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ORIGINAL ARTICLE

Predictive accuracy of comorbidity index models in assessing mortality risk among hemodialysis patients: A comprehensive single-center observational cohort study

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Abstract

Objectives: Comorbidity prediction models have been demonstrated to offer more comprehensive and accurate predictions of death risk compared to single indices. However, their application in China has been limited, particularly among maintenance hemodialysis (MHD) patients. Therefore, the objective of this study was to evaluate the utility of comorbidity index models in predicting mortality risk among Chinese MHD patients.

Methodology: The MHD patients in the First Affiliated Hospital of Guangzhou University of Traditional Chinese Medicine were taken as the subjects. Claims-based disease-specific refinements matching translation to ICD-10 and flexibility (CDMF-CCI) model and Liu model were selected as the candidate models for this verification research. Univariate and multivariate Cox regression calculations were used to analyze the independent predictive effect of the models on survival rate.

Results: Annually, nearly 500 patients undergo hemodialysis treatment. From January 2019 to June 2022, a total of 199 patients succumbed, with a mean age of 65.2 years. During these 4 years, the mortality rates were 13.04%, 9.68%, 11.69%, and 6.39%, respectively. The leading causes of death were sudden demise (82 patients, 41.2%), cardiovascular disease (48 patients, 24.1%), pulmonary infection (33 patients, 16.5%), and stroke (19 patients, 9.5%). When compared to individual indices, the CDMF-CCI model displayed more accurate and predictive results, with an HR of 1.190 ($P = 0.037$). Conversely, the Liu model failed to identify high-risk individuals.

Yanna Yu and Fen Li contributed equally.

Conclusion: The MHD patients face a significant risk of mortality. When compared to univariate parameters and the Liu model, the CDMF-CCI model exhibits superior predictive accuracy for mortality in MHD patients.

KEYWORDS
chronic kidney disease, end-stage kidney disease, maintenance hemodialysis, mortality, renal function

1 | INTRODUCTION

At the 2023 annual meeting of the Chinese Society of Nephrology, it was announced that the number of patients receiving dialysis treatment in China, who are registered in the Chinese National Renal Data System (CNRDS), has exceeded 1 million. As China's aging population continues to grow,[1] coupled with the extensive coverage of medical insurance policies and the relentless advancements in dialysis technology and equipment, the projected number of maintenance hemodialysis (MHD) patients is anticipated to surge significantly in the coming years.[2] Notably, MHD patients often experience shorter lifespans and heightened mortality risks compared to the general population, underscoring the urgent need for an accurate predictive tool to predict poor prognosis, thereby enabling the implementation of tailored health care and treatment strategies.[3]

The comorbidity evaluation models represent a significant shift away from the conventional approach, which solely focused on individual indicators, by placing comorbidity at the forefront as the primary determinant of mortality risk.[4] In recent times, these models have gained widespread recommendation as a prognostic prediction method in chronic disease management. They integrate pertinent data sourced from questionnaires, examination reports, medical record systems, and chronic disease databases, offering a comprehensive assessment of a patient's health status.[5] After over three decades of development and continuous refinement in line with the evolving disease spectrum and the International Classification of Diseases (ICD), these comorbidity evaluation models have garnered widespread adoption.[6–8] In recent years, Chinese scholars have gradually turned their attention to this domain.[9] However, there remains a scarcity of reported research exploring the value and applicability of comorbidity prediction models, specifically for the Chinese hemodialysis population. Consequently, the aim of this study was to demonstrate the superior predictive accuracy of comorbidity models over univariate approaches and to identify an optimal model tailored for MHD patients.

2 | METHODOLOGY

2.1 | Study design and settings

The cross-sectional type of observational study was conducted in the First Affiliated Hospital of Guangzhou University of Traditional Chinese Medicine from January 2019 to June 2022, in Guangzhou, China. Comprehensive patient information, encompassing general demographics, disease diagnoses, and laboratory test results, was gathered utilizing the electronic medical record system.

2.2 | Dialysis treatment protocol

The majority of patients underwent routine hemodialysis sessions three times weekly, each lasting for 4 h. During these sessions, anticoagulants such as heparin sodium, low-molecular-weight heparin, or citrate were administered. The blood flow rate was maintained at 200–300 mL/min, while the dialysate flow was set at 500 mL/min. The dialyzer membrane area employed ranged from 1.3 to 1.8 square meters, ensuring effective dialysis for the patients.

