

The Relationship of Aortic Knob Width and Prognosis in COVID-19 Patients

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ABSTRACT

Introduction: To investigate the relationship between aortic knob width (AKW) and prognosis in patients hospitalized due to coronavirus disease-2019 (COVID-19), and to determine whether AKW can be used as a predictor of in-hospital mortality.

Methods: This cross-sectional study included 222 patients who were hospitalized with COVID-19 following emergency department admission. Based on the clinical outcome, patients were categorized into two groups: those who died during hospitalization (group 1, n=64) and those who survived (group 2, n=158). Demographic, clinical, laboratory, and radiological data were collected retrospectively. AKW was measured on chest radiographs, and its association with in-hospital mortality was assessed through multivariate logistic regression and receiver operating characteristic curve analysis.

Results: AKW was significantly higher in deceased patients compared to survivors (45.1±8.8 mm vs. 36.7±6.7 mm; p<0.001). A cut-off value of 40 mm for AKW predicted in-hospital mortality with 76.6% sensitivity and 70.3% specificity. AKW was found to be an independent predictor of in-hospital mortality (odds ratio: 1.196, 95% confidence interval: 1.106-1.293, p<0.001). AKW showed significant correlations with age, inflammatory markers (C-reactive protein, ferritin, procalcitonin), and clinical severity parameters, such as oxygen saturation and respiratory rate.

Conclusion: AKW measured on chest X-rays at the time of admission is a non-invasive and accessible prognostic marker in hospitalized COVID-19 patients. Values above 40 mm may indicate increased mortality risk, and these patients should be monitored more closely during hospitalization.

Keywords: Aortic knob width, COVID-19, prognosis, mortality, chest radiograph

Introduction

The severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), which has been defined as causing SARS since December 2019, has affected the whole world and continues to affect it (1). The World Health Organization has stated that it will continue its efforts to make an impact globally (2). In Covid-positive patients, simple symptoms such as fever, fatigue, dry cough, headache, and diarrhea can be observed, as well as acute respiratory distress syndrome (ARDS) and related cardiovascular shock. Disruptions in hematologic and immune system functions are key contributors to both the development and progression of the disease (3). Some cases may result in death despite treatment (3,4). Advanced age, the presence of comorbid conditions, and immunodeficiency are all associated with increased risks of morbidity and mortality (5). For this reason, it is important to make the diagnosis of coronavirus disease-2019 (COVID-19), predict the prognosis of the patients at the time of application, and determine the severity of the disease.

The aortic knob is a contour of the aortic arch and can be easily visualized on a chest radiograph. Dilatation of the aorta, which undergoes various changes with normal aging, has also been associated with atherosclerotic changes such as enlargement and calcification of the aortic knob (6). Studies have shown that aortic knob width (AKW) is associated with target organ damage in many diseases, especially in hypertension and coronary artery disease, (7-9). This study examined the relationship between AKW and prognosis in individuals hospitalized for COVID-19, based on the effects of multiple comorbidities on mortality and morbidity. Additionally, the correlation of this relationship with parameters determining the severity of the disease, as well as immunological and hematological parameters, was evaluated in this study.

Methods

Subjects

Our study was designed as a cross-sectional study and included 222 patients (121 males, 101 females, mean age: 60.0±16.6 years) who



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applied to the emergency department with various complaints such as fever, cough, shortness of breath, and fatigue. Patients were hospitalized as a result of the examinations, and it was decided that they would be followed up and treated. Histories of the patients were taken, physical examinations were performed, and their information was recorded. The acute and chronic diseases of the patients, as well as the drug treatments they used, were recorded. Those with malignancy, rheumatological diseases, and chronic liver disease were identified as having systemic disease, and recorded. Temperatures of all patients were measured, and respiratory rates, systolic-diastolic blood pressures, pulses, and fingertip oxygen saturations were recorded by pulse oximetry. Venous blood samples were taken from all patients, and hemogram, D-dimer, alanine transaminase (ALT), aspartate transaminase (AST), urea, creatinine, lactate dehydrogenase (LDH), C-reactive protein (CRP), troponin, ferritin, and procalcitonin values were measured at the time of admission to the hospital. These values were also measured during follow-up in individuals who were recommended to be hospitalized. In addition to hemogram parameters, neutrophil-lymphocyte ratio, and systemic inflammatory index (SII) were calculated. SII was found as multiplying the neutrophil to lymphocyte ratio with the platelet count.

