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Cancer antigen-125 is a predictor of mortality in patients with pulmonary arterial hypertension

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ABSTRACT

Background: Carbohydrate antigen 125 (CA 125), known as a tumor marker for ovarian cancer, has been reported to increase and be associated with severity in heart failure and chronic obstructive pulmonary disease. Patients with pulmonary arterial hypertension may also die due to developing right heart failure. The aim of this study is to evaluate the prognostic role of CA-125 in PAH patients.

Methods: A total of 40 consecutive patients with PAH were evaluated prospectively. The mean age of patients was 52 ± 11 years (12% males, 88% females) with a median follow-up period of 16 months.

Results: After follow-up period, 12 out of 40 patients (30%) died. CA-125 levels were higher among those who died compared to those who survived [78.5 (11.0–292) vs. 27.5 (2.10–138) U/ml, p = 0.001]. The optimal cut-off value of CA-125 to predict mortality was found as 35.29 U/ml, with 85.7% specificity and 75% sensitivity. In multivariable Cox proportional-hazards model with forward stepwise method; CA-125 > 35.32 U/ml on admission (HR = 7.645, 95% CI: 1.356–43.121, p = 0.021), age (HR = 1.132, 95% CI: 1.040–1.233, p = 0.004), TAPSE (HR = 0.740, 95% CI: 0.549–0.998, p = 0.048) and uric acid (HR = 1.444, 95% CI: 1.022–2.042, p = 0.037) remained associated with an increased risk of death.

Conclusion: In this study, we showed for the first time that serum CA-125 values were an independent predictor for the long-term mortality in PAH patients.

1. Introduction

Pulmonary arterial hypertension (PAH) is a vasculopathy characterized by increased pulmonary arterial pressure that can lead to right heart failure due to its progressive course [1,2]. Although many treatments have appeared in recent years to improve symptoms and functional capacity, mortality rates in PAH patients are still quite high [3]. For this reason, early detection of the disease and accurate prognostic classification in diagnosed patients is very important. For guiding treatment decisions and making prognostic expectations more accurate, current guidelines recommend a risk class assessment in specific periods in PAH patients. Multi-parameter risk assessment methods, including clinical, echocardiographic, and hemodynamic variables, are used in daily practice [3,4]. New York Heart Association Functional Class (NYHA FC), 6-Minutes Walking Test (6-MWT), right atrial pressure (RAP), cardiac index (CI), and N-terminal pro-brain natriuretic peptide (NT-proBNP) are prognostic markers that have been shown to be effective in combined use [5]. Given the complex processes underlying PAH pathophysiology, studies on suitable and easily accessible biomarkers that can predict disease severity and survival are still not sufficient today.

Cancer antigen 125 (CA-125), which is a soluble glycoprotein with high molecular weight, releases from epithelial serosal cells and has been used as a tumor marker in gynecologic malignancies for a long time [6]. However, CA-125 serum levels have been shown to increase in many diseases such as coronary artery disease, heart failure, and chronic

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obstructive pulmonary disease (COPD) [7,8]. Also in recent studies; CA-125 was found to be correlated with clinical, hemodynamic, and echocardiographic variables in heart failure and could be used as a prognostic marker [9,10].

The negative effect of worsening right ventricular function on mortality in PAH patients has been shown in previous studies. A decrease in tricuspid annular plane systolic excursion (TAPSE) values, in particular, is associated with negative prognosis in PAH patients [11]. CA-125 is known to be a parameter indicating both right and left ventricular dysfunction [12]. For the first time in the literature, we investigated the relationship between serum CA-125 levels, which are indicative of RV dysfunction, and mortality in patients with PAH.

2. Methods

Forty patients, aged 18 and over, followed up due to diagnosis of idiopathic PAH through right heart catheterization (RHC) at Cardiology Clinic, were included in the study by obtaining informed consents during routine outpatient applications between 1 January 2017 and 1 January 2018. Patients with known malignancies, heart failure, pregnancy, recent kidney and liver failure, and a history of coronary artery disease, and patients whose RHC records could not be reached, were excluded from the study.