2.3 | Study sample and participants

The inclusion criteria for this study are as follows: Firstly, patients must have been undergoing dialysis for a duration exceeding 3 months and be aged 18 years or older. Secondly, their life expectancy must be anticipated to surpass 6 months. Thirdly, the patient's condition must have remained stable in the 3 months preceding their inclusion in the study. The exclusion criteria for this study are outlined as follows: Firstly, participants who are enrolled in interventional clinical trials are not eligible. Secondly, patients diagnosed with acute kidney injury (AKI), defined as an increase in serum creatinine by 0.3 mg/dL within 48 h, or exceeding 1.5 times the baseline value within 7 days, or presenting with urine output of less than 0.5 mL/kg/h for more than 6 h, are excluded. Thirdly, individuals with acute health conditions, including infections, fever, acute coronary syndrome, or acute exacerbations of chronic diseases, are not included. Lastly, patients who are infected with HIV or AIDS are also excluded from the study.

2.4 | Candidate comorbidity models

The claims-based disease-specific refinements matching translation to ICD-10 and flexibility (CDMF-CCI) model[10] and the Liu model[11] were chosen as potential candidates for analysis.

According to the grouping requirements of the models, the comorbidity score calculated from the CDMF-CCI scale categorized the patients into three distinct groups: a score of 0 indicating the absence of comorbidity, a CCI score less than 2 indicating low comorbidity, and a CCI score greater than 2 signifying high comorbidity. The comorbidity score calculated from the Liu model stratified the subjects into four groups: Group 1 (3 points or less), Group 2 (4 to 6 points), Group 3 (7 to 9 points), and Group 4 (10 or more points).

2.5 | Ethical statements and declarations

This research was granted approval by the Ethics Committee of The First Affiliated Hospital of Guangzhou University of Chinese Medicine, under the reference number K-2023-111. Additionally, the study has been registered with the Chinese Clinical Trial Registry (ChiCTR), with the registration number ChiCTR2000035328.

2.6 | Statistical analysis

Continuous variables were represented using the mean (standard deviation), while proportions were represented using percentages. Survival curves between groups were assessed using the Kaplan–Meier method and log-rank test to compare the predictive value of mortality between the two models. Univariate and multivariate Cox regression proportional hazard regressions were conducted to identify predictors of patient survival. Factors yielding $p \leq 0.05$ in the univariable models were included in the multivariable analyses. Hazard ratios (HRs) with 95% confidence interval (CI) and p values were reported. All these analyses were conducted utilizing the R software version 4.2.1 (Bell Laboratories).

3 | RESULTS

3.1 | Study overview and baseline information

Over the span of 4 years, from January 2019 to June 2022, an annual average of approximately 500 patients underwent hemodialysis treatment. During this period, a total of 199 patients passed away, comprising 131 males (65.5%) and 68 females (34.5%), with an average age of 65.22 ± 13.63 years. The mortality rates varied annually, reaching 13.04%, 9.68%, 11.69%, and 6.39%, respectively.

The primary causes of mortality were diverse, with sudden death accounting for the highest proportion (41.2%, 82 patients), followed by cardiovascular disease (24.1%, 48 patients), pulmonary infection (16.5%, 33 patients), and stroke (9.5%, 19 patients).

In the CDMF-CCI model, patients were categorized into three distinct comorbidity groups: non-comorbidity ($n = 11$), low comorbidity ($n = 97$), and high comorbidity ($n = 91$), with an average score of 1.65 ± 0.88. Meanwhile, the Liu model assigned scores ranging from under 3 points ($n = 81$) to over 10 points ($n = 4$), with an average score of 4.73 ± 2.63, further segmenting patients into four distinct groups based on their scores: 3 points or less, 4–6 points, 7–9 points, and above 10 points.

For a comprehensive overview of the patient demographics and characteristics, please refer to Table 1.

3.2 | Comparative analysis of dialysis patient survival using CDMF-CCI and Liu models

In the CDMF-CCI model, the survival curve for the low-risk comorbidity group (depicted in red) significantly surpassed those of the other two groups (green and blue), showcasing excellent discrimination as illustrated in Figure 1. Within this model, a lower score correlated with a shorter survival period for dialysis patients. Even patients categorized as intermediate risk, with scores above 2, faced a heightened mortality risk. The graph reveals that the survival rate for the intermediate-risk group dwindled to below 50% after 3 years and further decreased to less than 10% after 10 years.

Conversely, the survival curve did not exhibit a significant correlation with comorbidity in the Liu model (Figure 2).

TABLE 1 Characteristics of the study population ($n = 199$).

