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Integration of clinical and imaging data to predict death in hemodialysis patients

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Abstract

In a prior publication, we demonstrated that a model integrating clinical and simple imaging data predicted the presence and severity of coronary artery calcification in prevalent hemodialysis patients. Herein we report the ability of the same model to predict all-cause death. We assessed all-cause mortality in 141 consecutive maintenance hemodialysis patients from two dialysis centers followed for a median of 79 months from enrollment. Patients were risk stratified according to a simple cardiovascular calcification index (CCI) that included patient's age, dialysis vintage, calcification of the cardiac valves, and abdominal aorta. The mean patients' age was 55 ± 14 years. Abdominal aorta calcification was present in 57% of the patients, and 44% and 38% had aortic and mitral valve calcification, respectively. During follow-up, 75 deaths (93 deaths per 1000 person-years) were recorded. The CCI was linearly associated with risk of death, such that the unadjusted hazard risk (HR) increased by 12% for each point increase in CCI ($P < 0.001$). Further adjustments for age, sex, study center, diabetes mellitus, history of cardiovascular disease, hypertension, congestive heart failure, left ventricular hypertrophy, systolic, and diastolic blood pressure did not substantially change the strength of this association (HR 1.10; 95%CI: 1.00–1.21; $P = 0.03$). The CCI is a simple clinical model that can be used to risk stratify maintenance hemodialysis patients.

Key words: Cardiovascular calcification index, hemodialysis, outcome, risk stratification, imaging

INTRODUCTION

Because of the poor cardiovascular prognosis of patients undergoing maintenance hemodialysis, several methods have been proposed for risk stratification. In a prior publication, we proposed the use of a score that combined clinical data and information derived from simple imaging tests, such as an echocardiogram to demonstrate the presence of valvular calcification and a lateral abdominal X-ray to visualize calcification of the abdominal aorta.[1] Subsequently, the Kidney Disease: Improving Global Outcomes (KDIGO) working group suggested that these two imaging approaches are reasonable for the assessment of cardiovascular calcification because of the ease of performance, low cost, and low radiation exposure (for the planar abdominal X-ray).[2] After a follow-up of approximately 6 years from patient enrollment, we report the results of an analysis of all-cause death associated with our scoring system in the 141 hemodialysis patients that constituted the original cohort.

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METHODS

Patient selection

Adult patients receiving maintenance hemodialysis were recruited from two dialysis centers (Denver, Colorado and

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New Orleans, Louisiana). Patients were excluded if they were pregnant or planned a pregnancy within 6 months of anticipated enrollment, were receiving hemodialysis for less than 6 months, and were unable or unwilling to sign an informed consent. A total of 154 consecutive patients were enrolled. Thirteen subjects were excluded from the current analyses because they did not undergo an echocardiogram (n = 9) or a lateral lumbar X-ray (n = 10), leaving a cohort of 141 patients.

Data collection

Self-reported variables included age, sex, race, and smoking habit. Medical charts were reviewed to assess the presence of diabetes mellitus, history of atherosclerotic cardiovascular disease (ASCVD), and dialysis vintage. History of ASCVD included myocardial infarction, angina, and peripheral and cerebrovascular disease.

