AN OBSERVATIONAL STUDY ON RELATIONSHIP BETWEEN C-REACTIVE PROTEIN ALBUMIN RATIO (CAR) AND NEW-ONSET ATRIAL FIBRILLATION (AF) IN POST-OP CABG PATIENTS

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ABSTRACT:

Background: The association between systemic inflammatory markers and atrial fibrillation (AF) is an emerging area of interest. This study designed to evaluate the value of prediction based on C-Reactive protein (CRP) to Albumin Ratio (CAR), C-Reactive Protein, Ratio of Neutrophil-Lymphocyte (N/L), and ratio of Platelet-Lymphocyte (P/L) leading to postoperative AF (New-Onset POAF) occurrence among patients who underwent recent coronary artery bypass grafting (CABG).

Methodology: 306 patients, admitted with coronary artery disease (CAD) and Triple Vessel Disease (TVD) and underwent CABG at SRIHER, Chennai, between August 2022 and 2023, were included. The participants were divided into 2 groups: 1. Patients with normal sinus rhythm (n=187) and patients with New-Onset POAF (n=119). Demographic parameters, clinical parameters, and inflammatory markers were analysed using logistic regression and correlation tests.
Results: CAR is significantly higher along with inflammatory markers like CRP, N/L-ratio, and P/L-ratio in the New-Onset POAF group compared to sinus rhythm group. The logistic regression model revealed that these inflammatory markers were significant predictors of New-Onset POAF. Further correlation tests showed significant positive correlations between markers and New-Onset POAF.

Conclusion: Novel marker, CAR has significant potential in predicting New-Onset POAF in Indian patients who underwent CABG along with Markers of systemic inflammation, including CRP, N/L-ratio, and P/L-ratio. This novel insight underscores the possible role of systemic inflammation in New-Onset POAF development and opens avenues for better risk stratification and therapeutic interventions.

Keywords: Postoperative New-Onset Atrial Fibrillation, Coronary Artery Bypass Grafting, Inflammatory Markers, C-Reactive Protein-Albumin Ratio, C-Reactive Protein, Neutrophil-Lymphocyte Ratio, Platelet-Lymphocyte Ratio.

INTRODUCTION

Atrial fibrillation (AF) is a common condition with sustained dysrhythmiasobserved in medical practice. Even though there are advancements in treatment and prevention, AF remains as a cause ofhuge risk of mortality, elevated morbidity, frequent hospitalizations, and diminished quality of patient life.[1] While the exact causes of AF are not fully understood, gaining more knowledge about its pathogenesis could lead to new therapeutic approaches. Inflammation was shown to play a role in development of numerous cardiovascular problemslike unstable angina and heart strokes.[2] Similarly, evidence suggests a link between inflammation and initiation and progression of AF, inlight of the association of AF with inflammation of myocardium and response to systemic inflammation (SIR) following surgeries to the heart and bypass grafting of cardiopulmonary vessels.[3,4]Identifying patients at risk of New Onset postoperative AF (New Onset POAF) before surgery and taking appropriate precautions could potentially reduce mortality and morbidity rates. It is believed that AF initiation may result from fibrosis and necrosis as a result of inflammation, that trigger dysrhythmias mediated bypotential fluctuations in cell membrane. Many studies have focused on establishing a correlation between AF and inflammation by examining inflammatory biomarkers. Early observations showed a correlation between POAF and extent of inflammatory systemic response post CABG.[3]

Among these inflammatory biomarkers, C-reactive protein (CRP) was studied extensively and is known to be a prognostic condition for mortality in patients with inflammatory complications.[5] Additionally, the CRP/albumin ratio (CAR), a newer marker which reflects the interaction between dystrophy and SIR, has been identified as a valuable indicator for acute illness in various medical settings.[6] Recent evidence suggests that not only an increase in CRP levels but also an elevation in new markers of inflammation such as CAR are relatedto the progression of AF.[7] CAR outperforms CRP/albumin levels individually in determination of the status of inflammation in variousCVD's.[8,9]Literature review of works by Lo and colleagues[10] and Aviles and colleagues[11]displayed that a higher CRP baseline levels were related to an elevated risk of POAF. Patients with elevated quartiles of baseline CRP had a elevated likelihood of development of AF through the post-surgical period. Evaluating the CAR value, may offer early diagnosis of postoperative atrial fibrillation in high risk patients.[12]People with an elevated CAR need frequent closefollow-ups and intensive therapy. Also, as a readily measurable biomarker, the CAR offers the

upper hand of simplicity and standardization without requiring additional complex expenses, making it a cost-effective and convenient tool for prognostication.[7]

However, despite the extensive evidence highlighting the relationof CAR with AF, there is a lack of published studies specifically investigating the direct association between CAR and New Onset postoperative AF in the Indian population. Hence, the aim of the present study is to explore the potential usefulness of CAR in predicting the presence and development of New-Onset Postoperative AF in patients of India. This research focusses to contribute for the determination of the role of CAR as a predictive tool for postoperative AF and provide valuable insights for clinical practice.

