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Research Article

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The Value of CA 125 In Predicting Fluid Overload in Heart Failure

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Abstract

Background: *Congestion is the main mechanism leading to severe disease progression and is also an important treatment target in heart failure, so early detection of fluid overload and/or pulmonary congestion in heart failure patients is very necessary. CA 125 has been used as a marker in screening, diagnosis, monitoring, and prognosis in ovarian cancer patients. Recently, CA 125 has been reported to increase in fluid overload and/or pulmonary congestion in heart failure, but the cutoff of CA 125 to diagnose this condition still differs among researches, so we conducted the study "The value of CA 125 in predicting fluid overload in heart failure" with the following two objectives: 1. Determine the prevalence of fluid overload in heart failure. 2. Determine the cutoff point, AUC, sensitivity, specificity of CA 125 in predicting fluid overload in heart failure. 3. Determine predictors of fluid overload in heart failure.*

Materials and methods*: there were fifty-eight heart failure patients at the HCMC Hospital of Rehabilitation - Professional Diseases from September 1, 2023 to December 31, 2023. This was a cross-sectional study.*

Results*: there were 42 cases (prevalence 72.41%) with fluid overload, mean age 68.34 ± 13.71, men accounted for 55.2%.The median CA 125 value was 28.74 U/mL and the interquartile range (16 – 71.90), the value of CA 125 in predicting fluid overload was > 16 U/mL with an AUC ROC was 0.717 (95% CI 0.584-0.828, p=0.005), sensitivity 85.7%, specificity 56.2%.*

Conclusion*: CA 125 value has quite good accuracy in predicting fluid overload in heart failure. CA 125 > 16 U/mL remained the strongest independent predictor of fluid overload (OR 8.79; p = 0.011) in multivariable regression analysis.*

Keywords: *CA 125, fluid overload, heart failure.*

1. Introduction

Heart failure (HF) is one of the main cardiac diseases leading to intensive care unit (ICU) admission (18.6%)[1]. Organ congestion is a classical feature of HF[2-4] that is caused by excess fluid or fluid redistribution into the extravascular space[4]. In addition, during and after cardiac surgery (CS) or cardiac interventions, the infusion of considerable amounts of IV fluids may be necessary[5] due to cardiopulmonary bypass (CPB) induced inflammation[5], blood loss, myocardial depression, rhythm disturbances, and impaired vascular tone[6]. Therefore, additional iatrogenic fluid overload is common at ICU admission in patients with HF and may affect outcomes[7,8]. Further, patients with heart failure often suffer from extravascular over-hydration due to fluid re-distribution while actually being intravascular fluid depleted[4]. This may lead to the administration of further fluids for resuscitation purposes[2,9-11] and thus further aggravates organ dysfunction (heart, lung, and kidneys), leading to a vicious circle of organ failure[4].

CA125 (also known as MUC16) is a transmembrane protein that is highly glycosylated and has a high molecular weight. It is mainly composed of three parts: the N-terminal domain, tandem repeat domain, and C-terminal domain[12]. Research shows that CA125 is not expressed in tumor cells but instead originates from the cell surfaces of various tissues of the coelomic epithelium[13]. Its main function is to hydrate, lubricate and protect the surface of the epithelial cavity from physical pressure[14]. CA125 is considered a valuable biomarker for diagnosing ovarian cancer and evaluating the therapeutic prognosis of patients[15].