Chest X-ray and Pulmonary Thorax Tomography

In posteroanterior imaging, AC radiography and lung tomography were performed on all patients. Chest radiographs were evaluated by a physician who was unaware of the patient's clinical information. The width of the aortic knob was assessed by measuring the maximum transverse diameter along the horizontal line extending from the lateral border of the trachea to the lateral wall of the aortic knob.

Information about the patient's pulmonary involvement was obtained from pulmonary tomography.

COVID-19 Diagnosis and Hospitalization Indication

The diagnostic criteria of the Turkish Ministry of Health National Science Committee were used as the COVID-19 diagnostic criteria for the patients. A confirmed positive diagnosis was established in individuals presenting with at least one symptom-such as fever, cough, dyspnea, sore throat, headache, myalgia, diarrhea, or loss of taste or smell-unattributable to other known conditions, alongside either a history of recent travel to a high-risk area within the preceding 14 days, close contact with a confirmed COVID-19 case during that period, or a positive SARS-CoV-2 result via molecular testing. Individuals diagnosed with severe acute respiratory infections-characterized by fever, cough, dyspnea, tachypnea, hypoxemia, hypotension, altered consciousness, and common radiological findings on lung imaging in patients with an acute respiratory tract infection that developed within the last 14 days-were required hospitalization for follow-up. Patients who required respiratory support or mechanical ventilation due to respiratory failure, developed cardiovascular shock and multiple organ failure, and had neurological symptoms, especially loss of consciousness due to desaturation, were monitored in the intensive care unit. The number of days the patients were hospitalized was recorded. The medication administered during the hospitalization was also recorded. All treatments applied to patients with hospitalization indications were administered by considering

the treatment plan of the National Science Committee of the Turkish Ministry of Health (10). Also, the management of patients diagnosed with severe pneumonia, ARDS, sepsis, and septic shock during diagnosis and follow-up was carried out in accordance with the guidelines of the Ministry of Health of the Republic of Türkiye (11).

Out of 222 patients who were admitted to the hospital due to severe pneumonia, ARDS, sepsis, septic shock, and desaturation, 64 died. The study participants were divided into two groups: group 1, which consisted of 64 patients who resulted in death (mean age: 38 males, 69.2 ± 16.2 years), and group 2, which consisted of 158 patients who did not result in death (83 males, 56.3 ± 15.4 years).

An informed consent form was signed by the patients participating in the study, and the relatives of the individuals who were not in a position to give consent. The study was approved by the University of Health Sciences Türkiye, İstanbul Training and Research Hospital Clinical Research Ethics Committee (approval number: 46, date: 11.02.2022).

Statistical Analysis

Statistical analyses were conducted using SPSS version 22.0. Continuous variables were shown as mean $\pm$ standard deviation if normally distributed, and as median (25th-75th percentiles) if not. Categorical variables were presented as counts (n) and percentages (%). The Kolmogorov-Smirnov test was used to check if the numerical data had a normal distribution. Comparisons of continuous variables in two independent groups were made using the independent samples t-test and Mann-Whitney U test depending on the distributional characteristics of the parameters. Spearman's correlation analysis was used to evaluate the relationship between AKW and several other parameters. To assess the independent contribution of each variable, we performed a multiple logistic regression analysis that included all clinical variables with a $p < 0.05$ in the univariate analysis. Hosmer and Lemeshow tests were performed to choose the best regression model. Odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) were computed individually. To determine the AKW cut-off with optimal sensitivity and specificity for predicting mortality, receiver operating characteristic (ROC) curve analysis was employed. A p-value below 0.05 was regarded as statistically significant.

Regression analysis was performed to evaluate the independent effects on in-hospital mortality of demographic characteristics, admission physical examination findings, and laboratory findings. All variables that reached statistical significance ($p < 0.05$) in the univariate analysis were included in the multiple logistic regression model. OR and 95% CI were calculated. ROC curve analysis was used to calculate the AKW value, which predicts in-hospital mortality with the best specificity and sensitivity.

