

## Novel Predictor for Recurrent Atrial Fibrillation After Radiofrequency Catheter Ablation (RFCA): A Review of Literature to Explore The Role of Carbohydrate Antigen-125 (PCA-125) in Plasma

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### Abstract

*Atrial Fibrillation (AF), the most prevalent variety of arrhythmia has an overwhelming prevalence in people over 65 years old, rendering it among the leading cardiovascular concerns. A literature search up to 2012 was carried out, including the following data bases: Medline, Google Scholar and Web of Science. The boolean terms word of this search were "Plasma Carbohydrate Antigen-125 OR PCA-125" AND "Radiofrequency Catheter Ablation OR RFCA" AND "Atrial Fibrillation OR AF" AND "Recurrent". 36 articles are included in this review. Carbohydrate Antigen-125 (CA-125) expression shows its potency to predict a recurrent AF after RFCA procedures. CA-125 is released from mesothelial cells through protein cleavage, then released into body fluids, which play a role in protecting epithelial surfaces through lubrication and hydration processes. Myocardial remodeling results in pathological cardiomyocyte hypertrophy with re-expression of embryonic genes. During this process, proto-oncogenes are activated, which stimulate growth factors present in the embryonic heart, leading to increased CA-125 levels. Elevated levels of CA-125 in plasma may be an interesting option as an independent predictor of recurrent AF after RFCA.*

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### **Introduction**

Atrial Fibrillation (AF) is one of the most common type of arrhythmia commonly encountered in clinical practice and has a particularly high prevalence in individuals over 65 year of age, making it one of the major cardiovascular problems (Joglar et al., 2024); (Tzeis et al., 2024). The Global Burden of Atrial Fibrillation reported that the global prevalence of AF in 2010 was 33.5 million (Hindricks et al., 2021); (Vinter et al., 2024). Furthermore, the prevalence of AF in Indonesia in 2016 was approximately 600-699 cases per 100,000 population (Choi et al., 2023); (Stauffer et al., 2024)

The high incidence of AF can trigger stroke complications up to five times greater, resulting in 20% mortality and 60% disability.<sup>6</sup> Apart from that, AF can also increase the risk of heart failure, leading to an increase in hospitalization rates of up to 40% and increasing the risk of mortality (Vinter et al., 2024); (Stauffer et al., 2024). The high rates of morbidity, disability and mortality caused by AF are becoming a challenge that requires special attention for treatment and prevention.<sup>4</sup> It can occur as a supraventricular tachycardia caused by uncoordinated mechanical and electrical activity in the atrium, resulting in the atrium being unable to contract effectively (Choi et al., 2023); (Dretzke et al., 2020). Symptoms and signs of AF can vary from asymptomatic to fatigue, headache, palpitations, chest pain and dyspnea.<sup>8</sup> A diagnosis of AF is made through history taking and physical examination which is confirmed using an electrocardiogram (ECG) or ambulatory rhythm monitoring. Over the past few years, Radiofrequency Catheter Ablation (RFCA) has become one of the first-class recommended procedures in the clinical treatment of AF with high effectiveness and safety (Li, Chen, Wang, Su, & Ling, 2020). Nevertheless, the RFCA procedure has a fairly high recurrence rate ranging from 39.5-51.3% (Li et al., 2020); (Popa et al., 2022)

A systematic review of 10 studies showed the incidence of recurrent AF after RFCA was in the range of 16-64% (Packer et al., 2019). This implies the importance of having effective and accurate predictors to predict the likelihood of recurrent AF after RFCA so as to improve the success of AF case management (Hindricks et al., 2021); (El-Harasis et al., 2024). The latest research proves that Carbohydrate Antigen-125 (CA 125) in plasma has the potential to predict recurrent AF after RFCA (Hindricks et al., 2021). Carbohydrate Antigen-125 (CA-125) is a glycoprotein from the mucin family (MUC16) that has a protective function on epithelial surfaces through lubrication and hydration (Victoria Castro et al., 2022). The production of CA-125 occurs in mesothelial cells of the pericardium, pleura and mullerian epithelium as a response to inflammatory and mechanical stress (Hindricks et al., 2021). Formerly, CA-125 was widely used as a predictor of ovarian cancer, but in recent years, elevated CA-125 levels have been associated with cardiovascular disease including AF (Victoria Castro et al., 2022)