MATERIALS AND METHODS

The observational study was conducted in SRIHER, Chennai on patients who were admitted with CAD and TVDwho underwent CABG during 2022 and 2023. The patient's database was accessed and isolated based on inclusion and exclusion criteria. 400 patients whose age is between 40-70 years in sinus rhythm and New Onset AF post CABG were included. Those with valvular disease, preop-arrhythmias, heart failure, thyrotoxicosis and those who were implanted with permanent or temporary pace maker (PPI & TPI) were excluded from the study. Outof the 306 final cohort, 187 who had a normal sinus rhythm were grouped aside with 119 AF patients in another group. After explaining the protocol to the participants or care takers, consent was obtained before participation in the study.

Collection of blood and analysis

The blood was withdrawn from antecubital vein through a venal puncture with the help of sterile 21 guage syringe after 12 hr fasting duration. This was stored at 4^0C till further use in the ampules. Automatic blood cell counter (LH780) analysed the RBC, WBC, Haemoglobin (Hb), Platelets, Neutrophils, Lymphocytes and monocytes. N/L, P/L ratios were also dettermined accordingly. Serum was subjected to determination of CRP and ALB and resultant Novel marker of CAR was obtained by diving CRP by ALB values. The heart rhythms were monitored closely using ECG in the ICU and hospitalization period. Arrhythmias or dysrhythmias were noted and New Onset AF episodes lasting for at least a period of 5mins were considered as POAF.[13]

Statistical analysis

SPSS software package 16.0 was used for comparing various groups and for analysing data. Student's T test was employed for analysing Numerical variables and non-numerical data was compared using Chi-squared tests. The data was represented as mean±SD and the values for which p-value <0.001were considered significant. The correlation between markers was determined using Spearman or Pearson correlation testing and logistic regression testing was performed to predict the markers associated with the AF.

RESULTS

In Table 1, the demographic data of the study was demonstrated, categorized into two groups based on their cardiac rhythm status: normal sinus rhythm and New Onset postoperative atrial fibrillation (New Onset POAF). The table provides a summary of various demographic parameters and their comparison between the two groups.The average age of participants with regular sinus rhythm was 50.7 ± 10.3 years, whereas patients with New-Onset POAF had more mean age of 58.9 ± 12.1 years ($p<0.001$), indicating a significant relationof age with the development of New Onset POAF.Gender distribution revealed that a higher percentage of males (63.86%) experienced New Onset POAF compared to females (36.13%) ($p < 0.001$).

The presence of comorbidities was also analysed. Although the prevalence of diabetes showed a slightly higher proportion in the New Onset POAF group (63.02%) compared to the normal sinus rhythm group (57.75%), the relationwas not statistically significance ($p = 0.072$). However, hypertension (85.71% vs. 70.05%, $p<0.001$) and CHF (20.11% vs. 5.88%, $p<0.001$) were reletively more prevalent in the New-Onset POAF group. The history of stroke did not show a significant difference of the 2 groups ($p=0.091$).

Body mass index (BMI) was significantly elevated in participants with New-Onset POAF (31.33 ± 4.28) in comparison with normal sinus rhythm (27.18 ± 3.29) ($p < 0.001$), indicating a potential association between obesity and New Onset POAF.Regarding haematological parameters, the mean WBC was slightly elevated in the normal sinus rhythm group (8.934 ± 1.829) compared to the New Onset POAF group (8.638 ± 1.922) ($p = 0.044$). On the other hand, there was difference between neutrophil count (7.83 ± 0.12 vs. 4.77 ± 0.21, $p < 0.001$), lymphocyte count (4.76 ± 0.15 vs. 4.24 ± 0.18, $p = 0.023$), and platelet count (387.4 ± 7.7 vs. 154.4 ± 9.3, $p < 0.001$) between the New Onset POAF and normal sinus rhythm groups

