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Development and Validation of a Risk Nomogram Model for Predicting Cognitive Frailty in Patients with Stage 1–3 Chronic Kidney Disease

Shuzhi Peng, Xinyue Huang, Dichen Gao, Xinyu Gu, Jingwen Nie, Xin Zhang*

College of Health Management, Shanghai Jian Qiao University, Shanghai 201306, China

**Corresponding author:* Xin Zhang, zhangxin1816199@163.com*

Abstract: *Objective:* To construct a risk prediction model for cognitive frailty in patients with chronic kidney disease (CKD) and draw a nomogram, so as to provide a reference for clinical medical staff to predict the risk of cognitive frailty in these patients and take targeted nursing measures. *Methods:* In this study, patients with CKD in stages 1–3 were collected as a modeling set from October 2022 to April 2023 in the Nephrology Department of two hospitals in Shanghai. Through univariate analysis and multivariate logistic regression analysis, the risk factors of cognitive frailty in patients with CKD in stages 1–3 were screened out, and the risk prediction model was constructed according to the weight of risk factors, and the nomogram was drawn using Stata15.0 software. Bootstrap self-sampling method is used to repeat sampling 1,000 times to verify the built prediction model internally. According to the same inclusion and exclusion criteria, from October 2022 to April 2023, the patient case data of stages 1–3 CKD in the Nephrology Department, a cooperative hospital in Jiangsu Province, were selected as the verification set, and the model was externally verified. *Results:* In the modeling set (n = 600), cognitive frailty incidence was 38.8% (n = 233), and in the verification set (n = 200), it was 42.0% (n = 84). Independent risk factors include chronic disease count, depression, sleep quality, C-reactive protein, D-dimer, and parathyroid hormone in CKD patients. Internal test showed corrected C-statistic 0.779 (95% CI 0.742–0.816, $P < 0.01$), Hosmer–Lemeshow $\chi^2 = 5.794$, $P = 0.670 > 0.05$. DCA indicated the model provides positive benefits for intervention decisions. External verification yielded C-statistic 0.909 (95% CI 0.870–0.948, $P < 0.01$), Hosmer–Lemeshow $\chi^2 = 3.423$, $P = 0.904 > 0.05$. *Conclusion:* The incidence of cognitive frailty in patients with CKD is high. Patients with CKD with a large number of chronic diseases, severe depressive symptoms, poor sleep quality, abnormal C-reactive protein, abnormal D-dimer, and abnormal parathyroid hormone have a higher risk of cognitive frailty. The risk prediction model has good prediction efficiency, which can provide a reference for clinical medical staff to predict the risk of cognitive frailty in patients with CKD and formulate nursing countermeasures.

Keywords: Chronic kidney disease; Cognitive frailty; Risk factors; Risk prediction model

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1. Introduction

Frailty manifests psychologically as reduced ability to bear mental stress and physiologically as decreased body function, increasing susceptibility to stress, disease, and injury [1]. Cognitive impairment involves deficits in areas like memory, language, execution, calculation, understanding, and judgment, including mild cognitive impairment (MCI) and Alzheimer's disease (AD) [2]. Physical frailty accelerates cognitive decline in cognitively normal individuals and increases future MCI and AD risk [3,4]. Cognitive frailty enhances the prediction of adverse events, such as death, disability, hospitalization, and falls, in elderly patients [5,6].

In 2001, Paganini-Hill and his colleagues put forward the term "cognitive frailty" for the first time in a clock drawing test, and correlated cognitive frailty (CF) with the potential protective factors and risk factors of AD [7]. In 2004, the term "cognitive frailty" was used to refer to the cognitive impairment that appears with people entering old age, or cognitive impairment or pre-dementia related to other diseases [8]. In 2006, when Panza [9] studied the relationship between vascular regulatory factors and cognitive function, CF was only used as a clinical label. In 2013, the International Academy on Nutrition and Aging (I.A.N.A.) and the International Association of Gerontology and Geriatrics (I.A.G.G), defined cognitive frailty as physical frailty (at least one of which is consistent with the diagnosis of frailty phenotype) and decreased cognitive reserve function, which means that the clinical dementia rating (CDR) score is 0.5, and it is in the suspected period of dementia. In 2014, Dartigue [10] added the state before physical frailty to the judgment standard of CF. Among the five criteria of weight loss, fatigue, sedentary behavior, slow gait, and low muscle strength, three or more people are considered to be physically frail, while one or two people are considered to be in a state before physical frailty. In 2015, Ruan [11] proposed the concept of cognitive frailty, which can be divided into two subtypes, namely, reverse CF and potentially reversible CF. Among them, reversible cognitive decline must be subjective cognitive decline (SCD) caused by physical factors [12].

