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Is aortic knob width a novel predictor of mortality in hemodialysis patients?

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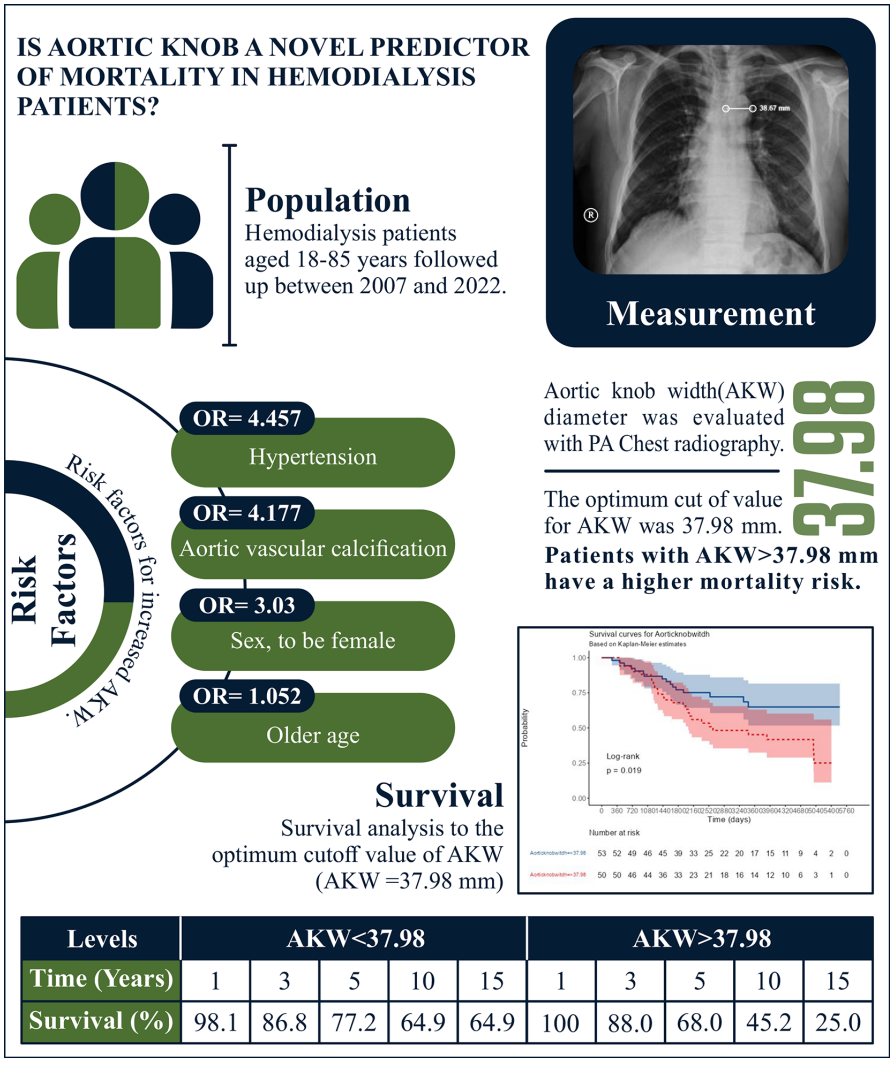
Abstract. – OBJECTIVE: Identifying reliable predictors of mortality in end-stage renal disease patients is crucial for patient outcomes. Aortic knob width is a radiographic parameter used to assess cardiovascular diseases and atherosclerosis. This study investigated the association between aortic knob width and mortality in hemodialysis patients.

PATIENTS AND METHODS: The study included data collected between 2007 and 2022 from 103 patients aged between 18 and 85 who had been undergoing hemodialysis treatment for at least one year. Patients were divided into two groups: survivors and deceased. The aortic knob width was measured using a posterior-anterior chest radiograph after midweek hemodial-



Levels	AKW<37.98					AKW>37.98				
Time (Years)	1	3	5	10	15	1	3	5	10	15
Survival (%)	98.1	86.8	77.2	64.9	64.9	100	88.0	68.0	45.2	25.0

Graphical Abstract. Aortic knob width in mortality prediction in hemodialysis patients.

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ysis. The relationship between aortic knob width and mortality was investigated.

RESULTS: **Deceased patients had significantly larger aortic knob widths compared with survivors. The deceased group's hemodialysis (HD) duration was shorter, median age was older, Kt/V, hemoglobin, and albumin levels were lower, and the frequency of patients with hypertension, diabetes, and aortic wall calcification was higher. Aortic knob width greater than 37.98 mm was identified as a predictor of mortality in hemodialysis patients. Survival rates for aortic knob width <37.98 mm are 98.1% for 1 year and 64.9% for 15 years. For aortic knob width larger than 37.98 mm, survival rates are 88% for three years, 68% for five years, 45.2% for ten years, and 25% for fifteen years. The most important risk factors for increased aortic knob width were age, male sex, aortic calcification, and hypertension.**

CONCLUSIONS: **Age, male gender, aortic calcification, and hypertension are the primary risk factors for increased aortic knob width in hemodialysis patients. Aortic knob width greater than 37.98 mm, which can be measured simply and rapidly using posterior-anterior chest radiography, may be a predictor of mortality.**

Key Words:
Aortic knob width, Hemodialysis, Mortality, Chronic renal disease, Atherosclerosis.