Results

Group 1 had significantly older age and longer hospitalization compared to group 2 when demographic variables were evaluated. While gender, number of vaccinated patients, systolic-diastolic blood pressure was similar between the groups, fever, pulse and respiratory rate were significantly higher in group 1 compared to group 2. Oxygen

saturation was markedly reduced in group 1 relative to group 2. When the existing diseases of the individuals were compared, the presence of hypertension, coronary artery disease, kidney failure, heart failure, and systemic diseases was significantly higher in group 1 than in group 2 (Table 1).

AKW was significantly higher in group 1 compared to group 2 (45.1 ± 8.8 mm vs. 36.7 ± 6.7 ; $p < 0.001$).

When laboratory values were compared, glucose, urea, creatinine, ALT, AST, LDH, CRP, ferritin, and D-dimer were significantly higher in group

1 compared to group 2. Procalcitonin and troponin values were similar between groups (Table 2). Among the hemogram parameters, white blood cells (WBC), hemoglobin, neutrophil, neutrophil to lymphocyte ratio, and SII were significantly higher in group 1 than group 2, while the monocyte value was significantly lower in group 1 compared to group 2. Lymphocyte and platelet values were similar between the groups (Table 1).

Pearson's correlation analysis showed a significant positive correlation with AKW and age, length of hospital stays, respiratory rate, heart rate,

Table 1. Demographic, laboratory features, hematological parameters, prognostic nutritional indices, systemic inflammatory indices of the groups

	Group 1 (n=64)	Group 2 (n=158)	p
Age (years)	69.2±16.2	56.4±15.4	<0.001
Gender (M,n)	38	83	0.355
Hospital stay duration (day)	17.4±11.5	9.1±6.5	<0.001
Temperature (°C)	37.4±0.99	36.9±0.71	<0.001
Oxygen saturation (paO ₂)	86.7±8.1	94.3±4.3	<0.001
Hypertension (n)	45	65	<0.001
Diabetes mellitus (n)	28	51	0.089
Coronary artery disease (n)	19	26	0.027
CHF (n)	21	18	<0.001
COPD (n)	8	16	0.607
CRF (n)	21	21	0.001
Vaccinated (n)	5	12	0.956
Systolic blood pressure (mmHg)	134.5±39.7	131.3±23.2	0.461
Diastolic blood pressure (mmHg)	77.5±17.1	78.3±12.7	0.684
Heart rate (beat/min)	103.9±14.6	95.2±13.0	<0.001
Respiratory rate (breath/min)	19.9±6.9	16.2±4.2	<0.001
Glucose (mg/dl)	185.8±94.4	140.0±68.4	<0.001
Urea (mg/dl)	82.9±56.1	42.2±35.1	<0.001
Creatinine (mg/dl)	1.63±1.45	1.11±1.10	0.013
ALT (U/L)	87.8±179.8	37.2±65.0	0.003
AST(U/L)	168.7±448.3	38.7±54.7	0.023
LDH (U/L)	649.5±664.2	275.6±170.1	<0.001
CRP (mg/L)	144.3±94.9	34.7±66.4	<0.001
Procalcitonin	5.7±39.7	4.2±11.5	0.772
Ferritin	1859.3±4115.8	271.0±405.1	<0.001
D-dimer (mg/L)	3.98±5.35	1.85±3.97	0.001
Troponin I (pg/mL)	12.6±46.1	23.8±131.4	0.513
WBC (x10 ⁹ /L)	13.48±10.38	7.89±4.04	<0.001
Platelet (x10 ⁹ /L)	222.7±106.6	229.1 ± 86.7	0.640
Hemoglobin (g/dl)	10.9±2.5	12.5±2.3	<0.001
Lymphocyte (x10 ⁹ /L)	1.84±0.79	1.73±2.34	0.873
Neutrophil (x10 ⁹ /L)	11.0±7.6	6.80±9.78	0.002
Neutrophil-to-lymphocyte ratio	21.33±23.70	6.23±10.60	<0.001
SII	4541.5±4872.7	1373.1±2494.0	<0.001
AKW (mm)	45.1±8.8	36.7±6.7	<0.001