CKD refers to a chronic kidney structural or functional disorder caused by many factors, which has the characteristics of a high prevalence rate, low awareness rate, and high medical expenses [13]. With the increasing aging of the world population, the incidence and mortality of CKD are increasing year by year, which has become a global public health problem affecting human health, and the prevalence rate of the general population in the world has reached as high as 14.3% [14]. The Chinese Center for Disease Control and Prevention (CCDC) investigated 31 provincial administrative regions in China, and obtained more than 170,000 samples of kidney indicators. It is estimated that there are 82 million adults with CKD in China, accounting for 8.2% of the total population in China [15]. CKD has brought a heavy economic burden to the government, society, and family.

Recent studies show that the incidence of cognitive impairment in CKD patients is as high as 58.8% [16], which may have an important impact on patients' health and reduce patients' compliance with treatment plans and quality of life. Coppolino [17] found that mild and moderate CKD patients are very common in the frail elderly, and the severity of renal insufficiency is independently related to the severity of cognitive impairment. Previous studies have found that people with CKD are at greater risk of cognitive frailty due to anemia, inflammation, cardiovascular diseases, and various metabolic disorders [18]. The increase of body toxins in CKD patients will lead to physical frailty and cognitive decline. The coexistence of the two will aggravate the decline of patients' self-management ability and medication compliance, and even develop into dementia, thus aggravating the progression of chronic renal failure patients. In patients with kidney disease, frailty and cognitive impairment are mostly studied separately, and there is little epidemiological evidence about CF. Studies have shown that CKD has a high incidence and poor prognosis, which is a risk factor for frailty and cognitive impairment. Frailty will also increase the risk of death in patients with CKD [19].

CKD patients with physical frailty and cognitive frailty show high prevalence, severe outcomes, and heavy burden. No drug fully cures CF, but it is reversible [20]. Early identification and intervention in high-risk CF patients can reverse CF, reduce adverse outcomes, and improve function and quality of life. Therefore, screening for cognitive frailty risk factors in CKD patients helps detect risks early, enabling timely intervention to reduce CF incidence, slow CKD progression, improve quality of life, and lessen family burden.

2. Materials and methods

2.1. Participants

Inclusion criteria: (1) Patients who meet the CKD in stages 1–3 criteria of the 2002 Quality Guidelines for Kidney Disease Prognosis (K/DOQI) [21]; (2) The course of CKD is more than 3 months; (3) Clear consciousness and normal communication skills [22]; (4) Informed consent and voluntary participation in this study. Exclusion criteria: (1) Patients who have been definitely diagnosed with dementia or other nervous system diseases; (2) Severe visual and hearing impairment; (3) Severe cardiovascular disease or liver and renal failure; (4) Accompanied by systemic infectious diseases.

2.2. Instruments and measurements

The questionnaire was designed through literature review, interviews, expert consultation, and group discussions, covering four parts: (1) General demographics: gender, age, BMI, marital status, education, and living conditions. (2) Disease data: CKD stages, duration, depressive symptoms (CES-D), drug types, and chronic disease count. (3) Lifestyle factors: smoking, alcohol, exercise, social interaction, sleep (PSQI), daily activities (BI), and fall history. (4) Blood indices: creatinine, urea, uric acid, CRP, albumin, hemoglobin, sodium, potassium, chlorine, cholesterol, fibrinogen, D-dimer, PT, PTH, procalcitonin.

