

# Cancer Antigen 125 is Associated with Length of Stay

in Patients with Acute Heart Failure

Hakki Kaya, MD  
Recep Kurt, MD  
Osman Beton, MD  
Ali Zorlu, MD  
Hasan Yucel, MD  
Hakan Gunes, MD  
Didem Oguz, MD  
Mehmet Birhan Yilmaz,  
MD, FACC

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**From:** Department of Cardiology (Drs. Beton, Kaya, Kurt, Yilmaz, Yucel, and Zorlu), Cumhuriyet University Medical School, 58140 Sivas; Cardiology Clinic, Sivas Numune Hospital (Dr. Gunes), 58040 Sivas; and Department of Cardiology (Dr. Oguz), Baskent University Medical School, 06500 Ankara; Turkey

**Address for reprints:**  
Hakki Kaya, MD, Department of Cardiology, Cumhuriyet University Medical School, Kayseri St. No:69, 58140 Sivas, Turkey

**E-mail:**  
drhakkikaya84@gmail.com

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*Length of stay is the primary driver of heart-failure hospitalization costs. Because cancer antigen 125 has been associated with poor morbidity and mortality rates in heart failure, we investigated the relationship between admission cancer antigen 125 levels and lengths of stay in heart-failure patients. A total of 267 consecutive patients (184 men, 83 women) with acute decompensated heart failure were evaluated prospectively. The median length of stay was 4 days, and the patients were classified into 2 groups: those with lengths of stay  $\leq 4$  days and those with lengths of stay  $> 4$  days. Patients with longer lengths of stay had a significantly higher cancer antigen 125 level of 114 U/mL (range, 9–298 U/mL) than did those with a shorter length of stay (19 U/mL; range, 3–68) ( $P < 0.001$ ). The optimal cutoff level of cancer antigen 125 in the prediction of length of stay was  $> 48$  U/mL, with a specificity of 95.8% and a sensitivity of 96% (area under the curve, 0.979; 95% confidence interval [CI], 0.953–0.992). In the multivariate logistic regression model, cancer antigen 125  $> 48$  U/mL on admission (odds ratio=4.562; 95% CI, 1.826–11.398;  $P=0.001$ ), sodium level ( $P<0.001$ ), creatinine level ( $P=0.009$ ), and atrial fibrillation ( $P=0.015$ ) were also associated with a longer length of stay after adjustment for variables found to be statistically significant in univariate analysis and correlated with cancer antigen 125 level. In addition, it appears that in a cohort of patients with acute decompensated heart failure, cancer antigen 125 is independently associated with prolonged length of stay. (Tex Heart Inst J 2017;44(1):22-8)*

**H**eat failure (HF) is a complex clinical syndrome with high mortality and morbidity rates.<sup>1</sup> Acute decompensated HF is among the most important causes of death all over the world and constitutes the most frequent cause of hospitalization, especially in patients older than 65 years of age.<sup>2-6</sup> Because of its high prevalence, poor clinical course, and heavy economic burden, it is important to classify the risk of this disease in hospitalized patients and to determine which patients are expected to have a long hospital stay.<sup>7-10</sup>

Cancer antigen 125 (CA-125) is a high-molecular-weight, soluble glycoprotein, which is released from coelomic or müllerian epithelium and has long been used as a tumor marker in ovarian cancers.<sup>11</sup> However, in the last decade, a correlation between serum CA-125 levels and cardiopulmonary diseases such as left- and right-sided HF, coronary artery disease, atrial fibrillation (AF), and chronic obstructive pulmonary disease (COPD), has been revealed.<sup>12-19</sup> Although serum CA-125 levels are significantly increased in HF and this increase correlates with the severity of the disease, the relationship between CA-125 and length of stay (LOS) in patients with HF has not yet been evaluated. This study is the first that attempts to evaluate the relationship between the duration of hospitalization and CA-125 levels in patients with HF.