Introduction

End-stage renal disease (ESRD), which is characterized by irreversible loss of kidney function and requires renal replacement treatment for survival, is an important global health problem affecting millions of people worldwide[1]. The causes of mortality in hemodialysis (HD) patients are cardiovascular diseases, infections, inflammation, and comorbidities[2-4]. The identification of reliable indicators of mortality in ESRD patients is critical for clinical treatment and improving patient outcomes. In recent years, there has been a growing interest in evaluating the potential association between aortic knob width (AKW), aortic calcification, and mortality risk in patients with ESRD[5-7].

AKW is a radiographic parameter used to assess the presence of cardiovascular diseases (CVD), such as atherosclerosis (AS), hypertension (HT), and vascular calcification[8-10]. AKW is best visualized on a posterior-anterior (PA) chest radiograph. It is the most distant section of the aortic arch and continues with the descending thoracic aorta. AKW is a simple and noninvasive measurement obtained by transverse measurement of the widest part of the aortic arch on the PA chest radiograph, which can provide valuable information about aortic structure, function, and related pathologies[11]. AKW enlargement is associated with CVD, such as AS, target organ damage, HT, cardiac dysfunction, aortic calcification, and coronary artery disease (CAD)[9,12-14]. AKW may reflect the burden of cardiovascular risk factors such as HT, AS, and vascular calcification, which are common in ESRD and contribute to increased mortality risk. Therefore, we think that it may be a potential marker for CVD and mortality in HD patients. It is also important to understand the processes of AKW and mortality in ESRD patients to develop possible treatment solutions.

Previous studies[5,7] have focused on the relationship between aortic vascular calcification and mortality rather than AKW in HD patients. In view of the lack of current information in the literature, we investigated the relationship between AKW and mortality in HD patients in this study.

Patients and Methods

This study evaluated the AKW effect on HD mortality using patient data. The study included all patients aged 18 to 85 who underwent HD treatment for ESRD for at least one year at a single center between 2007 and 2022. The sample size analysis determined that a minimum of 102 participants was required according to a reference effect size of 0.5, a type 1 error rate of 0.05, and an acceptable power of 80%.

Exclusion criteria included patients who had a history of malignancy, stage 3-4 heart failure, known aortic disease, cardiomyopathy, amyloidosis, chronic obstructive pulmonary disease, kyphoscoliosis, chest deformity, open heart or chest surgery, coronary artery bypass surgery, active infection and/or sepsis, hemodialysis treatment for less than a year, hypervolemia, or a PA chest radiograph that was not taken properly. Figure 1 displays a flow chart that illustrates the exclusion criteria for the patients.

This cohort was divided into two groups according to survival. Patient records were investigated to acquire information on height, weight, body mass index (BMI), date of first HD, Kt/V, and concomitant diseases such as diabetes mellitus (DM), CAD, and hyperlipidemia (HL). BMI (kg/m^2) was calculated as follows: weight (kg) and height (m^2).

HT was defined as using hypertension medication or systolic or diastolic blood pressure higher than 140/90 mmHg, and DM as using antidiabetic medication or fasting glucose above 126 mg/dL or HbA1C above 6.5%, HL was de-

