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CA125, Galectin-3 and FGF-23 are interrelated in heart failure with reduced ejection fraction

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ABSTRACT

Background

Carbohydrate Antigen 125 (CA125) is the most widely used biomarker in ovarian cancer screening. In p atients with heart failure (HF), increased levels of CA125 have been observed and related to disease severity. Our objective was to determine the association of CA125 levels with two biomarkers of adverse remodeling in HF patients with reduced ejection fraction (HFrEF).

Methods

CA125 circulating levels were determined with an electrochemiluminscent immunoassay. Concentrations of B-type natriuretic peptide (BNP), N-terminal proBNP (Nt-proBNP), Galectin-3 and Fibroblast Growth Factor 23 (FGF23) were also measured by immunoassays.

Results

CA125 levels were increased in HFrEF, were associated to disease severity according NYHA classes. Median CA125 concentration was also significantly related to cardiovascular mortality. CA125 concentrations were positively and significantly associated to Galectin-3 and FGF23.

Conclusions

Concentrations of CA125 are increased in patients with HFrEF, associated to disease severity and adverse cardiovascular outcomes. CA125 levels are also correlated to Galectin-3 and FGF-23, two biomarkers related to fibrosis and cardiovascular remodeling.

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The burden of heart failure (HF) is recognized worldwide (1,2). The sub-phenotyping of HF patients is important to anticipate potential adverse outcomes and adapt treatment. Biomarkers play an important role in the diagnosis of HF and natriuretic peptides, N-terminal pro B-type natriuretic peptide (NT-proBNP) and B-type natriuretic peptide (BNP), remain the first-choice biomarkers (1). Different classes of other biomarkers might inform on different aspects on HF development and provide additional valuable information about patients' risk (2). To this end, several tumor markers such as Carbohydrate Antigen 125 (CA125), CA 15-3, CA 19-9, carcinoembryonic antigen, alpha-feto protein and chromogranin, have been explored in HF (3).

The evidence about the involvement of CA125 in the pathophysiology of HF is accumulating. CA125, also known as MUC16, is a large glycoprotein synthesized by mesothelial cells and is the most widely used biomarker in ovarian cancer screening (3). In patients with HF, increased levels of CA125 have been observed, strongly associated with right-sided HF parameters, and related to disease severity as such with diagnostic and prognostic perspectives (3,4).

The hypothesis beyond the elevation of CA125 in HF patients include congestion and inflammation (5). CA125 is non-linearly and positively associated with intrarenal venous flow (IRVF) measured by Doppler ultrasound, a potential surrogate marker of renal congestion (6). Inflammatory process and remodeling might also trigger CA125 in HF (4).

Other biomarkers like Galectin-3 (Gal-3) and Fibroblast growth factor 23 (FGF-23) have been related to inflammation and adverse remodeling in HF. FGF-23 is produced by osteocytes, regulates phosphate homeostasis and has also been evaluated in HF and linked to adverse outcomes, inflammation, and fibrosis (7).

Our objectives were to assess CA125 levels in a group of HF patients with reduced ejection fraction (HFrEF) and to evaluate its association with Gal-3 and FGF-23.

This study is retrospective and blood samples were collected in 102 HF patients with reduced left ventricular ejection fraction. Each patient gave informed consent, and the protocol was approved by the local institutional review board. Demographic information including medical history (New York Heart Association [NYHA] class), clinical signs and standard laboratory data were recorded. All HF patients received optimal therapy and none of the female patients had ovarian cancer. CA125 concentrations were determined with a two-sites electrochemiluminescent automated assay on the Cobas® 8000 platform (Roche Diagnostics, Mannheim, Germany). The upper limit of the reference interval (URL) for the CA125 assay is 35 U/mL. N-terminal proBNP (NT-proBNP) was measured with automated electrochemiluminescent immunoassay also on the Cobas® 8000 platform. Gal-3 and FGF-23 concentrations

were determined with enzyme-linked immunosorbent assays as previously described (8).

