COMBINATION OF THORACIC AORTIC CALCIFICATION INDEX AND C-REACTIVE PROTEIN TO PREDICT ALL-CAUSE MORTALITY IN MAINTENANCE HEMODIALYSIS PATIENTS

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ABSTRACT

Objective: *The risk factors of all-cause mortality in maintenance hemodialysis (MHD) patients were investigated alongside the value of thoracic aortic calcification index (TACI) combined with C-reactive protein (CRP) levels to predict all-cause mortality in MHD patients.*

Methods: *A total of 312 MHD patients were followed up either until death or 30th November 2020.TACI were calculated semi-quantitatively using a blinded method, and demographic, clinical, and laboratory parameters including mineral metabolism markers were collected for each patient.*

Results: *TACI and CRP in the death group were both significantly higher than those in the survival group. Age, dialysis age, hemoglobin, corrected calcium, CRP, and TACI were independent risk factors for all-cause death in MHD patients. Kaplan-Meier survival analysis demonstrated that the 1-, 3-, and 5-year overall survival rates of patients in the TACI≥1.67% group were significantly lower than those with a TACI<1.67% (P<0.001). The decision tree (DT) model determined that a of TACI≥1.67% combined with a CRP>20.61mg/L were important determinant variables for predicting high all-cause mortality in MHD patients.*

Conclusion: *TACI combined with CRP can therefore aid prediction of all-cause mortality in MHD patients. TACI and CRP are therefore promising interventional targets for reducing all-cause mortality in MHD patients.*

Keywords: *Thoracic aortic calcification score, C-reactive protein, hemodialysis, all-cause mortality.*

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Introduction

In recent years, the incidence of chronic kidney disease (CKD) has increased year by year, increasing numbers of patients with CKD progress to end-stage renal disease (ESRD). The main renal replacement therapy for ESRD patients is hemodialysis, as dialysis technology has developed, the survival rates of MHD patients have significantly improved. Studies have shown that 50% of deaths in MHD patients are due to cardiovascular disease (CVD), which is one of the important causes of death in MHD patients[(1)]. Many studies have shown that the presence of thoracic aortic calcification (TAC) detected by computed tomography (CT) is a sign of subclinical atherosclerosis, in turn this is associated with an increased risk of cardiovascular events[(2-4)]. Following a 7.8 year follow-up of 4,544 patients who underwent full-body CT examination, it was found that thoracic aortic calcification was associated with overall mortality[(5)]. However, a specific quantitative value was not given to predict all-cause mortality.

In CKD patients (including those receiving MHD treatment), inflammation is a well-known indicator that can predict clinical outcome[6, 7]. This study aimed to explore using the combination of thoracic aortic calcification index (TACI) and c-reactive protein (CRP) to predict all-cause mortality in MHD patients, and to provide specific values of TACI and CRP to predict the risk of all-cause mortality.

Patients and methods

Patients

This study was a retrospective case-control study. The selected patients started MHD treatment at the Hemodialysis Center based in the Second Affiliated Hospital of Nantong University between November 2012 and November 2019. The selected patients were aged >18 years of age, had a dialysis term of ≥3 months, were in a stable condition, and had complete follow-up data.

The exclusion criteria were:

• Serious cardiovascular and cerebrovascular events which occurred within three months;

• History of malignant tumor;

• Acute and chronic infection within one month;

• Serious arrhythmia and severe arrhythmia within one month in patients with heart failure;

• Patients with glucocorticoid and immunosuppressant medication history within the previous six months; The Ethics Committee of the Second Affiliated Hospital of Nantong University reviewed and approved this study (approval number: 2019KW008).

Data collection

Data was collected relating to age, gender, primary disease, body mass index (BMI), dialysis age, dialysis adequacy (URR, spkt/V), predialysis systolic blood pressure (SBP), predialysis diastolic blood pressure (DBP), hemoglobin (Hb), Albumin (ALB), blood glucose (Glu), total cholesterol (TC), triglycerides (TG), low density lipoprotein (LDL), high density lipoprotein (HDL), corrected calcium (Ca), phosphorus (P), hypersensitive C-reactive protein (CRP), parathyroid hormone (PTH), thoracic aortic calcification index (TACI). Specimen collection consisted of fasting venous blood prior to each dialysis session. TACI was used to evaluate the degree of TAC. All enrolled patients in our hospital underwent a plain chest CT scan using a Siemens 64-row double-spiral CT. TACI was calculated semiquantitatively using a blinded method. Starting from the tracheal bifurcation, 20 layers of 0.5-cm thickness images were continuously scanned downwards up to a total of 10 cm. Each level was divided into 12 fan-shaped areas, and the number of areas occupied by calcification were calculated (CT value of 130 HU; calcified plaque was defined as an area exceeding 1mm^2).