Table 1, Prevalence of patient demographic data in New Onset POAF

Demographic parameter	**Group with normal sinus rhythm (n=187)**	**Group with New Onset POAF (n=119)**	**p-Value**
Age (years)	50.7±10.3	58.9±12.1	<0.001
Gender			
Male (n, %)	98 (52.4)	76 (63.86)	<0.001
Female (n, %)	89 (47.59)	43 (36.13)	<0.001
Condition			
Diabetes (n, %)	108 (57.75)	75 (63.02)	0.072
Hypertension (n, %)	131 (70.05)	102 (85.71)	<0.001
CHF (n, %)	11 (5.88)	24 (20.11)	<0.001
History of stroke (n, %)	9 (4.81)	9 (7.56)	0.091
Obesity (BMI)	27.18±3.29	31.33±4.28	<0.001
WBC (10^3/μL)	8.934±1.829	8.638±1.922	0.044
Neutrophil (10^3/μL)	4.77±0.21	7.83±0.12	<0.001
Lymphocytes (10^3/μL)	4.24±0.18	4.76±0.15	0.023
Platelets (10^3/μL)	154.4±9.3	387.4±7.7	<0.001

Table 2, Changes in the inflammatory markers in patients with New Onset POAF

Marker	**Group with normal sinus rhythm**	**Group with New Onset POAF**	**p-Value**
N/L ratio	1.125	1.644	0.021
P/Lratio	11.40	81.38	<0.001
C-Reactive Protein (CRP) (mg/L)	4.14±0.34	17.29±1.88	<0.001
Albumin (g/L)	3.42±0.29	3.87±0.41	0.048
CAR	1.19±0.22	4.63±0.75	<0.001

