PROJECT TITLE: Predicting Risk of Mortality in Dialysis Patients: Prognostic Value of a Simple Chest X-ray

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PROJECT SUMMARY:

Patients with kidney failure on dialysis are at high risk for cardiovascular disease and premature death in aggregate. Individual patient risk, however, varies widely. Improved ascertainment of individual risk could inform decisions about patient management and counselling. Since the majority of mortality of patients is driven by cardiovascular (CV) causes, CV risk factors such as heart size and aortic calcification are plausible prognostic markers. The objective of this study was to assess the value of simple, chest X-ray derived measures of cardiac size (Cardiothoracic Ratio) and vascular calcification (Aortic Arch Calcification), in predicting death in a prevalent cohort of hemodialysis (HD) patients.

Employing the Manitoba Renal Database, all patients starting dialysis in Manitoba from 2000-2010 and who received a chest X-ray were identified. Cardiothoracic ratio and aortic calcification values were determined by two independent reviewers for 824 prevalent patients.

The goals of the student were to 1) learn how to use a medical database 2) develop clinical chest X-ray reading skills and 3) become familiar with and use appropriate statistical tools to determine whether cardiothoracic ratio, aortic arch calcification, or both, were predictors of mortality, and whether they improved upon simpler prognostic models.

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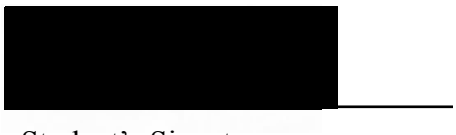

Student's Signature

Supervisor's Signature

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Introduction

Kidney failure is a major public health problem with increasing incidence and prevalence worldwide (1). Patients with kidney failure on dialysis experience poor overall survival, with an age and sex adjusted mortality several fold higher than patients not on dialysis (2). Although aggregate survival on dialysis is poor, variability in individual patient prognosis is substantial (3). This poses significant challenges for health care providers and patients alike. Survival estimates are a crucial part of informed discussions regarding starting or withdrawing from dialysis, and often inform decisions regarding the intensity of screening, monitoring and treatment of comorbid diseases for patients undergoing dialysis (4-6). Uncertainty about these outcomes can render such decisions more difficult for patients, families, and physicians.

In order to estimate survival, knowledge of risk factors is essential. Mortality in dialysis is driven primarily by cardiovascular (CV) disease (7,8). Consequently, major factors associated with cardiovascular disease on dialysis, such as echocardiographic left ventricular hypertrophy and CT evidence of coronary or aortic calcification are independent predictors of mortality and cardiovascular events in dialysis patients (9,10). However, the high cost and unknown benefit of intensive risk reduction strategies based on these procedures precludes routine implementation for the purposes of risk stratification in kidney failure (11). Preliminary data suggest that measures obtained from a routine posterior-anterior (PA) chest X-ray (CXR) may provide reasonable estimates of vascular calcification and left ventricular size, and could enhance risk prediction without the cost of a CT or echocardiogram (12,13). Data in the general population has shown aortic arch calcification (AAC) (14,15) and cardiothoracic ratio (CTR) (16-18), both obtained from a routine chest X-ray, to be predictors of CV outcome and mortality, respectively. The prognostic value of these simple measurements has not been studied in kidney failure, but if validated, chest X-ray based measurements could be easily and cheaply implemented with minimal inconvenience to patients and improve risk stratification in the dialysis unit as part of routine clinical care. In many hemodialysis units, chest X-rays are routine for providing information for central line placements, and surveillance for latent tuberculosis.

The objective of this study was to determine whether chest X-ray derived measurements of cardiac size (CTR) and vascular calcification (AAC score), could accurately predict mortality and improve simpler prognostic models in patients with kidney failure.