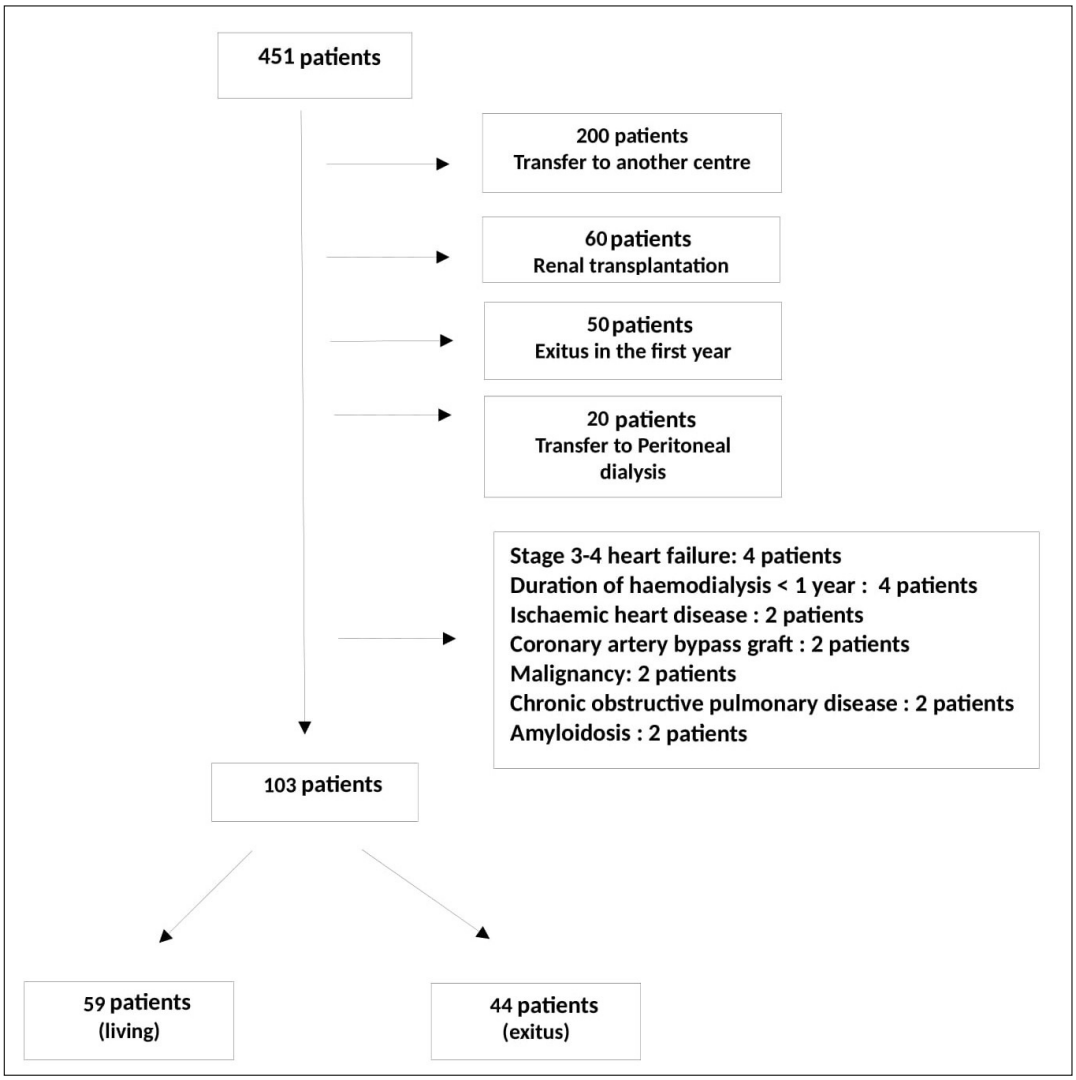

Figure 1. The flow chart used to exclude patients (n=451).

fined as high blood lipids (total cholesterol ≥200 md/dL, high-density lipoprotein (HDL) cholesterol <40 mg/dL, low-density lipoprotein (LDL) cholesterol ≥130 mg/dL, and triglycerides >500 mg/dL) and using hyperlipidemia medication, whereas CAD was >50% or greater coronary artery stenosis in anjiography or a history of myocardial infarction[11,15-17].

Evaluation of Laboratory and Posterior-Anterior Chest Radiographs

In the first year after the first dialysis treatment, our HD patients' serum albumin, ferritin, lipids (total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides), C-reactive protein (CRP), hemoglobin, and PA chest radiographs were evaluated.

Using a PA chest radiograph, AKW and cardiothoracic ratio (CTR) were measured after HD treatment was undertaken in the middle of the week.

AKW was measured along a straight line from the left lateral wall of the aortic arch to the lateral border of the trachea on a PA chest radiograph (Figure 2). One physician carried out the evaluation to mitigate potential bias. The CTR was calculated by dividing the largest horizontal cardiac diameter by the diameter of the thorax.

Statistical Analysis

The data were analyzed using SPSS 22 software (IBM Corp., Armonk, NY, USA).

The normality was assessed using the Kolmogorov-Smirnov test. Subsequently, the Mann-Whit-

Table I. Patient characteristics according to survival (n=103).