The total number for each level was divided by 12. The same method was used to evaluate the remaining levels. After addition of all of the levels, the resulting number was divided by 20 and multiplied by 100% to obtain the TACI. All calculations were performed by a single person. TACI was calculated three times, and the mean value was obtained. The following equation was used: TACI = (A/12+B/12+...T/12)/20×100%, where A, B... T represented the numbers of sectors occupied by calcification at each CT level (Figure 1)[8].

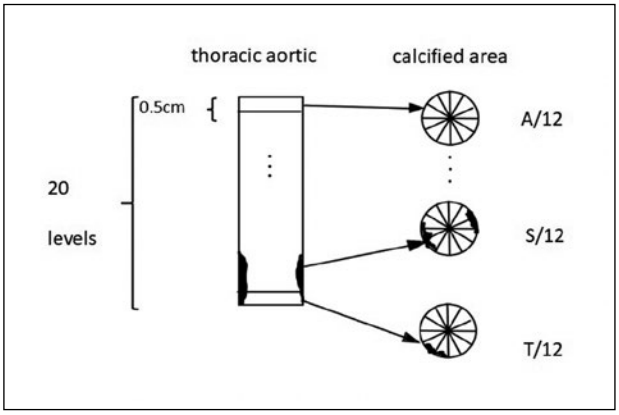

Figure 1: TACI=(A/12+B/12+…T/12)/20×100% A, B,… T represents the sector number of calcified areas on each CT slice.

Follow-up and study endpoint

In this retrospective case-control study, all patients were followed up from MHD treatment through to death, withdrawal from hemodialysis, kidney transplantation, loss at follow-up, or until the end of the study period (30 November 2020). The median follow-up time was 27.5 months.

The endpoints were all-cause mortality (cardiovascular disease, infection, tumor, accident, uremia, any other causes).

Grouping

According to the endpoint events, patients were divided into either a death group or a survival group. The receiver operating characteristic curve (ROC) was used to calculate the best cutoff value of TACI predicting all-cause mortality in MHD patients, and then divided into a TACI≥cutoff group and TACI<cutoff group.

Dialysis program

The frequency of dialysis for all patients was three times/week, 4h/time, the dialysate used bicarbonate dialysate, the dialyzer used Nipro 15G, the polysulfone membrane dialyzer had an area of 1.5m^2. Use low-molecular-weight heparin for anticoagulation during dialysis. The dialysate flow rate is 500ml/min, and the blood flow rate is 200~300ml/min.

Statistical analysis

SPSS 23.0, Graphpad prism 8.0 and MedCalc 19.1 software packages were used for statistical processing of data. Normally distributed measurement data was represented by x±s, and comparison between groups was tested by analysis of variance. Non-normal distribution data was represented by M (1/4,3/4), and a non-parametric test was used for comparison between groups. Enumeration data was expressed as a percentage or frequency, and comparison between groups was performed by x2 test.

The Kaplan-Meier method was used to draw the survival curve, and the Log-rank test was used to compare the differences in survival rates of patients. Cox regression analysis was used to analyze related risk factors. The ROC and Youden index were used to evaluate TACI's prediction of all-cause mortality in MHD patients, and the cutoff value was calculated. A decision tree model was used to determine the important determinant variables that predict all-cause mortality in MHD patients. P<0.05 was taken as the difference required for statistical significance.

Results

Baseline information

312 patients with MHD were enrolled into this study. The survival time, Hb, LDL, P, PTH, and DBP measurements in the death group were significantly lower than those in the survival group.

The Ca, CRP, and TACI were significantly higher in the death group than those in the survival group (P<0.05; Table 1).

Follow-up of outcomes and cause of death

Of the 326 patients with MHD, 14 (4.5%) withdrew from the study by the halfway point, therefore the final count saw 312 patients were enrolled, of which 8 (2.6%) received kidney transplantation and 6 (1.9%) were lost at follow-up. By the end of the follow-up period, 80 patients (25.6%) had died. The causes of death included: 56 deaths from cardiovascular disease (17.9%), 15 strokes (4.8%), and 2 severe infections (0.64%). There were 3 cases of organ failure (0.96%), 3 cases of gastrointestinal bleeding (0.96%), and 1 death related to a car accident (0.32%).