Materials and Methods

Study Population: The study was conducted in Winnipeg, Canada and was approved by the appropriate research ethics board at the University of Manitoba. We performed a retrospective cohort study utilizing a comprehensive prospective database of all patients initiating dialysis in Manitoba Canada between January 1, 2000 and August 1, 2010 (n=2368). This database is maintained by the Manitoba Renal Program, which provides dialysis and chronic kidney disease services for the entire province of Manitoba and areas of Northwestern Ontario (Catchment area approximately 1.5 million). Details of this database have been described in previous studies (19). Briefly, the database captures patient demographics, cause of ESRD, comorbid conditions, type of dialysis, initial dialysis access, initial blood work, modality transitions within the first 90 days,

small molecule clearance, and all outcomes until death, transplantation, or transfer out of province. All new starts and outcomes are adjudicated weekly at a multidisciplinary team rounds and recorded in the database by dedicated MRP personnel. A subset of this data is forwarded to the Canadian Organ Replacement Register (CORR) maintained by the Canadian Institute for Health Information. For the purposes of the present analysis, we included only adult (>18 years) chronic dialysis (on dialysis >90 days) patients. We examined all-cause mortality as the primary outcome.

X-ray measurements: Eligible patients identified in the MRP database were linked by PHIN (Personal Health Information Number) and date of birth to a province-wide registry of radiographic procedures (AGFA IMPAX 6) to identify chest X-rays. The earliest available (i.e. closest to date of dialysis initiation), technically adequate chest X-ray was chosen for review. We defined technical adequacy as a postero-anterior chest X-ray exhibiting defined heart borders and a defined aortic knob. Thus, chest X-rays with severe effusions, infiltrates, or anatomic or technique irregularities that precluded identification of cardiothoracic ratio or aortic arch calcification were excluded. Two adjudicators independently assessed technical adequacy, with disagreements resolved by consensus. Both film and digital X-rays were included.

The grade of aortic arch calcification was assessed using a previously validated scoring system: grade 0 (no visible calcification), grade 1 (small spots of calcification or single thin calcification of the aortic knob), grade 2 (one or more areas of thick calcification), and grade 3 (circular calcification of the aortic knob) (20). The cardiothoracic ratio was calculated as the ratio of maximum transverse cardiac diameter in millimeters to maximum thoracic diameter in millimeters. Both AAC grading and CTR measurement can be viewed in Figure 1. All measurements of AAC and CTR were assessed independently by two adjudicators, with disagreements resolved by a consensus measurement.

Statistical Methods: Summary statistics were presented as mean (SD) or median (IQR) as appropriate; categorical values were described as proportions. Univariate comparisons in patient characteristics were performed with ANOVA or Chi square test as appropriate.

Univariate Cox proportional hazards regression was used to estimate the unadjusted impact of AAC grade and CTR on all-cause mortality. Multivariable Cox Proportional Hazards Regression models were constructed to 1) to identify a parsimonious base prediction model (best base model, BBM) using clinical variables alone 2) to assess whether AAC and CTR were independent of these base model variables in prediction of death and 3) to calculate the improvement in model discrimination and reclassification after addition of AAC or CTR or both to the base model. The base prediction model for death was built from a pool of candidate clinical variables using forward selection; for the purposes of this analysis, variables in the base models were retained if they were associated with a $p<0.1$. Three enriched models were created: base plus CTR, base plus AAC, and base plus both AAC and CTR. We assessed model discrimination using Harrell's concordance statistic (C-statistic), and the integrated discrimination improvement index (IDI). The Harrell's C statistic corresponds to the area under the receiver-operating curve for the proportional hazards model, and is the standard measure of discrimination. The IDI measures the change in the discrimination slopes between two alternative models, and is considered a more sensitive measure of discrimination than the C-

statistic. We also examined model reclassification using the net reclassification index, NRI (21). NRI measures the ability of a new model to correctly reclassify patients without the outcome of interest (i.e. death) into lower risk categories and patients with the outcome of interest into higher risk categories. For the purpose of the present analysis, we used the following risk classification scheme: high risk, >10% risk of death; moderate risk, 5-10% risk of death; and low risk, <5% risk of death. To be judged clinically useful, the models incorporating AAC and CTR had to exhibit statistically significant improvements in two of the following three measures of predictive model performance: C-statistic, IDI>10%, and NRI>10% (22,23).

