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REVIEW ARTICLE

Increased serum interleukin-6 level as a predictive biomarker for atrial fibrillation: A systematic review and meta-analysis

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KEYWORDS
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Abstract
Background: Atrial fibrillation (AF) is related to a higher risk of thromboembolic events and mortality. Some studies have demonstrated that the inflammatory biomarker interleukin-6 (IL-6) is associated with a higher risk of higher thrombosis in AF patients, but the real effect of IL-6 remains a controversy.
Methods: We conducted a systematic review and meta-analysis to investigate the association between IL-6 and thromboembolic events, as well as bleeding events, acute coronary syndrome (ACS) events and all-cause mortality in AF.
Results: A total of five studies involving 22 928 patients met our inclusion criteria for the systematic review. The higher level of IL-6 in AF patients is related to long-term thromboembolic events including stroke (RR 1.44, CI 95% 1.09-1.90, p=0.01). IL-6 meant a higher risk of long-term bleeding risk (RR 1.36, CI 95% 1.06-1.74, p=0.02), ACS risk (RR 1.81, CI 95% 1.43-2.30, p<0.001) and all-cause mortality (RR 2.35, CI 95% 2.09-2.65, p<0.001).
Conclusion: A higher level of IL-6 may predict a greater number of long-term thromboembolic events and bleeding events, ACS events and mortality in AF patients. Further studies such as the cut-off point of IL-6 need to be conducted in the future.

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PALAVRAS-CHAVE
Firilhação auricular;
Interleucina-6;
Acidente vascular cerebral;
Prognóstico

Nível sérico elevado de Interleucina-6 como biomarcador preditivo de fibrilhação auricular: uma revisão sistemática e meta-análise

Resumo
Introdução: A fibrilhação auricular (AF) está relacionada com maior risco de eventos tromboembólicos e de mortalidade. Alguns estudos mostraram que o biomarcador inflamatório interleucina-6 (IL-6) estava associado a maior risco trombótico em doentes com AF, mas o efeito real da IL-6 continua controverso.
Métodos: Realizámos uma revisão sistemática e meta-análise para investigar a associação de IL-6 com eventos tromboembólicos assim como eventos hemorrágicos, eventos síndrome coronária aguda e mortalidade total na AF.
Resultados: Cinco estudos que envolveram 22 928 doentes preencheram os nossos critérios de inclusão para revisão sistemática. Maior nível de IL-6 em doentes com AF relaciona-se com eventos tromboembólicos em longo prazo, incluindo acidente vascular cerebral (RR 1,44, 95% CI 1,09-1,90, P 0,01), risco de ACS (RR 1,81, 95% CI 1,43-2,30, P<0,001) e mortalidade total (RR 2,35, 95% CI 2,09-2,65, P<0,001).
Conclusão: Um nível mais elevado de IL-6 pode prever um maior número de eventos tromboembólicos assim como de eventos hemorrágicos, eventos ACS e mortalidade em doentes com AF. Mais estudos sobre o ponto de corte de IL-6 necessitam ser realizados.

Atrial fibrillation (AF) is the most common sustained arrhythmia in clinical practice which can cause thromboembolic events such as stroke.[1–3] So far, anticoagulation therapy is the major strategy for AF treatment.[4] We applied CHA_2DS_2-VASc (Congestive Heart Failure, Hypertension, Age (≥75 years), Diabetes, Stroke/Transient Ischemic Attack, Vascular Disease, Age (65-74 years), Sex (Female)) score to assess the risk of stroke in AF patients. The patients with a high score (male ≥2, female ≥3) require anticoagulation therapy.[5] We used HAS-BLED (Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile INRs, Elderly, Drugs or alcohol) to estimate the bleeding risk in AF patients. A score ≥3 means there is a high risk of bleeding.

However, the area under curve (AUC) for CHA_2DS_2-VASc is approximately 0.660.[5] In our previous investigation, less than 30% patients received anticoagulation therapy before stroke. One of the important reasons was that the score before stroke was <2. There must be other factors such as biomarkers which lead to stroke and thromboembolism. Similarly, the AUC for HAS-BLED is approximately 0.60.[6] We also are unable to estimate the risk of other adverse events, such as cerebral infarction and mortality in AF patients by using these scores. It is necessary to discover other methods to assess the prognosis of AF patients.

Inflammation can cause AF and thrombosis. Several biomarkers have been studied in AF patients such as C-reactive protein (CRP)[7,8] and interleukin (IL),[9] while the role of IL-6 in AF and adverse events, especially thrombotic risk, remains controversial.[10,11] We therefore conducted a systematic review and meta-analysis to provide an overview of the association between IL-6 with thromboembolic and other adverse events in AF.

