermore, logistic regression is constrained by the assumption of linear relationships, making it less effective at handling complex nonlinear relationships. In contrast, machine learning, such as decision trees, support vector machines, and random forests, can mitigate the limitations of traditional methods and have shown excellent performance in improving prediction accuracy and automatically extracting features. Before being applied in clinical practice, prediction models should undergo both internal and external validation. However, the lack of model validation may be a common issue in current clinical risk prediction models. This may be attributed to difficulties in accessing clinical data, limited research resources, and infrequent collaboration between hospitals. Only one study [29] performed external validation, one study [33] used a combination of internal and external validation, and seven studies [22,26–28, 30,32,35] conducted internal validation. This highlights the limited generalizability of the models and the difficulty in validating their effectiveness. Compared to reconstructing models, performing external validation directly is more time- and cost-efficient. Therefore, future studies could focus on externally validating high-quality models from this research or combine traditional methods with machine learning to develop prediction models with superior performance. Additionally, In the reporting process, strict adherence to the TRIPOD (Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis) guidelines should be ensured for standardized reporting [41].

4.2. The prevalence of frailty in maintenance hemodialysis patients

This study reveals that the prevalence of frailty in maintenance hemodialysis patients is 32.2%, which is relatively high and aligns with the findings of previous studies [9,10,42]. The occurrence of frailty significantly worsens the prognosis of maintenance hemodialysis patients. Ddlgado et al. [43] demonstrated that, in the population initiating maintenance hemodialysis, frail patients have a two-fold higher risk of falls or fractures compared to non-frail patients. Another study found that frailty was significantly associated with increased mortality and hospitalization within 2 years among maintenance dialysis patients, suggesting that frailty may serve as an important prognostic indicator in this population [44]. Subgroup analysis showed that the method of frailty measurement was not a source of heterogeneity. Future research could explore the sources of heterogeneity through meta-regression or further in-depth subgroup analyses and interpretations.Thus, early identification and intervention for frailty should be emphasized, as they are critical for improving patient outcomes.

4.3. Predictors of frailty in maintenance hemodialysis patients

The results of the meta-analysis indicate that age, albumin, nutritional status, biologic sex, comorbidities, and depression are the six key predictors identified as factors influencing the occurrence of frailty in patients undergoing maintenance hemodialysis. As age increases, MHD patients experience a decline in physical function, reduced immune capacity, and diminished stress resilience, all of which increase their vulnerability to frailty. Additionally, poor physical health and the burden of chronic diseases can lead to psychological changes, such as feelings of aging and loneliness, further heightening the risk of frailty [45]. Albumin levels and nutritional status are significant factors influencing frailty in maintenance hemodialysis patients, which is consistent with previous studies [46,47]. Albumin serves as a protective factor against frailty, as it also reflects the patient's overall nutritional state. Prolonged dialysis results in decreased nutrient intake due to anorexia, dietary restrictions, etc., and increased metabolic rate, excessive nutrient loss, coupled with inflammation and uremic toxin accumations, resulting in protein-energy wasting (PEW), which leads to malnutrition [48]. Malnutrition leads to progressive depletion of skeletal muscle, muscle atrophy, and reduced physical activity, ultimately promoting the onset of frailty and significantly increasing the patient's risk of mortality [49]. Therefore, it is essential for maintenance hemodialysis patients to focus on balanced nutrition

and appropriate dietary intake, and if necessary, to consider intravenous infusion of nutritional solutions.

The Charlson Comorbidity Index (CCI) is considered the gold standard for assessing clinical comorbidities and is an effective tool for predicting patient mortality [50]. Studies have shown that frail patients with maintenance hemodialysis have a higher comorbidity burden compared to non-frail patients [51]. A higher CCI score indicates a greater number of comorbid conditions and poorer physical function, which makes patients more susceptible to frailty. Other studies have demonstrated a positive correlation between comorbidities and frailty in dialysis patients: the greater the number of comorbid conditions, the more severe the frailty [52]. Women, compared to men, have a higher risk of frailty, which is consistent with findings from previous studies [53]. The possible reasons are that, firstly, women generally have lower disease tolerance during illness, lower activity levels, and less muscle mass, making them more prone to sarcopenia, which increases the likelihood of developing frailty [54]. Secondly, this is related to endocrine hormones. After menopause, the sharp decline in estrogen levels in women may lead to osteoporosis and muscle atrophy, while in men, testosterone levels tend to decline gradually and more steadily [55]. Hemodialysis is a long-term treatment process that imposes significant psychological and financial stress on patients, with depression emerging as the most common psychological issue [56]. Depressed patients may face an increased risk of frailty due to reduced social interactions, decreased physical activity, and the potential onset of cognitive impairment [57]. John et al. showed that there was a significant correlation between depression and frailty, and that depression was independently correlated with mortality in dialysis patients [58]. Although the Activities of Daily Living (ADL) score did not show significance in this analysis, numerous studies have identified it as an important factor influencing frailty development [59,60]. Possible reasons for the lack of significance in this study may include the small sample size or lower quality of the included literature. A lower ADL score reflects greater physical dysfunction and poorer self-care ability, both of which can lead to disuse muscle atrophy, thereby promoting the development of frailty. In conclusion, clinicians and healthcare professionals should closely monitor six key factors—age, albumin levels, nutritional status, biologic sex, comorbidities, and depression—when managing long-term dialysis patients, and intervene promptly to improve patient outcomes.