Results

Of the initial 2368 potentially eligible patients, 824 had technically adequate PA chest X-rays for the study and were included in the analysis. The specific reasons for exclusion are summarized in Figure 2.

Study Population: The baseline characteristics of the study population have been summarized in Table 1. Data on age, sex, diabetic status, race, cause of renal disease, hemoglobin, serum creatinine, serum calcium, serum phosphate, serum albumin, other co-morbidities, and our primary outcome (all-cause mortality) were obtained from the Manitoba Renal Program database. The median age of the cohort was 60 [47, 71] years at the time of X-ray, with a median dialysis vintage of 1.3 years. Fifty-four percent of the cohort was male, and 35% were of aboriginal descent.

Of the 824 patients, 152 patients died at a median dialysis time of 2.5 years from initiation. Compared with survivors, patients who died were significantly older (68 years vs. 58 years, $p<0.001$) at the chest X-ray date, had a higher prevalence of CHF (22% vs. 14%, $p=0.01$), and had been on dialysis longer at the time of X-ray assessment. Interestingly, median serum creatinine at the start of dialysis (566 vs. 709, $p<0.001$) was lower in patients who died (Table 2).

Median CTR for the cohort was 0.53 [0.48, 0.58], and 67% had a CTR >0.5 (Table 3). The median CTR in patients who died was higher than among survivors (0.55 vs. 0.52, $p<0.001$) and 79% had a CTR>0.5. Overall, 46% had AAC>0, and among patients who died that proportion rose to 64% vs. 41% in patients who lived.

Comparison with missing data: To assess the possibility of a selection bias, we performed a sensitivity analysis comparing the characteristics of patients with and without an available X-ray (Table 1). On average, patients without X-rays were older by a decade, were more likely to be dialyzing outside of Winnipeg, and be of Caucasian descent. The study population had a higher rate of diabetes than patients without X-rays, but a lower rate of ischemic heart disease. Patients with X-rays also had, on average, higher starting levels of creatinine and phosphate, and lower levels of hemoglobin and serum albumin.

Risk prediction for all cause mortality: Cardiothoracic ratio (per 0.1 unit change) and aortic arch calcification were both strong univariate predictors of death on univariate proportional

hazards analysis (Table 4). The association between AAC and mortality was significantly decreased after adjustment for age, in multivariate Cox models (Table 5).

The predictive ability of CTR and AAC in addition to our base predictive model for mortality is presented in Table 5. As above, the CTR was independently associated with mortality when added to a best base model comprised of the variables age at chest X-ray, duration of hemodialysis, diabetes, heart failure, baseline serum creatinine and serum albumin (strongest predictors of survival in a base Cox model). However, CTR did not significantly increase the area under the curve of the base model (0.71 [0.66, 0.76] vs. 0.72 [0.67, 0.76]). Furthermore, it did not improve the IDI (IDI =0), nor did it improve net reclassification performance (NRI=0). For complete multivariate analysis, see Table 5.

Discussion

In our longitudinal study of 824 prevalent patients on hemodialysis, neither cardiothoracic ratio nor aortic arch calcification assessed on routine chest X-ray improved prediction of mortality. While CTR was independently associated with mortality in multivariable survival analysis, it did not consistently improve prediction of mortality risk. In contrast, AAC was not associated with mortality after adjustment for potential confounders, and appeared to be correlated with patient age at time of X-ray (Table 6).