Methods

Search strategy

We used electronic databases to identify relevant studies. The PubMed, EMBASE, Web of Science, and Cochrane databases were systematically searched for studies published up to January 2020. We used mesh terms including ''atrial fibrillation'' and ''interleukin 6'' and ''inflammation''.

Study selection

We enrolled the studies according to the the following criteria: (1) cohort studies (both retrospective and prospective) about stroke or thromboembolic risk in AF patients and (2) studies which focused on IL-6. In case of multiple publications, the most recent studies or studies of a larger population were used. Citations were selected by initially screening the title and abstract of the studies. We assessed the study quality using the Newcastle-Ottawa scale. The total scores ranged from 0 (worst) to 9 (best) for case-control or cohort studies.

Data extraction

Using standard data extraction forms, two reviewers (Zhou and Zhao) extracted data from the relevant studies. The following data were independently extracted: author's name, year of publication, type of study design, study population, sample size, mean duration of follow-up, study end points, risk ratio (RR) with 95% confidence interval (CI), cut-off

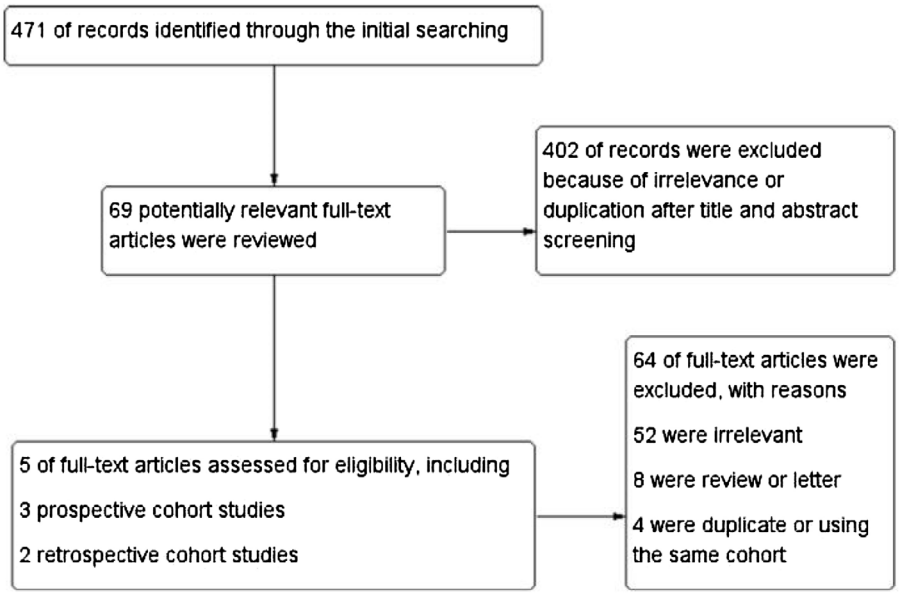

Figure 1 Flow diagram of the study selection.

value and reported adjustment for potential confounders. If the study provided the IL-6 level, we extracted the means and standard deviations in each group. If the study provided the medians and ranges instead of the means and standard deviations, we imputed the means and standard deviations using the method developed by Hozo et al.[12]

Data analysis

For cohort studies, we used pooled hazard ratio (HR) as a summary statistic to estimate the prognostic effect of IL-6 level on thromboembolic events in AF patients. An HR>1 indicated the correlation between elevated IL-6 and stroke and thromboembolic events.

Statistical heterogeneity across studies was assessed using the I^2 statistic. An $I^2 \geq 50\%$ suggests that there is significant heterogeneity between studies. The HR was pooled using a fixed-effects model to manage heterogeneity if it was insignificant ($I^2<50\%$); otherwise, a random-effects model was applied. A p value <0.05 was considered to be statistically significant. Statistical analyses were performed using the RevMan 5.3 software.

Results

Study characteristics

In total, 471 records were retrieved in our primary literature search by using the mesh term atrial fibrillation and interleukin-6. 402 records were excluded after screening the titles and abstracts. 69 potentially relevant full-text articles were reviewed, and five studies with a total of 22 928 participants were included in the final analysis (Figure 1), including two retrospective cohort studies and three prospective cohort studies (Table 1). Quality assessment is reported in Table 2.