Data collection, per protocol, included age, gender, admission CA-125 and other blood parameters, electrocardiogram, transthoracic echocardiography, Borg dyspnea score, 6-MWT, PAH-specific or supportive therapies, the cardiac catheterization findings and detailed physical examination. Serum levels of CA-125 were determined using a commercially available kit (AxSYM System, Abbott Laboratories, Abbott Park, IL). The AxSYM CA-125 assay is based on microparticle enzyme immunoassay; this technology uses a solution of suspended, submicron-sized latex particles to measure analytes.

2.1. Echocardiographic and invasive measurements

All records taken by Vivid E7 echocardiography device (GE Healthcare Ultrasound Systems, USA) and 2.5–5 MHz transducer from all patients were reported in accordance with current guidelines and recommendations [13]. Left ventricular Ejection Fraction (EF) was evaluated by the modified Simpson method using apical 4 cavity images. Standard morphological measurements included the left–right atrium (LA-RA) and left–right ventricle (LV-RV) diameters and RA area obtained from the 4-cavity image, and the inferior vena cava (IVC) diameter and respiratory change obtained from the subcostal window. Presence or absence of pericardial effusion was noted. Tricuspid regurgitation peak velocities and TAPSE were measured. Pulmonary artery systolic pressure (PAP) was calculated by adding RA pressure indirectly measured by IVC diameter and respiratory variation to the Bernoulli equation created using tricuspid peak velocity [14]. The right heart catheterization was performed earlier in accordance with current recommendations and included standard hemodynamic measurements [15]. During the RHC, cardiac output was calculated using the Fick method.

2.2. Outcome definitions

All-cause mortality was selected as the main endpoint. The information regarding patients' survival status was ascertained at each hospitalization, during office visits or telephone interviews. This study complied with the Declaration of Helsinki and was approved by the institutional review board of Sivas Cumhuriyet University.

2.3. Statistical analysis

Continuous variables were expressed as mean ± SD or median (min–max) in the presence of abnormal distribution, and categorical variables as percentages. The Receiver operating characteristic (ROC) curve analysis was performed to identify the optimal cut-off point of CA-125 (at which sensitivity and specificity would be maximal) for the prediction of mortality. Areas under the curve (AUC) were calculated as measures of the accuracy of the tests. We compared the AUC with the use of the Z test. Comparisons between groups of patients were made by use of the Chi-square test for categorical variables, independent samples *t* test for normally distributed continuous variables, and the Mann–Whitney *U* test when the distribution was skewed. The Kaplan–Meier curves were using to display mortality in two patient subgroups, defined as having no increased (Group I) or increased (Group II) CA-125 based on a cut-off value. We used univariable analysis to quantify the association of variables with mortality. Variables found to be statistically significant in univariable analysis and other potential confounders were used in a multivariable Cox proportional-hazards model with the forward stepwise method in order to determine the independent prognostic factors of mortality. All the statistical procedures were performed using SPSS software version 14.0 (SPSS Inc., Chicago, IL). p-value of 0.05 was considered as statistically significant.

In a study conducted by Matar et al., the measurement uncertainty for CA-125 was found to be 10% on average. For this reason, univariate and multivariate analyses were repeated with ± 10% values of the determined cut-off value. [16]

3. Results

The population of our study consisted of 35 females (88%), 5 males (12%), and the mean age of the patients was 52 years (minimum 23 – maximum 66). At the end of the mean 16-month (minimum of 2, maximum of 24 months) follow-up period, 12 (30%) patients died.

The main characteristics of the patients divided into 2 groups, including the deceased and the survivors, are seen in Table 1. Accordingly, the NYHA functional classes of deceased patients were worse than those who lived, the Borg dyspnea scores were higher and the 6-MWD were lower. The use of loop diuretic was more in the deceased patients group.

IVC diameter, RV diameter, and RA area from the echocardiographic parameters were higher and TAPSE was lower in the deceased patients group compared to the survivors group. Given the findings of the heart catheterization of patients, the cardiac index was lower in the deceased patients group, and RAP and LV end-diastolic pressure (LVEDP) were higher.

While total protein, albumin, and calcium values were lower in the deceased patients group, AST values were higher.

Serum CA-125 mean values were significantly higher in the deceased patients group (27.5 U/ml vs. 78.5 U/ml, p:0.001) (Table 1).