Examination procedures during the initial and follow-up study visits have been described in detail previously.[1] In brief, body mass index was calculated as the ratio of the weight in kilograms and height in square meters. Blood pressure was measured three times, after a 15- to 20-minute rest, using a manual aneroid sphygmomanometer with a 30-second rest between each measurement. Measurements were performed with participants in the supine position using the arm that did not contain an arteriovenous fistula or shunt. A technique similar to that described by Kauppila and colleagues[3] was employed to obtain images of the lower abdominal aorta. In brief, a lateral plain radiograph of the abdomen was obtained that included the last two thoracic vertebrae and the first two sacral vertebrae. A previously published semiquantitative scoring system was utilized to ascertain the degree of calcification present in the abdominal aorta.[3] Only the segments of abdominal aorta in front of the first to the fourth lumbar vertebra were considered. Points were assigned from 0 to 3 (0: none; 1: small; 2 moderate; 3: large) according to the length of each calcified plaque identified along the anterior and posterior profile of the aorta in front of each of the lumbar vertebrae. Using this numerical grading, the score could vary from 0 to 24 points with higher scores indicating a greater degree of calcification of the abdominal aorta. Two-dimensional echocardiography studies were performed utilizing a Sequoia 512 (Siemens, Erlangen, Germany) for patients in New Orleans and a Vivid 7 (General Electric, Milwaukee, WI, USA) echocardiographic equipment for patients in Denver. The presence or absence of aortic and mitral valve calcification, separately, was determined visually and only qualitatively. Measurements of end-diastolic posterior wall and interventricular septum wall thickness, as well as end systolic and end-diastolic left ventricular diameters were obtained on M-mode images with two-dimensional imaging confirmation in the long axis parasternal view of the left ventricle. Left ventricular hypertrophy (LVH) was defined as a left ventricular mass index ≥ 125 g/m^2, according to data previously published from the Framingham Heart Study.[4]

Cardiovascular calcification index (CCI)

The CCI was developed to provide a sensitive and quantitative prediction of coronary artery calcification as assessed with electron beam computed tomography (CT). As previously described several covariates (age, dialysis vintage, aortic and valve calcification, and abdominal aorta X-ray measures) were used to ascertain each participant's CCI score.[1]

Primary outcome

The primary outcome was all-cause mortality. Mortality was assessed searching the Social Security Death Index (http://ssdi.rootsweb.com/ssdi.rootsweb.com) master file using patients' names and social security numbers. Searches were conducted for mortality occurring through June 21, 2011.

Statistical analysis

To gauge the associations between demographic and clinical characteristics and the CCI score, participants were grouped into four approximately equally sized categories (CCI points: 0–2; 3–4; 5–7; 8–11). Characteristics of the study population were calculated overall and by CCI categories. For continuous variables, means and standard deviations were calculated and the statistical significance of linear trends across CCI categories was assessed via analysis of variance. For categorical variables, proportions were calculated and the statistical significance of linear trends was tested with chi-square tests. Follow-up time was calculated as the number of days between each participant's study examination and their date of death or June 21, 2011. Cumulative mortality curves were calculated by CCI category using the Kaplan–Meier method. Cox survival analyses were used to calculate the hazard associated with each CCI unit increase. Hazard ratios were calculated initially without adjustments. Subsequent models included adjustment for demographic variables (age, sex and study center) and for case mix (diabetes mellitus, ASCVD, hypertension, congestive heart failure, LVH, systolic, and diastolic blood pressure). A final analy-

sis assessed the ability of the CCI to discriminate individuals who subsequently died vs. those who did not die using c-statistics. C-statistics were calculated for progressively adjusted models. All analyses were completed using R version 2.9.2 (2009-08-24; The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The mean patients' age was 55 ± 14 years (Table 1). There were almost equal proportions of men and women and Caucasians and African Americans. The median dialysis vintage was 2.6 (interquartile range: 0.1–18.9) years and hypertension, diabetes mellitus, ASCVD, and congestive heart failure were prevalent (95%, 49%, 39%, and 21%, respectively). Cardiovascular calcification was prevalent and 57% had abdominal aorta calcification, while 44% and 38% had aortic and mitral valve calcification, respectively. The median abdominal aorta X-ray score was 1 (range: 0–24). When the study population was stratified according to CCI quartiles, higher CCI levels were significantly associated with older age, history of ASCVD, diastolic blood pressure as well as presence of abdominal aorta and valvular calcification (all P value < 0.05; Table 1). Gender, race, diabetes mellitus, dialysis vintage, and systolic blood pressure were not significantly associated with the CCI (Table 1).

During a median follow-up of 79 months, 75 deaths (93 deaths per 1000 person-years) were recorded. As shown in Figure 1, a linear association between the CCI and the risk of death was noted. For each CCI unit increase, there was a significant 12% increase in risk of death (Table 2). The association remained significant after adjustment for age, sex, study site, ASCVD, diabetes mellitus, congestive heart failure, hypertension, systolic and diastolic blood pressure, LVH (P = 0.035; Table 2 and Figure 2).