	Survivors (n=59) n (%) or $\bar{x}$ ± SD	Deceased (n=44) n (%) or $\bar{x}$ ± SD	*p*
Age, years	52.15±18.46	61.64±13.81	0.008
Gender (f/m)	28 (47.5)/31(52.5)	20 (45.5)/24 (54.5)	0.998
BMI, kg/m^2	23.81±5.20	24.74±5.09	0.453
HD duration, years	6.75±4.20	4.55±3.28	0.008
HT, N/Y	22 (37.3)/37 (62.7)	3 (6.8)/41 (93.2)	<0.001
DM, N/Y	49 (83.1)/10 (16.9)	26 (59.1)/18 (40.9)	0.013
HL, N/Y	53 (89.8)/6 (10.2)	36 (81.8)/8 (18.2)	0.260
CAD, N/Y	48 (81.4)/11 (18.6)	25 (56.8)/19 (43.2)	0.009
AKW, mm	35.73±6.23	39.49±5.97	0.003
CTR	0.51±0.07	0.54±0.07	0.051
Aortic wall calcification (N/Y)	40 (67.8)/19 (32.2)	12 (27.3)/32 (72.7)	<0.001
Albumin, g/dL	3.64±0.33	3.30±0.40	<0.001
Ferritin, mg/dL	588.48±342.79	655.68±446.54	0.653
LDL cholesterol, mg/dL	96.11±34.97	98.59±57.72	0.653
HDL cholesterol, mg/dL	33.27±8.47	33.54±8.14	0.872
Triglycerides, mg/dL	198.54±140.20	173.50±97.12	0.560
Hemoglobin, g/dL	11.12±2.09	10.45±1.95	0.047
Kt/V	1.74±0.34	1.45±0.30	<0.001
CRP/Albumin	0.22±0.22	0.44±0.56	0.090
Ferritin/Albumin ratio	163.46±100.61	212.61±176.55	0.235
AKW/BMI ratio	1.55±0.35	1.65±0.38	0.191
AKW/CTR ratio	69.27±11.69	74.62±15.20	0.028

AKW: aortic knob width, HD: hemodialysis, CTR: cardio-thoracic ratio, CAD: coronary artery disease, HT: hypertension, DM: diabetes mellitus, HL: hyperlipidemia, CRP: C-reactive protein, BMI: body mass index.

ney U test, *t*-test, Chi-square test, ROC analysis, Cox regression, binary logistic regression, and Kaplan-Meier analysis were employed. Statistical significance was assumed at a *p*-value lower than 0.05.

Results

The study included a total of 103 HD patients, of whom 55.4% were male. The average age of these patients was 56.20±17.22 years, ranging from 18 to 85 years. The patients were followed up for an average of 5.81±3.97 years, with a range of 1 to 15 years. Patients were divided into two groups according to survival. During the follow-up period, 44 patients passed away, while 59 patients survived. The leading causes of death were cardiovascular disease (31 cases, or 70.5%), infections (10 cases, or 22.7%), and malignancy (3 cases, or 6.8%). Patient characteristics according to survival are shown in Table I. The deceased group's HD duration was shorter, median age was older, Kt/V, hemoglobin, and albumin levels were lower, and the fre-

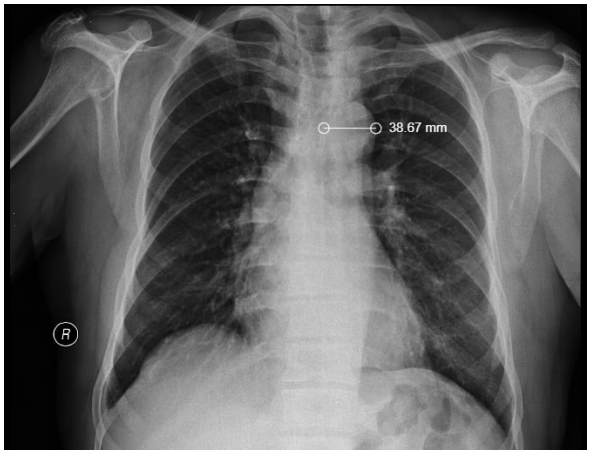

Figure 2. Posteroanterior chest radiography view of aortic knob width assessment.