Previous studies have shown that extent of vascular calcification reported from a chest X-ray is strongly associated with mortality, cardiac events, as well as coronary and other vascular calcification in non-ESRD patients (12,15). Using the grading system described previously, AAC detectable on CXR has been shown to be a strong independent predictor of new CV events beyond traditional risk factors (14). In a previous study of 401 incident patients on dialysis in Japan, only a borderline significant association between AAC and CV mortality (but not all cause mortality) was been identified (24). While this study found similar results, we examined a prevalent cohort with a larger sample size. Our study was unique in that, rather than examining AAC simply as a risk factor, we also sought to determine if it was a prognostic marker that might aid in risk stratification. As stated above, our results showed a correlation between AAC and all-cause mortality, but only a borderline association on multivariate analysis. This was due in large part to the confounding of age. Furthermore, AAC did not improve risk stratification.

Evidence supports CTR as a predictor of mortality in the general population. A high CTR is an indicator of an enlarged heart and is a predictor of poor outcome in heart failure patients (16-18). In the ESRD population, the evidence is less clear on whether CTR is an independent predictor of poor outcomes. In a study of 468 hemodialysis patients in Taiwan, CTR predicts both all-cause and CV 2-year mortality (25). Similarly, our results showed a correlation between CTR and all cause mortality on multivariate analysis, but in contrast, had a higher n and included people both with and without diabetes. In addition, our study examined cardiothoracic ratio as a prognostic marker, but found it did not improve risk stratification (IDI and NRI=0) in our prevalent cohort.

Our results imply that use of CTR and AAC obtained from PA chest X-rays do not add value beyond traditional means to improve prognostication of chronic hemodialysis patients. A caveat to this conclusion is that the population subset without X-rays was older, and had higher rates of ischemic heart disease. By analyzing a subset that is younger and has a lower rate of IHD, it is possible the association between CTR/AAC and mortality was underestimated, although we feel this is unlikely.

Strengths of the study include it's cohort design, large sample size, and analytical strategy. The prospect of a simple, inexpensive, routine imaging modality held promise as a cheap method of risk assessment. Our study population was unique in its size, its large aboriginal representation, and that all patients received dialysis through a unified program (Manitoba Renal Program). Another strength was the independent review process for CTR and AAC. Taking the mean of two independent CTR measurements per X-ray ensured precision, while settling by consensus all AAC discrepancies achieved the same result.

A limitation to the study was exclusion of a significant number of patients lacking available X-rays. A partial explanation for this high rate of exclusion may lie in the location of dialysis. The subset of the population without chest X-rays was more likely to have been dialyzed in a rural, satellite setting, where acquisition of a chest X-ray is improbable in the context of this study. Finally, it should be noted that this study used a prevalent cohort and therefore a survivor bias may be present.

In summary, our data do not support the clinical utility of simple plain X-ray measures of cardiac size and vascular calcification. While these methods may have reduced costs, they do not add additional value to risk prediction tools using demographic and comorbidity variables for mortality in patients on dialysis. More advanced imaging techniques such as cardiac MRI and coronary CT may be needed to improve prognostication in this population. However, we must recognize that a modifiable risk does not necessarily translate into a reduction in mortality. In one study, a previously proven reduced progression of coronary artery calcification by treatment with sevelamer over calcium-based phosphate binders, did not translate into better outcomes for patients (11,26). To summarize, while these tools may improve prognosis calibration, further study will be required to examine whether higher intensity risk reduction strategies can modify the course of patients at increased risk.