The ROC curve displaying the relationship between CA-125 level and mortality is shown in Fig. 1. According to the ROC curve analysis, an optimal cut-off value of CA-125 to predict mortality was found as 35.29 U/ml, with 75% sensitivity and 85.7% specificity (AUC 0.827, 95% CI 0.675–0.928, $p < 0.001$) (Fig. 1).

Furthermore, CA-125 levels were negatively correlated with TAPSE, cardiac index, total protein, albumin and 6-MWD and positively correlated with RV diameter, IVC diameter, presence of pericardial effusion, RAP, RA area, uric acid, use of loop diuretics, NYHA class III-IV and Borg dyspnea score (Table 2).

The results of the univariable and multivariable Cox proportional hazards analyses for mortality are depicted in Table 3. In the multivariable Cox proportional hazards model with the forward stepwise method, age, uric acid level, TAPSE, and CA-125 > 35.29 U/ml on admission remained associated with an increased risk of death after adjustment for variables found to be statistically significant in univariable analysis and were correlated with CA-125 level (Table 3).

Univariable and multivariable Cox proportional hazards analyses was repeated with 31.76 U/ml and 38.82 U/ml values, which were ± 10% of the cut-off value of 35.29 U/ml. Accordingly, CA-125 > 31.76 U/

Table 1
Baseline characteristics of study patients.

	Patients who survived (n:28)	Patients who died (n:12)	*p* Value
Baseline characteristics			
Mean age (years)	60.8 ± 13.5	70.6 ± 9.2	0.028
Sex (female) (%)	23 (82%)	12 (100%)	0.298
NYHA class III-IV, n (%)	5 (18%)	10 (83%)	<0.001
Borg dyspnea score	12.8 ± 2.5	16.2 ± 3.0	0.001
6-Minutes walking distance (m)	298 (145–480)	165 (60–445)	<0.001
Echocardiographic parameters			
LV ejection fraction (%)	55.6 ± 3.3	55.4 ± 3.3	0.190
sPAP (mmHg)	60.8 (25–123)	66.8 (50–113)	0.293
IVC diameter (mm)	15.8 ± 3.8	19.8 ± 4.0	0.004
RV diameter (mm)	49.2 ± 4.2	51.8 ± 2.4	0.047
TAPSE (mm)	19.1 ± 3.0	15.3 ± 3.7	0.001
Presence of pericardial effusion, n (%)	5 (18%)	3 (25%)	0.677
RA area (cm^2)	19.7 ± 3.0	24.3 ± 3.6	<0.001
Cardiac catheterization findings			
Cardiac index (L/min/m^2)	3.0 ± 0.5	2.6 ± 0.4	0.034
Mean PAP (mm/Hg)	40.1 (26–95)	43.2 (26–82)	0.469
PCWP (mm/Hg)	10.1 ± 3.1	12.0 ± 1.9	0.058
RAP (mm/Hg)	8.4 (4–18)	11.3 (4–15)	0.008
LV end-diastolic pressure (mmHg)	9.9 ± 2.8	12 ± 2	0.024
PVR (WU)	5.6 ± 3.1	6.3 ± 3.1	0.511
Laboratory findings			
Hemoglobin (g/dl)	13.7 ± 1.9	12.8 ± 2.7	0.253
Creatinine (mg/dl)	0.8 ± 0.2	1.1 ± 0.5	0.072
Uric acid (mg/dl)	3.8 ± 0.7	4.0 ± 0.5	0.349
Total protein (mg/dl)	6.7 ± 0.5	5.9 ± 0.7	<0.001
Albumin (mg/dl)	4.1 ± 0.4	3.6 ± 0.5	0.001
AST (U/l)	19.2 (10–48)	33.3 (14–127)	0.009
Calcium (mmol/l)	9.1 ± 0.5	8.7 ± 0.6	0.035
CA-125 (U/ml) (min–max)	27.5 (2.1–138)	78.5 (11.0–292)	0.001
CA-125 > 35.29 U/ml, n (%)	4 (14%)	9 (75%)	<0.001
Medical treatment at admission			
Endotelin receptor antagonists, n (%)	22 (79%)	9 (75%)	1.000
Phosphodiesterase 5 inhibitors, n (%)	4 (14%)	3 (25%)	0.410
Use of Loop diuretics, n (%)	15 (54%)	12 (100%)	0.004

NYHA, New York Heart Association; LV, left ventricle; LA, left atrium; sPAP, systolic pulmonary artery pressure; IVC, inferior vena cava; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; RA, right atrium; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; PVR, pulmonary vascular resistance; WU, wood units; AST, aspartat aminotransferase; CA-125, cancer antigen 125.