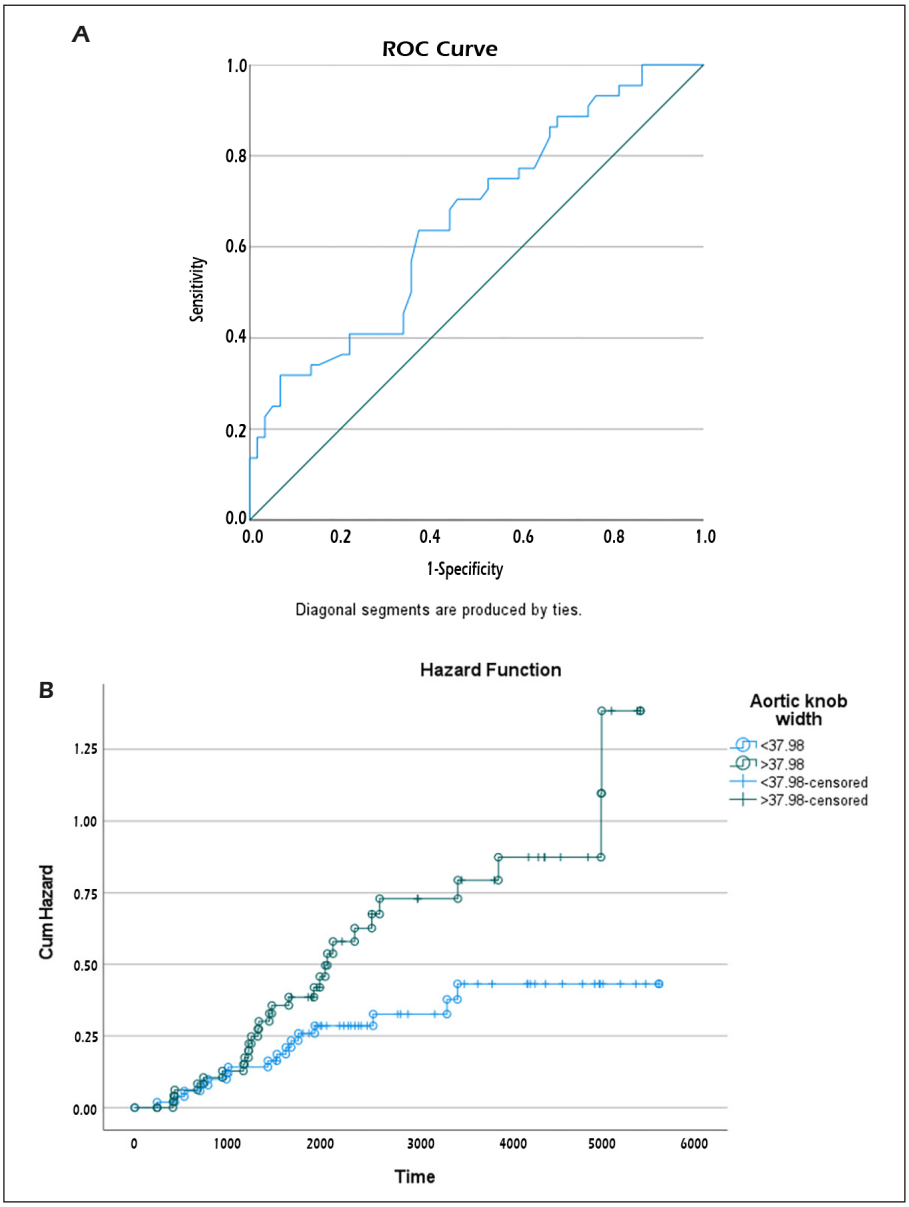

Figure 3. **A**, Area under the curve for aortic knob width. **B**, Survival analysis according to aortic knob width.

quency of patients with hypertension, diabetes, and aortic wall calcification was higher.

The mean AKW was calculated at 37.4±6.5 mm, which was larger in deceased patients (39.49±5.97 mm) than survivors (35.73±6.23 mm). In addition, the mean AKW was larger in males (38.2±7.3 mm) than in females (36.49±5.3 mm). There was also no significant difference between the two groups in terms of CTR (p=0.05).

Correlations between AKW and other measurements are shown in Table II. It was found that there was a weak negative correlation between AKW, Kt/V, and albumin values.

According to ROC analysis, when the role of AKW, AKW/CTR ratio, AKW/BMI ratio, CRP/albumin ratio, and ferritin/albumin ratio in the prediction of mortality was investigated, only the area under the curve for AKW was found to be significant (Figure 3A). AKW larger than 37.98 mm was demonstrated to be a moderately strong diagnostic test (AUC=0.661) and a predictor for mortality (Tables III, Figure 3B).

According to Kaplan-Meier survival analysis for our recommended optimal AKW value, survival rates for AKW <37.98 mm are 98.1% for 1 year and 64.9% for 15 years. For AKW greater than 37.98 mm, survival rates are 88% for three years, 68% for five years, 45.2% for ten years, and 25% for fifteen years (Table IV and Figure 4).

Table II. Correlations between aortic knob width and other measurements (n=103).

	AKW	Kt/V	Albumin	Ferrritin	Hb	LDL cholesterol	TG	HDL	CRP
AKW	—								
Kt/V	-0.199*	—							
Albumin	-0.203*	0.502	—						
Ferrritin	0.055	0.010	-0.228*	—					
Hb	0.009	0.249	0.360	-0.235**	—				
LDL cholesterol	0.070	0.221	0.067	-0.089	0.073	—			
TG	0.048	0.040	0.071	-0.011	0.078	0.305	—		
HDL cholesterol	-0.029	0.257	0.111	0.017	-0.019	0.313	-0.387***	—	
CRP	0.124	0.043	-0.272**	0.084	-0.023	0.133	0.130	-0.154	—

*p<0.05, ** p<0.01, *** p<0.001, one-tailed. AKW: aortic knob width, CRP: C-reactive protein, HB: hemoglobin, TG: triglycerides.

Table III. Area under the curve and optimum cut-off value for aortic knob width.