Studies have highlighted congestive HF as a special cause of increased serum CA125 levels. Moreover, CA125 levels are closely associated with the severity of congestion and are often accompanied by significant volume overload and fluid accumulation[16]. Indeed, up to two-thirds of patients with acute heart failure exhibit CA125 levels (35-200 U/mL) above the normal range[17], and in patients with stable HF is mostly lower than 35 U/mL. The mechanism behind the upregulation of serum CA125 in patients with congestive HF has not been confirmed. In the existing studies, mechanical stress and inflammatory stimulation are considered crucial factors in this process, and two hypotheses have been proposed: (1) Mesothelial cells are stimulated by the mechanical stress caused by tissue tension due to fluid overload, leading to the release of CA125[18]. (2) The overexpression of CA125 in mesothelial cells is stimulated by activation of the inflammatory cytokine network[17]. According to Colombo et al.[19], venous congestion leads to endothelial activation, upregulation of inflammatory cytokines, hepatic dysfunction, and intestinal villus ischemia. Intestinal villus ischemia can eventually cause abnormal function and loss of barrier function in intestinal epithelial cells, allowing the lipopolysaccharides and endotoxins produced by gram-negative bacteria in the intestinal lumen to enter the circulation. It further

aggravates the inflammatory environment that is already established by venous congestion and neurohormonal activity. Fluid overload and inflammatory processes interact to form a vicious cycle in congestive HF. It is crucial to provide a comprehensive explanation for elevated CA125 levels to differentiate between ovarian cancer and HF accurately. While fluid retention can cause tissue damage and elevate CA125 levels in both ovarian cancer and HF patients, the level of CA125 is considerably higher in ovarian cancer patients compared to HF patients[20]. Furthermore, it is important to note that CA125 alone is not an ideal diagnostic tool for either condition due to its limited specificity and sensitivity[20]. Therefore, for better clinical effectiveness in screening and early detection, it should be combined with symptoms/signs, other biomarkers or ultrasound and other multimodal methods. The cutoff of CA 125 to diagnose fluid overload and/or pulmonary congestion still differs among researches, so we conducted the study "The value of CA 125 in predicting fluid overload in heart failure" with the following three objectives: 1. Determine the prevalence of fluid overload in heart failure.

1. Determine the prevalence of fluid overload in heart failure.
2. Determine the cutoff point, AUC, sensitivity, specificity of CA 125 in predicting fluid overload in heart failure.
3. Determine predictors of fluid overload in heart failure.

2. Materials and methods

2.1. Study population:

2.1.1. We included adult patients admitted during the study period with heart insufficiency.

2.1.2. Inclusion criteria: heart failure patients at the HCMC Hospital of Rehabilitation - Professional Diseases from September 1, 2023 to December 31, 2023.

Definitions of fluid overload and/or pulmonary congestion: fluid overload was defined as a weight-adjusted cumulative fluid body (= total fluid in–total fluid out) at ICU discharge ≥5%; Dyspnoea, orthopnoea, fatigue, jugular venous pressure (JVP), rales, pedal oedema, increase pulmonary circulation and/or pulmonary edema in chest X-rays[21].

2.1.3. Exclusion criteria were as follow: patients younger < 18 years, insufficient data, no cancer.

2.2. Methods:

2.2.1. Study design: cross-sectional. This study complies with the Declaration of Helsinki and was approved by the local institutional review committees. All patients provided written informed consent.

Sample size:

$$n = Z^2_{1-\alpha/2} \frac{p(1-p)}{d^2}$$

Where: p = 8.6% according to Waskowski J et al[22].

We chose d = 0,1, n = $1{,}96^2$ x 0,086 x 0,914/$0{,}1^2$ = 30.2.

So minimum sample size was 31 cases.

2.2.2. Laboratory data: blood samples were taken within the first 24 h of hospital admission. The estimated glomerular filtration rate (eGFR) was calculated according to the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI). Plasma concentrations of CA125 were measured with the commercially available electrochemiluminescent sandwich immunoassay Roche ElecsysVR CA 125 assay). For CA125, the intra-assay precision (coefficient of variation) is 1.4–2.0%, and the inter-assay precision (coefficient of variation) is 0.0–0.9%, with an analytical range of 0.6–5000 U/mL.

