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Predictive Value of Carbohydrate Antigen-125 in Determining the Left Ventricular Diastolic Dysfunction

Sol Ventrikül Diyastolik Disfonksiyonunun Belirlenmesinde Karbonhidrat Antijeni-125'in Tahmini Değeri

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ABSTRACT

Aim: Carbohydrate antigen-125 (CA-125) is a well-known marker for mesenchymal cell activation. It is being investigated as a predictive marker for cardiac pathologies due to pericardial or pleural mesenchymal cell activation. In this study, the relationship between left ventricular diastolic diameter (LVDd) and ejection fraction (EF) and serum CA-125 levels was investigated.

Material and Method: Thirty-eight patients who underwent coronary artery bypass graft operation were included in the study. LVDd and EF values were calculated. Routine blood parameters and serum CA-125 levels were obtained from blood samples. Patients were divided into groups according to LVDd (LVDd <50mm vs. ≥50mm) and EF (EF <50% vs. EF≥50%).

Results: Among the low (<50%) and high (≥50%) EF groups, serum neutrophil, mean platelet volume (MPV), lactate dehydrogenase (LDH), aspartate aminotransferase (AST), troponin-I, triglyceride, and very low-density lipoprotein (VLDL) levels were statistically different ($p<0.05$). However, no statistical difference was observed between the low (<50mm) and high (≥50mm) LVDd groups in other blood parameters except for serum CA-125 levels ($p>0.05$). Higher serum CA-125 levels were obtained in patients with a high left ventricular diastolic diameter (≥50mm) ($p<0.05$). In addition, CA-125 was found to be an important predictor of left ventricular diastolic diameter with an optimal cut-off value of 0.644 kU/L (60% sensitivity and 78.3% specificity).

Conclusion: According to our results, increased serum CA-125 level is an independent predictor of higher LVDd and may be a good indicator of left ventricular functions.

Keywords: CA-125, left ventricle diastolic dimension, ejection fraction.

ÖZ

Amaç: Karbonhidrat antijeni-125 (CA-125), mezenkimal hücre aktivasyonu için iyi bilinen bir belirteçtir. Perikardiyal veya plevral mezenkimal hücre aktivasyonuna bağlı kardiyak patolojiler için öngörücü bir belirteç olarak araştırılmaktadır. Bu çalışmada sol ventrikül diyastolik çapı (LVDd) ve ejeksiyon fraksiyonu (EF) ile serum CA-125 seviyeleri arasındaki ilişki araştırıldı.

Gereç ve Yöntem: Koroner arter baypas greft operasyonu uygulanan 38 hasta çalışmaya dahil edildi. LVDd ve EF değerleri hesaplandı. Kan örneklerinden rutin kan parametreleri ve serum CA-125 seviyeleri elde edildi. Hastalar LVDd (LVDd <50mm vs. ≥50mm) ve EF'ye (EF <%50 vs. EF≥%50) göre gruplara ayrıldı.

Bulgular: Düşük (<%50) ve yüksek (≥ %50) EF grupları arasında serum nötrofil, ortalama trombosit hacmi (MPV), laktat dehidrogenaz (LDH), aspartat aminotransferaz (AST), troponin-I, trigliserit ve çok düşük yoğunluklu lipoprotein (VLDL) düzeyleri istatistiksel olarak farklıydı ($p<0.05$). Ancak düşük (<50mm) ve yüksek (≥50mm) LVDd grupları arasında serum CA-125 düzeyleri dışında diğer kan parametrelerinde istatistiksel fark gözlenmedi ($p>0.05$). Sol ventrikül diyastolik çapı yüksek (≥50mm) olan hastalarda serumda daha yüksek CA-125 seviyeleri elde edildi ($p<0.05$). Ayrıca, CA-125, 0,644 kU/L'lik optimal cut-off değeri (%60 duyarlılık ve %78,3 özgüllük) ile sol ventrikül diyastolik çapının belirlenmesinde önemli bir öngörücü belirteç olarak bulundu.

Sonuç: Sonuçlarımıza göre artmış serum CA-125 düzeyinin daha yüksek LVDd için bağımsız bir öngörücü olduğu ve sol ventrikül fonksiyonlarının iyi bir göstergesi olabileceği görülmektedir.

Anahtar Kelimeler: CA-125, sol ventrikül diyastol sonu çapı, ejeksiyon fraksiyonu.