Biomarkers were modelled as continuous variables. The non-parametric Spearman rank correlation coefficients were used to assess the relationships between biomarkers, age, EF and GFR. Multiple regression analysis was performed to test the independent associations between age, gender and the different biomarkers. Statistical analysis was performed using Medcalc software version 20.111 (Medcalc Software Ltd).

Patients' characteristics were as followed: mean age: 69 ± 13 years; males n=89; females n=23; NYHA II-IV; etiology: ischemic n=86, dilated cardiomyopathy n=26; mean left ventricular ejection fraction (EF): 23 ± 6%). The median circulating levels of NT-proBNP and BNP were 3356 ng/mL [76-33020] and 532 ng/L [range: 21-5017] respectively. Median circulating levels of Gal-3 and FGF23 were 17 ng/mL [range: 8-50] and 102 RU/mL [20-15000], respectively.

The mean CA125 in HF patients was 135 U/mL [range: 5-2587]. CA125 concentrations above the URL were observed in 57 % of the HFrEF patients. CA125 concentrations were significantly related to NYHA classes ($p<0.001$, Figure 1A) and geometric means were 23 U/mL in NYHA class II (n=45), 77 U/mL (n=44) in NYHA class III and 246 U/mL in NYHA class IV (n=12). CA125 significantly and negatively correlated to left ventricular ejection fraction ($r=-0.27$, $p<0.001$) and higher CA125 concentrations were related to the lowest survival rate (Figure 1B).

CA125 concentrations were positively and significantly associated to Galectin-3 ($r=0.31$, $p<0.001$) and FGF23 ($r=0.38$, $p<0.001$) (Figure 2A and Figure 2B). CA125 was also significantly related to natriuretic peptides. With multiple regression analysis the independent determinant of CA125 levels were age, BNP and Galectin-3.

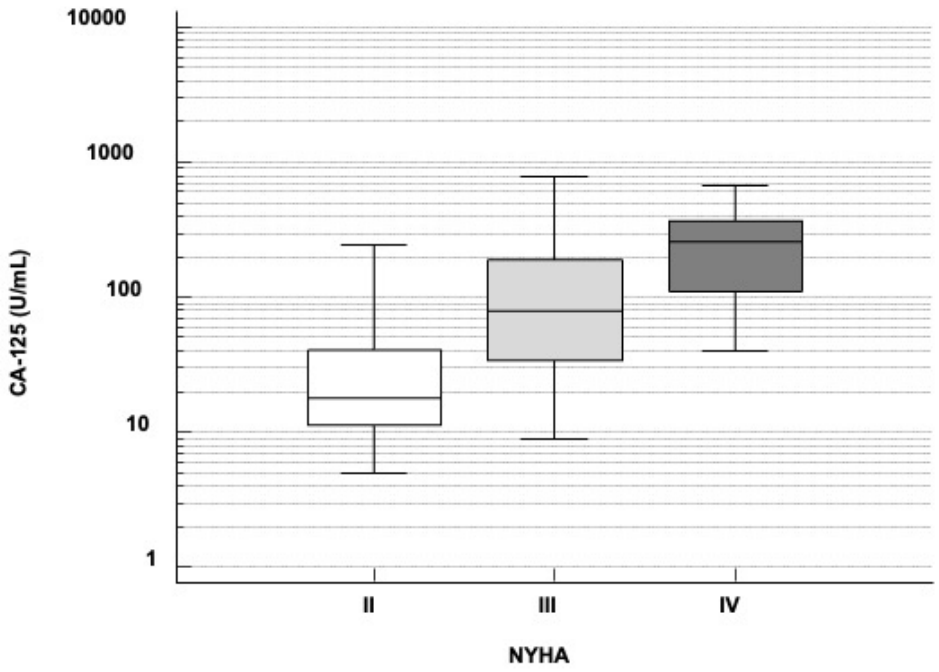
Our study showed, as already evident from literature, a raise of CA125 concentrations in HFrEF patients and association of CA125 with disease severity and prognosis. Interestingly, our study unrevealed significant and positive relationships between CA125 levels and two biomarkers of cardiovascular remodeling Gal-3 and FGF23.