Association between IL-6, stroke and thromboembolic events in AF

Where IL-6 was affected by other factors, such as antithrombotic therapy or comorbidity, the researchers adjusted the outcomes to determine whether IL-6 was an independent risk factor for stroke and thromboembolic events. We used the data after adjustment. Meta-analysis showed that elevated IL-6 meant a higher risk of long-term stroke and thromboembolic risk in AF patients with a pooled RR 1.44 (CI 95% 1.09-1.90, p=0.01) (Figure 2).

Association between IL-6 and other adverse events in AF

We conducted the analysis of major bleeding events (Figure 3A), acute coronary syndrome (ACS) (Figure 3B), all-cause mortality (Figure 3C) in AF and the level of IL-6. Three studies were eligible for the analysis. Meta-analysis showed that elevated IL-6 meant a higher risk of long-term bleeding risk (RR 1.36, CI 95% 1.06-1.74, p=0.02), ACS risk (RR 1.81, CI 95% 1.43-2.30, P<0.001) and all-cause death (RR 2.35, CI 95% 2.09-2.65, p<0.001).

Discussion

IL-6 is one of the inflammatory cytokines with a pleiotropic effect on immune response and inflammation. It is synthesized in immune cells such as macrophages and monocytes.[16] When pattern recognition receptors of immune cells are activated, a range of signaling pathways including factor kappa B are initiated to enhance the transcription of the message RNA of inflammatory cytokines such as IL-6, tumor necrosis factor (TNF), and IL-1β.[17] IL-6 can also be produced in endothelial cells as a result of the stimulation of IL-1, TNF and interferon-γ.[18]

Table 1 Studies on association between IL-6 and thromboembolic events in AF.

Study, year	Type of study	Average follow-up (months)	No. of patients, n	Cut-off point of IL-6 (ng/L)	End points	Variables adjusted for
Aulin, 2015[13]	Retrospective cohort study	24	6187	2.5	Stroke/systemic embolism, major bleeding, ACS	Other inflammation marker level, treatment, CHA2DS2-VASc score
Conway, 2004[14]	Prospective cohort study	76.8	77	20	Stroke, all-cause mortality	Age, antithrombotic therapy
Hijazi, 2016[11]	Retrospective cohort study	22.8	14 954	2.3	Stroke/systemic embolism, major bleeding, ACS, all-cause mortality	Other inflammation marker level, study treatment, CHA2DS2-VASc score
Rivera, 2019[6]	Prospective cohort study	78	940	3.7	Stroke, major bleeding	Other inflammation marker level, CHA2DS2-VASc and HAS-BLED score
Roldan, 2012[15]	Prospective cohort study	31.9	770	3.35	Stroke/TIA, ACS, all-cause mortality	CHA2DS2-VASc score

AF: atrial fibrillation; TIA: transient ischemia attack; ACS: acute coronary syndrome; CHA_2DS_2-VASc: Congestive Heart Failure, Hypertension, Age (≥75 years), Diabetes, Stroke/Transient Ischemic Attack, Vascular Disease, Age (65-74 years), Sex (Female).

Table 2 Newcastle scale for scoring studies.

Study, year	Newcastle-Ottawa Scale			
	Selection	Comparability	Outcome/Exposure	Total
Aulin, 2015	***	**	***	7
Conway, 2004	**	**	***	6
Hijazi, 2016	***	*	**	5
Rivera, 2019	***	*	***	7
Roldan, 2012	***	*	*	5

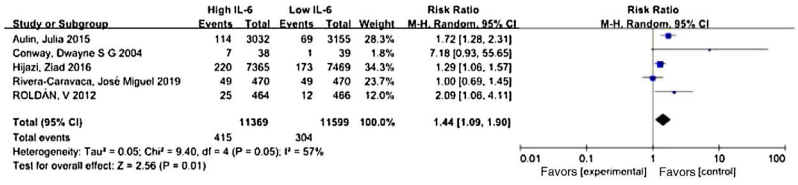

Figure 2 Forest plots of risk ratio (RR) and CI 95% for the association between IL-6 and stroke and thromboembolic events in AF.