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INTRODUCTION

Myocardial infarction and similar pathologies cause complex alterations in the ventricular structure. Subsequent neurohormonal activations lead to deterioration of ventricular functions by stimulating ventricular remodeling. In the myocardial area where infarctions exist along with an abnormal dilation and tissue weakening, hypertrophication of normal myocardial areas and dilations can be detected [1]. Early diagnosis of left ventricular failure is crucial for managing patients who develop myocardial infarction and coronary artery disease. Thus, determining the predictive data for left ventricular remodeling and diagnosing maladies with non-invasive, simple and reliable methods, along with an efficient treatment, are also crucial.

Carbohydrate antigen-125 (CA-125) is a glycoprotein spotted on ovarian tumor cells which is used to diagnose and follow-up patients with ovarian cancer [2,3]. CA-125 synthesis is not only limited to ovarian cancer. It is also secreted from fetal coelomic epithelial derivatives and mesothelial cells such as endometrium, fallopian tube, peritoneum and pleural pericardium [4]. High CA-125 levels have been determined in heart failure patients [2, 5-7] and elevated CA-125 levels were found to be associated with functional capacity in cardiac insufficiency [5].

In this study, the relationship between serum CA-125 levels and left ventricular functions consisting of left ventricular diastolic diameter (LVDd) and ejection fraction (EF), was investigated in coronary artery bypass graft surgery patients.

MATERIAL and METOD

Ethics and Patient Selection

After designation of study steps, ethical approval was obtained from the local ethical committee (Date 07.06.2021, Session No. 11 and Decision No. 11- HRU/21.11.11) and written informed consent from the patients. Thirty-eight patients who had coronary bypass operation were included to the study. Patients with advanced heart failure (EF<30), concomitant heart valve disease, chronic kidney disease, chronic liver disease, systemic inflammatory disease, chronic obstructive pulmonary disease and malignancy, were excluded from the study.

Transthoracic Echocardiography and CA-125 Measurements

The standard echocardiographic (Vivid S6, GE Vingmed Ultrasound, Horten, Norway) examinations were made by single cardiologist with 2.5–5 MHz probes. Measurements were retrieved by long axis and apical 4 spaces with standard criteria. The modified Simpson method was used for calculation of ejection fraction (EF). Cardiac chamber sizes and other echocardiographic parameters were detected according to previous guidelines [8].

Blood samples was taken from patients and placed in sterile anticoagulant tubes. The tubes were delivered to the laboratory by maintaining the cold chain. Blood samples were centrifuged at 4 000 rpm for 10 minutes. Supernatant plasma was taken into Eppendorf tubes and stored at -80°C. Plasma samples were studied with Human Carbohydrate Antigen-125 (CA-125) ELISA Kit. Results were recorded as kU/L units. Patients were divided into two groups according to EF values (EF< %50 vs. EF≥ %50) and Left ventricular end-diastolic dimension (LVDd) (< 50mm vs. ≥ 50mm) similarly as described in previous studies [9]. Obtained blood parameters and plasma CA-125 levels were compared in each group.

Statistical Analyze

All statistical analyses were calculated by the SPSS 22.0 for Windows. The normal distribution was determined by the Kolmogorov-Smirnov test and histogram. Non-parametric tests were used for calculations. The continuous variables were expressed as median (min-max). The categorical variables were expressed as n (%). The differences of continuous variables were calculated by the Mann Whitney-U test and the Wilcoxon test was used for repeated measures. The Chi-Square test was used to determine the difference between groups of categorical variables. ROC analysis is done for the effect of CA-125 on LVDd measurement and also cut-off point was calculated. $p<0.05$ were considered as statistically significant.

RESULTS

There is no significant difference between LVDd (LVDd < 50mm vs. ≥ 50mm) and EF (EF < 50% vs. EF ≥ 50%) groups in regards of demographic variables, except hypertension. Arterial blood pressure was high in low LVDd group (< 50 mm) (p: 0.006) (Table-1). The mean ages were found to be similar in for all groups (Table-2). Serum neutrophil values were statistically high in low EF group when compare with high EF [(median (min-max): 5.84 (3.8-9.62) vs. 5.07 (2.46-7.55)] (p: 0.048). Mean platelet value (MPV) is higher in low EF group [(median (min-max): 9.17 (7.06-10.27) vs. 7.77 (0-12.4)] (p: 0.040). Similarly lactate dehydrogenase (LDH), aspartate transaminase (AST), troponin-I levels were statistically higher in low EF group (p<0.05). Oppositely triglyceride and VLDL levels were significantly higher in high EF group. Other complete blood counting parameters were statistically not significant between groups (p>0,05) (Table-2). There was no difference in according to blood tests between LVDd groups (< 50mm vs. ≥ 50mm) except CA-125 levels. Incremental CA-125 values were found in high LVDd (≥ 50mm) group when compare with low LVDd (< 50mm) group (p: 0.032). The comparison of CA-125 levels was demonstrated in Figure-1-A and Figure-1-B in regards of LVDd and EF.