Recently, a study revealed that elevated plasma CA-125 (PCA 125) levels prior to RFCA therapy are associated with a high risk of AF recurrence and can be used as an independent predictor of AF recurrence 12 months following RFCA. Notably, the PCA-125 test has several advantages such as using a blood sample and affordable cost.<sup>3</sup> This review aimed to explore the potential of PCA-125 as a biomarker predictor of AF recurrence after RFCA to prevent complications and thus reduce morbidity, disability and mortality.

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### **Method**

A literature search up to 2012 was carried out, including the following data bases: Medline, Google Scholar and Web of Science. The boolean terms word of this search were “Plasma Carbohydrate Antigen-125 OR PCA-125” AND “Radiofrequency Catheter Ablation OR RFCA” AND “Atrial Fibrillation OR AF” AND “Recurrent”. 114 articles were found. Case reports, case series, and animal studies were excluded from analysis. Only articles written in English language were considered eligible. All articles were initially screened for title and abstract, and 36 eligible articles for full text reading were subsequently selected and included in this paper. All the work in this manuscript does not use any artificial intelligence tools.

### **Result and Discussion**

#### **1. Result**

##### **Atrial fibrillation and radiofrequency catheter ablation (RFCA)**

AF contributes to one-third of all patients who are subsequently discharged with arrhythmia as the primary diagnosis (Liu et al., 2019). It is caused by focal ectopic impulses and re-entry mechanisms in the atrium. Ectopic impulses arise from myocytes in the pulmonary veins and are triggered by diastolic  $\text{Ca}^{2+}$  leakage from the sarcoplasmic reticulum causing myocyte depolarization due to  $\text{Na}^{+}$  current through the  $\text{Na}^{+}$   $\text{Ca}^{2+}$  channel. The re-entry mechanism is promoted by the slow conduction velocity of the depolarization wave and the shorter refractory period of cardiac myocytes (Huang et al., 2020); (Wang, Dang, Liu, & Hui, 2021) AF can lead to serious complications including stroke and heart failure, and stroke is currently the second leading cause of disability, increasing morbidity and mortality (Stauffer et al., 2024)

The risk of such complications is strongly associated with the incidence of recurrent AF (Choi et al., 2023); (Dretzke et al., 2020). The recurrent category in AF is when the patient has two or more episodes of AF confirmed by ECG (Núñez et al., 2022); (Marinescu et al., 2024). It can be categorized as paroxysmal (returning to sinus rhythm within 7 days), persistent (lasting more than 7 days), or long persistent (lasting more than 12 months). Also, permanent AF is when a decision is made to take no further action to restore or maintain sinus rhythm (Dretzke et al., 2020)

Some of the causes of recurrent AF are due to remodeling of the structure, electrophysiology, and mechanics of the atria resulting in loss of contractile function (Liu et al., 2019); (Marinescu et al., 2024). The risk of complications due to recurrent AF will increase if not managed appropriately and adequately. While anti-arrhythmic drugs are widely used as first-line therapy in the treatment of AF, the recurrence rate is still relatively high. In a study of 629 patients, the recurrence rate within 12 months was 59.2% (Zhang, Jin, Han, & Hou, 2023)

The management that is currently widely utilized and considered level one evidence in the guidelines for the treatment of AF and recurrent AF is Radiofrequency Catheter Ablation (RFCA) (Choi et al., 2023). The patients treated with RFCA generally have a lower recurrence rate than those treated with anti-arrhythmic drugs (36.4% vs. 59.2%) (Zhang et al., 2023). A meta-analysis of nine studies also showed a lower post-ablation recurrence rate compared to the group using anti-arrhythmic drugs (258/849 vs. 369/693,  $P < 0.01$ , OR 0.31, 95% CI: 0.24-0.39) (Sánchez et al., 2020)