Test result variable(s): aortic knob width				
Area	Std. Error[a]	p	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
0.661	0.054	0.005	0.556	0.767
Positive if greater than or equal to	Sensitivity	Specificity	LR(+)	LR(-)
37.98	0.636	0.627	1.70	0.58

[a]under the nonparametric assumption.

Table IV. According to Kaplan-Meier analysis, 1, 3, 5, 10, and 15-year survival ratios according to aortic knob width groups.

					95% Confidence Interval	
Levels	Time (years)	Number at risk	Number of events	Survival (%)	Lower (%)	Upper (%)
AKW <37.98	1	52	1	98.1	94.5	100.0
AKW <37.98	3	46	6	86.8	78.1	96.4
AKW <37.98	5	39	5	77.2	66.6	89.4
AKW <37.98	10	17	4	64.9	51.7	81.6
AKW <37.98	15	2	0	64.9	51.7	81.6
AKW >37.98	1	50	0	100	100	100
AKW >37.98	3	44	6	88.0	79.4	97.5
AKW >37.98	5	33	10	68.0	56.2	82.2
AKW >37.98	10	14	9	45.2	32.4	63.0
AKW >37.98	15	1	3	25.0	11.2	56.0

AKW: aortic knob width.

Table V. Aortic knob width groups' life expectancy by cause of death.

Aortic knob width groups		Mean (days)				
				95% Confidence Interval		
		Estimate	Std. Error	Lower Bound	Upper Bound	*p*
All causes	<37.98	4,238.636	284.255	3,681.496	4,795.775	**0.019**
	>37.98	3,197.520	279.509	2,649.683	3,745.357	
	Overall	3,736.051	210.353	3,323.759	4,148.343	
Cardiovascular*	<37.98	1,656.700	210.353	996.567	2,316.833	0.747
	>37.98	1,815.545	210.353	1,316.721	2,314.370	
	Overall	1,770.331	205.656	1,367.246	2,173.416	
Other (infection and malignancy)*	<37.98	1,770.625	441.962	904.380	2,636.870	
	>37.98	2,131.333	564.738	1,024.446	3,238.220	
	Overall	1,955.373	342.902	1,283.286	2,627.461	

* Adjusted for mortality causes.

Table VI. Cox regression and logistic regression analyses are used for the prediction of aortic knob width.

Model 1	B	*p*	O.R.	95% C.I. for EXP(B)	
				Lower	Upper
Age, years	0.051	**0.010**	1.052	1.013	1.094
Gender, male	-1.101	**0.045**	0.333	0.113	0.977
HD duration, year	0.067	0.298	1.069	0.943	1.212
BMI, kg/m^2	0.051	0.339	1.053	0.947	1.170
Aort calcification, yes	1.430	**0.016**	4.177	1.299	13.433
HT, yes	1.494	**0.021**	4.457	1.251	15.873
DM, yes	-0.305	0.597	0.737	0.238	2.283
CAD, yes	-0.774	0.206	0.461	0.139	1.529
HL, yes	-0.115	0.870	0.891	0.224	3.542
Constant	-4.841	0.005	0.008		
Model 2					
AKW group Ref: <37.98, Risk: ≥37.98	0.718	0.022	2.050	1.109	3.791
KtV adjusted					
AKW group Ref: <37.98, Risk: ≥37.98	0.709	0.028	2.031	1.078	3.826

HD: hemodialysis, CAD: coronary artery disease, HT: hypertension, DM: diabetes mellitus, HL: hyperlipidemia, BMI: body mass index. Model 1: Logistic regression analysis for prediction of aortic knob width. Model 2: Cox regression analysis results according to aortic knob width groups.

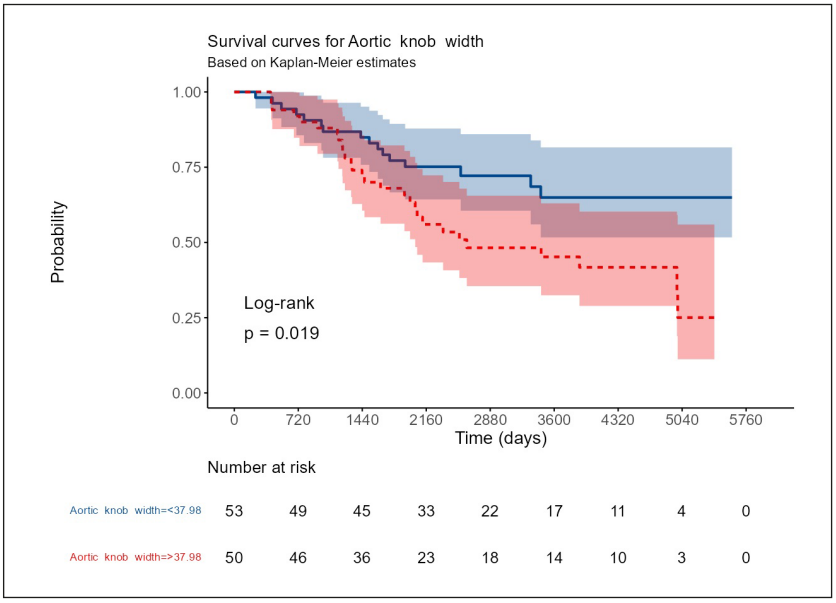

Figure 4. Survival graph for all causes of death by aortic knob width groups.