The CCI score improved the prediction of outcome compared to other factors. As shown in Table 3, when the CCI score was added to age, clinical data, and LVH, this allowed for the prediction of approximately 80% of fatal events during follow-up (c-statistic for discriminating mortality: 0.79 [95% confidence interval (CI): 0.72–0.87]).

DISCUSSION

The very high morbidity and mortality of patients on maintenance dialysis has stimulated the search for and the proliferation of new markers of risk.[5,6] Among the numerous markers identified, vascular calcification (VC) has emerged as an accurate predictor of risk.[7–11] Nonetheless, the debate on how to perform assessment of VC and how to integrate this piece of information in clinical practice is still open.[2]

The gold standard for VC quantification is CT.[12,13] Nonetheless, the routine use of cardiac CT is not recommendable because of its high cost and radiation exposure

Table 1 Clinical characteristics of the study population by cardiovascular calcium index score (n = 141)

	Overall population	Cardiovascular calcium index score				
	n = 141	0–2 (n = 42)	3–4 (n = 29)	5–7 (n = 38)	8–11 (n = 32)	P trend
Age, years	55 (14)	46 (12)	54 (14)	56 (14)	66 (8)	<0.001
Dialysis vintage	2.6 (0.1–18.9)	2.2 (0.1–18.4)	2.5 (0.2–7.0)	3.5 (0.1–18.3)	2.9 (0.6–18.9)	0.15
Women, %	49	51	48	61	38	0.57
White, %	40	33	41	50	50	0.19
Diabetes mellitus, %	49	43	55	47	44	0.36
Congestive heart failure, %	21	14	17	32	25	0.11
Hypertension, %	95	95	93	97	94	0.99
ASCVD, %	39	21	45	50	44	0.02
SBP, mmHg	146 (25)	143 (22)	148 (27)	146 (27)	147 (25)	0.53
DBP, mmHg	78 (14)	81 (15)	81 (12)	77 (15)	72 (12)	0.008
Median abdominal aorta X-ray score	1 (0.24)	0 (0–4)	1 (0–7)	2.5 (0–14)	11 (3–24)	<0.001
Valvular calcification						
Aortic valve, %	44	0	24	45	100	<0.001
Mitral valve, %	38	12	34	63	69	<0.001

Numbers in table are mean (standard deviation), percent, or median (minimum and maximum value). ASCVD = atherosclerotic coronary vascular disease; DBP = diastolic blood pressure; SBP = systolic blood pressure.