The receiver operator characteristic (ROC) curve analysis revealed that the optimal cut-off point 0.644 kU/L of CA-125 level shows 60% (32.9%-82.5%) sensitivity and 78.3% (55.8%-91.7%) specificity (Figure-2) for predicting the disrupted LVDd (≥50mm) [p=0.032 and AUC=0.709 (0.539-0.879; 95%CI].

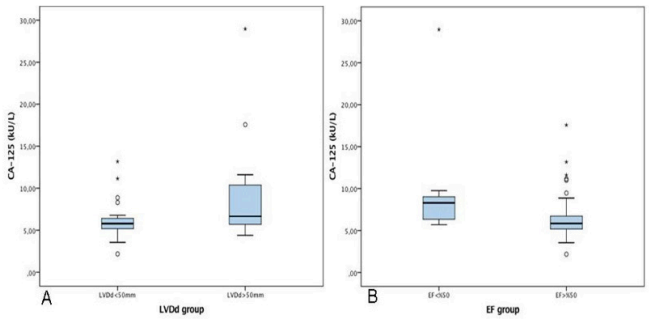
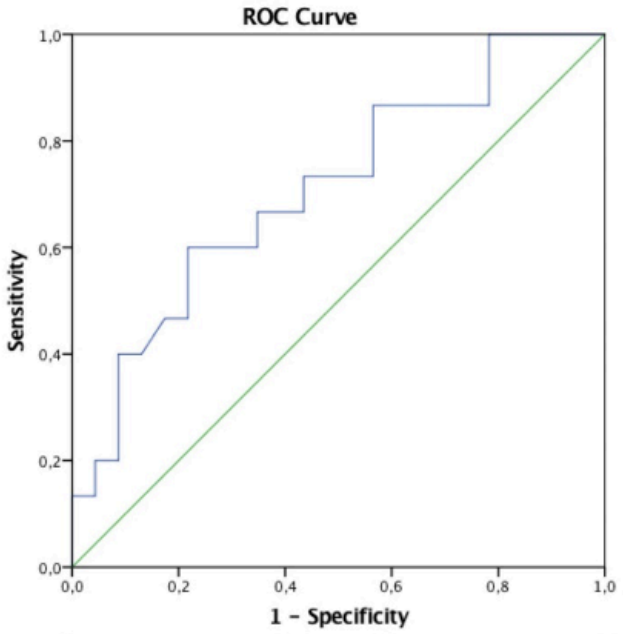


Figure 1. Comparison of CA-125 levels between groups. A= Box-plot graphic of Left Ventricular end-diastolic dimension (LVDd) group. B= Box-plot graphic of ejection fraction (EF) groups.



Area Under Curve

Test Result Variable	Area	Asymptomatic 95% Confidence Interval Lower Bound	Upper Bound
CA-125	0.709	0.539	0.879

Figure 2. ROC curve analyze of CA-125 levels for predicting LVDd (optimal cut-off value of 0.644 kU/L with 60% sensitivity and 78.3% specificity)

DISCUSSION

Serum CA-125 is a biomarker for ovarian carcinomas with peritoneal involvement for decades [10]. CA-125 is a high molecular weight glycoprotein that is similar to mucin and highly detected in disorders with peritoneal irritation. It is released by mesenchymal cells and thus the elevation of this marker is also detected in other sites which include mesenchymal cells, such as pericardium and pleura [11]. Therefore, higher CA-125 levels are detected in pelvic inflammatory disease, cirrhosis with peritoneal acid, and also congestive cardiac failure that have deteriorated with pleural and pericardial effusion [11,12]. After detection of CA-125 expression at epicardial tissue, increased levels of this marker were observed in cardiac pathologies [12]. The first findings of blood cancer markers were reported by Nagele et al. in chronic heart failure patients with heart transplantation and they were first to describe the relationship between heart

Table-1. Comparison of the demographic variances in regards of Left Ventricular end-diastolic dimension (LVDd) and ejection fraction (EF) groups.