Diagnostic criteria for cognitive frailty follow international standards, using Frailty Phenotype (FP), Montreal Cognitive Assessment-Basic (MoCA-B), and Clinical Dementia Rating (CDR) for data collection.

FP assesses frailty across five domains; score 0 = no frailty, 1–2 = pre-frailty, 3–5 = frailty; $\alpha = 0.897$, KMO = 0.890, $P < 0.05$.

MoCA-B screens cognition; total 30 points, ≥26 = normal, <26 = impairment; $\alpha = 0.839$, KMO = 0.895, $P < 0.05$.

CDR evaluates dementia severity; score 0 = healthy, 0.5 = suspicious, 1 = mild, 2 = moderate, 3 = severe; $\alpha = 0.890$, KMO = 0.898, $P < 0.05$.

The criteria for judging CF in this study are as follows: (1) the FP score is 3–5; (2) MoCA-B scale score is <26; (3) CDR scale score is 0.5, and there is no dementia diagnosis. The above criteria must be met at the same time.

2.3. Data collection

This study collected CKD stage 1–3 patients from Shanghai hospitals' nephrology departments (October 2022 to April 2023) as a modeling set, and used data from a Jiangsu hospital as a verification set. Investigators received unified training on skills, tool scoring, and precautions before conducting face-to-face surveys. After patient consent, questionnaires were issued; self-evaluation scales were self-completed or investigator-assisted. CDR scale scores were evaluated via semi-structured interviews with patients and caregivers. General data like gender and age came from electronic records, while blood indices were from initial admission tests. Pace was assessed as the average of two 4.5 m walks at normal speed. Grip strength was measured twice with the dominant hand in a standing position, averaging results [23]. Medical staff screened eligible CKD patients via HIS and CKD platforms, supplementing missing data through phone or in-person follow-ups.

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Review Committee of the Shanghai University of Medicine and Health Sciences (No. 2023-hxxm-01-612401197903300537). Informed consent was obtained from all participants in the study.

2.4. Data analysis

SPSS25.0 and Stata15.0 were used for statistical analysis and nomogram creation. Variables with $P < 0.05$ in univariate analysis underwent logistic regression; model variables were selected via the backward stepwise method and the model was built. Internal validation utilized Bootstrap resampling (1,000 times) to calculate C-Index for nomogram prediction performance. Discrimination was assessed via AUC of ROC curve, and calibration by the calibration curve and the Hosmer–Lemeshow test [24]. If C-Index and AUC exceed 0.75, our nomogram has good predictive performance. Calculating chi-square yields *P*; a higher *P* indicates better calibration, while $P < 0.05$ shows the prediction differs from the actual. Decision curve analysis (DCA) evaluates net benefit, and sensitivity, specificity, and accuracy assess practical efficiency. Stata15.0 visualizes the model via a nomogram for easy interpretation and patient evaluation [25]. External validation uses another brand-new data set to validate the model, and the patients in the data set are from completely different research centers [26]. In this study, the case data of cooperative hospitals were used as the verification set.

3. Results

3.1. Descriptive analyses (Table 1)

There are 600 samples in the modeling set, including 233 (38.8%) with cognitive frailty and 367 (61.2%) with non-cognitive frailty. The age ranged from 19 to 59, with an average age of 48.03 ± 7.843. There are 200 people in the verification set, including 84 (42.0%) with cognitive frailty and 116 (58.0%) with non-cognitive frailty. The age ranged from 22 to 59, with an average age of 48.84 ± 8.556 (See **Table 1**).