CHF: Congestive heart failure, COPD: Chronic obstructive pulmonary disease, CRF: Chronic renal failure, AST: Aspartat transaminase, ALT: Alanine transaminase, LDH: Lactate dehydrogenase, CRP: C-reactive protein, WBC: White blood cells, SII: Systemic inflammatory index, AKW: Aortic knob width

procalcitonin, CRP, ferritin, D-dimer, neutrophil to lymphocyte ratio, and SII (Table 2). There was a significant negative correlation between fingertip oxygen saturation and the variable of interest (Table 2).

In-hospital mortality-related factors identified through univariate and multivariate logistic regression analyses are detailed in Table 3. It was found to be predictive for in-hospital mortality in univariate analyses. Multivariate logistic regression was used to identify independent predictors of in-hospital mortality, utilizing variables that showed significance in univariate analyses. According to the multivariate logistic regression analysis, hypertension (OR =3.729, 95% CI: 1.194-11.645, $p=0.023$), low oxygen saturation (OR =0.904, 95% CI: 0.835-0.979, $p=0.013$), elevated LDH levels (OR =1.003, 95% CI: 1.000-1.005, $p=0.020$), increased ferritin (OR =1.001, 95% CI: 1.000-1.002, $p=0.008$), and greater AKW (OR =1.196, 95% CI: 1.106-1.293, $p<0.001$) were found

to be independently associated with higher in-hospital mortality. ROC analysis showed that the area under the curve for AKW in predicting in-hospital mortality was 0.822 (95% CI: 0.758-0.886, $p<0.001$) (Figure 1). The cut-off value for AKW, which predicts in-hospital mortality, was 40.0 mm with a sensitivity of 76.6% and a specificity of 70.3%.

Discussion

The main result of our study is that AKW, which can be easily measured on a posteroanterior chest X-ray, is associated with end-organ damage in various patient groups in previous studies. AKW is closely associated with mortality in COVID-19 patients requiring hospitalization. It is also closely linked to lab findings that reflect disease severity and to several markers of inflammation.

The structural and physical properties of the aortic wall change with age, and it loses its normal structure and function to certain degrees. It has been shown that the increase in aortic knob diameter is associated with age, body surface area, and gender, with a particularly strong association with hypertension. It has been stated that AKW may be an important indicator of the generalized atherosclerotic process due to its close relationship with coronary artery calcification and Framingham risk score (12,13). It was thought to be associated with target organ damage (14).

Individuals with severe COVID-19 are high-risk patients and often present with a high heart rate, low oxygen saturation, and a clinical picture of infiltrates of more than 50% of the lung on imaging (15). It is known that approximately 25% of patients who need to be hospitalized due to COVID-19 require intensive care (16,17). In serious COVID-19 cases, common complaints like fever, cough, sore throat, and breathing difficulties can worsen over time, leading to conditions such as ARDS,

Table 2. Pearson's correlation analysis between AKW and several parameters

	rho	p
Oxygen saturation	-0.35	<0.001
Respiratory rate	0.35	<0.001
Heart rate	0.27	<0.001
C-reactive protein	0.35	<0.001
Procalcitonin	0.32	<0.001
D-dimer	0.34	<0.001
Ferritin	0.27	<0.001
Neutr-to-lymphocyte	0.37	<0.001
SII	0.34	<0.001

SII: Systemic inflammatory index, AKW: Aortic knob width.

Table 3. Univariate and multivariate regression analysis showing the parameters related with in-hospital mortality