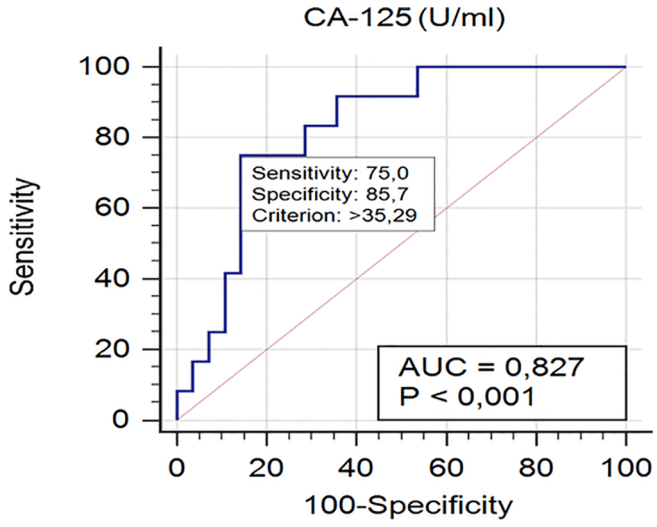

Fig. 1. ROC curve of CA-125 to predict long-term mortality.

Table 2
Spearman correlation coefficients for CA-125.

	CA-125	*p* Value
TAPSE (mm)	−0.558	<0.001
RV diameter (cm)	0.457	0.003
IVC diameter (mm)	0.588	<0.001
Presence of pericardial effusion	0.338	0.033
RAP (mm/Hg)	0.466	0.002
Cardiac Index (L/min/m^2)	−0.370	0.019
RA area (mm^2)	0.652	<0.001
Uric acid (mg/dl)	0.367	0.020
Total protein (mg/dl)	−0.456	0.003
Albumin (mg/dl)	−0.326	0.040
Use of loop diuretics	0.383	0.015
6-Minutes walking distance (m)	−0.565	<0.001
NYHA class III-IV	0.581	<0.001
Borg dyspnea score	0.494	0.001

TAPSE, tricuspid annular plane systolic excursion; RV, right ventricle; IVC, inferior vena cava; RAP, right atrial pressure; RA, right atrium; NYHA, New York Heart Association.

ml was found associated with a statistically significant increased risk of death (p:0.002, HR:7.827, CI: 2.097–29.210). CA-125 > 38.82 U/ml was also found statistically significantly associated with an increased risk of death in univariate and multivariate analysis ($p < 0.001$, HR: 11.185, CI:2.973–42.083)

Kaplan–Meier analysis yielded diverging survival curves for two previously defined subgroups of CA-125 with a threshold of 35.29 U/ml ($p < 0.001$) (Fig. 2).

4. Discussion

To the best of our knowledge, this is the first study to demonstrate that CA-125 aids in the prognosis of patients with PAH. We also revealed that high CA-125 levels were associated with poor hemodynamic and echocardiographic parameters such as RV dysfunction, decreased 6-MWD, poor NYHA class, and worsened the Borg dyspnea score.

Advanced age, Low 6-MWD, poor NYHA functional class, decreased cardiac index, presence of pericardial effusion, high PAP and presence of RV dysfunction have been shown in many studies to increase mortality in PAH patients [5,17,18]. In our study, advanced age was determined as an independent predictor for mortality in both univariable analysis and multivariable analysis. Although parameters such as cardiac index, RA area, LVEDP were found to be associated with mortality in univariable analysis, they were not independent predictors in multivariable analysis. NYHA FC, 6-MWD, and Borg dyspnea scores, which are parameters that can be used to evaluate pulmonary capacity and lung function in PAH patients, were found to be worse in the deceased patients group. Although these parameters were associated with mortality in univariable analysis, they were not found to be independent predictors of mortality after multivariable analysis.