Characteristics	Population	Death group	Survival group	t/Z/X^2	P-Value
	n=312	n=80 (25.6%)	n=232 (74.4%)		
Male,%	174 (55.8%)	51 (63.8%)	123 (53.0%)	2.278	0.096
Age, y	60.10±14.91	67.68±11.90	57.49±14.96	6.159	<0.001
Dialysis age [m, M(1/4, 3/4)]	36.5 (22,56)	32 (15.5,54)	38 (23,56)	-1.660	0.097
Primary kidney disease, %					
Glomerulonephritis	116 (37.2%)	14 (17.5%)	102 (44.0%)	19.593	<0.001
Diabetes	107 (34.3%)	32 (40.0%)	75 (32.3%)		
Other	89 (28.5%)	34 (42.5%)	55 (23.7%)		
BMI, kg/m2	23.85±4.06	23.09±4.53	24.11±3.86	-1.878	0.061
URR (%)	66.32±7.82	65.81±7.45	66.49±7.95	-0.575	0.566
spkt/V	1.33±0.26	1.32±0.23	1.33±0.27	-0.278	0.781
Survival time [m, M(1/4, 3/4)]	27 (18.25,40)	17(6,33.5)	30(20,43)	-5.711	<0.001
Hb, g/L	91.27±18.65	87.49±15.96	92.58±19.35	-2.117	0.035
Alb, g/L	34.69±5.62	33.93±5.01	34.95±5.80	-1.400	0.163
Glucose, mmol/L	5.46±1.51	5.67±1.62	5.39±1.46	1.443	0.15
TG, mmol/L	1.83±0.57	1.79±0.50	1.84±0.60	-0.555	0.579
TC, mmol/L	4.07±1.13	3.96±1.10	4.10±1.15	-0.920	0.358
LDL, mmo/L	2.35±0.66	2.22±0.57	2.40±0.68	-2.105	0.036
HDL, mmol/L	1.05±0.30	0.99±0.28	1.06±0.31	-1.820	0.070
Ca, mmol/L	2.17±0.26	2.23±0.19	2.14±0.28	2.692	0.007
P, mmol/L	1.76±0.57	1.56±0.49	1.83±0.58	-3.786	<0.001
CRP (mg/L)	23.47±11.28	33.18±14.54	19.77±6.76	11.854	<0.001
PTH [pg/ml, M(1/4, 3/4)]	261.15 (151.68,455.58)	215.3 (117.6,325.7)	286 (169.7,497.7)	-2.940	0.003
Systolic blood pressure, mmHg	152.99±24.03	150.54±26.70	153.84±23.04	-1.058	0.291
Diastolic blood pressure, mmHg	83.16±14.89	79.23±12.33	84.53±15.47	-2.775	0.006
TACI (%)	1.25% (0,7.5%)	3.75% (0.63%,20.20%)	0.8333% (0,5.42%)	-4.88	<0.001

Table 1: Comparison of general data and laboratory parameters between the MHD patient death and survival groups.

BMI=body mass index; Hb=hemoglobin; Alb=albumin; TG=triglyceride; TC=total cholesterol; LDL=low-density lipoprotein; HDL=high-density lipoprotein; P=phosphorus; Ca,=corrected calcium; CRP=C-reactive protein; PTH=parathyroid hormone; TACI = thoracic aortic calcification score.

Analysis of risk factors for all-cause death

Multiple factors Cox regression analysis showed that age, dialysis age, Hb, Ca, CRP, and TACI were independent risk factors for all-cause death in MHD patients (P<0.05; Table 2). For every 1mg/L increase

in CRP, the all-cause mortality of MHD patients increased by 7.1%, and for every 1% increase in TACI, the all-cause mortality rate increased by 2.6%.

	Univariate analysis			Multivariate analysis		
	OR	95%CI	P-Value	OR	95%CI	P-Value
Gender	1.81	1.141-2.87	0.012	1.541	0.932-2.548	0.092
Age	1.05	1.031-1.069	<0.001	1.040	1.017-1.064	0.001
BMI	0.948	0.894-1.005	0.073			
Dialysis age	0.981	0.97-0.992	0.001	0.968	0.957-0.979	<0.001
Systolic blood pressure	0.995	0.986-1.005	0.355			
Diastolic blood pressure	0.977	0.962-0.993	0.005	1.000	0.980-1.021	0.997
URR	0.974	0.942-1.006	0.114			
spkt/v	0.68	0.278-1.658	0.396			
Hbg/L	0.984	0.971-0.998	0.023	0.980	0.965-0.996	0.012
Alb	0.97	0.934-1.008	0.126			
Glucose	1.098	0.958-1.258	0.181			
TG	0.911	0.626-1.326	0.626			
TC	0.883	0.717-1.088	0.242			
LDL	0.749	0.523-1.073	0.115			
HDL	0.618	0.287-1.332	0.22			
Ca	3.551	1.39-9.071	0.008	7.163	2.139-23.992	0.001
P	0.464	0.294-0.732	0.001	0.765	0.464-1.261	0.293
CRP	1.064	1.05-1.077	<0.001	1.071	1.053-1.089	<0.001
PTH	0.999	0.998-1	0.048	1.000	0.999-1.001	0.469
TACI	1.032	1.02-1.045	<0.001	1.026	1.011-1.042	0.001

Table 2: Univariate and multivariate Cox regression analysis results of all-cause mortality in maintenance hemodialysis patients.