## Patients and Methods

A total of 300 consecutive patients, admitted to the emergency unit and then hospitalized at Cumhuriyet University Hospital (Turkey) for decompensated HF from January 2011 through January 2015, were prospectively considered for enrollment in this study. Subsequently excluded from the 300 were 33 patients: 11 patients with previous diagnoses of malignancies, 3 with previous diagnoses of cirrhotic hepatic disease, 5 with diagnoses of active inflammatory diseases, 1 with a diagnosis of nephrotic syndrome, 8 with a high CA-125 level ( $\geq 300$  U/mL, suspected malignancy), and

5 with diagnoses of gynecologic diseases (Fig. 1). The remaining 267 patients (184 men and 83 women) were enrolled in the study after giving their informed consent. The study was performed in accordance with the Declaration of Helsinki for Human Research, and was approved by our hospital's institutional review board.

Decompensated HF was diagnosed on the basis of recent deterioration of symptoms in combination with signs of HF, as suggested in published guidelines.<sup>20,21</sup> Blood samples for CA-125 and other routine testing were taken within 30 minutes of admission. The samples were stored under appropriate conditions, then serum CA-125 levels were determined with use of the AxSYM® Plus Immunoassay Analyzer (Abbott Laboratories; Abbott Park, Ill). The AxSYM CA-125 assay has its basis in microparticle enzyme immunoassay, a technology that uses a solution of suspended, submicron-sized latex particles for the purpose of measurement. Throughout their hospitalizations, all patients were monitored by a cardiologist who was blinded to the study and to the treatment methods; the time of discharge was decided by this cardiologist. Each patient's LOS, chronic HF medications, in-hospital medications—including positive inotropic agents (dopamine, dobutamine, or both)—and other data at admission, were obtained by the same cardiologist. Hypertension was defined as

blood pressure  $\geq 140/90$  mmHg on more than 2 occasions during official measurements or as the patient's being on antihypertensive therapy. Diabetes mellitus (DM) was defined as a fasting blood glucose level  $\geq 126$  mg/dL or as the patient's being on antidiabetic therapy.

Transthoracic echocardiographic examinations were undertaken by experienced echocardiographers, blinded to the study, via the Vivid 7® cardiac ultrasonography system (GE VingMed Ultrasound AS; Horten, Norway) with 2.5- to 5-MHz probes. The left ventricular ejection fraction (LVEF) was calculated with use of the modified Simpson method, in line with the most recent European Society of Cardiology guidelines.<sup>21</sup> Chamber sizes were defined in accordance with published guidelines.<sup>22</sup> Systolic pulmonary artery pressure (SPAP) was calculated by using the peak velocity of tricuspid regurgitation and an estimate of right atrial pressure.<sup>23,24</sup> The presence or absence of pericardial effusion was noted.