It is known that worsening renal function in PAH patients negatively affects survival [19]. However, in our study, no statistical was found in creatinine values between the two groups. Although there was a statistically significant difference in albumin and calcium values between the two groups, there was no clinical significance. In addition, the need for loop diuretic treatment is greater in the deceased patients group. However, these parameter were not determined as an independent predictor for mortality in our study. There is a study conducted by Simpson et al. with a group of scleroderma-associated PAH patients and showing that serum uric acid levels can be used to determine the prognosis of the disease [20]. In our study, the usability of uric acid levels as an independent predictor of mortality in PAH patients appears to be consistent with the results of this study.

CA-125 is a glycoprotein that has an extremely complex structure and high molecular weight and is synthesized by epithelial serous cells. It is known that CA-125 levels have increased in many malignant and

Table 3
Univariable and multivariable Cox regression analyses for predicting mortality.

Variable	Univariable			Multivariable		
	p Value	HR	(95% CI)	*p* Value	HR	(95% CI)
Statistically significant variables						
CA-125 > 35.29 U/ml	<0.001	11.185	2.973–42.083	0.021	7.645	1.356–43.121
Age (years)	0.026	1.089	1.010–1.173	0.004	1.132	1.040–1.233
LV end-diastolic pressure (mmHg)	0.042	1.265	1.009–1.587			
Creatinine (mg/dl)	0.012	3.429	1.314–8.948			
AST (U/l)	0.024	1.020	1.003–1.038			
Calcium (mmol/l)	0.027	0.294	0.099–0.872			
Variables which correlated with CA-125						
TAPSE (mm)	<0.001	0.725	0.602–0.873	0.048	0.740	0.549–0.998
RV diameter (mm)	0.081	1.118	0.986–1.268			
Presence of pericardial effusion	0.482	1.611	0.427–6.081			
IVC diameter (mm)	0.007	1.198	1.051–1.366			
RA area (cm^2)	0.001	1.280	1.110–1.477			
RAP (mmHg)	0.012	1.206	1.042–1.397			
Cardiac Index (L/min/m^2)	0.027	0.231	0.063–0.843			
Uric acid (mg/dl)	0.003	1.444	1.131–1.842	0.037	1.444	1.022–2.042
Total protein (mg/dl)	<0.001	0.195	0.080–0.474			
Albumin (mg/dl)	0.001	0.173	0.061–0.492			
Use of loop diuretics	0.137	0.024	0.000–3.269			
6 Minutes walking distance (m)	0.002	0.983	0.973–0.994			
NYHA class III-IV	0.001	13.137	2.853–60.491			
Borg dyspnea score	0.001	1.515	1.185–1.937			

CA-125, cancer antigen 125; LV, left ventricle; AST, aspartat aminotransferase; TAPSE, tricuspid annular plane systolic excursion; RV, right ventricle; IVC, inferior vena cava; RA, right atrium; RAP, right atrial pressure; NYHA, New York Heart Association.

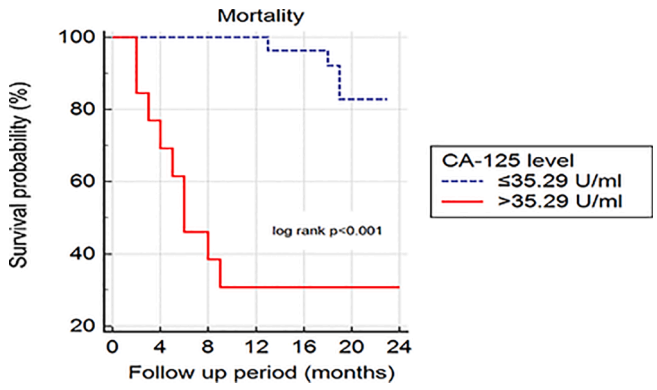

Fig. 2. Kaplan–Meier curve for long term mortality.

non-malignant cases, mainly ovarian cancer [21,22]. It has previously been shown that CA-125 is released by mesothelioma cells in the pericardium, peritoneum and pleura [23]. Prognostic value of increased CA-125 levels has been shown, particularly in heart failure. There are studies showing diagnostic and prognostic benefits of serum CA-125 levels in some pulmonary pathologies [24]. Increased venous system pressure and especially inflammation induced in the pulmonary bed are common in the pathophysiology of both PAH and heart failure. The most important triggers of CA-125 release from epithelial surfaces are also mechanical stress and inflammation. This may explain the rise of CA-125 in our patient group. However, long-term prospective studies with control groups are needed to demonstrate this fully.