Table 1. Survey results of general demographic factors

Variables		Modeling set (*n* = 600)		Verification set (*n* = 200)	
		Non-CF (*n* = 367)	CF (*n* = 233)	Non-CF (*n* = 116)	CF (*n* = 84)
Age in years		48.01 ± 8.07	48.03 ± 7.84	47.4 ± 9.552	50.83 ± 6.493
Gender	Male	223 (37.2%)	131 (21.8%)	73 (36.5%)	55 (27.5%)
	Female	144 (24.0%)	102 (17.0%)	43 (21.5%)	59 (14.5%）
BMI (kg/m^2)	<18.5	50 (8.3%)	36 (6.0%)	11 (5.5%)	99 (4.5%)
	18.5–24	152 (25.3%)	99 (16.5%)	69 (34.5%)	54 (27.0%)
	≥24	165 (27.5%)	98 (16.3%)	36 (18.0%)	21 (10.5%)
Marital status	Married	226 (37.7%)	161 (26.8%)	67 (33.5%)	40 (20.0%)
	Unmarried	26 (4.3%)	4 (0.7%)	17 (8.5%)	12 (6.0%)
	Divorced	41 (6.8%)	16 (2.7%)	14 (7.0%)	11 (5.5%)
	Widowed	74 (12.3%)	52 (8.7%)	18 (9.0%)	21 (10.5%)

Table 1 (Continued)

Variables		Modeling set (*n* = 600)		Verification set (*n* = 200)	
		Non-CF (*n* = 367)	CF (*n* = 233)	Non-CF (*n* = 116)	CF (*n* = 84)
Education	Illiterates	20 (3.3%)	12 (2.0%)	16 (8.0%)	15 (7.5%)
	Primary school	68 (11.3%)	59 (9.8%)	41 (20.5%)	35 (17.5%)
	Junior school	132 (22.0%)	72 (12.0%)	37 (18.5%)	24 (12.0%)
	Senior high school	86 (14.3%)	47 (7.8%)	11 (5.5%)	2 (1.0%)
	College or above	61 (10.2%)	43 (7.2%)	11 (5.5%)	8 (4.0%)
Living conditions	Live in solitude	71 (11.8%)	44 (7.3%)	32 (16.0%)	22 (11.0%)
	Live with spouse	82 (13.7%)	52 (8.7%)	43 (21.5%)	25 (12.5%)
	Live with children	59 (9.8%)	39 (6.5%)	6 (3.0%)	11 (5.5%)
	Live with spouse and children	98 (16.3%)	72 (12.0%)	34 (17.0%)	21 (10.5%)
	Live with other caregivers	57 (9.5%)	26 (4.3%)	1 (0.5%)	5 (2.0%)

3.2. Results of logistic regression analysis

In the modeling set, risk factors underwent univariate analysis, with significant variables ($P < 0.05$) shown in **Table 2**. These variables were analyzed multivariately, and significant predictive factors were included in the model. Based on independent factors entering the regression model, a cognitive frailty risk prediction model for chronic kidney disease patients was constructed, with a nomogram presented in **Figure 1**. Independent variable distributions are in **Table 3**, showing only nomograph variables.

Table 2. Results of logistic regression analysis

Variables	Modeling set OR (95% CI)		Verification set OR (95% CI)	
	Univariate analysis	Multivariate analysis	Univariate analysis	Multivariate analysis
Number of chronic diseases	1.181 (1.062~1.313)	1.134 (1.004~1.28)	2.793 (2.075~3.76)	0.272 (0.085~0.874)
CES-D score (<15)				
CES-D score1 (6–19)	2.453 (1.604~3.753)	2.571 (1.613~4.099)	2.92 (1.479~5.764)	7.709 (2.424~24.514)
CES-D score (≥20)	4.575 (2.88~7.268)	4.678 (2.811~7.784)	3.244 (1.541~6.83)	8.134 (2.159~30.645)
PSQI score (0–5)				
PSQI score (16–21)	7.13 (3.222~15.784)	7.916 (3.328~18.828)	7.750 (2.736~21.955)	19.993 (3.888~102.801)
PSQI score (11–15)	5.54 (2.517~12.226)	4.935 (2.095~11.628)	4.632 (1.667~12.871)	9.134 (1.89~44.131)
PSQI score (6–10)	3.687 (1.640~8.289)	3.583 (1.491~8.612)	3.157 (1.136~8.778)	4.807 (0.892~25.905)
C-reactive protein	2.401 (1.715~3.360)	1.958 (1.342~2.857)	2.090 (1.163~3.757)	2.431 (0.886~6.672)
D-dimer	3.366 (2.209~5.129)	2.894 (1.822~4.599)	3.071 (1.550~6.082)	9.132 (2.764~30.169)
PTH	2.020 (1.437~2.839)	1.741 (1.188~2.55)	0.684 (0.381~1.226)	
Procalcitonin	1.748 (1.218~2.507)		2.250 (1.231~4.111)	

