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Prognostic value of pleural effusion, CA-125 and NT-proBNP in patients with acute decompensated heart failure

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Abstract

Background: Acute decompensated heart failure (HF) is a serious complication associated with significant morbidity and mortality. The CA-125 and NT-proBNP levels have been shown in some studies to predict the outcome, however, the prognostic value of other simple clinical parameters such as pleural effusion has not been established yet.

Aim: To assess the prognostic value of pleural effusion regarding in-hospital and 6-month follow-up outcome in patients with acute decompensated HF and the relationship between pleural effusion and CA-125 and NT-proBNP levels.

Methods and results: The CA-125 and NT-proBNP levels were measured at baseline and the presence of pleural effusion was examined on chest radiograms. One hundred patients were prospectively followed until the occurrence of cardiac death, defined as death from worsening HF or sudden cardiac death, or completion of follow-up period. There were 27 deaths over the course of 6 months of follow-up. An insignificant trend towards higher values of CA-125 was found in patients with pleural effusion. Univariate Cox regression analysis showed that there was no relationship between pleural effusion and in-hospital outcome as well as mortality during 6-month follow-up. The CA-125 and NT-proBNP levels predicted mortality. Multivariate Cox regression analysis showed that only CA-125 was an independent predictor of the 6-month outcome (RR: 1.2; 1.04–1.4; $p = 0.001$).

Conclusions: In patients with acute decompensated HF, accompanying pleural effusion did not predict mortality or rehospitalisation during the 6-month follow-up. The increased CA-125 level was found to be an independent predictor of poor outcome, irrespective of pleural effusion.

Key words: decompensated heart failure, pleural effusion, CA-125, NT-proBNP, prognosis

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INTRODUCTION

Chronic heart failure (CHF) is a severe clinical condition, associated with high mortality and morbidity rates. Chronic heart failure is considered a clinical syndrome occurring not only as a result of the pumping action failure, but also due to complex neurohormonal activation and inflammatory changes [1–5]. The prognosis in CHF remains poor despite advances in treatment. Half of the CHF patients die within 3–4 years, while more than 50% of those with severe CHF die within one year [2, 4]. Worsening of heart failure in the setting of CHF is called decompensation. Patients with heart failure frequently experience episodes of acute decompensated heart failure (ADHF), leading to hospital admission, which account for approximately 80% of cases [5].

As a consequence of a better understanding of the pathophysiology of ADHF, the search for novel biomarkers with potential use in the management of these patients has become an interesting and exciting field. Most of knowledge re-

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garding biomarkers focused on natriuretic peptides, particularly B-type natriuretic peptide (BNP). However, many other potential biological markers have emerged and are now under intensive research [6]. Lack of consensus for the use of appropriate biomarkers in addition to high healthcare costs limit the use of those markers in general practice. Clearly, reliable radiographic and clinical markers, additional to the plasma biomarkers, that would predict the outcome and guide therapeutic approach, are needed.

Pleural effusion is a complication which is frequently seen during ADHF. To date, clinical and prognostic value of pleural effusion accompanying ADHF has not been examined. Therefore, we tested the hypothesis whether concomitant pleural effusion in ADHF can predict in-hospital and 6-month outcome.

Recently, carbohydrate antigen 125 (CA-125), a glycoprotein synthesised by epithelial serous cells, has emerged as a potential biomarker in ADHF, by showing correlations with clinical and echocardiographic parameters indicative of the severity of the disease [7, 8]. The secondary purpose of this study was to examine whether serum levels of CA-125 and NT-proBNP correlated with pleural effusion in patients with ADHF and to assess their prognostic value in ADHF.

METHODS

Patients' selection and assessment of pleural effusion

Between December 2007 and July 2008, we had prospectively studied consecutive patients with ADHF secondary to ischaemic or idiopathic dilated cardiomyopathy. All patients were screened; the study cohort consisted of 100 consecutive patients who were admitted to the Coronary Care Unit (CCU) and who met the following criteria:

- symptomatic CHF associated with underlying structural heart disease (Stage C) or advanced structural heart disease and marked symptoms of CHF at rest despite maximal medical therapy (Stage D);
- unable to carry on any physical activity without discomfort. Symptoms at rest. If any physical activity is undertaken, discomfort is increased (NYHA functional classic IV);
- evidence of systolic dysfunction on echocardiographic examination on admission — left ventricular ejection fraction (LVEF < 40%);
- physical signs of pulmonary oedema on admission: crackles or rales over lungs, effusion, tachycardia, tachypnoea.