It is known that CA-125 has a positive correlation with RAP in heart failure patients [25]. In our study, RAP values were higher in the deceased patients group. In addition, TAPSE, one of the indicators of RV dysfunction, was found to be worse in the deceased patients group. In addition, both RAP and TAPSE were associated with mortality in univariable analysis. However, only TAPSE was identified as an independent predictor for mortality after multivariabe analysis. Right ventricular morphology and ejection dynamics differ from the left ventricle. Longitudinal contractions of the RV free wall constitute an important part of RV systolic functions. TAPSE is important in monitoring RV dysfunction because it accurately reflects longitudinal functions and is easily and frequently reproducible. In PAH patients, the prognostic importance of TAPSE has been demonstrated in many studies. In a study in which 50 PAH patients were included, Ghio et al. observed that negative outcomes were significantly higher in the group with TAPSE value of 15 mm and below at the end of a 1-year follow-up [11]. Yılmaz et al. showed that CA-125 values were significantly higher in the presence of RV dysfunction accompanying heart failure [26]. In PAH, the resulting RV dysfunction activates the cascade of inflammation, making peripheral congestion even more pronounced. CA-125 also increases with the effect of congestion in the mesothelial areas. In our study, low TAPSE and high CA-125 values were associated with mortality in regression models.

In our study, CA-125 cut-off value was 35.29 U/ml which can predict mortality in PAH patients. In many previous studies, a value of >35 U/ml was found to be associated with poor outcomes in heart failure patients [27,28]. These data are observed to be compatible with the cut-off value of 35.29 U/ml determined in our study.

Epiney et al. showed that CA-125 levels are particularly high in pleural effusion, pericardial effusion, and in case of the presence of increased free fluid in the peritoneum [29]. In our study, the presence of pericardial effusion and the need for loop diuretics were significantly correlated with CA-125 levels. This led to the idea that the management of diuretic therapy could be carried out under the guidance of CA-125 consecutive measurements. Nunez et al. investigated the management of diuretic therapy based on CA-125 levels in patients with acute decompensated heart failure and found that all-cause mortality and recurrent hospitalizations were significantly less in the CA-125-guided treatment group [30]. There are no studies investigating the usability of CA-125 in diuretic treatment management for congestive symptoms of PAH patients. We thought that the findings in our study will provide a solid basis for the studies that can be done in this area.

Very different values can be obtained in CA-125 measurements using different analyzers. For this reason, the cut-off values found in our study cannot be generalized to all measurement methods and laboratories. As our study shows, if CA-125 is intended to be used to predict mortality in PAH, researchers must determine their own cut-off values using their existing tests. In our study, 10% more and fewer values of the cut-off value we determined to eliminate the measurement uncertainty were

also subjected to univariate and multivariate cox regression analyzes. The fact that both values are associated with a statistically significant increased risk of death increases the detection power of the cut-off value in particular for the method we use.

4.1. Study limitations

There are some limitations to the present study. The most important limitations were the relatively small sample size and the lack of a control group without PAH. B-type natriuretic peptides are established biomarkers in HF; however, this was not examined in our study. Another limitation of our study is that there are different results for CA-125 with different analysis methods and the analysis system we use is inaccessible in some countries. Because of this limitation, the values we found cannot be generalized for use in other centers. Finally, the follow-up period is also short. For this reason, there is a need for longer follow-up studies with a greater number of patients.