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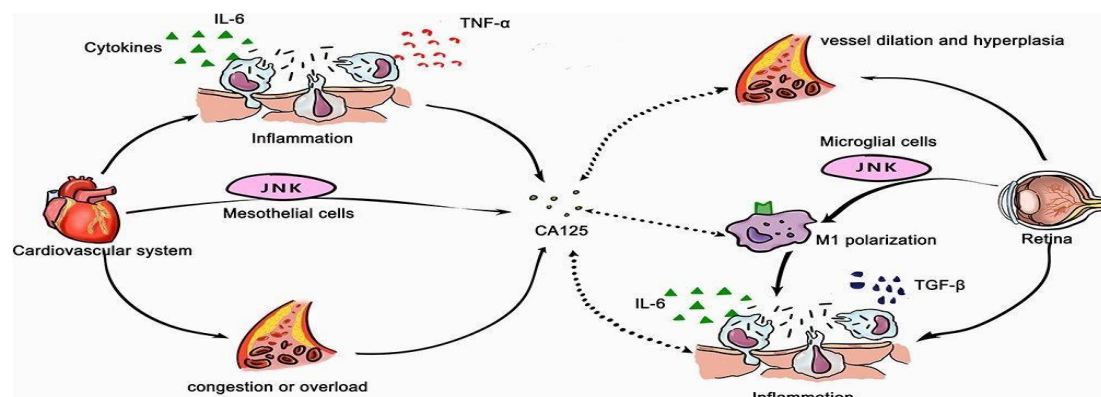
Despite the fact that RFCA is a first-class recommendations in AF management and demonstrated a lower recurrence rate than the use of anti-arrhythmic drugs, the recurrence rate was still quite high. Out of 353 patients who underwent RFCA, 85 patients (24.1%) experienced recurrence within 12 months of follow-up (Choi et al., 2023); (Li et al., 2020); (Zhang et al., 2023)

### Carbohydrate Antigen-125 (Ca-125)

*Carbohydrate antigen-125* (CA-125), a glycoprotein belonging to the mucin family (MUC16) produced by epithelial cells in body cavities, such as pericardium, pleura, peritoneum, and mullerian epithelium. CA-125 is released from mesothelial cells through protein cleavage, then released into body fluids, which play a role in protecting epithelial surfaces through lubrication and hydration processes (Hindricks et al., 2021); (Victoria Castro et al., 2022); (Brundel et al., 2022)

The secretion of CA-125 occurs due to mechanical stress, such as fluid accumulation and inflammation exhibiting a high expression state. It has been reported that CA-125 concentration associated with serum TNF- $\alpha$ , IL-6, IL-10, IL-1 $\beta$ , and Escherichia coli LPS, although the exact mechanism is unknown (Linz et al., 2024); (Ohlrogge, Brederbecke, & Schnabel, 2023)

In normal circumstances, mesothelial cells maintain proliferation in accordance with cell death. This balance becomes disturbed when mesothelial cells are exposed to mechanical stress or inflammation. Mechanical and inflammatory stress-induced damage is transmitted into the cytoplasm via the c-Jun N-terminal kinases (JNK) pathway. Aside from that, there is an increased synthesis of hyaluronan and cytoplasmic fibers in mesothelial cells in response to damage and cell death. Cell membrane morphocytology and stability were also altered. The cytoplasmic end of CA-125 is connected to the actin cytoskeleton through the ERM family, which consists of Ezrin, Radixin, Moesin, and Merlin. To accommodate the changes in the mesothelial cytoskeleton and the ongoing inflammatory or mechanical stress, the extracellular glycosylated MUC16 will be released from the mesothelial cell surface resulting in an increase in CA 125 levels in the plasma (Figure. 1) (Ohlrogge et al., 2023); (Starek et al., 2023)