		LVDd group		p	EF group		p
		LVDd<50mm	LVDd≥50mm		EF<%50	EF≥%50	
Gender	Female	6 (60%)	4 (40%)	1.000	3 (30%)	7 (70%)	0.351
	Male	17 (60.7%)	11 (39.3%)		4 (14.3%)	24 (85.7%)	
Age		65 (40-77)	61 (48-73)	0.559	58 (48-73)	65 (40-77)	0.692
Smoking	Absent	17 (68%)	8 (32%)	0.191	4 (16%)	21 (%84)	0.672
	Present	6 (46.2%)	7 (53.8%)		3 (23.1%)	10 (76.9%)	
Hypertension	Absent	8 (40%)	12 (60%)	0.006	4 (20%)	16 (80%)	1.000
	Present	15 (83.3%)	3 (16.7%)		3 (16.7%)	15 (83.3%)	
Diabetes mellitus	Absent	14 (56%)	11 (44%)	0.429	4 (16%)	21 (84%)	0.672
	Present	9 (69.2%)	4 (30.8%)		3 (23.1%)	10 (76.9%)	

*Chi-square test

Table-2. Comparison of the blood parameters in regards of Left Ventricular end-diastolic dimension (LVDd) and ejection fraction (EF) groups. (RBC: Red blood cell, WBC: White blood cell, RDW: Red cell distribution width, CA-125: Carbohydrate antigen-125, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, WBC: White Blood Cell, VLDL: Very Low-density lipoprotein, AST: Aspartate transaminase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase, PLT: Platelet)