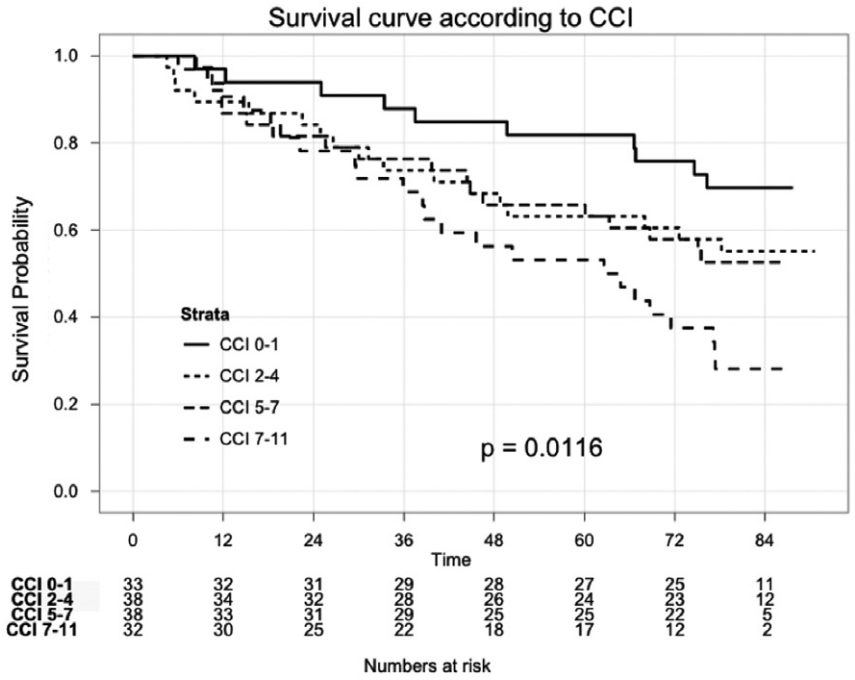

Figure 1 Kaplan–Meier survival analyses comparing mortality according to quartile of cardiovascular calcification index (CCI). CCI scores 0–2, 3–4, 5–7, 8–11 define low, mid-low, mid-high, and high scores, respectively.

for the patient. As a consequence, the recent KDIGO-Clinical Practice Guidelines for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD)[2] after acknowledging the high risk inherent with VC, suggested that easily performed in-office imaging tests, such as planar X-ray of the abdomen to detect aortic calcification or echocardiography to detect valvular calcification, may be desirable options.[2]

In a prior publication, we showed a close association between VC of the abdominal aorta and cardiac valves with coronary artery calcification (CAC).[14] The likelihood of detecting a clinically meaningful burden of CAC was significantly increased among patients with evidence of cardiac valve calcification (in the presence of calcification of either cardiac valve the likelihood ratio for a CAC greater than 100 was 1.79; 95% CI: 1.09-2.96) or participants with severe calcification of the abdominal aorta (likelihood ratio for a CAC score greater than 100: 7.50; 95% CI: 2.89, 19.5).[14]

We subsequently developed a CCI that integrated the information derived from demographic and clinical data and simple measures of VC to provide an alternative for predicting CAC in the absence of cardiac CT.[1] For

Table 2 Hazard ratios for mortality associated with each one point increase in the cardiovascular calcification index (CCI) score

Model	Beta	HR (95% confidence interval)	P value
Cardiovascular calcification index (CCI) score (per unit increase)			
Unadjusted	0.121	1.12 (1.04–1.21)	0.001
Adjusted for age, sex, gender, center, systolic blood and diastolic blood pressure, history of atherosclerotic cardiovascular disease, diabetes mellitus, hypertension and congestive heart failure, left ventricular hypertrophy	0.100	1.10 (1.00–1.21)	0.035

HR = hazard ratio.

Table 3 C-index of different models

Model	C stat	95% confidence interval
Demographic variables (age, sex, site)	0.72	0.63–0.80
+ Case mix (ASCVD, CHF, hypertension, systolic and diastolic blood pressure)	0.77	0.69–0.85
+ LVH	0.77	0.70–0.85
+ CCI	0.79	0.72–0.87

ASCVD = atherosclerotic coronary vascular disease; CCI = cardiovascular calcification index; CHF = congestive heart failure; LVH = left ventricular hypertrophy.

example, we demonstrated that a CCI score ≥ 9, nearly quadruples the probability of finding a severe CAC burden (likelihood ratio of detecting a CAC > 1000 given a CCI ≥ 9: 3.83; 95% CI: 1.85–7.93).[1]

The current report adds to the existing body of evidence by showing that the CCI has a strong association with the risk of all-cause mortality. Indeed, the current results document an almost linear increase in the mortality risk associated with increasing CCI. Every unit increase in the CCI score corresponded to about a 10% higher risk of death during follow-up. Notably, adjustment for potential confounders did not attenuate the statistical significance of the association. Taken together, these data support the notion that imaging findings represent the integrated effect of several risk factors affecting vascular health over a long period of time.

A tool accurate and easy to apply, such as the CCI, has several potential applications that might appeal to the clinician. In fact, over the past decade, the population receiving dialysis has grown older and sicker.[15] Thus, it has become difficult to assess an individual's risk relying solely on clinical data. By integrating an anatomical evaluation of the arterial tree with clinical data, the CCI offers an opportunity to refine risk assessment, thus identifying the patients in need of more aggressive preventive measures including treatments that prevent further expansion of soft tissue calcification.