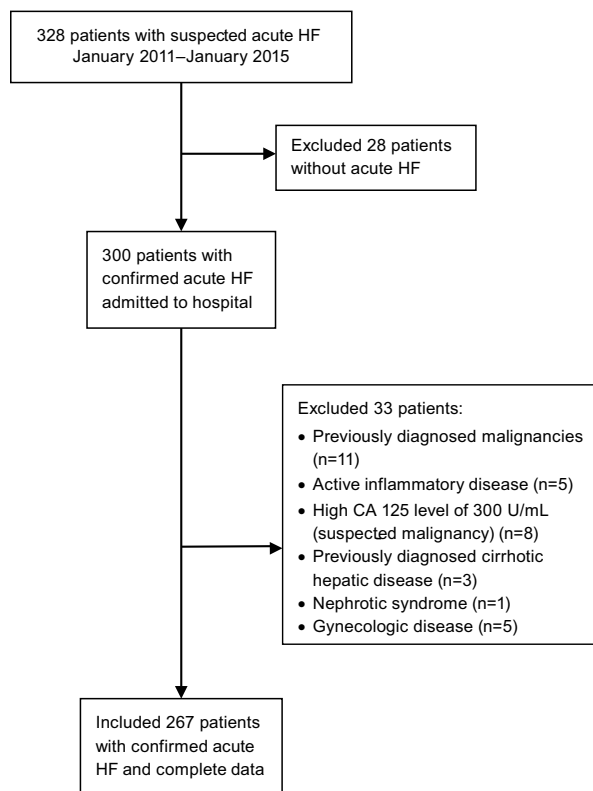
### Statistical Analysis

Data management and analysis were performed with use of SPSS version 14 (IBM Corporation; Armonk, NY), and a 2-sided  $P$  value  $\leq 0.05$  was considered statistically significant. Continuous data are expressed as mean  $\pm$  SD or as median, and categorical data are expressed as percentages. Means were compared via an independent-sample  $t$  test, and, in the event of no normal distribution, via a Mann-Whitney U test with median. Categorical data were evaluated by using the  $\chi^2$  test, as appropriate. Correlation was evaluated by means of the Spearman correlation test. A receiver operator characteristic curve analysis was performed to identify the optimal cutoff point of CA-125 for the prediction of prolonged LOS. The area under the curve (AUC) with 95% confidence interval (CI) was calculated in prediction of prolonged LOS. The optimal cutoff value of CA-125 was defined as the value associated with the highest sum of sensitivity and specificity-1 (Youden index). We used univariate analysis to quantify the association between variables and prolonged LOS. The variables found to be statistically significant in the univariate analysis, and other potential confounders, were used in a multivariate logistic regression model with forward stepwise method in order to determine the independent prognostic factors of prolonged LOS.

### Results

The mean age of the patients was  $68 \pm 11$  years. The median LVEF was 0.37, and there were 144 HF patients with reduced LVEF and 123 HF patients with preserved LVEF. The median CA-125 level was 46 U/mL. The median LOS was 4 days, and the mean LOS was  $4.7 \pm 3$  days (range, 1–15 d).

Patients were classified into 2 groups on the basis of median LOS (LOS  $\leq 4$  d versus  $>4$  d). Table I shows



**Fig. 1** Flow chart shows the patient selection process.

CA-125 = cancer antigen 125; HF = heart failure

the baseline clinical characteristics of the patients in terms of that LOS. Patients with LOS >4 days had higher CA-125 levels than did patients with LOS ≤4 days (114 [range, 9–298] U/mL vs 19 [range, 3–68] U/mL; *P*<0.001). Moreover, patients with LOS >4 days were older and had larger left atrial diameters, higher SPAP measurements, and higher blood urea nitrogen (BUN) and creatinine levels. In addition, the presence of DM, AF, right ventricular dilation, and pericardial effusion—together with the rate of using positive inotropic drugs—were higher in patients with LOS >4 days. However, LVEFs, blood levels of sodium, potassium, and albumin, and the rates of prehospital use of β-blockers and diuretics were lower in patients with LOS >4 days.

In HF patients, CA-125 levels correlated positively with age, SPAP, left atrial diameter, and BUN and creatinine levels; they were associated with the presence of DM, AF, right ventricular dilation, and pericardial effusion, and with the use of positive inotropic agents while in the hospital. Conversely, CA-125 was negatively cor-

related with sodium, potassium, albumin, and hemoglobin levels, and with LVEF; it was associated with the prehospital use of β-blockers and diuretics (Table II).

The optimal cutoff level of CA-125 in the prediction of prolonged LOS was found to be >48 U/mL, with specificity of 95.8% and sensitivity of 96% (AUC=0.979; 95% CI, 0.953–0.992; *P*=0.0001 (Fig. 2).

Table III shows the results of the univariate and multiple logistic regression analyses of prolonged LOS. A CA-125 level >48 U/mL on admission and many other factors had prognostic significance in univariate analysis, whereas in the multiple logistic regression model, using the forward stepwise method, CA-125 level >48 U/mL (OR=4.562; 95% CI, 1.826–11.398; *P*=0.001), sodium level (OR=0.727; 95% CI, 0.655–0.807; *P*<0.001), creatinine level (OR=2.004; 95% CI, 1.193–3.367; *P*=0.009) and the presence of AF (OR=2.073; 95% CI, 1.149–3.74; *P*=0.015) remained associated with an increased risk of prolonged LOS, after adjusting for the variables found to be statistically significant in