2.2.3. Statistical analysis: we performed all statistical analyses using the software SPSS for Windows (version 26; SPSS Inc., Chicago, IL, USA). We tested for normal distribution using the Kolmorgorov– Smirnov test or the Pearson's chi-squared test. Student's t-test for normally distributed data and the Mann–Whitney U test for non-normally distributed data were used to compare quantitative variables between groups. Chi square test or Fisher's exact test were used for qualitative variables, as appropriate. The diagnostic performance of CA125 for identifying fluid overload was tested using the receiving operating curve (ROC). The optimal cut-point (best balance between sensitivity and specificity) was tested with the Youden method. Independent factors associated with

Fluid overload were assessed by multivariate logistic regression analyses using univariate factors with a value of $p < 0.05$. A final model was derived by using backward stepwise selection. Statistical significance was assumed for $p < 0.05$.

3. Results

From September 1, 2023 to December 31, 2023 there were 58 patients who met the inclusion criteria and had no exclusion criteria.

3.1. Baseline characteristics

58 patients were enrolled and included in the analysis. The mean age of the sample was 68.34 ± 13.71 years, 32 (55.2%) were male, 18 (31%) had an LVEF ≤ 40%, 34 (58.6%) had a prior history of heart failure, 8 (13.8%) had a prior history of chronic kidney disease, 5 (8.6%) had acute pulmonary edema, 14 (24.1%) acute decompensated heart failure, NT-proBNP was 1603 pg/ml (595-3897), CA 125 was 28.74 U/ml (16-71.90), respectively. A total of 42 subjects (72.4%) had a fluid overload. Baseline characteristics across fluid overload and non-fluid overload patients are summarized in **Table 1**. There were differences between fluid overload group and non-fluid overload group, except NT-proBNP value and sodium level

Table 1. Baseline characteristics.

Varables	Total (n=58)	Fluid overload (n=42) (72.4%)	Non-Fluid overload (n=16) (27.6%)	P value
Demographics and medical history				
Age (years)	68.34 ± 13.71	68±13.61	69,25±14.36	0.759
Male sex	32 (55.2)	25 (43.1)	7 (12.1)	0.285
BMI (kg/m^2)	21.25 [19.59 – 24]	20.90 [19.4-24]	21.9 [20.22-24.92]	0.504
HTA	48 (82.8)	34 (58.62)	14 (24,18)	0.559
Dyslipidemia	38 (65.5)	27 (46.55)	11 (18.95)	0.751

HF	34 (58.6)	25 (43.1)	9 (15.5)	0.823
DM	17 (29.3)	14 (24.14)	3 (5.16)	0.279
CAD	29 (50)	22 (37.93)	7 (12.07)	0.560
CKD	8 (13.8)	8 (13.8)	0 (0)	0.0623
Vital signs				
SBP, mmHg	115 [100-130]	115 [100-130]	115 [100-130]	0.913
DBP, mmHg	70 [60-70]	70 [60-70]	70 [65-80]	0.262
HR, b.p.m	90.21 ± 18.02	89.31 ± 17.00	92.56 ± 20.88	0.544
NYHA on admission				
NYHA II	7 (12.1)	5 (8.62)	2 (3.48)	0.212
NYHA III	30 (51.7)	19 (32.76)	11 (18.94)	
NYHA IV	21 (36.2)	18 (31.03)	3 (5.17)	
Laboratory				
LVEF (%)	50 [35.75-60.25]	46 [33.75-60]	53 [47-61]	0.120
Sodium (mmol/L)	**138.93 ± 6.78**	**137.57 ± 6.90**	**142.50 ± 5.07**	**0.012**
Creatinine (µmol/L)	85.6 [73.8-111.3]	85.6 [75-118.3]	87.7 [73.6-110.8]	0.689
eGFR (mL/min/1.73m^2)	75.05 [50.3-89.6]	83.05 [50-89.7]	67.4 [53.5-84.1]	0.797
Ure (mmol/L)	6.22 [4.63-8.64]	6.21 [4.31-9.54]	6.22 [5.56-6.86]	0.717
Hemoglobin (g/dL)	12.45 ± 2.65	12.28 ± 2.59	12.89 ± 2.82	0.437
NT-proBNP (pg/mL)	**1603 [595-3897]**	**2429.5 [753-6750]**	**789.50 [290.55-1227]**	**0.020**
CA 125 (U/mL)	28.74 [16-71.90]	38.10 [20.33-87]	15.90 [10.90-30.04]	0.197