Characteristics	Statistics
Male, *n* (%)	131 (65.5%)
Female, *n* (%)	68 (34.5%)
Age (years)	65.22 ± 13.63
Weight (kg)	60.89 ± 9.25
Height (cm)	166.81 ± 5.83
Hemoglobin (g/L)	96.31 ± 21.77
Hematocrit	0.30 ± 0.08
Serum calcium (mmol/L)	2.16 ± 0.22
Serum albumin (g/L)	36.87 ± 5.19
Serum uric acid (mmol/L)	446.04 ± 124.33
Serum urea (mmol/L)	26.06 ± 10.42
Serum creatinine (μmol/L)	829.70 ± 299.74
Serum ferritin (mmol/L)	530.01 ± 704.35
Serum phosphorus (mmol/L)	1.98 ± 0.71
Alanine aminotransferase (mmol/L)	15.14 ± 21.66
CDMF-CCI model	1.65 ± 0.88
Liu model	4.73 ± 2.63

Note: CDMF-CCI model: Claims-based disease-specific refinements matching translation to ICD-10 and flexibility. Liu model: Named by the first author, which was meticulously crafted using extensive data from 33,077 American dialysis patients diagnosed with 11 distinct medical conditions. Prior to the initiation of hemodialysis treatment, the comprehensive array of biochemical indicators above were gathered from these patients.

3.3 | The COX regression analysis

Univariate COX regression analysis indicated that a high CDMF-CCI score was associated with a lower survival rate, with a hazard ratio (HR) of 1.216 (Table 2). Furthermore, the relationship remained significant even after adjusting for other variables, with an HR of 1.190 (Table 3).

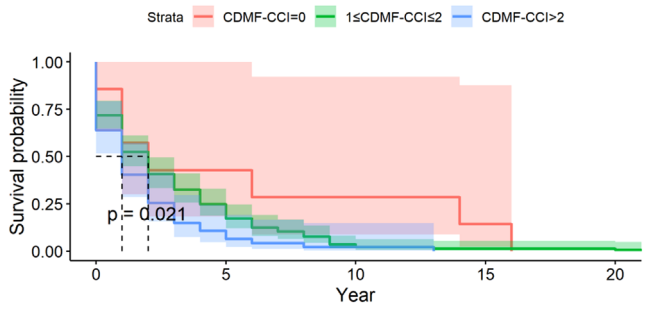

FIGURE 1 Death prediction of CDMF-CCI model for hemodialysis patients. Group 1 (red, no comorbidity): Patients with a CDMF-CCI score of 0. Group 2 (green, low-risk comorbidity): Patients with a CDMF-CCI score less than 2. Group 3 (blue, high-risk comorbidity group): Patients with a CDMF-CCI score of 2 or more.

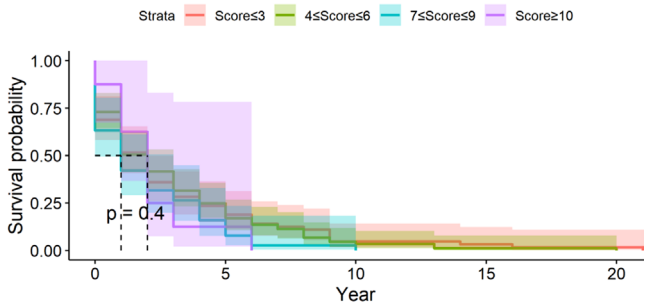

FIGURE 2 Death prediction of Liu model for hemodialysis patients. Group 1 (red, low-risk comorbidity): Patients with 3 points or less. Group 2 (green, moderate-risk comorbidity): Patients with 4 to 6 points. Group 3 (blue, significant risk comorbidity): Patients with 7 to 9 points. Group 4 (purple, major risk comorbidity): Patients with 10 points or more.

4 | DISCUSSION

In 1987, the first comorbidity prediction model, known as the Charlson comorbidity index, was developed using medical data from 559 patients. This model was later validated using a separate set of 685 patients who were followed up for 10 years to assess the model's accuracy in predicting 10-year survival.[12]

The final model encompassed 19 "diseases" and assigned values of 1, 2, 3, and 6 points, respectively, to calculate comorbidity scores. Additionally, considering age as an independent risk factor, the value was incremented by 1 point starting at the age of 50 years. Subsequently, the 10-year survival rate was calculated. In the past 30 years, researchers and health professionals have widely utilized CCI models to aid in the diagnosis and assessment of death risk among patients with coexisting conditions in various medical care settings, including communities and nursing homes. These models have also been employed to determine the prognosis of patients in the community, nursing homes, and other medical environments.[13–15] We believe that the CCI model takes into account both age and kidney disease, making it more suitable for prognostic assessment in hemodialysis patients. However, several points need to be further confirmed: Firstly, it is necessary to consider whether the American disease spectrum of 33 years ago is still suitable for our current conditions. Secondly, hemodialysis patients may not only have "moderate–severe nephropathy" as captured in the model but may also suffer from renal anemia, endocrine abnormalities, chronic kidney disease–mineral, and bone abnormalities. Therefore, the assignment of 2 points in the model may not be entirely appropriate. Thirdly, considering that the 10-year forecast period may be too long for elderly individuals over the age of 70, it could be beneficial to have more flexible forecast years, such as 3 or 5 years.