**Figure 1.** The release of Carbohydrate Antigen-125 (CA-125) from mesothelial cells (Ohlrogge et al., 2023)

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Previously, a high level of CA-125 was identified in ovarian, lung and gastrointestinal malignancies. In patients with ovarian cancer, several studies have shown that serum CA-125 levels provide great assistance in further cancer monitoring especially in risk stratification and prognosis after treatment (Brundel et al., 2022)

CA-125 < 35 U/mL can clearly distinguish between healthy individuals and patients with ovarian cancer, while 65 U/mL is the maximum cutoff in distinguishing between patients with benign disease and ovarian carcinoma. Therefore, CA-125 levels > 35 U/mL became the most widely accepted cutpoint (Rillig et al., 2021); (Pinzon & Karunawan, 2020)

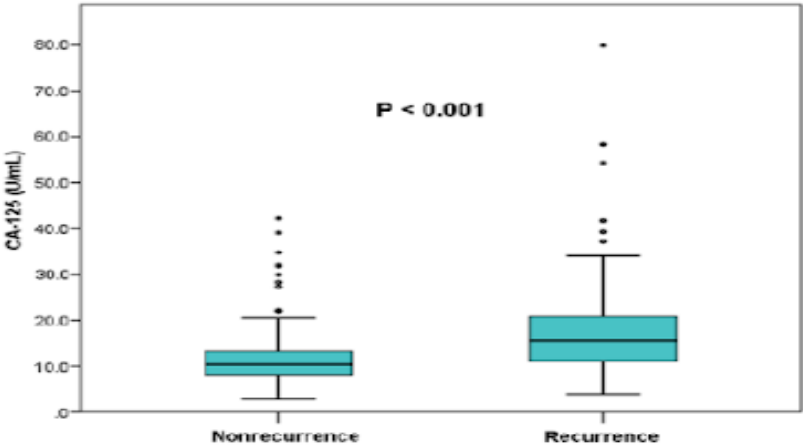
Nowadays, CA-125 is not only used to screen and monitor malignancies, but also linked to cardiovascular diseases, such as heart failure, pericarditis, coronary heart disease, and atrial fibrillation (Rillig et al., 2021). Serum CA-125 levels were first associated with the cardiovascular system in cases of pericardial effusion (Pfenniger, Yoo, & Arora, 2024). Further research has developed, including a systematic review between clinical heart failure status, hemodynamic signs, prognosis and serum CA-125 levels reported by Nägele et al. This marker increases in parallel with the neurohormones norepinephrine and atrial natriuretic peptide (Chen et al., 2024). Increased serum CA-125 concentrations were found to correlate with cardiac function in CAD and showed good potential in the identification of subclinical atherosclerosis in CAD (Lilla Szuromi, Orsolya Hajas, Edina Nagy-Baló, Ildikó N Forgács, László T Nagy, Miklós Fagyas, Attila Tóth, Béla Nagy Jr, János Kappelmayer, 2023)

### **Ca-125 Expression for Predictor of Atrial Fibrillation Recurrency after Radiofrequency Catheter Ablation**

In recent years, elevated CA-125 levels have been associated with cardiovascular disease, one of which is AF. A meta-analysis showed elevated CA-125 levels in AF patients compared to sinus rhythm with a mean difference of 16 U/mL (95%CI: 2-20 U/mL,  $P < 0.05$ ). In addition, the risk of AF associated with elevated CA-125 levels was 1.39 times more likely to experience AF (95%CI: 1.06-1.82,  $P < 0.05$ ) (Rillig et al., 2021)

Recent studies have shown the potential of plasma CA-125 levels as an independent predictor of AF recurrence after RFCA. A cohort study conducted by Wang et al. reported plasma CA-125 as a predictor of post-RFCA AF recurrence in 353 patients divided into 96 (27.2%) with PeAF and 257 (72.8%) with PAF. Results showed that PeAF patients had higher PCA-125 levels than PAF patients ( $15.59 \pm 11.59$  U/mL vs.  $12.12 \pm 6.59$  U/mL,  $P = 0.01$ ).