Simple imaging methods to detect VC and to test the independent contribution of vascular and valvular calcification to outcome prediction have been used in a few other studies.[8,16–19] Similar to ours, those studies suggested that the presence of VC portends a poor prognosis among prevalent dialysis patients independent of age and comorbidities. However, the CCI is the first attempt to condense clinical and imaging information to provide the clinical nephrologist with a practical tool to implement in his clinical practice.

This study suffered from a few limitations worth mentioning. The study data were collected from prevalent hemodialysis patients followed at two high-volume centers and the results should be confirmed in other

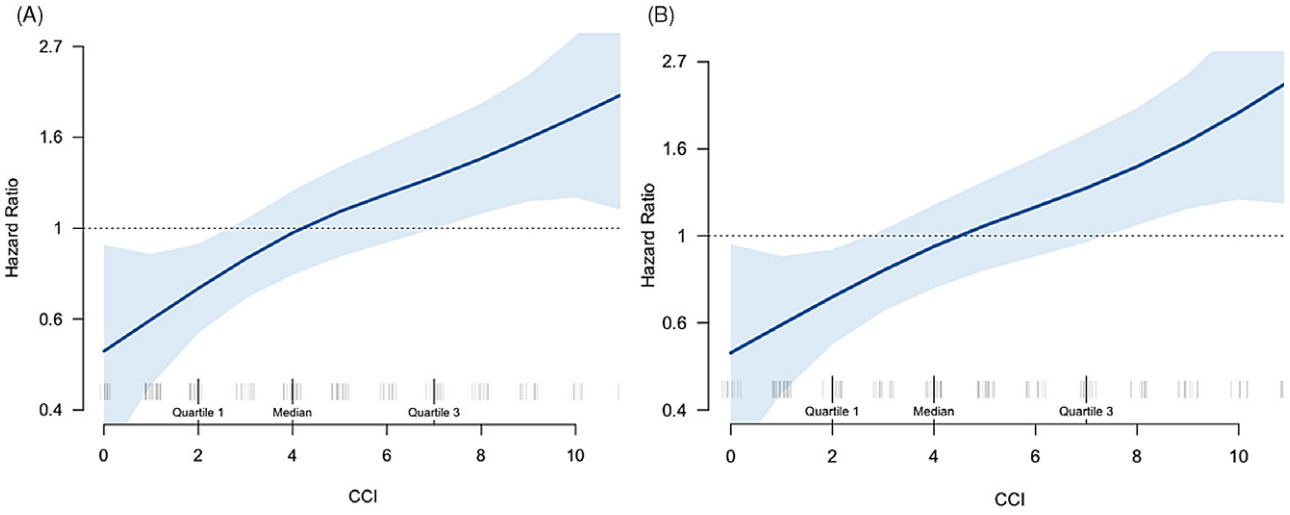

Figure 2 Overall likelihood of dying from all cause during follow-up according to severity of cardiovascular calcification index (CCI). (A) The hazard ratio (HR) is unadjusted. (B) The HR is adjusted for age, sex, study center, diabetes mellitus, history of cardiovascular disease, hypertension, congestive heart failure, left ventricular hypertrophy, systolic, and diastolic blood pressure. The solid line represents the HR according to increasing CCI severity; the light blue area represents the 95% confidence intervals (CI).

cohorts. Similarly, future endeavors should be undertaken to test whether the CCI is associated with mortality in incident hemodialysis as well as peritoneal dialysis patients. Finally, we did not have information on cause-specific outcomes. As such, we were unable to assess the association of the CCI with CV mortality and morbidity.

In conclusion, the current study shows that the integration of clinical data with information derived by a lateral–lateral planar X-ray of the abdomen and an echocardiogram can predict the risk of death of prevalent hemodialysis patients. Simple tools such as the CCI could enhance the ability of clinical nephrologists to perform more accurate risk estimates on their patients. Additionally, they may enhance the awareness of practicing physicians of the frequency and extent of cardiovascular calcification (CVC). The outcome may be a more focused intervention on the modifiable factors believed to impact CVC progression and—hopefully—the morbidity and mortality of this group of extremely high-risk patients.

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