5. Conclusions

Non-invasive risk assessment in the follow-up of PAH patients plays a key role in determining prognosis and treatment targets. In this study, for the first time in the literature, serum CA-125 values were found to be an independent predictor in predicting mortality in PAH patients. Larger scale studies are needed to support the use of CA-125 in the risk classification of PAH patients as a cheap and easily accessible biomarker.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] M. Humbert, O. Sitbon, G. Simonneau, Treatment of pulmonary arterial hypertension, N. Engl. J. Med. 351 (14) (2004) 1425–1436.
[2] N. Galiè, M. Humbert, J.-L. Vachiery, et al., 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS)Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT), Eur. Respir. J. 46 (4) (2015) 903–975, https://doi.org/10.1183/13993003.01032-2015.
[3] R.L. Benza, D.P. Miller, M. Gomberg-Maitland, et al., Predicting survival in pulmonary arterial hypertension: insights from the registry to evaluate early and long-term pulmonary arterial hypertension disease management (REVEAL), Circulation 122 (2) (2010) 164–172, https://doi.org/10.1161/CIRCULATIONAHA.109.898122.
[4] N. Nickel, H. Golpon, M. Greer, et al., The prognostic impact of follow-up assessments in patients with idiopathic pulmonary arterial hypertension, Eur. Respir. J. 39 (3) (2012) 589–596, https://doi.org/10.1183/09031936.00092311.
[5] A. Boucly, J. Weatherald, L. Savale, et al., Risk assessment, prognosis and guideline implementation in pulmonary arterial hypertension, Eur. Respir. J. 50 (2) (2017) 1700889, https://doi.org/10.1183/13993003.00889-2017.Supp2.
[6] C. Whitehouse, E. Solomon, Current status of the molecular characterization of the ovarian cancer antigen CA125 and implications for its use in clinical screening, Gynecol. Oncol. 88 (1) (2003) S152–S157, https://doi.org/10.1006/gyno.2002.6708.
[7] X. Li, M. He, J. Zhu, et al., Higher carbohydrate antigen 125 levels are associated with increased risk of coronary heart disease in elderly Chinese: a population-based case-control study, PLoS One 8 (11) (2013) e81328.
[8] S.F. Man, J.E. Connett, N.R. Anthonisen, et al., C-reactive protein and mortality in mild to moderate chronic obstructive pulmonary disease, Thorax 61 (10) (2006) 849–853.
[9] N.T. Kouris, D.D. Kontogianni, E.P. Papoulia, et al., Clinical and prognostic value of ele- vated CA125 levels in patients with congestive heart failure, Hellenic J. Cardiol. 47 (5) (2006) 269–274.
[10] J. Nunez, S. Juan, B. Vicent, et al., Improvement in risk stratification with the combination of the tumour marker antigen carbohydrate 125 and brain natriuretic peptide in patients with acute heart failure, Eur. Heart J. 31 (14) (2010) 1752–1763.
[11] S. Ghio, C. Klersy, G. Magrini, A.M. D'Armini, L. Scelsi, C. Raineri, M. Pasotti, A. Serio, C. Campana, M. Viganò, Prognostic relevance of the echocardiographic assessment of right ventricular function in patients with idiopathic pulmonary arterial hypertension, Int. J. Cardiol. 140 (3) (2010) 272–278, https://doi.org/10.1016/j.ijcard.2008.11.051.
[12] M.B. Yilmaz, M. Nikolaou, A. Cohen Solal, Tumour biomarkers in heart failure: is there a role for CA-125? Eur. J. Heart Failure 13 (6) (2011) 579–583, https://doi.org/10.1093/eurjhf/hfr022.
[13] M. Galderisi, C. Bernard, E. Thor, et al., Standardization of adult transthoracic echocardiography reporting in agreement with recent chamber quantification, diastolic function, and heart valve disease recommendations: an expert consensus document of the European Association of Cardiovascular Imaging, Eur. Heart J.-Cardiovascular Imaging 18 (12) (2017) 1301–1310.
[14] M. Schneider, T. Binder, Echocardiographic evaluation of the right heart, Wien. Klin. Wochenschr. 130 (13-14) (2018) 413–420, https://doi.org/10.1007/s00508-018-1330-3.