Exclusion criteria were as follows: renal dysfunction (serum creatinine > 1.5 mg/dL with or without haemodialysis treatment), cirrhotic liver disease, hypoalbuminaemia, malignancy, rheumatic valve disease, constrictive pericarditis, hypothyroidism, rheumatoid arthritis, systemic lupus erythematosus, parapneumonic effusion and empyema, history of tuberculosis, pulmonary embolism and history of exposure to asbestos.

All patients were treated according to the European Society of Cardiology guidelines for management and treatment of CHF [5]. The patients were discharged from the CCU when clinical status improved (between 2 and 21 days after the acute episode). The criteria of the improvement included: (a) subjective improvement measured by NYHA class with no orthopnoea; (b) hemodynamic stability: systolic blood pressure > 90 mm Hg and < 120 mm Hg; (c) heart rate < 100 bpm; (d) pulse oxymetry in ambient air > 90%; (e) normal diuresis > 1000 mL/day [9].

Study subjects were divided into two groups: patients with signs of pleural effusion and those without pleural effusion. Pleural effusion is usually seen on chest radiogram when > 200 mL of fluid is present [10]. Chest radiograms were performed on admission and after stabilisation of heart failure. The pleural effusion was quantified as follows. If detectable blunting of the posterior costophrenic angle was evident on the PA chest radiography, the quantity of pleural effusion was classified as small which was reported to correlate with pleural effusions in the range of 25 to 525 mL. Effusions were classified as moderate in size if the effusion comprised the lower part of the hemithorax but did not extend above the fourth rib on the PA view. This correlates with pleural effusions greater than 525 mL. Massive effusions were detected when expanded above the level of the fourth anterior rib on the PA view [11].

The investigation conformed to the principles outlined in the Declaration of Helsinki. The study was approved by the institutional committee and informed consent was obtained from all study participants.

Echocardiography

Complete transthoracic echocardiography was performed in all subjects (Vivid 7, GE Vingmed Ultrasound AS, Horten, Norway). Transthoracic echocardiography was performed by experienced echocardiographers without any knowledge of the biochemical and radiological data after achievement of clinical stability. All patients underwent a comprehensive examination, including M-mode, 2-dimensional and Doppler echocardiography. The left atrial diameter was estimated from the parasternal long-axis view. The left ventricular end-systolic and end-diastolic volumes, and LVEF were measured from the apical 4-chamber view using the modified Simpson's single plane method.

Biochemistry

Blood was sampled from a short polyethylene cannula placed in an antecubital vein. Test tubes were placed on ice and centrifuged immediately. Plasma samples were stored at – 80°C until analysis. Levels of serum CA-125 were determined using commercially available assay kits (Immulite 2000 Analyzer, Los Angeles, USA). Plasma NT-proBNP levels were measured by Stratus CS STAT Fluorometric Analyzer (Dade Behring, Newark, USA).

Follow-up

Patients were prospectively followed in the outpatient clinic for 6 months. The cardiac death, defined as death from worsening of CHF or sudden cardiac death, was the study outcome. The review of medical records and follow-up regular telephone interviews were performed monthly by cardiologists, who were blinded to blood examination data and radiological findings. Additionally, in-hospital outcome (duration, mortality) was also assessed in all patients.

Statistical analysis

Data were analysed using SPSS (Statistical Package for Social Sciences) version 10.0. Numerical values are reported as mean ± standard deviation, or as a proportion of the sample size. The differences in normally distributed parameters were assessed using Student t-test. In the case of variables with more than two categories, the one-way ANOVA test was carried out. Discrete variables were expressed as counts or percentages, and compared using a χ^2 test. As the measured data were markedly skewed (CA-125 and NT-proBNP), all values are expressed as median — interquartile range. Analysis of the differences between subgroups was performed using the non-parametric Mann-Whitney test. The correlation between two variables was studied with the Pearson test, depending on whether the variables had a normal (parametric) distribution, or not. Cumulative mortality curves were estimated using the Kaplan-Meier method. A univariate and multivariate model to identify potential risk factors for end points was assessed using the Cox regression analysis. In all analyses a p value < 0.05 was considered statistically significant.