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Figures

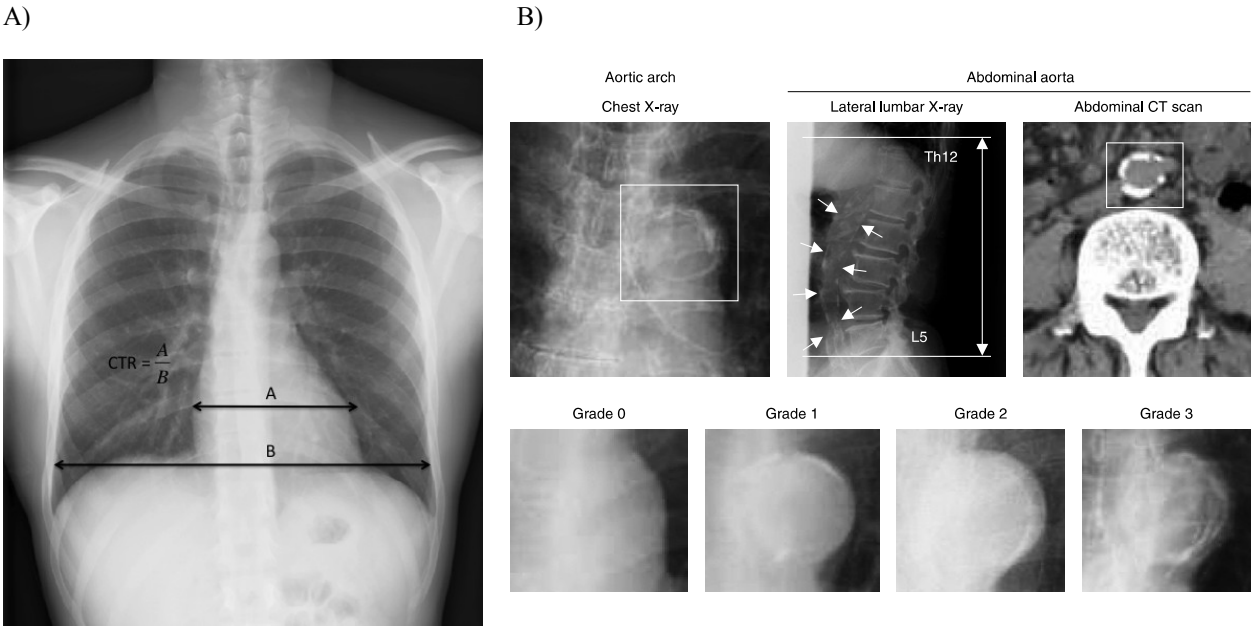

Figure 1: Clinical assessment of cardiothoracic ratio and aortic arch calcification
(A) Measurement of cardiothoracic ratio (CTR)
(B) Assessment of aortic calcification using chest x-ray (lateral lumbar and abdominal CT for comparison), with examples of grade 0-3 shown. Permission pending for reproduction of this image (12).