	Univariate			Multivariate		
	OR	95% CI	p value	OR	95% CI	p value
Age	1.057	1.034-1.080	<0.001			
Hypertension	3.389	1.818-6.317	<0.001	3.729	1.194-11.645	0.023
CAD	2.144	1.084-4.237	0.028			
CHF	3.889	1.897-7.972	<0.001			
CRF	3.186	1.590-6.385	0.001			
Saturation	0.816	0.764-0.871	<0.001	0.904	0.835-0.979	0.013
Heart rate	1.049	1.024-1.074	<0.001			
Glucose	1.007	1.003-1.011	<0.001			
Creatinin	1.361	1.076-1.723	0.010			
LDH	1.005	1.003-1.008	<0.001	1.003	1.000-1.005	0.020
CRP	1.012	1.008-1.016	<0.001			
Ferritin	1.002	1.001-1.003	<0.001	1.001	1.000-1.002	0.008
D-dimer	1.106	1.028-1.190	0.007			
WBC	1.168	1.094-1.248	<0.001	1.099	0.994-1.215	0.064
Hemoglobin	0.757	0.666-0.861	<0.001			
AKW	1.177	1.117-1.239	<0.001	1.196	1.106-1.293	<0.001

CAD: Coronary artery disease, CHF: Congestive heart failure, CRF: Chronic renal failure, AST: Aspartat transaminase, ALT: Alanine transaminase, LDH: Lactate dehydrogenase, CRP: C-reactive protein, WBC: White blood cells, SII: Systemic inflammatory index, AKW: Aortic knob width, CI: Confidence interval, OR: Odds ratio

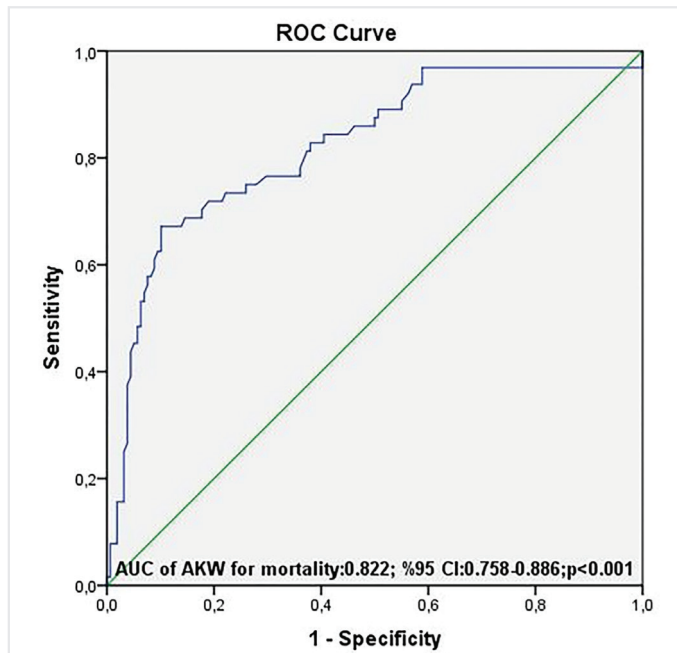


Figure 1. ROC curve of AKW to predict in-hospital mortality in patients with COVID-19

AKW: Aortic knob width, ROC: Receiver operating characteristic, CI: Confidence interval, AUC: Area under the curve, COVID-19: Coronavirus disease-2019

organ failure, circulatory shock, metabolic problems, and in some cases, death (18,19). Studies have suggested numerous parameters that can predict the prognosis in these patients.

In a local study by Burhamah et al. (20) in Kuwait, parameters that could affect the prognosis were investigated in 133 patients who were admitted to intensive care due to COVID. As a result of the study, mechanical ventilation during admission to the hospital, development of in-hospital complications, presence of kidney failure, leucocytosis, LDH, and urea levels were found to be closely associated with in-hospital mortality. In another study conducted by Nasrullah et al. (21) on 58 patients in Pennsylvania; they found the in-hospital mortality rate to be 32.8% and investigated the factors associated with mortality. The analysis demonstrated that multiple variables were markedly linked to an increased likelihood of death. These included advanced age, elevated Charlson comorbidity score, rapid breathing, low lymphocyte count at admission, higher APACHE ratings, circulatory collapse, onset of ARDS, need for ventilatory support, and corticosteroid administration.