IL-6 synthesized in the inflammatory lesion is released to the blood and moves to the liver, which means IL-6 is the major regulator of acute phase response in human hepatocytes.[19] A series of acute phase proteins were then induced such as CRP, fibrinogen and plasminogen activator inhibitor-1.[19] IL-6 promotes megakaryocyte maturation after reaching the bone marrow, thus leading to the release of platelets and thrombocytosis.[20] IL-6 may induce the expression of tissue factor,[21,22] factor VIII[23] and von Willebrand factor.[24] In addition, an increased interleukin-6 level decreases the natural inhibitors of hemostasis such as antithrombin, protein S[25] and thrombomodulin.[26] Elevated IL-6 is related to enhanced coagulation function and weakened anticoagulation function to establish a prothrombotic state, which in turn is linked to thrombotic risk and ACS. IL-6 also induces excess production of vascular endothelial growth factor, leading to enhanced angiogenesis and increased risk of bleeding.[16]

Emerging studies have proved that AF is a kind of inflammation, containing inflammatory cells and inflammatory cytokines. Thrombogenesis of AF is also associated with inflammation. CRP level is significantly associated with stroke risk in AF patients.[7] In AF patients, platelet P-selectin levels and adenosine diphosphate -induced platelet aggregation are significantly higher in the left atrium compared to the right atrium,[27] which may be related to the different inflammation level. IL-6 level is positively related to the CHA_2DS_2 score, while anticoagulation

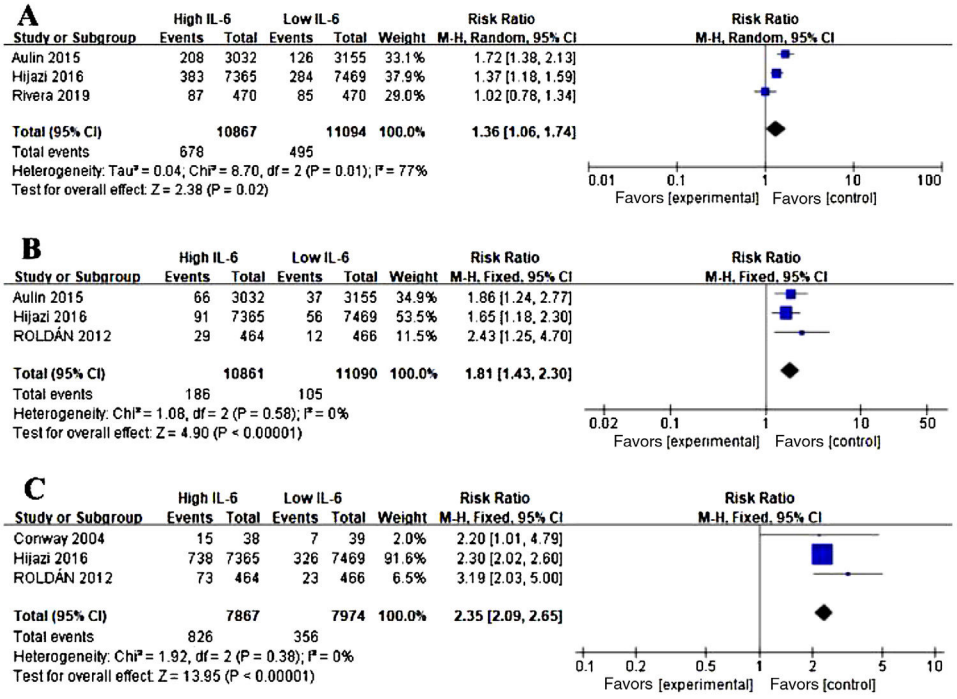

Figure 3 Association of IL-6 and other adverse events in atrial fibrillation (AF). (A) Forest plots of risk ratio (RR) and CI 95% for the association between IL-6 and major bleeding events in AF. (B) Forest plots of RR and CI 95% for the association between IL-6 and acute coronary syndrome events in AF. (C) Forest plots of RR and CI 95% for the association between IL-6 and all-cause mortality in AF.

therapy can decrease the IL-6 level.[28,29] Inflammation can cause endothelial dysfunction, platelet and endothelial cell activation, and coagulation cascade activation.[9]

In our meta-analysis, a higher IL-6 level may predict a higher thrombotic risk as well as a higher bleeding risk, ACS risk and mortality risk in AF patients. It is possible to assess the thromboembolic risk and bleeding risk by adding IL-6 into theCHA_2DS_2-VASc score and HAS-BLED score. Anti-inflammation or anti-IL-6 therapy may be administered in AF patients. Further research needs to be conducted such as the cut-off point of IL-6.

There areeveral limitations in our study. The participants' baseline characteristics, such as age and complications were various and the mean follow-up time and cut-off point were all different among the studies. Publication bias was not detected because of the limited number of studies. Publication bias might exist in this study.

Conclusion

Our meta-analysis showed that higher level of IL-6 may predict a greater number of long-term thromboembolic events, as well as bleeding events, ACS events and mortality in AF patients. Further studies such as the cut-off point of IL-6 need to be conducted in the future.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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