BMI=body mass index; Hb=hemoglobin; Alb=albumin; TG=triglyceride; TC=total cholesterol; LDL=low-density lipoprotein; HDL=high-density lipoprotein; P=phosphorus; Ca=corrected calcium; CRP=C-reactive protein, PTH=parathyroid hormone; TACI=thoracic aortic calcification score.

The predictive of TACI in all-cause mortality in MHD patients

ROC was used to determine the cut-off value of TACI to predict all-cause mortality in MHD patients. When the cutoff level was 1.67%, the area under the ROC curve was 0.680, the sensitivity was 66.23% and the specificity was 61.23%.

Comparison of overall survival

The best cut-off value for predicting all-cause mortality of MHD patients was TACI=1.67%, therefore patients were divided into two groups, TACI≥1.67% and TACI<1.67%. The 1-, 3-, and 5-year overall survival rates were 93.6%, 87.7%, and 66.7% for the TACI<1.67% group, and 86.5%, 61.5%, 46.5% for the TACI≥1.67% group respectively. The differences between the two groups were significant (P<0.05; Figure 2).

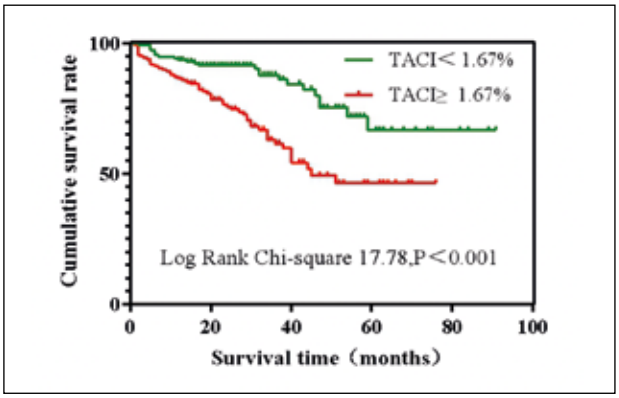

Figure 2: Comparison of overall survival rates of patients grouped by TACI cutoff value (Kaplan-Meier survival curve).

DT identifies patients at high risk of all-cause mortality

In the DT model, the best cutoff value of TACI ≥1.67% was determined as the variable for the initial split in groups. Among patients recorded with TACI <1.67%, 15.4% of the patients had all-cause deaths.

Among patients with TACI≥1.67%, 35.9% died from all causes. CRP was determined as the variable for the second split, with the best critical value set at >20.61 mg/L. When the patient's CRP>20.61mg/L, 55.8% of the patients had all-cause death, while only 11.4% of the patients with CRP≤20.61mg/L had all-cause death. According to the classification of DT, two groups of patients with a high risk of all-cause death were identified (P<0.05; Figure 3).

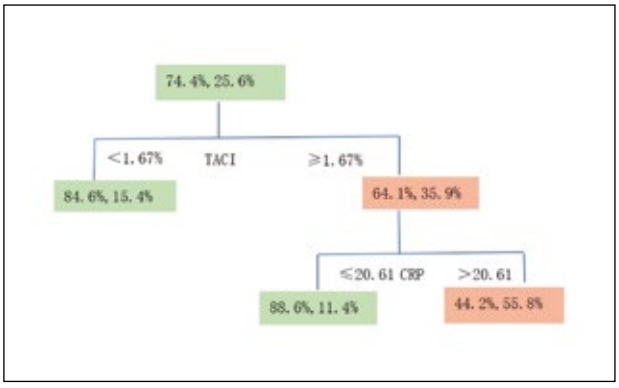

Figure 3: DT model: Represents the incidence of all-cause deaths in MHD patients identified from classification and regression tree analysis. The decimals on the right and left of the box represent the percentage of patients who survived and died, respectively.