The available evidence of the role of CA125 in the pathophysiology of HF is increasing with related perspectives to forward the diagnosis of HF (4). This was observed in our study with a significant proportion of HFrEF patients having significant increase of CA125. Two hypotheses are formulated in literature to explain such elevation of CA125 in HF, congestion, and inflammation. Data show that CA125 can predict the presence of a congestive intrarenal venous flow in patients with acute HF (6). The involvement of CA125 in the inflammatory process and remodeling in HF is also documented in the literature. Experimental data have also suggested a potential molecular interaction between CA125 and Gal-3; however, the biological and clinical relevance of this interaction is still uncertain (9). We reinforce this hypothesis through the significant relationships that we found in our study between CA125 and both Gal-3 and FGF-23. The participation of CA125 to such remodeling pathways can confirm interactions representing therapeutical targets. This is already a perspective for high-grade serous ovarian cancers and other MUC16/CA-125-expressing malignancies where targeting Gal-3 with a high-affinity antibody has been proposed (10).

CA125 testing offers several advantages in HF, which are presented in figure 3. Nevertheless, if the analytical and clinical value can be estimated as high, as different assays for CA125 are available but not standardized, it is important to mention that the decision limits need to be adapted to each method.

Our study is preliminary and has several limitations. A first one is a clear limited number of

Figure 1 **Association of CA125 circulating levels and New York Heart Association (NYHA) classes (A) and survival of HF patients (B)**



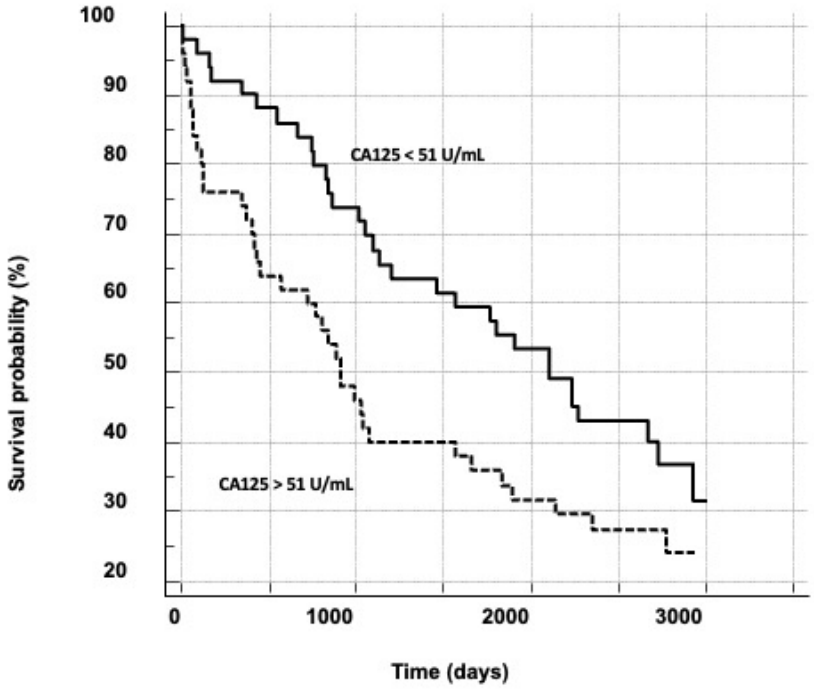
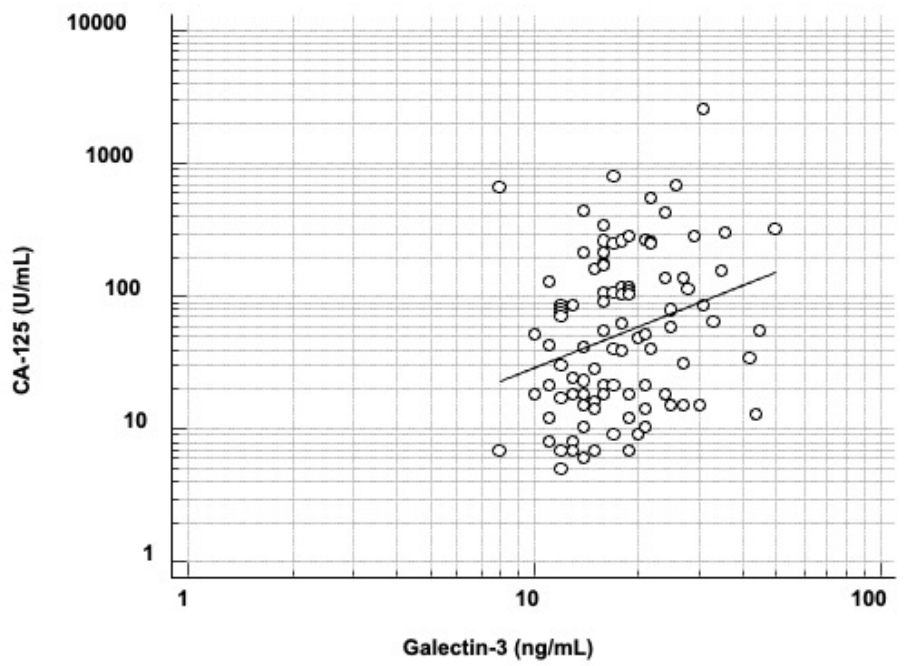