		Total	LVDd group		p*	EF group		p*
			LVDd<50mm	LVDd≥50mm		EF<%50	EF≥%50	
			Median (min-max)			Median (min-max)		
Age (at diagnosis)		63 (40-77)	65 (40-77)	61 (48-73)	0.559	58 (48-73)	65 (40-77)	0.692
Complete blood count	RBC(×10⁶/mm3)	5.01 (2.78-5.71)	5.02 (4.3-5.71)	4.99 (2.78-5.38)	0.226	4.85 (3.92-5.28)	5.02 (2.78-5.71)	0.266
	Hemoglobin (g/dL)	13.1 (9.72-16.2)	13.3 (10.6-16.2)	13.1 (9.72-15.9)	0.378	13.1 (10-14)	13.1 (9.72-16.2)	0.522
	Hematocrit (%)	40.15 (30.8-49)	40.6 (33.9-49)	39.5 (30.8-48)	0.250	39.7 (31.4-43.9)	40.5 (30.8-49)	0.486
	WBC (×10³/mm3)	8.55 (4.56-12.8)	8.58 (4.56-12.8)	8.52 (6.45-11.7)	0.633	9.43 (6.01-12.8)	8.42 (4.56-12.3)	0.127
	Neutrophil (×10³/mm3)	5.16 (2.46-9.62)	4.98 (2.46-9.62)	5.48 (3.25-7.54)	0.124	5.84 (3.8-9.62)	5.07 (2.46-7.55)	0.048**
	Lymphocyte (×10³/mm3)	2.19 (1.02-6.34)	2.2 (1.19-6.34)	2.17 (1.02-4.33)	0.601	2.26 (1.02-3.18)	2.17 (1.19-6.34)	0.925
	Monocyte (×10³/mm3)	0.53 (0.23-1.11)	0.52 (0.3-0.98)	0.54 (0.23-1.11)	0.929	0.56 (0.23-0.91)	0.52 (0.32-1.11)	0.778
	Basophil (×10³/mm3)	0.07 (0.04-0.13)	0.06 (0.04-0.12)	0.07 (0.05-0.13)	0.521	0.07 (0.06-0.1)	0.07 (0.04-0.13)	0.283
	Eosinophil (×10³/mm3)	0.15 (0-0.87)	0.14 (0-0.51)	0.15 (0.01-0.87)	0.940	0.14 (0.01-0.87)	0.15 (0-0.51)	0.970
	PLT (×10³/mm3)	234.5 (152-376)	229 (152-376)	258 (164-372)	0.580	229 (173-372)	240 (152-376)	0.970
	Mean platelet volume (MPV) (fL)	7.87 (0-12.4)	8 (6.57-11)	7.73 (0-12.4)	0.411	9.17 (7.06-10.27)	7.77 (0-12.4)	0.040**
	RDW (fL)	15.15 (12.33-30.7)	15.3 (12.33-30.7)	14.9 (12.78-18.5)	0.238	15.1 (12.33-15.4)	15.2 (12.91-30.7)	0.152
	Neutrophil/Lymphocyte ratio	2.36 (0.78-7.01)	2.17 (0.78-4.25)	2.6 (1.37-7.01)	0.179	2.35 (1.75-7.01)	2.37 (0.78-4.21)	0.292
	Monocyte/Lymphocyte ratio	0.26 (0.07-0.82)	0.26 (0.1-0.66)	0.25 (0.07-0.82)	0.799	0.28 (0.07-0.82)	0.25 (0.1-0.66)	0.692
Laboratory Results	Albumin (g/dL)	3.6 (1.9-4.1)	3.5 (1.9-4.1)	3.6 (2.2-3.8)	0.810	3.79 (1.9-4.1)	3.6 (2.9-4.1)	0.296
	Urea (mg/dL)	36.5 (23-73)	38 (26-60)	35 (23-73)	0.869	38 (30-73)	35 (23-60)	0.235
	Creatinine (mg/dL)	0.85 (0.69-2.33)	0.84 (0.72-1.63)	0.88 (0.69-2.33)	0.940	0.83 (0.69-2.33)	0.86 (0.72-1.63)	0.807
	Na (mEq/dL)	136 (133-141)	136 (133-141)	136 (133-140)	0.762	136 (133-140)	136 (133-141)	0.924
	K (mEq/dL)	4.05 (3.3-5.3)	4 (3.3-5.2)	4.1 (3.6-5.3)	0.177	4.1 (3.9-4.6)	4 (3.3-5.3)	0.416
	Ca (mEq/dL)	9 (7.5-10)	9 (8.1-10)	9.2 (7.5-9.7)	0.242	9.2 (7.5-9.5)	9 (8.1-10)	0.720
	LDH (U/L)	214.5 (132-998)	199 (132-998)	217 (153-679)	0.446	350 (217-998)	207 (132-423)	0.004**
	ALT (U/L)	20.5 (7-91)	20 (10-91)	21 (7-55)	0.676	27 (9-55)	20 (7-91)	0.749
	AST (U/L)	22 (10-174)	24 (10-72)	19 (11-174)	0.169	35 (19-174)	21 (10-72)	0.026**
	Triglyceride (mg/dL)	184.5 (50-721)	195 (93-721)	158 (50-584)	0.226	118 (63-155)	197 (50-721)	0.003**
	Cholesterol (mg/dL)	182 (102-253)	184 (119-248)	172 (102-253)	0.455	198 (102-248)	180 (109-253)	1.000
	HDL (mg/dL)	31 (15-54)	31 (15-54)	31 (16-43)	0.952	34 (16-54)	30 (15-41)	0.059
	LDL (mg/dL)	110.8 (21.6-400)	111.8 (38.6-400)	109.8 (21.6-400)	0.550	125.4 (51-184)	105 (21.6-400)	0.777
	VLDL (mg/dL)	38.6 (10-144)	41.2 (18.6-144)	31.6 (10-116.8)	0.174	23.6 (12.6-31)	41.2 (10-144)	0.003**
	CK-MB (ng/mL)	1.95 (0.7-93.6)	1.7 (0.8-25.1)	2 (0.7-93.6)	0.570	1.7 (0.8-93.6)	2 (0.7-25.1)	0.572
	Troponin-I (ug/L)	0.03 (0-40.38)	0.03 (0-6.72)	0.02 (0-40.38)	0.880	0.45 (0.01-40.38)	0.02 (0-6.72)	0.013**
	Sedimentation Rate	16.5 (3-39)	14 (3-39)	19 (5-39)	0.146	26 (11-39)	15 (3-39)	0.137
	CA-125 (kU/L)	6 (2.17-28.96)	5.79 (2.17-13.17)	6.66 (4.39-28.96)	0.032**	8.3 (5.7-28.96)	5.84 (2.17-17.57)	0.062