RESULTS

The study population consisted of 100 patients (59 males and 41 females, mean age of 65 ± 10 years). Baseline clinical characteristics, risk factors, medications, laboratory, and echocardiographic parameters of the patients with or without pleural effusion are presented in Table 1. Age and gender were equally distributed. Forty seven subjects had pleural effusion. Distribution of pleural effusion was as follows: mild effusion (n = 29; 13 were localised in the right hemithorax, 16 were bilateral); moderate effusion (n = 15; 3 were present in the right hemithorax, 1 was localised in the left hemithorax, and 11 were bilateral); and massive effusion (n = 3; 2 were bilateral, 1 was isolated in right hemithorax).

During a 6-month follow-up period there were 27 deaths (13 in group 1 and 14 in group 2, NS). There were no differences between the two groups in terms of echocardiographic characteristics and routine biochemistry findings. The serum CA-125 and NT-proBNP levels in patients with or without pleural effusion are shown in Table 2. A trend towards higher values of CA-125 was found in patients with pleural effusion.

The relationship between pleural effusion and in-hospital mortality as well as hospitalisation is shown in Table 2. There was no impact of pleural effusion on mortality and duration of hospitalisation. There was a significant correlation between CA-125 and NT-proBNP levels, which was independent from the presence of pleural effusion (Fig. 1).

The 6-month prognosis was similar in patients with or without pleural effusion. The survival curves for patients with or without pleural effusion are shown in Figure 2.

The Univariate Cox regression analysis showed that there was no effect of pleural effusion on mortality during a 6-month follow-up ($p = 0.400$). Every 50 U/L increase in level of CA-125 increased probability of death by 1.29 (1.13–1.47); $p < 0.001$; every 1000 pg/dL increase in NT-proBNP level increased probability of death by 1.08 (1.03–1.14); $p = 0.004$ (Table 3).

The multivariate Cox regression analysis showed that pleural effusion had no significant effect on prognosis and the effects of NT-proBNP on prognosis, seen in the univariate Cox regression model, disappeared using a multivariate model. The CA-125 level was the only independent predictor at cardiac death during a 6-month follow-up period (Table 4).

DISCUSSION

In the present study, we showed that: 1) pleural effusion concomitant with ADHF had no influence on the length of hospitalisation, mortality or rehospitalisation during 6 months of follow-up, 2) there is a trend towards higher values of CA-125 in patients with pleural effusion, 3) NT-proBNP levels were similar in patients with or without pleural effusion, 4) CA-125 levels strongly correlated with NT-proBNP levels, independent from the presence of pleural effusion, 5) univariate analysis showed that CA-125 and NT-proBNP levels were independent factors to predict adverse clinical outcome and 6) multivariate analysis demonstrated that only CA-125 level was an independent factor predicting 6-month mortality.

Despite high mortality following an episode of CHF decompensation, patients' risk stratification is not performed routinely, due to limited availability of biomarkers. Clearly, clinical or reliable plasma biomarkers, which could help in accessing the severity of ADHF, guide therapeutic approach, and predict clinical outcome of chronic heart failure, would be highly beneficial [6]. Although there are many causes of pleural effusion, the most common remains CHF [11]. Patients with CHF frequently experience episodes of ADHF requiring immediate therapy. Normally the amount of fluid in the pleural space is < 20 mL. Increased pleural capillary filtration occurs in patients with right or left HF. In these patients either elevated capillary hydrostatic pressure, or increased absorption of pulmonary interstitial oedema leads to the formation of a transudate which results in excess fluid accumulation in this space and can not be removed through nor-

Table 1. Baseline clinical characteristics, risk factors, medications, laboratory and echocardiographic parameters of the study patients

Parameter	Patients with pleural effusion	Patients without pleural effusion	P
Age [years]	66 ± 10	64 ± 9	NS
Women [%]	36	45	NS
Diabetes mellitus [%]	57	51	NS
Insulin usage [%]	25	22	NS
DCM [%]	89	88	NS
Hypertension [%]	27	24	NS
Smoking [%]	48	18	0.003
History of CABG [%]	17	22	NS
Beta-blocker [%]	53	69	0.08
ACEI [%]	87	70	0.03
Digoxin [%]	53	43	NS
Diuretics [%]	100	85	0.005
Statins [%]	14	26	NS
Amiodarone [%]	4	2	NS
AF [%]	17	8	NS
VT	1	2	NS
Hgb [g/dL] (mean)	12 ± 1.7	13 ± 1.9	NS
Total cholesterol (mean)	160 ± 59	168 ± 52	NS
LDL-colesterol (mean)	97 ± 41	113 ± 88	NS
HDL-cholesterol (mean)	35 ± 10	39 ± 22	NS
Triglyceride (mean)	153 ± 77	185 ± 38	NS
Creatinine (mean)	1.1 ± 0.9	1.2 ± 0.7	NS
EF [%]	34 ± 7	33 ± 7	NS
LVEDD [cm]	5.8 ± 09	5.7 ± 08	NS
LVESD [cm]	4.1 ± 1.3	4.2 ± 1.2	NS