**TABLE I.** Baseline Characteristics of the Patients

Variable	All Patients (n=267)	Length of Stay		P Value
		≤4 Days (n=142)	>4 Days (n=125)	
<b>Baseline characteristics</b>				
Age (yr)	68 ± 11	66 ± 12	70 ± 10	0.005
Male/female	184/83	96/46	88/37	0.623
Hypertension	144 (54)	81 (57)	63 (50)	0.277
Diabetes mellitus	75 (28)	32 (22)	43 (34)	0.031
Current smoking	90 (34)	43 (30)	47 (38)	0.174
Atrial fibrillation	102 (38)	40 (28)	62 (50)	<0.001
<b>Echocardiographic findings</b>				
Left atrial diameter (cm)	4.5 (2.7–6.9)	4.3 (2.7–6.4)	4.5 (3–6.9)	<0.001
LV ejection fraction	0.37 (0.10–0.65)	0.39 (0.10–0.65)	0.35 (0.10–0.64)	0.044
LV diastolic diameter (cm)	5.3 ± 0.8	5.3 ± 0.8	5.4 ± 0.8	0.529
Right ventricular dilation	172 (64)	65 (46)	107 (86)	<0.001
SPAP (mmHg)	36 (12–90)	32 (12–90)	40 (14–80)	<0.001
Pericardial effusion	41 (15)	13 (9)	28 (22)	0.005
<b>Laboratory findings</b>				
CA-125 (U/mL)	46 (3–298)	19 (3–68)	114 (9–298)	<0.001
Hemoglobin (g/dL)	2.9 ± 2.2	13.2 ± 2.2	12.7 ± 2.2	0.054
Blood urea nitrogen (mg/dL)	26 (6–103)	23 (9–103)	32 (6–91)	0.002
Creatinine (mg/dL)	1.1 (0.5–6.5)	1 (0.5–5.7)	1.3 (0.5–6.5)	<0.001
Sodium (mmol/L)	133 ± 4	134 ± 3	131 ± 3	<0.001
Potassium (mmol/L)	4.2 ± 0.6	4.3 ± 0.6	3.9 ± 0.6	<0.001
Albumin (g/dL)	3.9 ± 0.7	4 ± 0.6	3.7 ± 0.7	<0.001
ALT (U/L)	20 (4–1,353)	21 (4–1,164)	20 (6–1,353)	0.538
<b>Chronic medication</b>				
ACEI/ARB	216 (81)	119 (84)	97 (78)	0.258
β-blocker	222 (83)	128 (90)	94 (75)	0.002
Diuretic	204 (76)	118 (83)	86 (69)	0.006
<b>In-hospital medication</b>				
Positive inotropic agents	49 (18)	10 (7)	39 (31)	<0.001

ACEI/ARB = angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; ALT = alanine aminotransferase; CA-125 = cancer antigen 125; LV = left ventricular; SPAP = systolic pulmonary artery pressure

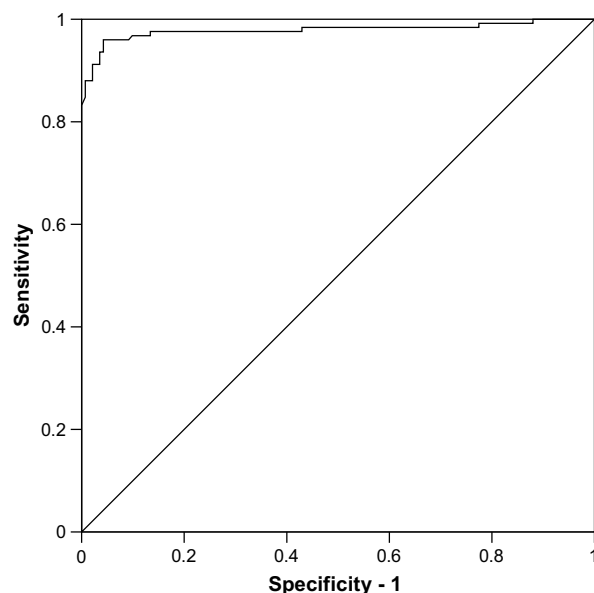
Data are presented as mean ± SD, number and percentage, or median and range. *P* ≤ 0.05 was considered statistically significant.

**TABLE II.** Spearman Correlation Coefficients for CA-125

Variable	CA-125	P Value
Age	0.149	0.015
Diabetes mellitus	0.143	0.02
Atrial fibrillation	0.359	<0.001
SPAP	0.258	<0.001
Right ventricular dilation	0.477	<0.001
Left atrial diameter	0.292	<0.001
Pericardial effusion	0.185	0.002
Blood urea nitrogen	0.272	<0.001
Creatinine	0.302	<0.001
Sodium	-0.415	<0.001
Potassium	-0.314	<0.001
Albumin	-0.278	<0.001
Hemoglobin	-0.145	0.018
LV ejection fraction	-0.134	0.029
β-blocker	-0.209	0.001
Diuretic	-0.228	<0.001
Positive inotropic support	0.365	<0.001

CA-125 = cancer antigen-125; LV = left ventricular; SPAP = systolic pulmonary artery pressure

$P \leq 0.05$  was considered statistically significant.