TABLE 2 Univariate COX regression analysis for hazard ratio in survival analysis.

Variables	Coefficient estimates	HR (95% CI)	*P*-value
Male	0.079	1.082 (0.803–1.458)	0.604
Age	0.005	1.005 (0.993–1.017)	0.398
Hematocrit	−4.874	0.008 (0.001–0.071)	<0.001*
Serum calcium	−1.664	0.189 (0.099–0.399)	<0.001*
Serum albumin	−0.057	0.945 (0.919–0.972)	<0.001*
Serum ferritin	−0.000	1.000 (0.999–1.000)	0.007*
Serum phosphorus	−0.122	0.885 (0715–1.096)	0.264
Alanine aminotransferase	0.004	1.004 (0.998–1.010)	0.163
CDMF-CCI	0.195	1.216 (1.034–1.430)	0.018*

Note: CDMF-CCI is the comorbidity index model used to calculate scores. The biochemical indicators were drawn prior to hemodialysis.

*$p < 0.05$ indicating statistical significance.

TABLE 3 Multivariate Cox regression to analyze the independent predictive effect of CCI on survival.

Variables	Coefficient estimates	HR (95% CI)	*P*-value
Hematocrit	−2.753	0.064 (0.006–0.691)	0.024*
Serum calcium	−1.087	0.337 (0.150–0.760)	0.009*
Serum albumin	−0.032	0.969 (0.939–1.000)	0.050
Serum ferritin	−0.000	1.000 (0.999–1.000)	0.001*
CDMF-CCI	0.174	1.190 (1.010–1.401)	0.037*

Note: CDMF-CCI is the comorbidity index model used to calculate scores. The biochemical indicators were drawn prior to hemodialysis.
*$p < 0.05$, indicating statistical significance.

With the release of the ICD-10 in 2019, Glasheen et al. updated the CCI model to create the CDMF-CCI model. After comparison, we found several differences between the CCI and CDMF-CCI models, although the CDMF-CCI model still comprises 19 items.

The differences between the CCI and CDMF-CCI models are as follows: (1) Disease classification: The term "coronary heart disease" has been replaced with "myocardial infarction" in the CDMF-CCI model. Additionally, "any tumor, leukemia and lymphoma within 5 years" has been reclassified as "malignancy." Furthermore, "mild to moderate kidney disease" and HIV infection (without AIDS) have been added to the list of diseases. (2) Assignment: The CDMF-CCI model assigns the same points as the CCI model for most diseases, with some exceptions. For example, the new "mild to moderate kidney disease" is assigned 1 point, HIV infection (without AIDS) is assigned 3 points, and "dementia" has been reduced to 1 point. (3) Calculation formula: The calculation formula remains the same for both models. After considering the characteristics of both the CCI and CDMF-CCI models, we ultimately chose the updated CDMF-CCI as the validation model. Our results suggest that CDMF-CCI is well suited for identifying high-risk comorbid patients, outperforming univariate indicators, and is a valuable tool for clinicians.

All the subjects in this study were hemodialysis patients. Prior to this study, several comorbidity models had been developed for end-stage kidney disease (ESKD) patients. In 1993, Wright-Khan et al. established a comorbidity model based on 375 ESKD patients.[16] Two years later, Davies enrolled 97 ambulatory peritoneal dialysis patients to establish a comorbidity prediction model.[17] In 2000, Athienites et al. developed the index of coexistent disease (ICED) model, which was based on peritoneal dialysis and hemodialysis patients.[18] In 2002, van Manen et al. proposed that the CCI model was superior to the Khan model and the Davies model in assessing the risk of death in ESKD patients.[19]

In 2004, Miskulin et al. conducted a study using data from the United States Renal Data System (USRDS) from 1997 to 2000, including 1779 patients. They compared the predictive value of four comorbidity models: ICED, Wright-Khan, Davies, and CCI.[20] The accuracy (area under the curve) of these models was 0.72, 0.68, 0.68, and 0.67, respectively. After adjusting for race and serum albumin, the accuracy was adjusted to 0.77, 0.75, 0.74, and 0.75, respectively. Although the predictive efficacy of ICED was slightly better than the other three models, it still needed improvement. Additionally, ICED required more time for data collection. Finally, Miskulin emphasized that fewer but better "comorbidity indexes," accurate assignment, and appropriate selection of diseases are key to effectively improving the accuracy and practical value of comorbidity models.