DCM — dilated cardiomyopathy; CABG — coronary artery bypass grafting; ACEI — angiotensin converting enzyme inhibitor; AF — atrial fibrillation; VT — ventricular tachycardia; Hgb — haemoglobin; EF— ejection fraction; LVEDD — left ventricular end-diastolic diameter; LVESD — left ventricular end-systolic diameter

Table 2. Comparison of CA-125 and NT-proBNP levels as well as in-hospital course in patients with or without pleural effusion

	Pleural effusion		P
	Negative (n = 53)	Positive (n = 47)	
CA-125 [U/L]	27.8 (79.7)	63.9 (211.1)	0.074
NT-proBNP [g/dL]	6640.8 (13368.6)	6737.1 (16108.2)	0.310
In-hospital mortality	3 (7.7%)	1 (2.1%)	0.325*
Duration of hospitalisation [days]	9 (1–74)	8 (2–55)	0.975**

Data are given as median (min–max); *Fisher's Exact test; **Mann-Whitney U test

mal processes [10]. When CHF is complicated by pleural effusion, assessment and planning care for the patient becomes more complicated.

Pleural effusion which is generally associated with dyspnoea, may reduce lung volume and may compromise the cardiovascular system [12]. Until now, the prognostic value of pleural effusion in ADHF has not been examined. Our study showed that pleural effusion has no predictive value.

We also sought to determine the contribution of CA-125 to the pleural effusion and its relation with the NT-proBNP levels. Although we showed only a trend towards higher values of CA-125 in patients with pleural effusion, CA-125 oc-