**Fig. 2** This receiver operating characteristic curve shows that the optimal cutoff level of CA-125 in the prediction of prolonged length of stay was >48 U/mL, with specificity of 95.8% and sensitivity of 96% (area under the curve=0.979; 95% confidence interval, 0.953–0.992;  $P=0.0001$ ).

the univariate analysis and for the variables correlated with the CA-125 level.

## Discussion

To our knowledge, for the first time in the medical literature, we have illustrated that high CA-125 levels are independently associated with prolonged LOS in patients hospitalized with acute decompensated HF. This decompensation has an increased prevalence in developed countries because of the higher average ages there; and the prolonged and frequent hospitalizations create a severe financial burden.<sup>25-29</sup> In addition, prolonged hospitalization leads to hyponatremia, hypoalbuminemia, hypokalemia, renal and hepatic insufficiency, anemia, embolic and hemorrhagic sequelae, and increased nosocomial infections—further increasing morbidity and mortality rates in patients with HF.<sup>30-35</sup>

Together with identifying patients who are expected to have prolonged hospitalizations, we need to develop new strategies for the follow-up and treatment of these patients, which would create both economic and clinical advantages. Although limited in number, there are studies that relate to the predictors of LOS in HF patients. One such study<sup>36</sup> associated chronic renal failure, COPD, and DM with LOS. Another<sup>37</sup> grouped patients in accordance with economic status and evaluated LOS predictors: in multivariate analysis, chronic renal failure was associated with LOS in all economic groups. Whellan and colleagues' study<sup>27</sup> of 70,000 patients found that factors such as AF, COPD, DM, chronic renal failure, female sex, low systolic blood pressure, high heart rate, and low levels of hemoglobin, high levels of BUN, and high levels of brain natriuretic peptide were associated with prolonged LOS. Sahin and associates<sup>38</sup> found that low systolic blood pressure, high BUN, anemia, and severe mitral insufficiency at the time of admission were independently associated with LOS. In patients older than age 65 years, only female sex and poor functional class at the time of hospitalization were found to be correlated with LOS.<sup>39</sup> Finally, low sodium and albumin values at the time of hospital admission and history of hypertension were independently associated with hospitalization longer than 10 days.<sup>40</sup>

As did the previous studies, our current study found that presence of AF and higher creatinine levels were independently associated with hospitalization longer than 4 days. In addition, we found that high CA-125 levels and low sodium levels were associated with prolonged LOS. Although other studies have identified female sex, DM, anemia, and lower albumin levels to be independent predictors, these factors were significant only in the univariate analysis in our study, not in the multivariate analysis. Distinctive from the other investigators of this topic, we evaluated the effects upon LOS

**TABLE III.** Univariate and Multivariate Analyses for Prolonged Length of Stay

Variable	Univariate		Multivariate	
	OR (95% CI)	P Value	OR (95% CI)	P Value
<b>Statistically significant variables</b>				
CA-125 >48 U/mL	3.881 (1.741–8.65)	0.001	4.562 (1.826–11.398)	0.001
Atrial fibrillation	2.51 (1.512–4.165)	<0.001	2.073 (1.149–3.74)	0.015
Sodium	0.722 (0.655–0.796)	<0.001	0.727 (0.655–0.807)	<0.001
Creatinine	1.893 (1.226–2.924)	0.004	2.004 (1.193–3.367)	0.009
Age	1.032 (1.009–1.056)	0.007	—	—
Diabetes mellitus	0.555 (0.323–0.952)	0.032	—	—
Left atrial diameter	2.058 (1.41–3.005)	<0.001	—	—
Right ventricular dilation	7.042 (3.87–12.813)	<0.001	—	—
SPAP	1.034 (1.013–1.056)	0.001	—	—
Pericardial effusion	2.864 (1.41–5.818)	0.004	—	—
Blood urea nitrogen	1.018 (1.004–1.032)	0.011	—	—
Potassium	0.298 (0.183–0.485)	<0.001	—	—
Albumin	0.449 (0.304–0.664)	<0.001	—	—
β-blocker	0.332 (0.167–0.658)	0.002	—	—
Diuretic	0.449 (0.251–0.801)	0.007	—	—
Positive inotropic support	5.986 (2.839–12.621)	<0.001	—	—
<b>Variables correlating with CA-125</b>				
LV ejection fraction	0.983 (0.963–1.003)	0.095	—	—
Hemoglobin	0.897 (0.803–1.003)	0.056	—	—