For all causes of mortality, there was a statistically significant difference in mean life expectancy between AKW groups (p=0.019), with a shorter life expectancy in patients with AKW >37.98 mm. When adjusted for the causes of death, there was no significant difference between cardiovascular and other causes (Table V).

Cox regression analysis results according to aortic knob width groups are shown in Table VI. The Cox regression analysis designed for the assessment and risk of mortality according to AKW was shown to be important, and as a result, patients with an AKW of 37.98 mm or larger had a 2.05 (hazard ratio=2.05) times higher likelihood of death during the follow-up period. AKW was a predictor of death when patients were adjusted to Kt/V, independent of HD adequacy.

Logistic regression analysis for the prediction of AKW is shown in Table VI. The model was found to be significant (omnibus test, p<0.001). The independent variables included in the model are age, gender, and duration of HD, BMI, HT, DM, CAD, and HL. AKW is the model's dependent variable (ref: 37.98, risk: 37.98). The dependent variable of the model is AKW (ref: <37.98, risk: ≥37.98). Independent variables explain 41.2% of the change in dependent variables, and the accuracy rate of the model is 70.9%. The risk of AKW over 37.98 mm increases 1.05 times for each 1 unit increase in age, 0.3 times for being male, 4.17 times for calcification in the ascending aorta, and 4.45 times for HT.

Discussion

The present study found that AKW was significantly associated with many significant factors, including advanced age, male gender, aortic calcification, and hypertension, and that AKW greater than 37.98 mm increased the risk of death in HD patients.

The aortic diameter is usually less than 40 mm in healthy adults. It is affected by various factors such as age, gender, height, weight, body surface area, and blood pressure. It is larger in males and increases by 0.9 mm in males and 0.7 mm in females per decade of life[18].

AKW was found to be less than 3 cm in adults in the United States of America in 1973[19]. More recently, in a study[20] of 650 Indian individuals, the mean average AKW was 3.10±3.34 cm in males and 3.076±3.9 cm in females. In a 2017 study[21] from Turkey, it was reported that AKW had a cut-off value of 3.5 cm in normotensives and 4 cm in hypertensives and that AKW was associated with HT. In another study[22] in Turkey, the authors found that the mean AKW was higher in HD pa-

tients (n=91; 35.0±5.8 mm) compared with controls (n=65; 26.6±4.3 mm).

A limited number of previous studies[8,9,12-14] have evaluated the association between AKW and AS, HT, vascular calcification, and CVD. To the best of our knowledge, this is the first study to investigate the relationship between AKW and mortality in HD patients. The results of this study indicate that the mean AKW of HD patients was 37.4±6.5 mm and was higher in the deceased (39.49±5.97 mm) than in the living (35.73±6.23 mm).

One of our important findings is that the mean AKW is larger in hypertensive, male, and elderly HD patients. It is well known that AKW is larger in males than in females and that it expands with age[9,18,23]. Due to the age-related increase in the prevalence of HT, it is possible that vascular stiffness and AS explain the association between AKW and HT. Aortic dilatation and thus expanded AKW can arise as a result of chronic hypertension, which is frequent in dialysis patients[10,22]. The majority of studies[12,13,22] on HT and AKW are cross-sectional and neglect the potential deleterious effects of both transient and persistent changes in blood pressure on the aortic wall. In order to mitigate this, our cross-sectional study included patients who had been treated with HD for at least one year, and some of them had lived for as long as fifteen years. Prospective, controlled studies are necessary to clearly confirm this association.

In our study, the mean AKW was found to be larger in male HD patients. In previous studies[9,18,20,22,24], males had a larger AKW than females in healthy individuals and HT and HD patients. In contrast, in a study conducted in Jamaica[25], a larger AKW was reported in females than in males. These findings have been attributed to higher blood pressure in females than in males. This may be due to the difference in study populations.

AS is a progressive disease that causes asymmetric focal thickening of the intima, also known as atheromatous plaque, characterized by the deposition of fats, cholesterol, and fibrous elements on the inner walls of the arteries[26,27]. These plaques develop larger as a result of the expansion of fibrous tissues and surrounding smooth muscle, which in turn reduces the amount of blood flow[28]. Fibroblast calcification and connective tissue development in atherosclerotic plaques stiffen arteries. Finally, ulceration on the luminal surface further complicates them. The rough inner surface promotes clotting and thrombosis, decreasing blood flow to tissues[28]. The development of AS is attributed to factors such as high blood pressure, DM, obesity, smoking, aging, genetic predisposition, and environmental factors[28,29]. AS is the most common cause of morbidity and mortality in ESRD patients[30,31]. In the pathogenesis of AS in HD patients, traditional and non-traditional risk factors play a role[32]. AKW has been associated with AS for a long time[33]. A study of 374 patients showed that an AKW larger than 41 mm may predict subclinical AS[8,12]. Early identification of AS and CVD may reduce HD mortality.