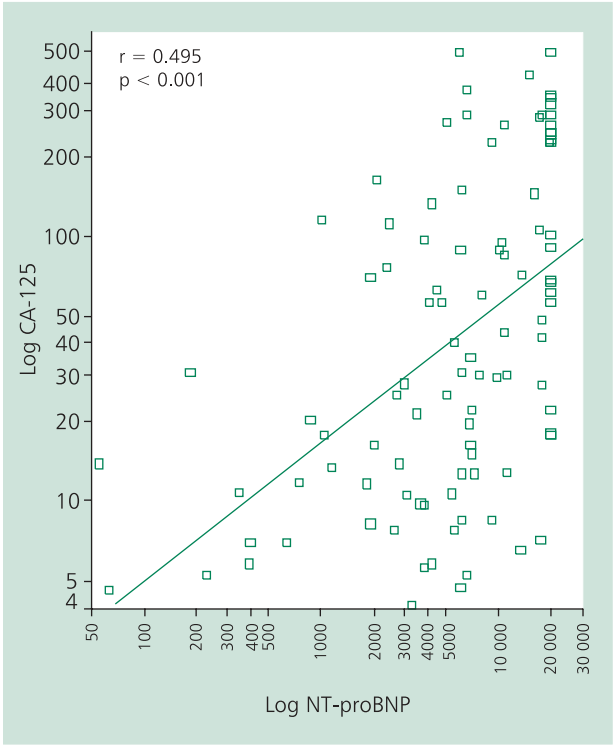

Figure 1. Correlation between CA-125 and NT-proBNP

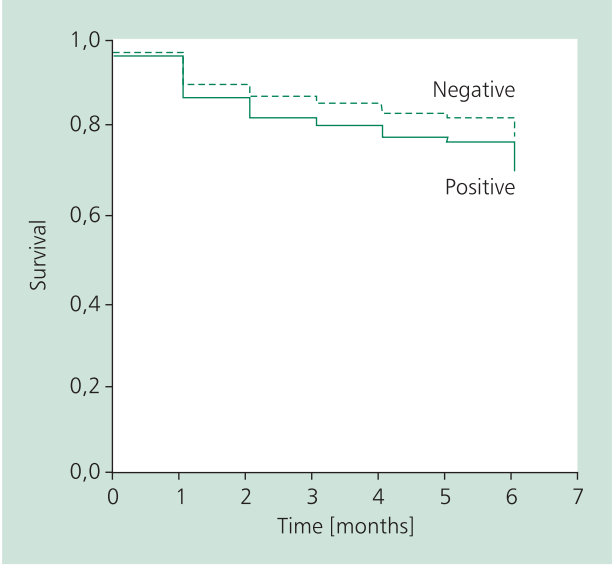

Figure 2. Survival curves for patients with and without pleural effusion

curred to be a prognostic parameter. Our study confirmed results of previous reports demonstrating the adverse prognostic risk of increased CA-125 level in ADHF patients [13, 14]. In one of these studies serum levels of CA-125 were shown to be an independent predictor of mortality during a 6-month follow-up, however, diagnostic accuracy of CA-125 was not correlated with NT-proBNP [14]. In another study of 95 patients with advanced CHF, serum level of CA-125 was associated with the severity of CHF and was independent predictive marker for re-hospitalisation. However, in contrast to our study, CA-125 did not predict mortality [13]. This discrepancy might be due to the fact that our subjects had more advanced CHF. Similar to our results, a trend towards higher values of CA-125 was reported [13].

In our study 5 patients had evidence of mild to moderate pericardial effusion on echocardiography. In these patients' levels of CA-125 were high, identically to the other studies [15, 16].

The cause of rising levels of CA-125 in CHF remains unknown. The CA-125 level is increased in patients with pericardial, pleural and peritoneal effusions [15, 17, 18]. We found only a non-significant trend towards higher values of CA-125 in patients with pleural effusion. However, the CA-125 was found as a prognostic marker independent from pleural effusion in the present study. Thus, we can speculate that the main source of CA-125 is beyond pleural fluid production capacity, which was suggested by Turk et al. [18].

Pleura is one of the sources of CA-125. It contains mesothelial cells which are able to synthesise CA-125 in response to increase in systemic and pulmonary venous pressure [18]. Moreover, it has been speculated that, even in the absence of fluid accumulation, increased cytokine stimulation, which are seen in CHF, may trigger production of CA-125 from mesothelial cells [19, 20]. In fact, our study confirmed this suggestion. Numerous reports have highlighted that plasma levels of inflammatory markers are increased in CHF [21, 22]. In our study we found increased level of CA-125 even in the absence of significant pleural effusion. It has been suggested that interleukin-6 plays an important role in production of CA-125, since there are data showing that proliferation of CA-125-producing cells is stimulated by this cytokine [19, 20]. Recently, Duman et al. [23] reported a close relationship between increased CA-125 levels and severe mitral stenosis compared to healthy controls. Previously we have reported that serum inflammatory cytokines were increased and stron-

Table 3. Influence of pleural effusion, CA-125, and NT-proBNP on 6-month survival (Univariate Cox regression analysis)

	Relative risk	Wald	P	95% confidence interval (RR)
Pleural effusion	1.393	0.709	0.400	0.644–3.014
CA-125*	1.288	13.811	< 0.001	1.127–1.473
NT-proBNP**	1.083	8.360	0.004	1.026–1.143

*Every increase of 50 U/L in the level of CA-125; **every increase of 1000 pg/dL in the level of NT-proBNP

Table 4. Influence of pleural effusion, CA-125, and NT-proBNP on 6-month survival (multivariate Cox regression analysis)

	Relative risk	Wald	P	95% confidence interval (RR)
Pleural effusion	1.200	0.211	0.646	0.552–2.611
CA-125*	1.222	6.430	0.011	1.047–2.611
NT-proBNP**	1.049	2.432	0.119	0.988–1.113

*Every increase of 50 U/L in the level of CA-125; **every increase of 1000 pg/dL in the level of NT-proBNP

gly correlated with functional capacity in severe chronic rheumatic valve disease [24, 25]. Taken together, we believe that one of the important underlying mechanisms of increased CA-125 in advanced CHF is activation of inflammatory cytokines.