Table 3. Independent variable assignment

Variable	Evaluation
PTH	Normal = 0, Abnormal = 1
D-dimer	Normal = 0, Abnormal = 1
C-reactive protein	Normal = 0, Abnormal = 1
PSQI score (6–10)	PSQI score (0–5) = 0, PSQI score (6–10) = 1
PSQI score (11–15)	PSQI score (0–5) = 0, PSQI score (11–15) = 1
PSQI score (16–21)	PSQI score (0–5) = 0, PSQI score (16–20) = 1
CES-D score (≥20)	CES-D score (<15) = 0, CES-D score (≥20) = 1
CES-D score (16–19)	CES-D score (<15) = 0, CES-D score (16–19) = 1

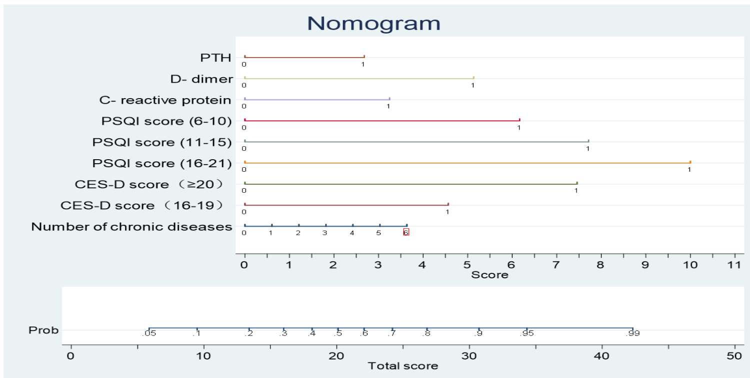

Figure 1. Nomogram of risk for cognitive frailty

3.3. Discrimination and calibration verification

Internal verification used bootstrap self-sampling to verify the nomogram risk prediction model. After 1000 bootstrap repetitions, the corrected C-statistic was 0.779 (95% CI: 0.742–0.816, $P < 0.001$), indicating good discrimination. ROC curve shows model discrimination (**Figure 2**).

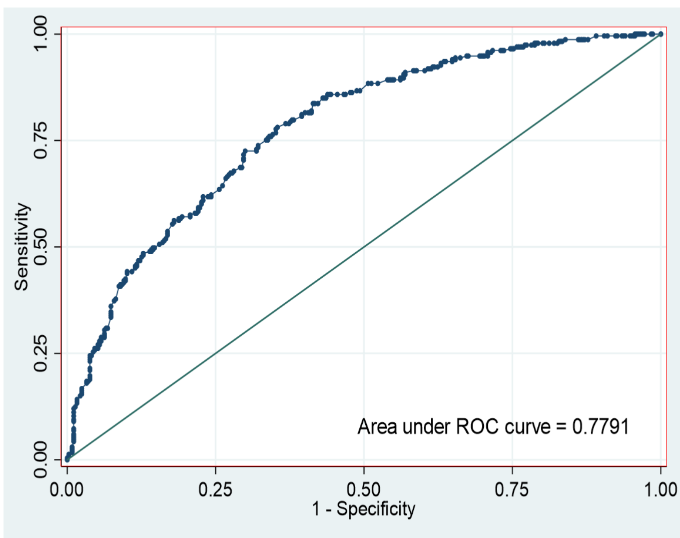

Figure 2. ROC curve of internal verification

External verification uses verification set data to evaluate the discrimination of the cognitive frailty risk assessment model via the area under the ROC curve (AUC). The prediction model from the modeling set was applied to the verification set, yielding an AUC of 0.909 (95% CI: 0.870–0.948, $P < 0.01$), as in **Figure 3**. The cognitive frailty risk prediction model for CKD patients shows good predictive performance.