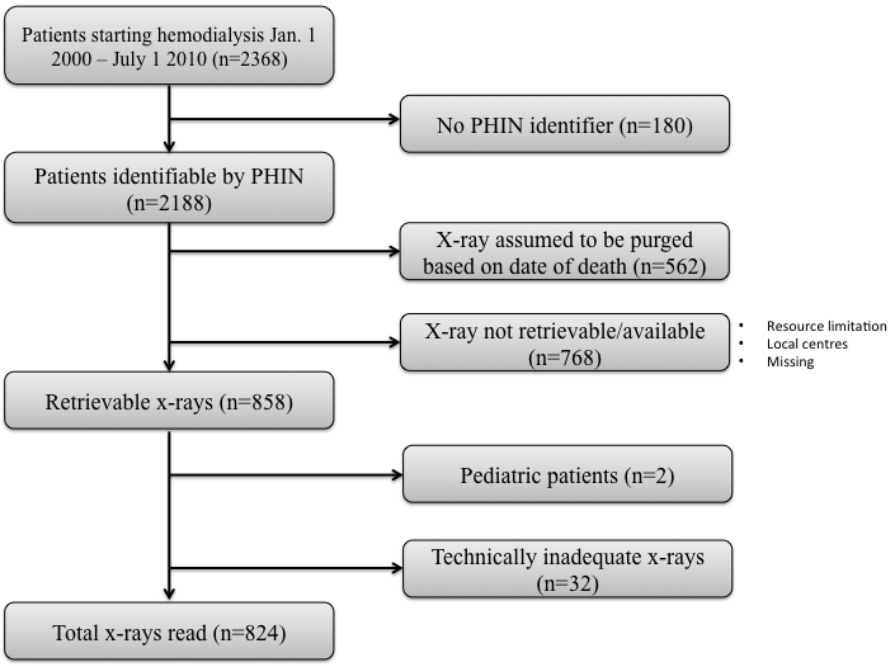

Figure 2: Process of patient exclusion from database

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Table 1: Characteristics of patients with and without an available chest X-Ray

Characteristics	X-ray available	X-ray not available	p
Proportion alive at end of follow-up	672/824	444/800	<0.001
Age at dialysis start	57.3 [45.0, 68.1]	63.8 [53.0, 74.8]	<0.001
Age at chest x-ray	59.7 [47.3, 70.7]	-	-
Sex (M)	54%	56%	0.64
Race			
Caucasian	47%	59%	<0.001
Aboriginal	35%	28%	0.003
Other	18%	13%	0.01
BMI	32.5 [28.5, 38.8]	33.0 [28.2, 38.3]	0.99
Diabetes	25%	20%	0.01
CHF	15%	18%	0.14
Hypertension	67%	70%	0.17
IHD	15%	20%	0.003
Hemoglobin	93 [81, 106]	97 [84, 110]	0.001
Creatinine	678 [529, 876]	632 [495, 815]	0.001
Urea	31 [25, 40]	32 [24, 39]	0.93
CO_2	20 [16, 23]	20 [17, 24]	0.03
Calcium	2.1[1.8, 2.3]	2.1 [1.8, 2.3]	0.97
PO_4	2.1[1.7, 2.6]	2.0 [1.6, 2.5]	0.01
Albumin	29 [24, 34]	30 [25, 35]	0.01
HD days at chest x-ray	463 [9, 1520]	N/A	-
Follow-up days	1173 [585, 2266]	1112 [453, 1926]	0.001
Older Vintage (start year<2005)	29%	30%	0.91
Urban dialysis	83%	68%	<0.001

Table 2: Characteristics of x-rayed patients, alive and dead

Characteristics	Alive	Dead	p
n	672/824	152/824	-
Age at chest x-ray	58.0 [46.1, 68.7]	67.5 [58.7, 78.4]	<0.001
Sex (M)	55%	49%	0.05
Race			
Caucasian	46%	51%	0.35
Aboriginal	34%	38%	0.34
Other	20%	11%	0.02
BMI	32.6 [28.5, 38.8]	31.4 [28.2, 39.4]	0.32
Diabetes	27%	18%	0.03
CHF	14%	22%	0.01
Hypertension	66%	71%	0.24
IHD	14%	20%	0.05
Hemoglobin	93 [80, 106]	95 [85, 105]	0.26
Creatinine	709 [555, 892]	566 [477, 723]	<0.001
Urea	31 [25, 39]	31 [23, 41]	0.91
CO_2	20 [16, 23]	20 [16, 23]	0.28
Calcium	2.1 [1.8, 2.3]	2.1 [1.8, 2.3]	0.32
PO_4	2.1 [1.7, 2.7]	2.1 [1.6, 2.5]	0.06
Albumin	29 [24, 34]	29 [24, 34]	0.94
HD days at chest x-ray	401 [4.0, 1589]	608 [76, 1327]	0.61
Follow-up days	1257 [626, 2411]	912 [402, 1664]	<0.001
Older Vintage (start year<2005)	30%	28%	0.77

Table 3: Distribution of cardiothoracic ratio and aortic arch calcification grade across study population				
Variable	Overall	Patients alive at end of follow-up	Patients dead at end of follow-up	p-value
Cardiothoracic ratio (CTR)	0.53 [0.48, 0.58]	0.52 [0.48, 0.57]	0.55 [0.51,0.59]	<0.001
CTR>0.5	67%	64%	79%	<0.001
Aortic Arch Calcification Grade (%)				<0.001
0	54%	59%	36%	
1	24%	22%	34%	
2	17%	16%	20%	
3	5%	4%	11%	