The elasticity of arterial walls diminishes as individuals age. Aortic stiffness serves as an initial indicator of both structural and functional alterations in the vessel wall and thus represents a significant marker for the presence of CVD and mortality. Aortic stiffness is a predictor of CVD and mortality and is one of the first detectable indicators of structural and functional changes in the artery wall[34,35]. Slow but progressive aortic dilatation with advancing age is assumed to be caused by increased arterial stiffness and pulse pressure, as well as a high collagen-elastin ratio[36,37]. Increased arterial stiffness is a well-established risk factor for mortality in chronic kidney disease patients[38-40]. Contributors to increased arterial stiffness in ESRD patients include vascular calcification, chronic volume overload, chronic microinflammation, lipid peroxidation, oxidative stress, sympathetic overactivity, and activation of the renin-angiotensin system[41,42]. The most prominent clinical consequences of arterial stiffness are arterial HT, high pulse pressure, CAD, myocardial hypertrophy, and heart failure. Identifying patients at high risk of CVD and requiring preventive and interventional strategies is an important step in the management of HD patients[43]. We did not evaluate arterial stiffness in our HD patients, but we evaluated AKW, which can be considered a surrogate marker, with a simple PA chest radiograph. We evaluated the long-term effect of aortic diameter changes on survival status and AKW and observed that an AKW larger than 37.98 mm increased the risk of mortality. Furthermore, the median survival rates for AKW less than 37.98 mm and greater than 37.98 mm were 64.9% and 25%, respectively, after 15 years of follow-up.

In our study, all-cause mortality was associated with AKW. However, no significant difference was found between the causes of death (cardiovascular and other causes). This may be because

the majority of the causes of death were cardiovascular disease, and other causes (such as infection or malignancy) were less common.

Our study shows the calcification of the aortic vascular wall and HT are the two significant factors contributing to increased AKW. In HD patients, arterial stiffness, AS, and vascular calcification are associated with each other[44,45]. Several risk factors have been identified for the development of vascular calcification. These include advanced age, male gender, prolonged duration of dialysis treatment, presence of DM and HT, smoking, alcohol consumption, hyperphosphatemia, hypercalcemia, hyperparathyroidism, high dosage of vitamin D, inflammation, and hypoalbuminemia[46]. Vascular calcification is also an independent predictor of mortality in HD patients[47].

In our study, we found no correlation between AKW, ferritin, or CRP. The inflammatory process in an atherosclerotic artery can cause blood to have more inflammatory cytokines and other acute phase reactants[26,48]. We excluded patients with acute infections from our study, and chronic factors such as age, HT, and vascular calcification may play a greater role in AKW in our HD patients.

We studied high-risk ESRD patients with HT, DM, HL, and CAD.

Our study was constrained to assess the association between clinical and laboratory findings and mortality one year after the initiation of HD treatment. We believe that including patients who have been on HD for at least one year reduces the likelihood that AKW will be affected by short-term changes.

Limitations

The study exhibits several limitations. Firstly, its cross-sectional design hinders the determination of causal relationships. Secondly, the reliance on a single center may introduce selection bias. Thirdly, the small sample size may pose challenges in interpreting the results.

Conclusions

A simple and accessible PA chest radiograph can detect AKW enlargement, which is associated with mortality in ESRD patients. Age, male gender, aortic calcification, and hypertension have been found to be the most important risk factors for increased AKW, and management of these risk factors may increase life expectancy in hemodialysis patients.

Conflict of Interest

The authors declare that they have no conflicts of interest.

Funding

The authors received no financial support for this study.

Informed Consent

Written informed consent was obtained from the study participants.

Ethics Approval

This study was conducted in accordance with the principles of the Declaration of Helsinki. The ethics committee of Çukurova University Faculty of Medicine approved this study (June 3, 2022, No. 123).

Data Availability

Data will be provided upon reasonable request to the corresponding author.

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Authors' Contributions

Bulent Kaya: concept, design, supervision, data collection, literature search, writing manuscript, critical review, analysis and interpretation, and resources. Burak Mete: data collection, analysis, literature review, manuscript writing, critical review. Mustafa Balal: concept, design, supervision, critical review, analysis. Neslihan Seyrek: concept, design, supervision, critical review, analysis. Ibrahim Karayaylali: concept, design, supervision, critical review, analysis.

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