Discussion

The main cause of death in patients with end-stage renal disease (ESRD) is cardiovascular disease (CVD), and the thoracic aortic calcification index (TACI) is one of the common signs of subclinical aortic atherosclerosis[9, 10]. Previous studies have shown that TACI is associated with an increased risk of cardiovascular events([2-4]). In this study, the TACI of the all-cause death group was significantly higher than that of the survival group, and multivariate Cox regression analysis showed that TACI is an independent risk factor for all-cause death in maintenance hemodialysis (MHD) patients. The importance of TACI was further confirmed in the DT model. These results were consistent with recent studies showing that the aortic vascular calcification of long-term dialysis patients is considered to be a risk factor for cardiovascular disease morbidity and mortality[11-15]. CRP is a protein that binds to the capsular C polysaccharide of Pneumococcus pneumoniae to form a complex, and is mainly synthesized in the liver. CRP is considered as a powerful biomarker of chronic systemic inflammation[16]. In 2000, Schoming et al. proposed that there is a "micro-inflammatory state" in patients with uremia, and elevated inflammatory response markers in the blood can predict the occurrence of cardiovascular events, and CRP is one of the main markers[17].Kaysen et al. showed that 35%-65% of patients on regular hemodialysis have a chronic persistent micro-inflammatory state[18]. In 2002, Caglar put forward the concept of malnutrition-inflammation-atherosclerosis syndrome. Micro inflammation is of great significance in the development of atherosclerosis, indeed Henze et al. believe that systemic inflammation can promote vascular calcification, and the incidence and mortality of CVD in uremia patients are closely related to the degree of body inflammation[19-21].

Inflammatory cells and inflammatory factors in the vascular wall are activated and released into the blood circulation to produce an oxidation cascade reaction, which initiates bone formation, thereby causing and accelerating vascular calcification[22]. It is reported that CRP is deposited on the arterial wall during the formation of atherosclerosis[23-24]. Furthermore, CRP mediates the uptake of low-density lipoprotein by macrophages[25]. These studies showed that CRP played special roles in the development of atherosclerosis. In our study, CRP was an independent risk factor for all-cause death in MHD patients. The importance was further confirmed within the DT model. Hemoglobin (Hb), albumin, blood lipids, and other factors can be used to assess the nutritional status of patients. In this study, Hb and low-density lipoprotein (LDL) in the death group were significantly lower than those in the survival group. Hb was seen to be an independent risk factor for all-cause death in MHD patients. This is also in line with the concept of malnutrition-inflammation-atherosclerosis syndrome.

In this study, the corrected calcium in the death group was significantly higher than observed in the survival group. Corrected calcium is an independent risk factor for all-cause death in MHD patients. High levels of calcium can lead to the formation and development of a large number of hydroxyapatite crystals. The higher the calcium, the easier it becomes for vascular calcification to develop. In previously published DOPPS study, when the corrected calcium concentration was 1.90-2.38mmol/L, the risk of death was considered the lowest[26].

In order to explore the predictive value of TACI for all-cause mortality in MHD patients, we used ROC curve to determine the cutoff values of TACI. We compared the overall survival rates based on the predicted value of TACI. The 1-, 3-, and 5-year overall survival rates were 93.6%, 87.7%, and 66.7% for TACI<1.67%, and 86.5%, 61.5%, 46.5% for TACI≥1.67%. In patients with TACI≥1.67% plus CRP>20.61mg/L was identified as an important decisive variable. Our data may help reduce the risk of all-cause mortality in MHD patients and guide doctors towards further evaluation and treatment of patients. TACI and CRP are promising targets to prevent and reduce the risk of all-cause mortality in MHD patients. We usually suggest that patients should use less calcium, reduce their levels of blood calcium, control blood phosphorus and parathyroid hormone to reach the standard, so as to delay the progress of vascular calcification. At the same time, we need to pay attention to the patients' micro nutritional status and quality of life.

Since this study was a retrospective case-control study with a retrospective bias, further prospective studies are needed to verify the key findings. Secondly, this study only measured the baseline levels of TACI and CRP in MHD patients, and did not dynamically observe TACI and serum CRP. There are limitations which cannot accurately reflect the trend of TACI and CRP over time. In short, in addition to confirming the importance of age, dialysis age, Hb, and corrected calcium,

our study also showed that TACI and CRP are independent predictors of all-cause mortality in MHD patients. It has been determined that in the population with TACI≥1.67% and CRP>20.61mg/L, patients with high mortality risk of MHD can be identified. Therefore, in preventing and reducing the risk of all-cause mortality in MHD patients, TACI and CRP may be important clinical goals. Further study is needed to confirm whether optimized medical therapies modify TACI and CRP, enabling improvement of outcomes in ESRD patients treated with MHD.

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