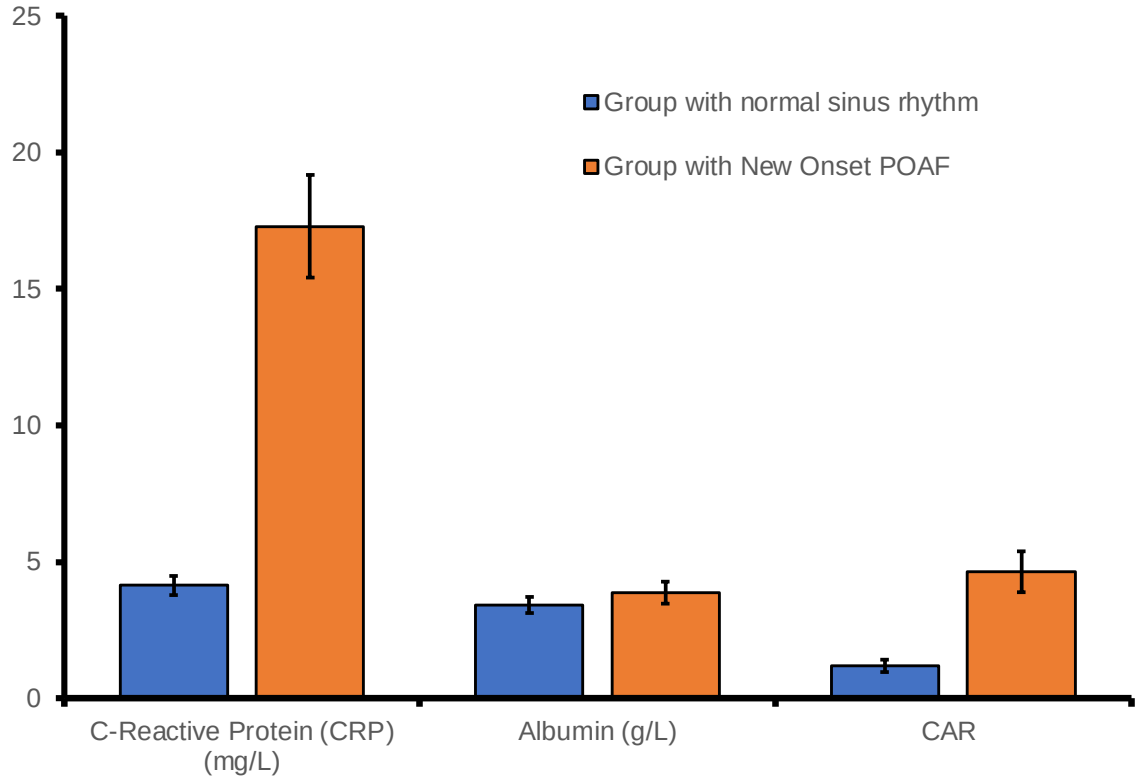

Figure 1, Detection of CAR, CRP and albumin in New-Onset POAF

The N/L ratio, was significantly elevated in the New-Onset POAF (1.644) in comparison to the normal sinus rhythm group (1.125) ($p = 0.021$). This suggests that an increased N/L ratio may be related with a increased risk of developing New-Onset POAF. Similarly, the P/L ratio, indicating the platelet-to-lymphocyte ratio, was significantly elevated in the New Onset POAF group (81.38) compared to the normal sinus rhythm group (11.40) ($p<0.001$). This reading suggested that a higher P/L ratio may be indicative of increased inflammation and a greater likelihood of New Onset POAF development. The CRP levels were elevated in the New Onset POAF (17.29 ± 1.88 mg/L) compared to the normal sinus rhythm group (4.14 ± 0.34 mg/L) ($p < 0.001$). This demonstrates a clear relationship between the increased CRP and the occurrence of New-Onset POAF, indicating that SIR plays a role in pathogenesis of New Onset POAF.

The albumin levels were slightly higher in the New Onset POAF group (3.87 ± 0.41 g/L) compared to the normal sinus rhythm group (3.42 ± 0.29 g/L) ($p = 0.048$). Although the difference was modest, it suggests that lower albumin levels may contribute to the inflammatory processes associated with New Onset POAF. Of particular interest is CARreflecting the interactive associationofdystrophy with SIR. The CAR value was significantly higher in the New Onset POAF group (4.63 ± 0.75) compared to the normal sinus rhythm group (1.19 ± 0.22) ($p < 0.001$) as shown in figure 1. This indicates that an elevation in CAR is strongly relatedto the progression of New Onset POAF, providing further evidence of inflammatory roles in POAFprognosis. Taken together, these findings highlight the significance of SIR in determining the occurrence of New Onset POAF. Elevated N/L-ratio, P/L-ratio, CRP, and CAR are all related with a higher risk of developing New-Onset POAF. Monitoring these markers may aid in recognising patients at higher risk for New-Onset POAF and enable timely interventions to mitigate adverse outcomes.

The logistic regression analysis provided odds ratios for these predictors, which can help us understand how changes in these variables might affect the likelihood of experiencing New Onset POAF. The age predictor has an odds-ratio of 1.05 meaning with an increment in 1 year of age there is a 5% increment in the chances of occurrence of New-Onset POAF. Similarly, the hypertension predictor has an odds ratio of 1.57, which means hypertensive patients have 57% higher odds of developing New Onset POAF than non-hypertensive patients, all else being equal.C-Reactive Protein (CRP) has an odds ratio of 1.49, suggesting the odds of New Onset POAF occurrence increase by 49%.However, Albumin shows an odds-ratio of 0.61, indicating the odds of New Onset POAF occurrence decrease by 39% (since 1-0.61=0.39), implying a protective effect.

In Table 3, the inflammatory markers and demographic parameters with significant correlations ($p < 0.05$) and high absolute values for the Pearson's r (linear relationships) or Spearman's rho (monotonic relationships) (closer to -1 or 1) have strong relationships with New Onset POAF occurrence. Like CAR, CRP has a significant p-value (<0.001), and its correlation coefficients (Pearson's r = 0.35 and Spearman's rho = 0.34) demonstrate a significant positive correlation with New-Onset POAF occurrence. CAR in the table has relatively high correlation coefficients (0.45 for Pearson's r and 0.43 for Spearman's rho) and a significant p-value, indicating a strong relationship with New-Onset POAF occurrence. The CAR value has a positive Beta coefficient and an odds ratio of 2.22. This suggests the odds of New Onset POAF occurrence more than double, assuming all other predictors are held constant. In summary, higher levels of CAR and CRP, both measures of SIR, are relatedto theelevated risk of New Onset POAF, suggesting that these inflammatory markers might be indicative of underlying pathological processes that predispose to New Onset POAF. However, higher levels of Albumin, an acute negative phase protein often reduced in systemic inflammation, is related to a lowered risk of New Onset POAF. The association of these markers with New Onset POAF could reflect the involvement of SIRs in the progression of New Onset POAF. These markers can be employed to identify people at high risk of occurrence ofNew Onset POAF and could provide targets for therapeutic interventions.