In 2010, Jiannong Liu et al. developed a comorbidity model based on 33,077 American dialysis patients with 11 diseases, which received international attention. This model, known as the Liu model, is the largest reported sample size in the field of comorbidity among dialysis patients.[11] The researchers found that the primary cause of renal failure is not predictive of death, hospitalization costs, and length of stay. They also observed interactions between age and comorbidity, leading them to conclude that age did not need to be included in the model.

In our study, we found that the Liu model was less accurate than the CDMF-CCI model in identifying patients at high risk of death. The possible reasons for this are as follows: 1. The number of comorbidity parameters was fewer in the Liu model compared to the CDMF-CCI model. 2. The characteristics of the population may not be suitable for the application of the Liu model. 3. The exclusion of age as a factor in the Liu model may be its biggest limitation.

These findings suggest that the CDMF-CCI model may provide more accurate risk assessment for dialysis patients compared to the Liu model. However, further validation studies are needed to confirm these findings in different populations and settings.

The mean age of the subjects in this study exceeded 65 years old, indicating that the population primarily consisted of older individuals. According to the clinical practice guideline published by the European Renal Best Practice (ERBP) in 2016, accurate risk assessment of death in hemodialysis patients is crucial for treatment planning. For instance, patients who are frail or near to death may benefit more from conservative treatment and palliative care, while those with a low risk of death may be candidates for more aggressive treatment to improve quality of life and dialysis adequacy.[21]

To assess the risk of death in hemodialysis patients, the renal epidemiology and information network (REIN) developed a 3-month risk of death model. The model was derived from data obtained from the REIN database, which included over 12,500 French dialysis patients aged 75 years or older. One-third of these patients had heart failure, and one-quarter had peripheral vascular disease. The validation group consisted of an additional 11,848 dialysis patients registered with the REIN library. Internal and external validation results showed that the REIN model had high accuracy in predicting death risk.

After rigorous analysis, the REIN study found that several factors, including diabetes mellitus, ischemic heart disease, cerebrovascular disease, chronic respiratory disease, physical fitness index, and body surface area, were not strongly associated with the risk of death at 3 months and were thus excluded from the model. Five general parameters (age, sex, daily behavior, mobility, and serum albumin level) and four comorbid parameters (congestive heart failure, peripheral vascular disease, arrhythmia, and malignancy) were

ultimately included in the model to predict the risk of death in hemodialysis patients.

Therefore, the initial recommendation for managing older patients with CKD stage 3b or higher advises that physicians utilize the REIN scoring system to estimate the risk of mortality in patients with CKD stage 5 (2B). However, it is important to note that the REIN model necessitates an assessment of a patient's mobility and behavioral abnormalities, and it only predicts a patient's survival rate over a 3-month period. Given that our database is still in the process of being refined, there is a potential for retrospective studies to suffer from recall bias regarding these specific factors. Therefore, the REIN model was not validated in this particular study.

5 | STRENGTH AND LIMITATION

This study has several limitations, including a small sample size, single-center design, and a focus on only two comorbidity models for comparison. Nevertheless, it represents a crucial first step in developing comorbidity prediction models for the Chinese hemodialysis population.

6 | CONCLUSION

The higher the comorbidity index in elderly hemodialysis patients, the higher the risk of death. The CDMF-CCI model exhibits superior predictive accuracy to the Liu scale for mortality in MHD patients. Nevertheless, the evaluation metrics of the present comorbidity models are intricate, with varying parameters and weights, posing hurdles for applicability to Chinese cohorts, notably dialysis patients. Amid China's medical informatics advancements, blood purification registry enhancements, and AI/mathematical algorithm support, we envision the establishment of tailored comorbidity models as an achievable milestone.

AUTHOR CONTRIBUTIONS

Xiaohua Pei: Conception, design, review, and editing. **Yanna Yu**: Original draft and provision of study materials or patients. **Fen Li**: Formal analysis. **Zhibin Ni** and **Shu Zhang**: Data curation. **Zhan Wang** and **Fen Li**: Data analysis and interpretation. **Weihong Zhao**: Supervision. All authors: Final approval of manuscript.

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CONFLICT OF INTEREST STATEMENT

There are no conflicts of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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