4.4. Inspiration for future research

In recent years, risk prediction models have become increasingly prevalent in healthcare; however, challenges persist due to factors such as insufficient sample sizes, lack of validation, and the difficulty of applying research results to clinical practice. The occurrence of frailty is a complex, multifactorial issue, influenced by a combination of biological, psychological, and social factors [61]. One study showed that the Edmonton Frailty Scale, based on multidimensional assessment, demonstrated higher accuracy in evaluating frailty in community-dwelling elderly individuals compared to frailty phenotype and FRAIL scales [62]. Furthermore, all of the included risk prediction models in this review are diagnostic prediction models. Diagnostic prediction models estimate the probability of adverse outcomes based on clinical symptoms and characteristics of the study subjects, helping healthcare providers to intervene early and prevent negative outcomes. As such, the comprehensive inclusion of frailty predictors for maintenance hemodialysis patients is crucial to ensuring the accuracy and generalizability of the model's performance. Improving model performance not only depends on the selection of predictors but also requires more sophisticated model algorithms. Beyond the use of machine learning techniques, advancements in deep learning technologies have introduced more complex and powerful algorithms, such as Convolutional Neural Networks (CNN) and Deep Neural Networks (DNN), which have shown excellent predictive capabilities. Consequently, the future development of risk prediction models urgently requires interdisciplinary collaboration, with teams comprising experts in clinical medicine, statistics, and computer science. Medical experts bring in-depth knowledge to establish a solid theoretical foundation for model construction and accurately identify key risk factors. Statisticians apply advanced statistical methods to extract valuable insights from complex data and uncover potential relationships between variables. Meanwhile, computer scientists focus on developing efficient algorithms that improve the model's operational efficiency and processing capacity.

After model development, external validation is a crucial step in assessing its generalizability. This is also the biggest limitation of most current risk prediction models, and the solution lies in teamwork and data integration. By pooling data from various sources and breaking down data silos, it becomes possible to integrate dispersed data, creating more comprehensive and enriched datasets. These datasets provide ample training and validation data for the model, which can subsequently improve its predictive performance and generalizability. However, it is also clear that many academic research findings are challenging to apply in clinical practice, primarily because their application methods are not sufficiently integrated with the realities of clinical work. Healthcare professionals are already busy with their work, and if the application methods are not simple and convenient, they will likely not be widely used in clinical practice and may even become a burden. Therefore, models should be presented through online calculators, mobile apps, or integrated with electronic medical record systems to better meet the needs of healthcare providers. Lastly, there is currently no universally gold standard for diagnosing frailty, and it is closely associated with various adverse health outcomes such as disability, dependence, and death [61]. In the future, consideration could be given to establishing a universal diagnostic standard for frailty, as well as developing prognostic risk prediction models that incorporate frailty as a key predictor for adverse outcomes.

5. Limitations

In this review, we conducted a comprehensive analysis of predictive models for assessing the risk of frailty in patients with MHD in china. However, it is important to acknowledge several limitations that may have influenced our conclusions: (1) All studies included in the research were conducted in China, which may introduce regional limitations and may not be representative of the broader population. (2) Most predictive models lack external validation, which may limit their generalizability. (3) The use of different measurement tools (frailty phenotype or FRAIL scales) for outcome assessment may introduce potential bias in the results of the meta-analysis. (4) Due to the variability in the completeness of the included studies and methodological differences, we are unable to conduct a quantitative analysis of the model performance metrics or explore the sources of heterogeneity in the pooled results of the predictive factors.

6. Conclusion

This study included fourteen studies, with a total of sixteen risk prediction models for frailty in patients with maintenance hemodialysis, which demonstrated good predictive performance. However, all the studies were assessed as having a high risk of bias, and most of the models lacked external validation. Age, albumin levels, nutritional status, sex, comorbidities, and depression are key predictors of frailty in maintenance hemodialysis patients, and these factors should be closely monitored. It is recommended that future researchers conduct large-scale, multi-center prospective studies, with a priority on external validation, or consider using advanced modeling algorithms to build risk prediction models. At the same time, researchers should strictly adhere to the TRIPOD guidelines for standardized study design and reporting processes, and further assess the effectiveness and feasibility of the models in clinical practice.

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Author contributions

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Xinran Zhou: methodology, writing - review & editing.

Qiong Li: investigation, methodology, writing-review and modifying.

Guodong Wang: supervision, writing - review & editing.

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