Table 4: Relationship between x-ray variables and death			
Variables	**Hazard Ratio**	**Model p**	**Model AUROC**
Model 1		<0.001	0.60 [0.55, 0.65]
CTR	1.78 [1.40, 2.27]		
Model 2		<0.001	0.63 [0.58, 0.68]
AAC	-		
0	referent		
1	2.43 [1.64, 3.61]		
2	2.22 [1.41, 3.49]		
3	4.35 [2.48, 7.66]		
Model 3		<0.001	0.65 [0.60, 0.70]
CTR	1.52 [1.17, 1.97]	0.002	
AAC		<0.001	
0	referent		
1	2.16 [1.45, 3.24]		
2	1.81 [1.13, 2.89]		
3	3.49 [1.17, 1.97]		

Table 5: Multivariate analysis			
Model and variables	Hazard Ratio	P value	Model AUROC
Best Base Model (BBM)		Model P < 0.0001	0.71 [0.66, 0.76]
Age at chest x-ray	1.04 [1.03, 1.05]	<0.001	
Duration of hemodialysis	0.94 [0.87, 1.01]	0.07	
Diabetes	0.61 [0.39, 0.95]	0.03	
Heart Failure	1.42 [0.96, 2.09]	0.08	
Creatinine	1.00 [1.00, 1.00]	0.08	
Albumin	0.97 [0.95, 1.00]	0.04	
Best Base Model + CTR		Model P < 0.0001	0.72 [0.67, 0.76]
Age at chest x-ray	1.04 [1.02, 1.05]	<0.001	
Duration of hemodialysis	0.94 [0.87, 1.01]	0.07	
Diabetes	0.60 [0.38, 0.94]	0.03	
Heart Failure	1.33 [0.90, 1.97]	0.2	
Creatinine	1.00 [1.00, 1.00]	0.10	
Albumin	0.97 [0.95, 1.00]	0.05	
CTR	**1.43 [1.11, 1.85]**	**0.01**	
Best Base Model + AAC		Model P<0.0001	0.71 [0.67, 0.76]]
Age at chest x-ray	1.03 [1.02, 1.05]	<0.001	
Duration of hemodialysis	0.92 [0.69,1.96]	0.02	
Diabetes	0.58 [0.37, 0.92]	0.02	
Heart Failure	1.40 [0.95, 2.08]	0.09	
Creatinine (per 100 mcM)	0.94 [0.88, 1.01]	0.09	
Albumin (per 10 g/L)	0.76 [0.59, 0.99]	0.04	
AAC		**0.05**	
0	**referent**		
1	**1.48 [0.96, 2.28]**	**0.08**	
2	**1.16 [0.69, 1.96]**	**0.6**	
3	**2.29 [1.19, 4.38]**	**0.01**	

Table 6: Analysis of confounding: the impact of AAC is dramatically reduced by adjustment for age and other variables

Variable	Unadjusted Hazard ratio	P value	Age-adjusted Hazard ratio	P value	Fully adjusted Hazard ratio*	P value
AAC		<0.001		0.06		0.05
0	referent		referent		referent	
1	2.43 [1.64, 3.61]		1.52 [0.99, 2.33]		1.48 [0.96, 2.28]	
2	2.22 [1.41, 3.49]		1.15 [0.69, 1.92]		1.16 [0.69, 1.96]	
3	4.35 [2.48, 7.66]		2.00 [1.07, 3.75]		2.29 [1.19, 4.38]	

*Adjusted for all variables in the best base model: Age at X-ray, duration of dialysis, diabetic status, history of heart failure, serum albumin and serum creatinine at initiation of dialysis