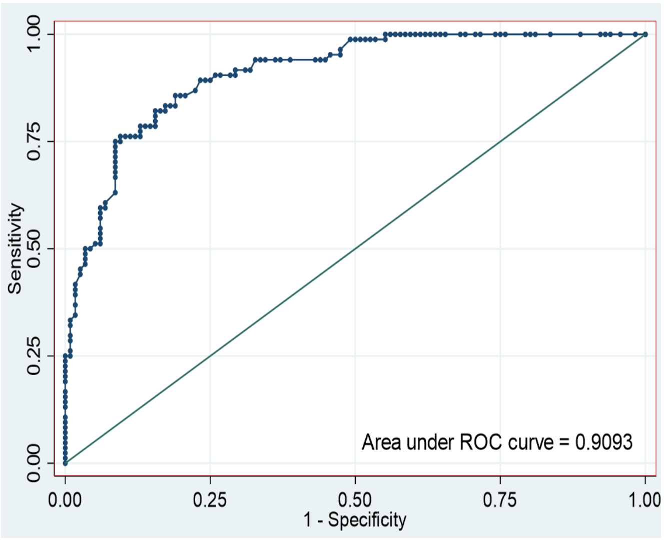

Figure 3. ROC curve of model external verification

The calibration chart of internal verification shows that the probability of CF predicted by the nomogram of the model is in good agreement with the actual probability of CF. Hosmer–Lemeshow test $\chi 2 = 5.794$, $P = 0.670 > 0.05$, which shows that the calibration of the model is good (See **Figure 4** for details).

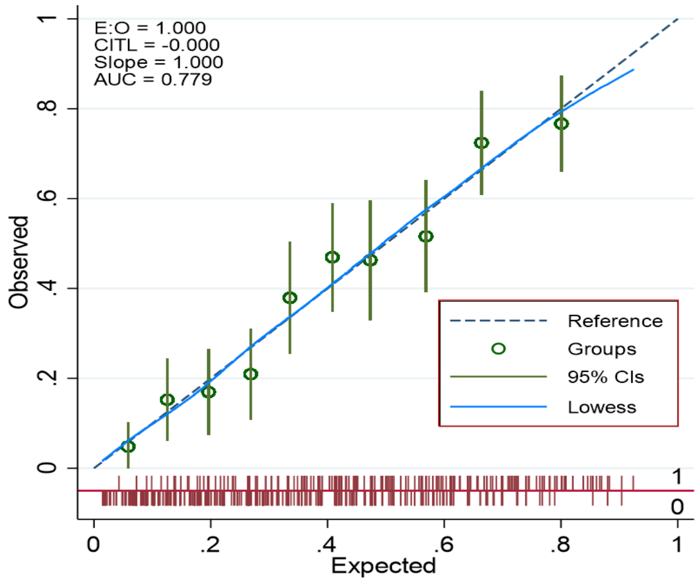

Figure 4. Internal verification calibration curve

The model, built in the modeling set, was tested on the verification set for calibration. The Hosmer–Lemeshow test ($\chi 2 = 3.423$, $P = 0.904 > 0.05$) showed no significant difference, indicating good fit for our cognitive frailty risk prediction model in CKD patients. The calibration chart confirms good agreement between predicted and observed values (**Figure 5**).