[15] S. Rosenkranz, I.R. Preston, Right heart catheterisation: best practice and pitfalls in pulmonary hypertension, Eur. Respiratory Rev. 24 (138) (2015) 642–652.
[16] G. Matar, B. Poggi, R. Meley, et al., Uncertainty in measurement for 43 biochemistry, immunoassay, and hemostasis routine analytes evaluated by a method using only external quality assessment data, Clin. Chem. Lab. Med. 53 (11) (2015) 1725–1736.
[17] G. Savarese, S. Paolillo, P. Costanzo, et al., Do changes of 6-minute walk distance predict clinical events in patients with pulmonary arterial hypertension? J. Am. College Cardiol. 60 (13) (2012) 1192–1201, https://doi.org/10.1016/j.jacc.2012.01.083.
[18] J.R. Swiston, S.R. Johnson, J.T. Granton, Factors that prognosticate mortality in idiopathic pulmonary arterial hypertension: a systematic review of the literature, Respiratory Med. 104 (11) (2010) 1588–1607, https://doi.org/10.1016/j.rmed.2010.08.003.
[19] F. Haddad, E. Fuh, T. Peterson, et al., Incidence, correlates, and consequences of acute kidney injury in patients with pulmonary arterial hypertension hospitalized with acute right-side heart failure, J. Cardiac Fail. 17 (7) (2011) 533–539, https://doi.org/10.1016/j.cardfail.2011.03.003.
[20] C.E. Simpson, R.L. Damico, L. Hummers, et al., Serum uric acid as a marker of disease risk, severity, and survival in systemic sclerosis-related pulmonary arterial hypertension, 204589401985947, Pulm. Circ. 9 (3) (2019), https://doi.org/10.1177/2045894019859477.
[21] C. Miralles, M. Orea, P. Espana, et al., Cancer antigen 125 associated with multiple benign and malignant pathologies, Ann. Surg. Oncol. 10 (2) (2003) 150–154, https://doi.org/10.1245/ASO.2003.05.015.
[22] T.J. O'Brien, H. Tanimoto, I. Konishi, M. Gee, More than 15 years of CA 125: what is known about the antigen, its structure and its function, Int. J. Biol. Markers 13 (4) (1998) 188–195, https://doi.org/10.1177/172460089801300403.
[23] F. Huang, K. Zhang, J. Chen, et al., Elevation of carbohydrate antigen 125 in chronic heart failure may be caused by mechanical extension of mesothelial cells from serous cavity effusion, Clin. Biochem. 46 (16-17) (2013) 1694–1700, https://doi.org/10.1016/j.clinbiochem.2013.09.008.
[24] H. Kaya, A. Zorlu, H. Yucel, et al., Cancer antigen-125 levels predict long-term mortality in chronic obstructive pulmonary disease, Biomarkers 20 (2) (2015) 162–167, https://doi.org/10.3109/1354750X.2015.1045033.
[25] H. Nägele, M. Bahlo, R. Klapdor, et al., CA 125 and its relation to cardiac function, Am. Heart J. 137 (6) (1999) 1044–1049, https://doi.org/10.1016/S0002-8703(99)70360-1.
[26] M.B. Yilmaz, A. Zorlu, O.T. Dogan, et al., Role of CA-125 in identification of right ventricular failure in chronic obstructive pulmonary disease, Clin. Cardiol. 34 (4) (2011) 244–248, https://doi.org/10.1002/clc.20868.
[27] A. D'Aloia, P. Faggiano, G. Aurigemma, et al., Serum levels of carbohydrate antigen 125 in patients with chronic heart failure, J. Am. College Cardiol. 41 (10) (2003) 1805–1811, https://doi.org/10.1016/S0735-1097(03)00311-5.
[28] J.Y. Yoon, D.H. Yang, H.J. Cho, et al., Serum levels of carbohydrate antigen 125 in combination with N-terminal pro-brain natriuretic peptide in patients with acute decompensated heart failure, Korean J. Intern. Med. 34 (4) (2019) 811–818, https://doi.org/10.3904/kjim.2017.313.
[29] M. Epiney, C. Bertossa, A. Weil, et al., CA-125 production by the peritoneum: in-vitro and in-vivo studies, Human reproduction 15 (6) (2000) 1261–1265.
[30] J. Núñez, P. Llàcer, V. Bertomeu-González, et al., Carbohydrate antigen-125–guided therapy in acute heart failure: CHANCE-HF: a randomized study, J. Am. College Cardiol. Heart Failure 4 (11) (2016) 833–843.