Limitations of the study

First, the number of patients is relatively small. Nonetheless, we were able to show significant independent predictive value of CA-125. Secondly, because we excluded patients with chronic renal disease, our data should not be generalised to all patients with CHF and renal failure. Thirdly, we did not perform diagnostic thoracentesis routinely. Large effusions, those > 200 mL, are easily identified on the posterior-anterior chest film. After clinical exclusion of other possible causes of pleural effusion, in our view, diagnostic thoracentesis is not necessary in the setting of advanced CHF. In addition, in the presence of persistent effusion, the Light's criteria would not enable to differentiate transudate from exudate more accurately, since the pleural protein is unhelpful in this setting. Additionally, it is not ethical to perform routine thoracentesis for the diagnostic purpose in patients with advanced CHF except in the presence of high clinical suspicion of exudative cause. In all our cases, clinical judgement was concordant with transudative pleural effusion. Thoracentesis was performed only in 3 patients who had massive effusion and required invasive evacuation of fluid. Fourthly, we did not include hospitalisation due to aggravation of CHF as an and-point during follow-up because the reasons for hospitalisation were not always clear and could have introduced additional confusion. Finally, there was a statistically important correlation between NT-proBNP and CA-125, and they were both were included in the multivariate analysis. We believe that due to that correlation, the prognostic significance of NT-proBNP in the multivariate model could be artificially decreased.

CONCLUSIONS

It is interesting to note that only CA-125 was an independent predictor of prognosis at 6-month follow-up. According to our findings, CA-125 is more reliable prognostic marker than NT-proBNP. If these data are replicated in larger studies, CA-125 may be utilised for risk stratification in CHF patients in the future.

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Wartość prognostyczna płynu w opłucnej oraz stężenia antygenu CA-125 i NT-proBNP u pacjentów z ostrą dekompensacją niewydolności serca

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Streszczenie

Wstęp: Ostra dekompensacja niewydolności serca jest poważnym powikłaniem związanym z istotną chorobowością i śmiertelnością. W niektórych badaniach wykazano, że stężenia antygenu CA-125 i N-końcowego fragmentu propeptydu peptydu natriuretycznego typu B (NT-proBNP) pozwalają przewidywać rokowanie, ale dotychczas nie ustalono wartości prognostycznej innych prostych parametrów klinicznych, takich jak płyn w opłucnej.

Cel: Celem pracy była ocena wartości prognostycznej płynu w opłucnej w odniesieniu do wewnątrzszpitalnych i 6-miesięcznych wyników leczenia u pacjentów z ostrą dekompensacją niewydolności serca, a także zależności między obecnością płynu w opłucnej a stężeniem antygenu CA-125 i NT-proBNP.

Metody i wyniki: Stężenia antygenu CA-125 i NT-proBNP oznaczano na początku obserwacji, a obecność płynu w opłucnej oceniano na zdjęciu rentgenowskim klatki piersiowej. Obserwowano prospektywnie 100 pacjentów aż do wystąpienia zgonu z przyczyn sercowych, zdefiniowanego jako zgon z powodu nasilenia niewydolności serca bądź nagły zgon sercowy, lub do zakończenia okresu obserwacji. W trakcie 6-miesięcznej obserwacji wystąpiło 27 zgonów. Wśród pacjentów z płynem w opłucnej stwierdzono nieistotną statystycznie tendencję w kierunku większych wartości stężenia antygenu CA-125. W jednozmiennej analizie regresji Coxa nie wykazano zależności między obecnością płynu w opłucnej a wewnątrzszpitalnymi wynikami leczenia oraz umieralnością w 6-miesięcznej obserwacji. Stężenia antygenu CA-125 i NT-proBNP pozwalały przewidywać umieralność. W wielozmiennej analizie regresji Coxa wykazano, że niezależnym wskaźnikiem predykcyjnym wyników leczenia po 6 miesiącach było tylko stężenie antygenu CA-125 (ryzyko względne 1,2; przedział ufności 1,04–1,4; $p = 0,001$).

Wnioski: U pacjentów z ostrą dekompensacją niewydolności serca współistnienie płynu w opłucnej nie pozwalało przewidywać umieralności oraz ryzyka ponownej hospitalizacji w ciągu 6-miesięcznej obserwacji. Stwierdzono, że zwiększone stężenie antygenu CA-125 było niezależnym wskaźnikiem predykcyjnym niekorzystnego rokowania, którego wartość prognostyczna nie wykazywała związku z obecnością płynu w opłucnej.

Słowa kluczowe: dekompensacja niewydolności serca, płyn w opłucnej, CA-125, NT-proBNP, rokowanie

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