CA-125 = cancer antigen 125; CI = confidence interval; LV = left ventricular; OR = odds ratio, SPAP = systolic pulmonary artery pressure

$P \leq 0.05$  was considered statistically significant. All the variables from Table I were examined; only those significant at  $P < 0.05$  and correlated with CA-125 are shown for the univariate analysis. Multivariate logistic regression analysis including all the variables in univariate analysis with enter method.

of pre-hospital use of oral diuretics and β-blockers for HF and of in-hospital use of positive inotropic agents: the absence of prehospital diuretics and β-blockers and the presence of in-hospital inotropic use were found to be significant for LOS in univariate analysis, but the use of these agents was not independently associated with LOS in multivariate analysis. The prolongation of hospitalization through the use of positive inotropic agents is an expected result, yet prolonged hospitalization in the absence of β-blockers and diuretics could arise from poor clinical conditions or poor prognosis.

Recent studies<sup>12,14-16</sup> have shown that CA-125, long useful as a tumor marker, has prognostic importance in many cardiovascular diseases, especially HF. In studies related to HF, CA-125 values correlated with pulmonary artery pressure, pulmonary artery capillary wedge pressure, left atrial volume index, LVEF, brain natriuretic peptide values, New York Heart Association functional class, and pericardial effusion.<sup>14,15,17</sup> In our study, CA-125 values correlated with SPAP, LVEF, and pericardial effusion.

Basically, the prognostic importance of CA-125 in the pathophysiology of HF can be explained by 2 mechanisms. First, the mechanical stress on mesoendothelial cells, which is produced by increased congestion, leads to CA-125 release from these cells. Second, the neurohormonal effect that develops in HF activates the sympathetic nervous system and the renin-angiotensin-aldosterone system, thus increasing cytokine release and stimulating the inflammatory process—thereby changing the morphology and cell membrane stability of mesoendothelial cells and causing CA-125 release.<sup>35,41,42</sup> According to this sequence, higher CA-125 levels and longer LOS in patients—with high volume loads and increased neurohormonal activation—is the logical result.

Study results show that AF increases left ventricular filling pressures and further impairs systolic and diastolic function in HF patients, thereby increasing mortality rates, stimulating inflammatory activity, and increasing the levels of some cytokines and of CA-125. It is not surprising, therefore, to find that AF, in the

current study, is an independent predictor for prolonged hospitalization in patients with HF.<sup>14,17,19,43,44</sup> In addition to high CA-125 levels and the presence of AF, lower sodium levels and higher creatinine levels are associated with prolonged LOS. This result, consistent with previous studies, is not surprising. It can be claimed that patients who have lower sodium levels and higher creatinine levels are more hypervolemic and produce less urine, because of diuretic resistance.

### Study Limitations

Some limitations arise from our analysis of a case series. Although the decisions related to treatment and to the time of hospital discharge were made by cardiologists who were blinded to the study, those different options regarding treatment protocol and different opinions regarding discharge times in HF patients could have affected the results of the current study, for which discharge criteria and treatment protocols were not standardized. In addition, the findings are those of a single center and need to be replicated in multicentric cohorts. Finally, some hemodynamic measurements—such as blood pressure and heart rate at admission—were not provided, because of problems at our center with storage of nurses' observations.

### Conclusion

We conclude that the levels of CA-125, sodium, and creatinine, and the presence of AF, are associated with LOS upon the admission of HF patients to the hospital. It seems that high CA-125 levels (>48 U/mL) on admission can by themselves determine which patients will need prolonged LOS. However, it remains to be established whether the intensification of medical therapy for acute-HF patients with high CA-125 can alter the in-hospital prognosis; we think that these patients should be monitored closely at admission for likely signs of prolonged LOS. When previous studies related to CA-125 and HF are taken into consideration—together with the multicentric, large-scale studies that can be conducted in the future—it might well become possible to use CA-125 as a regular biomarker in the follow-up of HF.

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