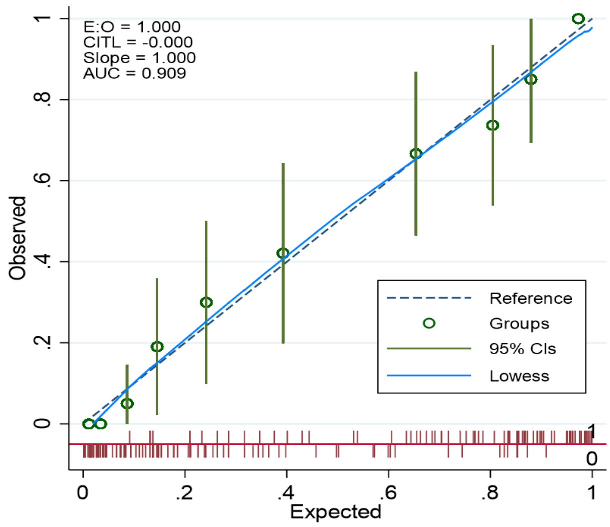

Figure 5. Calibration curve for external verification of model

3.4. Clinical application

The analysis of decision curves of the nomogram of the clinical application in the modeling and verification groups is shown in **Figures 6** and **7**. As can be seen from the figure, it can bring positive benefits to decide whether to take intervention measures according to the prediction model constructed in this study.

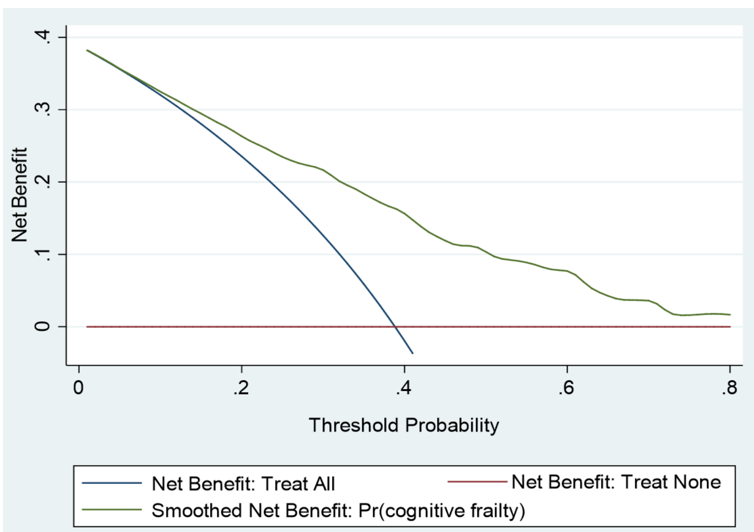

Figure 6. DCA curve of internal verification

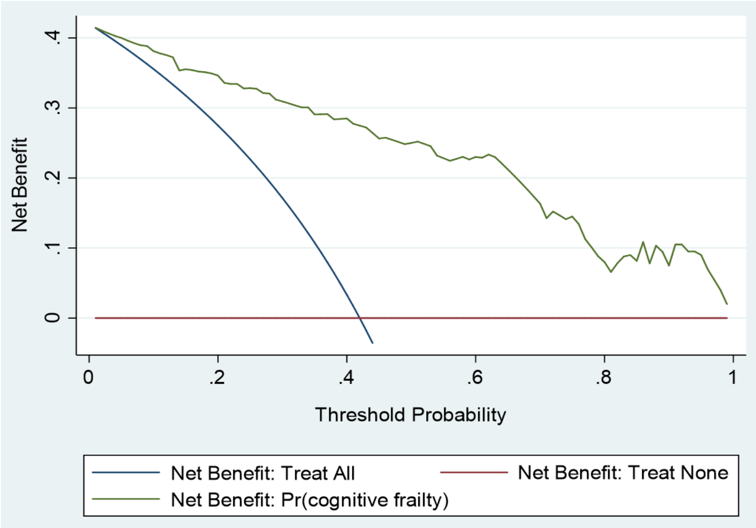

Figure 7. Decision curve of model external verification

4. Discussion

4.1. Current situation of cognitive decline

In this study, 800 patients with chronic kidney disease in stages 1–3 in the modeling set and the verification set were analyzed. The median and quartile of age were 49 (44, 54) years old, and 317 patients had CF, with the incidence of CF being 39.6%. Chang investigated 1,015 elderly CKD patients and found that the prevalence of CF was 15.2% [27]. Luo used the FP, MoCA, and CDR to evaluate the occurrence of CF, and the study found that 21.9% of elderly CKD patients had CF [28]. This shows that the incidence of CF in patients with CKD is higher than that in the general elderly population.