After a 12-month follow-up after RFCA, PCA-125 levels in recurrent AF were higher than those in the non-recurrent group ( $18.71 \pm 12.63$  U/mL vs.  $11.27 \pm 5.40$  U/mL,  $P < 0.001$ ) (Fig. 2) (Hindricks et al., 2021)



**Figure 2.** Carbohydrate Antigen-125 (CA-125) levels in the non-recurrent and recurrent groups

A similar study was conducted by Huang et al., in 422 patients with recurrent AF after RFCA occurred in 96 patients (22.75%). CA-125 levels also showed an association with AF recurrence rate where there was a significant increase in CA-125 in recurrent AF after RFCA compared to the group without recurrence ( $30.71 \pm 50.50$  U/ml vs.  $10.90 \pm 45.77$ U/ml,  $P < 0.0001$ ). Meanwhile, higher CA-125 levels were significantly associated with an increased risk of AF recurrence only in persistent AF (PeAF) ( $17.59 \pm 35.82$  U/ml vs.  $14.32 \pm 52.44$ U/ml) but there was no difference for paroxysmal AF (PAF) (El-Harasis et al., 2024)

**Table 1**  
The accuracy of CA-125 as a biomarker predictor of AF recurrence at fitting

| Author, Year      | Study Design | Country | Patient Characteristics    |          | CA-125 Sample                 | Analysis                            | AUC   | SEN   | SPE   | Cut-off    |
|-------------------|--------------|---------|----------------------------|----------|-------------------------------|-------------------------------------|-------|-------|-------|------------|
|                   |              |         | Recurrent/Non recurrent AF | PeAF/PAF |                               |                                     |       |       |       |            |
| Huang et al, 2019 | Cohort       | China   | 96/326                     | 176/80   | Plasma<br>Blood<br>Peripheral | Beckman<br>Coulter<br>OV<br>Monitor | 0.803 | 65.6% | 85.0% | 11.5 U/mL  |
| Wang et al, 2021  | Cohort       | China   | 85/268                     | 96/257   | Plasma<br>Blood<br>Peripheral | Beckman<br>Coulter<br>OV<br>Monitor | 0.748 | 61.2% | 79.1% | 13.75 U/mL |

Receiver operative characteristic curve (ROC Curve) analysis showed that CA-125 has sensitivity, specificity, AUC values to predict the occurrence of recurrent AF after RFCA of 61.2%, 79.1% and 0.748, respectively, with an optimal cut-off at a level of 13.75 U/mL (Hindricks et al., 2021)

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**Table 2**

Univariate and multivariate analysis of Carbohydrate Antigen-125 (CA-125), high sensitivity C-Reactive Protein (hs-CRP), and Left Atrial Diameter (LAD)

| Marker        | Univariate |             |         | Multivariate |             |         |
|---------------|------------|-------------|---------|--------------|-------------|---------|
|               | OR         | 95% CI      | P value | OR           | 95% CI      | P value |
| CA-125 (U/mL) | 1.129      | 1.083-1.177 | <0.001  | 1.121        | 1.075-1.169 | <0.001  |
| Hs-CRP        | 1.145      | 1.050-1.248 | 0.002   | 1.103        | 1.005-1.210 | 0.040   |
| LAD           | 1.108      | 1.055-1.162 | <0.001  | 1.096        | 1.042-1.153 | <0.001  |

These results were supported by a similar study with a sensitivity of 65.6%, specificity of 85% and AUC of 0.803 at an optimal cut-off at 11.5 U/mL (Table 1). According to Wang et al., multivariate analysis showed that CA-125 levels were superior to hs-CRP and LAD as independent predictors of recurrent AF after RFCA (Table 2)