Data are expressed as n (%); medium± SD; median [interquartile range] as appropriate.
CA125, antigen carbohydrate 125; CAD, coronary artery disease; DBP, diastolic blood pressure, DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, heart rate; HTA, hypertension; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; CKD: Chronic kidney disease was defined as eGFR eGFR <60 mL/min/1.73 m^2 using creatinine obtained at the admission

3.2. The value of CA 125 in predicting fluid overload

The diagnostic accuracy of the CA 125 was evaluated using receiver operating characteristic (ROC) curve analysis. The optimal cut-off point of CA 125 to predicting fluid overload was > 16 U/mL, the area under the AUC curve is 0.717 (95% CI 0.584-0.828, p=0.005), sensitivity 85.7%, specificity 56.2%, The result was displayed in **Figure 1**.

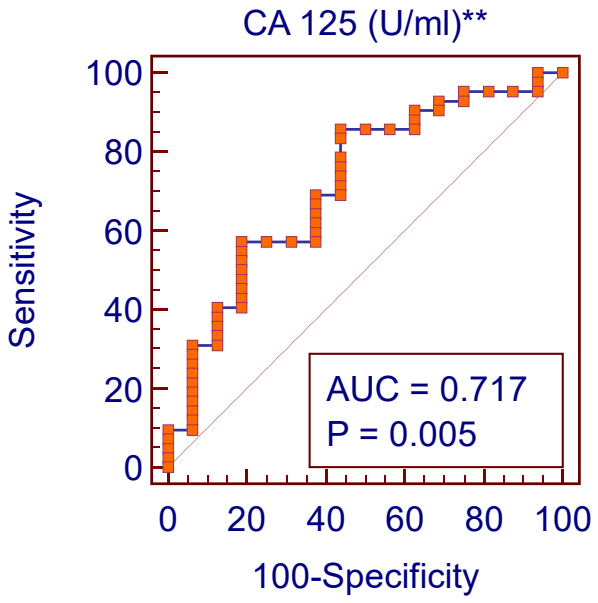

Figure 1. Cut-off point, AUC, sensivity, specificity of CA 125 in predicting fluid overload.

3.3. Univariate and multivariate logistic regression analyses for predictors of fluid overload

The variables correlated with fluid overload were analysed by univariable logistic regression. The variables with p value < 0.1 were selected in the multivariate logistic regression model by the Wald test with backward-stepwise method. During multivariable regression analysis, CA 125 > 16U/mL remained the strongest independent predictor of fluid overload (OR 8.79; p = 0.011). The result was presented in **Table 2**.

Table 2. Univariate and multivariate logistic regression analyses for predictors of fluid overload.

Univariate logistic regression			**Multivariate logistic regression**	
Variables	**p**	**OR**	**p**	**OR**
Age	0.754	1.007		
Gender	0.284	1.89		
BMI	0.498	1.065		
SBP	0.911	1.002		
DBP	0.266	1.041		
HR	0.205	0.972		
Na+	**0.019**	**1.15**	**0.033**	**1.21**
Hb	0.432	1.092		
Creatinine	0.684	0.997		
Ure	0.715	0.976		
NT-proBNP	**0.028**	**0.99**	0.062	0.99
CA 125 > 16 U/mL	**0.002**	**7.71**	**0.011**	**8.79**