Figure 2 **Relationships between Galectin-3 and CA125 concentrations (A) and FGF-23 and CA125 concentrations (B) in HFrEF patients**



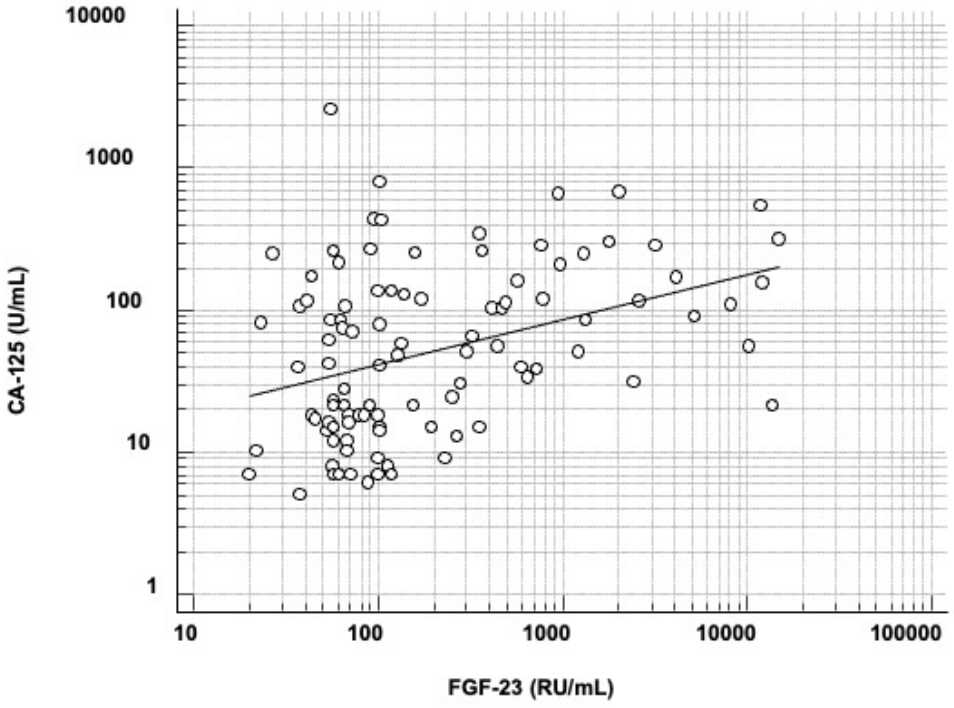
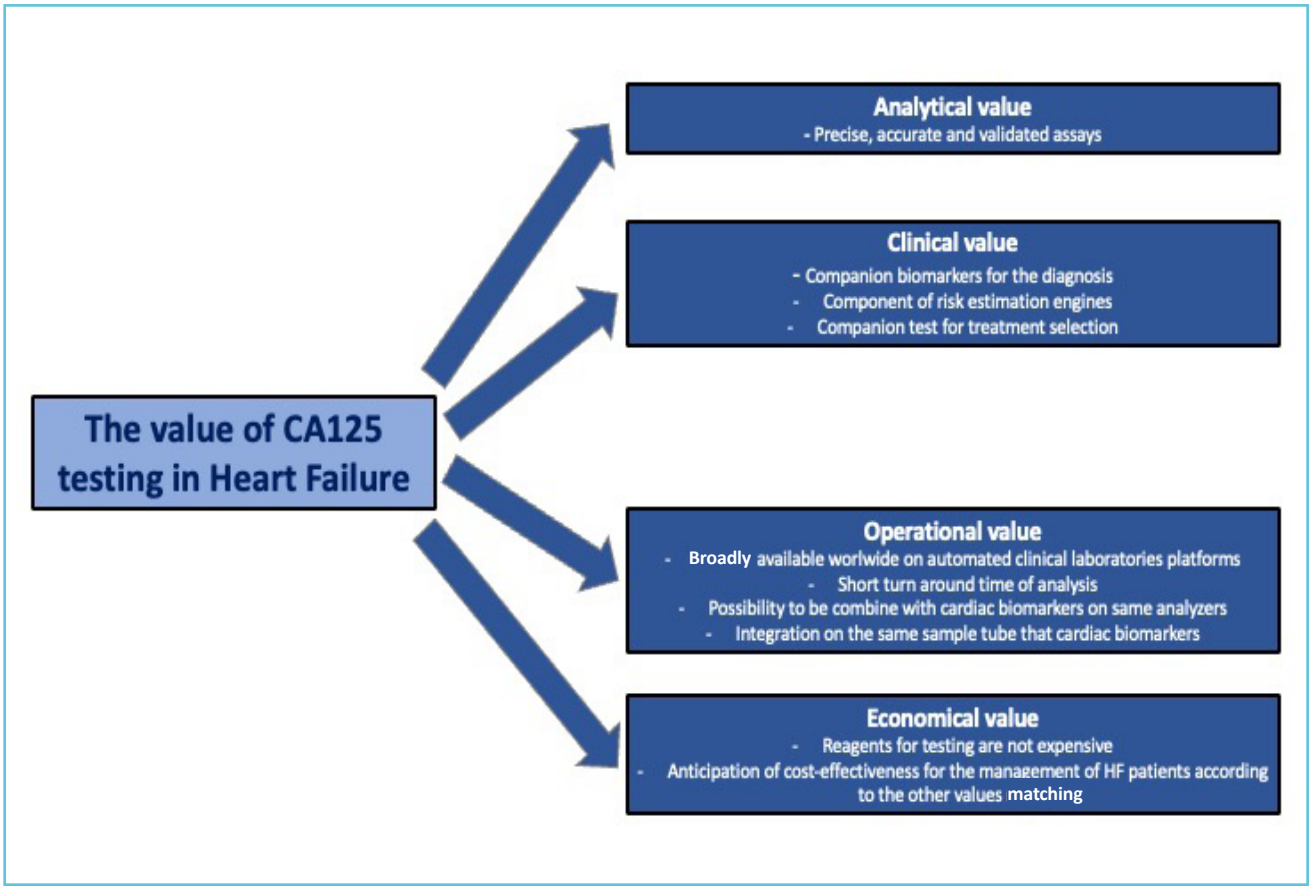


Figure 3 The potential value of CA125 testing in HF according to analytical, clinical, operational, and economic criteria



patients, even if the cohort was homogenous. Our observations will have to be confirmed on larger cohorts of patients. A second, is the lack of data from imaging to correlate fibrosis and remodeling to blood biomarkers.

In conclusion, our study showed increased CA125 concentrations in patients with HFrEF and a relation with disease severity. CA125 is also significantly and positively correlated to Galectin-3 and FGF-23, two biomarkers related to fibrosis and cardiovascular remodeling.

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Author contributions

Damien Gruson performed experimental design, conducted the experiments, analyzed and interpreted the results. Michel Rouseau, Sylvie Ahn and Anne-Catherine Pouleur were involved in the experimental design and read and approved the final version of the paper. Diane Maisin helped with analyses and interpretation of the results, and approved the final version.

Conflict of interest statement

The authors confirm that this paper content has no conflict of interests.

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