*Mann-Whitney-U test, **p<0.05 is statistically significant

functions and serum CA-125 levels [13]. Initial studies reported a faint relation between right ventricle functions and serum CA-125 levels, and insignificant prediction power of serum CA-125 levels for left cardiac functional changes [14]. However, conflicting results were reported in further studies. Varol et al. found that the levels of CA-125 were increased in patients suffering from heart failure with advanced pericardial effusion, in comparison to those suffering from heart failure with not-so-advanced pericardial effusion [7]. Turk et al. showed more pronounced CA-125 levels in patients with heart failure and pleural effusion [15]. D'Aloia et al. detected higher levels of serum CA-125 in heart failure patients with pleural, peritoneal, and pericardial effusion and advanced heart failure patients without effusion [16]. In another study, a relation was described between heart failure functional class and serum CA-125 [5]. Seo et al. detected higher levels of CA-125 in 65% of heart failure patients with different etiologies [17]. They found increased levels of CA-125 in patients with more effusion and echocardiographically witnessed that levels of CA-125 decreased and/or came down to normal levels, following decreased and/or disappeared effusion level. In the same study, they painted the pericardial autopsy material with anti-CA-125 and meaningfully detected higher levels of serum and pericardial CA-125 in anti-CA-125 positive patients. Judging from these results, they commented that CA-125 is a pericardial fluid producer. Kouris et al. evaluated the relationship between heart failure functional classes and tumor markers [6]. They found higher levels of CA-125 in patients with heart failure. At the same time, they observed elevated levels of CA-125 in correlation with functional class. They could not detect any relationship between CA-125 and left ventricular EF, EDV (end-diastolic volume) and the medical treatment provided. Battaloğlu et al. studied the effectiveness of plasma CA-125 and carcinoembryonic antigen (CEA) values in patients that underwent cardiopulmonary bypass surgery. They formed two groups: on-pump and off-pump. They could not find a meaningful difference in levels of CEA in any of the groups. But CA 125 values elevated significantly both on-pump and off-pump groups. They commented that cardiopulmonary bypass caused elevated levels of serum CA-125 [18]. Durak – Nalbantic et al. found that serum CA-125 levels were higher in patients with pleural or pericardial fluid [19]. Vizzardi et al. found that elevated serum CA-125 levels were an effective long-term prognostic marker in patients with mild-to-moderate heart failure, in patients with cardiovascular events [20]. Rong X et al. detected that elevated serum CA-125 levels could help to predict short-term cardiac insufficiency in patients with coronary artery disease [21]. Li J. et al. showed that increased perioperative serum CA-125 levels were an independent predictor of worse clinical outcomes at the one-year follow-up, after off-pump coronary artery bypass surgery [22]. In all of these studies, increased serum CA-125 levels were associated with heart failure.

Changes in cardiac workload alter left ventricular dimensions through adaptive remodeling of the myocardium. Therefore, end-diastolic volumes are considered to be a determinant of remodeling and a good indicator of functional capacity [23]. In patients with heart failure, left ventricular systolic and diastolic cavity dilations are signs of deterioration of ventricular functions and have a significant effect on mortality. Studies have shown that left ventricular dilation is one of the markers of cardiac dysfunction. Increased left ventricular cavity sizes aggravate mortality rates. A positive correlation is observed between patients with high LVDd values and mortality in patients with similar comorbidities [24].

We found incremental CA-125 values in patients with LVDd≥50mm. Furthermore, our results showed that CA-125 levels (optimal cut-off point of 0.644 kU/L) indicate disrupted LVDd with 60% sensitivity and 78.3% specificity. The relationship between LVDd - which is a predictable parameter of left ventricular dysfunction - and CA-125 values were evaluated. The increase in ventricular size and decrease in functional capacity at the end of diastole has been observed to increase CA-125 levels. These results suggest that CA-125 values above a certain level may indicate remodeling and related left ventricular enlargement.

Limitations

The first limitation is the low number of patients participating in our research. The second limitation is that plasma CA-125 levels are not compared

with healthy individuals. Finally, CA-125 values were not studied in pericardial fluid and pericardial tissue samples, as was done in some previous studies.

CONCLUSION

Our results indicated that increased CA-125 level is an independent predictor for higher LVDd. Moreover, screening of serum CA-125 levels can be useful for left ventricular diastolic dimension with an acceptable sensitivity and specificity. Increased levels of CA-125 may be one of the serious markers of left ventricular dysfunction and cardiac remodeling. Studies with larger patient groups are thought to provide a more detailed understanding of CA-125 and ventricular functions.

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ORCID and Author Contributions: NK (0000-0001-7111-7503): Concept and design, materials, practices, data collection and processing, interpretation, literature search, writing, critical review.

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