Table 3, Correlation of inflammatory markers and demographic parameters on the prediction of New-Onset POAF

Predictor	**Beta (SE)**	**Wald**	**p-Value**	**Odds-Ratio (95% CI)**	**Pearson's r-value**	**Spearman's rho**
Age (yrs)	0.05 (0.01)	25.00	<0.001	1.05 (1.03-1.07)	0.38	0.35
Gender (Male)	0.30 (0.20)	2.25	0.13	1.35 (0.92-1.98)	0.12	0.10
Diabetes	0.25 (0.20)	1.56	0.21	1.28 (0.86-1.91)	0.17	0.16
Hypertension	0.45 (0.21)	4.62	0.03	1.57 (1.04-2.37)	0.28	0.26
CHF	0.80 (0.30)	7.11	0.008	2.22 (1.21-4.06)	0.20	0.19
History of stroke	0.35 (0.30)	1.36	0.24	1.42 (0.78-2.58)	0.09	0.08
Obesity (BMI)	0.07 (0.02)	12.25	<0.001	1.07 (1.03-1.11)	0.36	0.32
/L ratio	0.20 (0.08)	6.25	0.01	1.22 (1.04-1.42)	0.20	0.18
P/L ratio	0.35 (0.10)	12.25	<0.001	1.42 (1.15-1.76)	0.33	0.31

C-Reactive Protein (CRP)	0.40 (0.12)	11.11	<0.001	1.49 (1.18-1.88)	0.35	0.34
Albumin	-0.50 (0.15)	11.11	<0.001	0.61 (0.44-0.85)	-0.32	-0.31
CAR	0.80 (0.20)	16.00	<0.001	2.22 (1.49-3.31)	0.45	0.43

DISCUSSION

Our investigation explored the link between inflammatory markers and demographic features in forecasting postoperative atrial fibrillation (New Onset POAF) in patients in India who had undergone CABG. We primarily assessed the CAR, CRP, Albumin, N/L-ratio, and P/L-ratio. Key outcomes from our logistic regression study indicated significant relationships between these variables and the occurrence of New-Onset POAF.

The CAR is a Novel compound marker indicative of both CRP and Albumin. The former, CRP, is an acute phase reactant associated with systemic inflammation. Its level elevates during inflammation, infection, or tissue damage, and it has been implicated in both the onset and maintenance of AF.[14] In contrast, an elevation in Albumin levels seems to confer protection against POAF.[15]Consequently, lower Albumin levels could signify increased inflammation, explaining the inverse correlation seen in our study. Elevated CAR values, resulting from an increase in CRP and a decrease in Albumin, imply heightened systemic inflammation, which has been associated with a higher risk of AF, consistent with previous findings.[14] Elevated CAR values reflect increased systemic inflammation, potentially exacerbating the anatomical and neural remodelling of the atrium, thereby predisposing to AF.[16]

Additionally, our study suggested a strong correlation between elevated CAR levels and a higher incidence of New Onset POAF. CRP is a known inflammation marker and has been linked to increased AF risk in previous studies.[17] Elevated CRP levels may indicate a heightened state of systemic inflammation, which could enhance the susceptibility of the myocardium to perioperative stressors, leading to a greater risk of New Onset POAF. Various works have shown a relationship of elevated CRP with recurrences of AF post catheterization and ablation, which corroborates our findingsshowing CRP>2 times elevated than normal in AF.[18] Our study observed a similar CRP value trend, peaking at 5mg/l in the normal group, but ranging up to 17 mg/l in the New Onset POAF group. Notably, those who had experienced AF for three months and exhibited no CRP level changes after successful electrical cardioversion were more likely to experience recurrence of AF.[19] Preoperative CAR levels were significantly higher in those who encountered postop AF after CABG than in those maintained postoperative normal sinus rhythm. A higher CAR was identified to be an important predictive factor for postoperative atrial fibrillation.[12]

Epidemiologic studies have shown that hyperlipidaemia, chronic smoking, hypertension, and DM are related with increased CRP levels and other SIR's.[20] However, it remains unclear whether lowering CRP levels would affect the occurrence or progression of AF positively. Latestworks suggest that CAR levels can be modulated using antihyperlipidemic, anti-diabetic, anti-cholesterol, and anti-inflammatory drugs such as aspirin, implying that CRP-reducing drugs or anti-inflammatory agents might enhancePOAF prevention in postoperative patients with higher CRP.[21]