4.2. Risk factors of cognitive frailty in patients with CKD

The occurrence of cognitive frailty is influenced by many factors. The results of this study show that the occurrence of CF in patients with CF in stages 1–3 is related to the number of chronic diseases, C-reactive protein (CRP), D-dimer (D-D), parathyroid hormone (PTH), depression, and sleep quality.

CKD is an important risk factor for cerebrovascular disease, while CKD patients are often complicated with other chronic diseases such as diabetes, hypertension, and gout, so the incidence of cognitive impairment will increase significantly [29,30]. Modeling set analysis shows chronic disease count is an independent CF risk factor, consistent with our verification set. More diseases increase CF risk. While uncontrollable by staff, identifying and training patients with multiple chronic diseases in physical and cognitive function can greatly reduce CF occurrence.

The sample analysis in the modeling set of this study shows that CRP abnormality is also an independent risk factor for CF, which has been verified in our verification set data. Many studies have shown that the frailty clinical phenotype is related to inflammation [31]. Blood tests and indices related to inflammation include hypoalbuminemia, low-density lipoprotein cholesterol reduction, and CRP increase, among which CRP is an important inflammatory biomarker and the most common inflammatory index in the clinic [32]. Gillett [33] pointed out that the hemostatic biomarker D-D is related to cognitive frailty, and vascular diseases and their risk factors have more and more obvious effects on cognitive function. Douglas also found that D-D was significantly related to frailty. Our study found the CF probability in CKD patients with abnormal D-D was 2.894 times higher than in normal D-D patients, a statistically significant difference. In clinical nursing, D-D monitoring can evaluate CF risk, and early dynamic monitoring supports clinical treatment [34].

PTH can cross the blood-brain barrier, and PTH receptors are all over the human brain [35]. PTH regulates circulation and intracellular calcium levels, and may induce apoptosis due to calcium overload, which causes the poor cognitive function of patients, including memory and attention disorders [36]. Murthy found that the high PTH level was independently related to the high number of falls and the clinical components of physical frailty of the older adults in the community [37]. The results of this study show that there are 144 (18%) CKD patients with depressive symptoms, which is higher than the prevalence rate of 8.1% reported by Zhu [38]. Many studies have confirmed that depression is an important risk factor for CF [39,40]. There are similar pathological mechanisms between depression and CF [41].

Previous studies have shown that sleep disorder is one of the important risk factors leading to CF. With the continuous development of sleep disorders, the possibility of CF progressing to mild cognitive impairment and AD is further increased [42]. Peng also found that the physical frailty of the elderly has a direct predictive effect on cognitive function and is mediated by sleep quality [43]. Sleep quality mediates cognitive dysfunction and physical frailty in CKD patients, where sleep disorders, frailty, and cognitive decline are common but ignored. Though not life-threatening, their long-term presence increases dementia risk, affects quality of life, and interacts with CKD. Improving sleep quality can reduce cognitive frailty.

4.3. Strengths and limitations

Currently, few studies address CF in CKD patients, lacking effective risk assessment tools. This study developed a risk prediction model using a nomogram for intuitiveness, readability, and ease of use by clinical staff. Risk factors are common in CKD diagnosis services, obtainable via hospital information systems without added costs, ensuring good applicability, accessibility, and controllability. The model was internally validated with Bootstrap resampling (1,000 times) and externally with CKD patients from other regional hospitals.

Although the model performs well, limitations include a sample limited to Shanghai and Jiangsu, requiring multi-center validation for broader applicability; fewer risk factors included, necessitating more in future studies to improve prediction; and time constraints preventing use of the latest CF definition to diagnose cognitive decline subtypes.

5. Conclusion

A large number of chronic diseases, severe depressive symptoms, abnormal CRP, abnormal D-D, and abnormal PTH can increase the risk of cognitive frailty in patients with CKD. Therefore, according to the risk prediction model we have built, clinical medical staff can provide preventive intervention measures for patients with these risk factors in line with their work and life characteristics.

Disclosure statement

The authors declare no conflict of interest.

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