## **2. Discussion**

As a single biological indicator, CA-125 shows moderate accuracy and could potentially be a predictor of AF recurrence after RFCA. Recent research has shown a difference in the optimal cut-off, which is based on the yellowing effect of the Huang et al. study, where 67.5% of the sample received long-term statin therapy, so the anti-inflammatory effect of statins may be the cause of the lower PCA-125 level of 11.05 U/mL, which is lower than the cut-off of 13.75 U/mL (Hindricks et al., 2021)

Thus, it suggests that patients with CA-125 levels below 13.75 U/mL have a lower likelihood of experiencing post-procedure AF recurrence, providing greater benefit to patients. CA-125 concentrations were higher in recurrent AF after RFCA, proving that CA-125 concentrations are highly correlated with the AF process. Popa et al. compared blood samples from 60 idiopathic AF patients with samples from 120 healthy patients in sinus rhythm (SR) and found that CA-125 levels were significantly higher in idiopathic AF patients than SR controls. Multivariate analysis showed that CA-125 levels (OR, 1.68; 95% CI: 1.07-2.64; P=0.026) were independently associated with idiopathic AF. This indicates that CA-125 may be a marker for AF in patients without structural heart disease (Yao et al., 2020)

However, the underlying pathophysiologic mechanism of this increase is still debated. Some studies suggest that the incidence and development of AF recurrence after RFCA is related to myocardial remodeling. Based on current developments in molecular biology, myocardial remodeling results in pathological cardiomyocyte hypertrophy with re-expression of embryonic genes. During this process, proto-oncogenes are activated, which stimulate growth factors present in the embryonic heart, leading to increased CA-125 levels (Zeid Nesheiwat; Amandeep Goyal; Mandar Jagtap, 2023); (Linhart M, Baman TS, Trivedi A, et al., 2022)

This suggests that plasma CA-125 levels are highly correlated with the incidence and progression of AF post RFCA. Results showed that PeAF patients had higher PCA-125 levels than PAF patients ( $15.59 \pm 11.59$  U/mL vs.  $12.12 \pm 6.59$  U/mL, P = 0.01). It was also significantly associated with an increased risk of recurrence in PAF. Previous

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data shows that the postoperative AF recurrence rate after RFCA varies from 14-35% in PAF and up to 70% in persistent AF, even though RFCA has become standard therapy (Yao et al., 2020); (Park J, Joung B, Uhm JS, et al., 2021). Therefore, identifying patients with persistent AF may help determine the optimal time for re-ablation and improve clinical outcomes.

As a biomarker, CA-125 has many advantages. First, compared to other biomarkers predictor, CA-125 is also superior to hs-CRP because it is more stable and has a longer half-life of 10.4 days and lasts up to 21 days compared to hs CRP which is only 19 hours. Second, CA-125 levels were not significantly influenced by gender, age BMI, and renal function. Third, according to a cohort study with 353 samples, the CA-125 examination procedure is standardized, non-invasive and relatively easy because it does not require special preparation for the patient to be examined. In addition, the cost required for CA-125 examination is also relatively affordable (Hindricks et al., 2021); (Krittanawong C, Padmanabhan S, Virk HUH, et al., 2021); (Weng LC, Rienstra M, Benjamin EJ, Magnani JW., 2021)

**Conclusion**

By considering the advantages, sensitivity, and specificity of CA-125, we conclude that elevated plasma levels of CA-125 may be an interesting option as an independent predictor of recurrent AF after RFCA. This review can be used as a basis for consideration for research on similar topics. Due to the fact that CA-125 has previously been utilized as a predictor of malignancy cases, in post-RFCA AF patients with elevated CA-125 who do not show clinical symptoms suggestive of AF, other supporting examinations suggestive of malignancy should be considered to confirm the diagnosis

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**CONFLICT OF INTEREST**

There is no conflict of interest



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