Moreover, a new oxygen requirement at discharge was observed in 44.7% of individuals who could be discharged from the intensive care unit, and this was also important in terms of showing the severity of the disease. In another local study, the relationship of hematological parameters and comorbidities with COVID-19 severity in patients hospitalized for COVID-19 was investigated. In this study involving 306 participants, patients were categorized as either severe or non-severe COVID-19 cases. The findings indicated that CRP, D-dimer, and ferritin levels at the time of hospital admission were significantly associated with disease severity (22). Chauhan et al. (23) conducted a study involving 125 hospitalized COVID-19 patients, exploring how admission-time demographic

characteristics and laboratory findings were associated with patient outcomes. They found that advanced age, presence of ischemic heart disease, smoking history, as well as high D-dimer and LDH levels at admission, and low lymphocyte counts were associated with mortality.

Inflammation plays an important role in COVID-19 infection. In their study of 720 COVID-19 patients who presented to the emergency department and were found to have PCR positivity, Toori et al. (24) concluded that neutrophil-lymphocyte ratios measured at the time of admission were associated with mortality as well as the severity of the disease. They suggested that the neutrophil to lymphocyte ratio has the important advantage of being inexpensive and easily available 24/7. In a study conducted in China, researchers showed that high NLR and LDH levels are closely related to the severity and course of the disease, and especially combining these two parameters will increase the sensitivity of the diagnosis (25). In a separate study involving 695 patients, Asan et al. (26) examined the link between hematologic markers and both disease severity and prognosis in COVID-19. They found that NLR, PLR, and $LYM \times PLT$ values measured at admission were significantly associated with disease severity and held predictive value for patient outcomes. Similarly, in our study, we found that NLR levels as well as SII, were associated with AKW levels, which are associated with prognosis.

In a study similar to ours, Luchian et al. (27) reported that a coronary artery calcium score of zero observed in 280 COVID-19 patients who underwent chest CT might be linked to an increased risk of major adverse cardiovascular events. They concluded that a calcium score of 0 in these individuals had a negative predictive value of 84.5%.

In our study, we investigated the relationship between AKW and mortality in COVID-19 patients, which is a non-invasive method that can be easily calculated and is inexpensive. As a result of our study, the width of the aortic knob, which is closely related to atherosclerosis and is known to be associated with end-organ damage in studies, may be associated with mortality in hospitalized COVID-19 patients. We concluded that in these patients, AKW greater than 40 mm can predict mortality, and AKW values correlate with hematological and laboratory parameters known to affect prognosis. We found a correlation between patients' ages, lengths of hospital stays, d-dimer, NLR, SII, procalcitonin, ferritin, CRP levels, and AKW values.

Study Limitations

First, our study is a cross-sectional single-center study, and patients suitable for hospitalization during a specific period were included. For this reason, local factors must be considered before generalizing our results to wider populations. The treatments applied to hospitalized patients may differ between countries. Additionally, the measurement of AKW may be subject to observer dependence, and inter-observer variability was not assessed in this study. The treatments of the patients in our study were applied in line with the guidelines of the Ministry of Health. During the period when the research records were obtained, vaccination was not yet widespread in our country. Therefore, the number of vaccinated cases in both patient groups was very low and was similar between the groups. For this reason, it is necessary to evaluate the results of the study independently of vaccination procedures.

Conclusion

The chest X-ray obtained at the time of hospital admission in almost all COVID-19 patients, which guides the diagnosis and treatment, is inexpensive, easily applicable, and accessible. It contains valuable information that may be related to their prognosis. AKW measurements appear to correlate with factors that are potentially predictive of mortality in individuals diagnosed with COVID-19. In these individuals, AKW measurement should be made at the time of admission, and individuals with values higher than 40 mm should be followed more carefully throughout the hospitalization process.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Türkiye, İstanbul Training and Research Hospital Clinical Research Ethics Committee (approval number: 46, date: 11.02.2022).

Informed Consent: An informed consent form was signed by the patients participating in the study, and the relatives of the individuals who were not in a position to give consent.

Footnotes

Authorship Contributions: Surgical and Medical Practices - M.S.Ç.; Concept - M.S.Ç., M.S.A.; Design - M.S.Ç.; Data Collection or Processing - M.S.Ç., M.S.A.; Analysis or Interpretation - M.S.Ç.; Literature Search - M.S.Ç., M.S.A.; Writing - M.S.Ç.

Conflict of Interest: No conflict of interest was declared by the authors.

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