The N/L-ratio is a SIR, which in a multitude of studies, has been discovered to be linked with the incidence of POAF.[15] In the context of acute inflammation, neutrophils, which are the principal white blood cells, are elevated, whereas lymphocytes are relatively diminished under conditions of stress. Hence, an escalated N/L ratio signifies a state of increased inflammation, which could potentially instigate the onset of AF. In a similar pathway, the P/L ratio has surfaced as a marker of inflammation, providing insight into both platelet activation and the lymphocytic response to inflammation and stress.[22] The consensus suggests that an elevated P/L ratio hints at a state of increased inflammation and heightened platelet activity, both integral to the pathophysiology of AF. Further reinforcing this, our study discovered that both the N/L and P/L ratios bore significant associations with the onset of New Onset POAF. As a well-established marker, an elevated N/L-ratio has been relatedto a poorer prognosis in a variety of cardiovascular conditions.[23] Likewise, a high P/L-ratio has been associated with less favourableresutls in coronary artery disease, possibly attributable to the involvement of platelets in inflammatory processes.[22] However, while our study's findings are encouraging, they should be viewed within the context of the study's limitations. These include its observational nature and the potential impact of factors that have not been accounted for. As a result, further multi-centre, prospective studies are required to validate our results and clear the potential mechanisms at play in the observed associations.

LIMITATIONS

While our study's observational design allowed us to identify associations, it's important to remember that this does not directly infer causality. Despite the discovery of significant links between inflammatory markers and the incidence of New Onset POAF, it's essential that further experimental research is undertaken to conclusively determine cause-and-effect relationships. Another important point to consider is the potential limitation on the applicability of our findings. The research was designed at a solo medical facility in Chennai, India, which can possibly restrict the broadness of its conclusions. To validate these findings, additional studies across multiple centres with a more diverse patient population would be beneficial. There's

also the possibility of selection bias, as patients were excluded those withcomorbid conditions like valvular heart disorder, preoperative arrhythmias, CHF, and thyrotoxicosis. The inclusion of these patients may have altered our results, considering the known relationships between these conditions and inflammation. Lastly, our assessment of CRP was only conducted at baseline, meaning we were unable to analyse the impact of changing levels over time or the influence of CRP levels post-intervention. Such measures might have offered a more comprehensive view of the patients' underlying inflammatory states. These are all considerations for future research in this area.

FUTURE PROSPECTS

Although our research identified substantial correlations between inflammatory markers and New Onset POAF, the specific mechanisms facilitating these associations largely remain to be clarified. Future research should concentrate on uncovering these underlying mechanisms, which could serve a dual purpose: reaffirming the validity of these markers and possibly revealing novel targets for therapeutic intervention. In addition, a more in-depth examination of other inflammatory markers could contribute to a more holistic understanding of role of inflammationin the manifestation of New-Onset POAF. If these markers do indeed play a part in the onset of New-Onset POAF, it suggests the potential effectiveness of interventions aimed at curtailing inflammation to reduce the incidence of New Onset POAF. Given this, future research could profitably investigate clinical trials of anti-inflammatory therapies, representing a promising avenue for the development of novel and effective treatment strategies.

CONCLUSION

Our research enlightens the possible role of systemic inflammation in predicting New Onset postoperative atrial fibrillation (POAF), using Novel markers such as CAR and other markers like CRP, N/L-ratio, and P/L-ratio. These findings contribute to the expanding knowledge that associates systemic inflammatory markers (CAR) with the New onset of atrial fibrillation. Notably, these easily obtainable markers may offer clinicians an invaluable tool to classify the risk of New Onset POAF in CABG patients, thereby enabling superior patient management, individualized treatment strategies, and potentially enhanced outcomes. Moreover, the potential implications of our findings extend beyond merely prognostic capabilities. By deepening our comprehension of the underlying pathophysiology of New Onset POAF, our research may serve as a platform for developing novel, targeted anti-inflammatory therapeutic strategies aimed at novel CAR marker to lower the occurrence of New Onset POAF and associated morbidity. In a broader context, our research highlights the necessity for ongoing investigation in this field to further reveal and substantiate the intricate interaction between CAR and new onset Postoperative atrial fibrillation. Ultimately, such research efforts will help refine management strategies for patients undergoing cardiac surgeries.

ACKNOWLEDGMENTS

Author's Choice

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