4. Discussion

CA125 has emerged as a valuable biomarker of congestion in AHF[23]. Although the pathophysiological mechanisms responsible for the increase of the synthesis of CA125 in AHF are not fully understood, mesothelial cells activation in response to increased hydrostatic pressure, mechanical stress and/or cytokine activation have been suggested as the crucial mechanisms[23]. Recently, our group reported that the most important factors related to CA125 in patients with AHF were, in order of importance, the presence of pleural effusion and the severity of tricuspid regurgitation[24]. Thus, we envision CA125 levels as a proxy of fluid overload and right-sided HF[24]. Thus, given that presence of fluid overload is highly prevalent in decompensated HF patients, it seems feasible to speculate that higher CA125 identifed more advanced patients with greater congestion and a higher risk of new HF decompensations. Conversely, natriuretic peptides are the standard HF biomarker accurately refecting the high flling ventricular pressures and myocardial stretch[25]. The role of natriuretic peptides in AHF has been extensively evaluated in patients with HFrEF, and the evidence is scarcer for HFpEF. Most prior studies in HFpEF evaluated mortality or the composite of death and readmission, with a prognostic value not diferent from those with HFrEF. The reasons behind the lack of predictive ability of NT-proBNP for predicting total AHF readmission in this sample remain elusive. However, some reasons have been postulated. The higher prevalence of right-sided dysfunction and systemic congestion in HFpEF over HFrEF has been previously reported. Thus, the relevance of CA125 can be expected to be a surrogate of systemic congestion over NT-proBNP as a proxy of left-sided filling pressure for predicting morbidity burden in this population. Thus, patients with HFpEF and predominant right-sided HF CA125 but not NTproBNP has been associated with worse outcomes. Patients with HFpEF are frequently elderly and display a higher prevalence of renal dysfunction, situations in which natriuretic peptides are elevated regardless of the severity of HF. Indeed, a recent study from our group showed that the main factors associated with NT-proBNP in HF patients were renal dysfunction, LVEF, and age[24]. Conversely, clinical parameters of congestion and the severity of tricuspid regurgitation were the most important predictors for CA125[24]. Additionally, there is compelling evidence that natriuretic peptides are not accurate or reliable markers of tissue congestion[25]. NT-proBNP was measured early during hospitalization. Prior studies have suggested predischarge natriuretic peptides assessment might have greater prognostic ability. Beyond the pathophysiology supporting the positive association between CA125 and burden of total HF admission, we envision that the assessment of CA125 during decompensation might be a helpful complementary tool for predicting the risk of subsequent new HF decompensations. Thus, circulating levels of CA125 may play a role in planning the intensity of depletion therapy, length of stay, and frequency of postdischarge monitoring as reported in recent studies in which high CA125 identified patients that benefit from more intensive diuretic regimens, longer hospital stays and close postdischarge follow-up. Our study expands the relevant role of CA125 as a circulating biomarker in patients with HF by confirming its value for predicting fluid overload in heart failure. The diagnostic accuracy of the CA 125 was evaluated using receiver operating characteristic (ROC) curve analysis. The optimal cut-off point of CA 125 to predicting fluid overload was > 16 U/mL, the area under the AUC curve is 0.717 (95% CI 0.584-0.828, p=0.005), sensitivity 85.7%, specificity 56.2%. During multivariable regression analysis, CA 125 > 16U/mL remained the strongest independent predictor of fluid overload (OR 8.79; p = 0.011). CA125 because it long-half life (7–12 days) is a biomarker of delayed response to acute hemodynamic changes, for patients with decompensated HF, CA 125 is a reliable surrogate that reflects fluid status over the past few weeks.

Limitations

Several limitations need to be acknowledged. First, this study has the inherent limitations of being a single-center observational study. Second, due to the limited sample size, some of the negative results could be explained by type II error (insufficient statistical power). Third, we did not perform an invasive haemodynamic assessment, so we cannot establish

direct correlations between fluid overload patterns and invasive right-sided filling pressures. Lastly, CA125 biomarker was measured at early hospitalzations, we did not evaluate the CA125 levels variation over time.

5. Conclusion

There were 42 cases (prevalence 72.41%) with fluid overload in heart failure patients. CA 125 value > 16 U/mL has quite good accuracy in predicting fluid overload in heart failure. CA 125 > 16 U/mL remained the strongest independent predictor of fluid overload (OR 8.79; p = 0.011) in multivariable regression analysis.

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