




SYSTEMATIC REVIEW

Interleukin 6 as a Predictive Biomarker for Atrial Fibrillation after Coronary Bypass Grafting: A Systematic Review

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ABSTRACT

Atrial fibrillation (AF) progresses after coronary bypass grafting in 11–40% of patients. Plasma biomarkers such as interleukin 6 (IL-6) can assess the risk of AF development. We performed a systematic review using as sources: PubMed, LILACS, and Cochrane Library databases were investigated using Boolean operators and MeSH terms (Medical Subject Headings Terms) “Atrial Fibrillation AND Interleukin AND Biomarkers”. As the following eligibility criteria: observational studies, studies with coronary artery bypass grafting with plasma levels of IL-6 recorded after screening, 11 articles were selected. Three studies met the inclusion and exclusion criteria. Results: IL-6 levels on AF group - Ishida et al. reported the plasma levels of IL-6 during the post-operative period as 360 ± 143 pg/mL, while Pretorius et al. reported it to be 380.6 ± 151.1 pg/mL. Lastly, Ziabakhsh-Tabari et al. reported a post-operative plasma IL-6 level of 38.2 ± 32 pg/mL. It is considered that new studies about the object are necessary, and these studies should be more standardized. Preferably, it would be important for the daily measurement of IL-6 and its correlation with AF development for statistical analysis to set the best time for sample collection and cut-off value.

KEYWORDS: Atrial Fibrillation; Interleukin-6; Coronary Artery Bypass; Biomarkers; Inflammatory Process; Systematic Review

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INTRODUCTION

Atrial fibrillation (AF) develops after coronary bypass grafting in 11–40% of the patients, usually between the second and fifth days after the procedure; this rate can vary based on the definition of AF and the diagnostic protocols used (1,2).

Plasma biomarkers, such as inflammatory biomarkers, vascular pathology, myocyte damage, atrial fibrosis, and impaired cardiac function, when associated with clinical events such as surgery, have been shown to be relevant for assessing the risk of developing AF. Among the inflammatory biomarkers, interleukin 6 (IL-6) has achieved promising results and may help to comprehend AF pathogenesis and predict future risk (3–6).

IL-6 is a signaling molecule associated with adaptive and immune responses. It is synthesized by monocytes, endothelial cells, fibroblasts, and others, in response to microorganisms, other cytokines, trauma, or stress factors. (3,7). There is evidence that inflammation may

be associated with AF pathogenesis. IL-6 has been shown to be linked to AF in patients without a history of AF (1,3,5,6,8,9).

This study aimed to investigate the role of IL-6 as a plasma biomarker for predicting AF after coronary bypass grafting.

MATERIALS AND METHODS

The objective of this study was to examine the role of IL-6 as a plasma biomarker for predicting AF after CABG. The following eligibility criteria were used: 1) observational studies, 2) studies including patients older than 18 years, 3) submitted to coronary bypass grafting, with or without extracorporeal circulation, 4) studies that present plasma levels of IL-6 after the surgery, 5) that performed statistical correlation between AF and IL-6; 6- studies written in English, Portuguese, French, Spanish, and German, 7) published on any date. The exclusion

criteria were as follows: 1) studies with pre-surgical drug intervention to prevent AF without a control group without intervention. Only the control group was eligible for review.

PubMed (US National Library of Medicine), LILACS (Latin American and Caribbean Center on Health Sciences), and Cochrane Library databases were searched using Boolean operators and MeSH terms (Medical Subject Headings Terms) "Atrial Fibrillation AND Interleukin AND Biomarkers". The titles and abstracts of all articles were read separately by two authors (ALADL

and RGDM) and manually selected based on the eligibility and exclusion criteria.

Any disagreements were resolved by consensus with the third author (A. D. S. M. J). Studies that caused doubts concerning the eligibility and exclusion criteria during title and abstract screening were selected for full-text reading.

Articles selected after title and abstract screening were read in full and were judiciously scrutinized about the eligibility and exclusion criteria by all three authors, as seen in Figure 1.

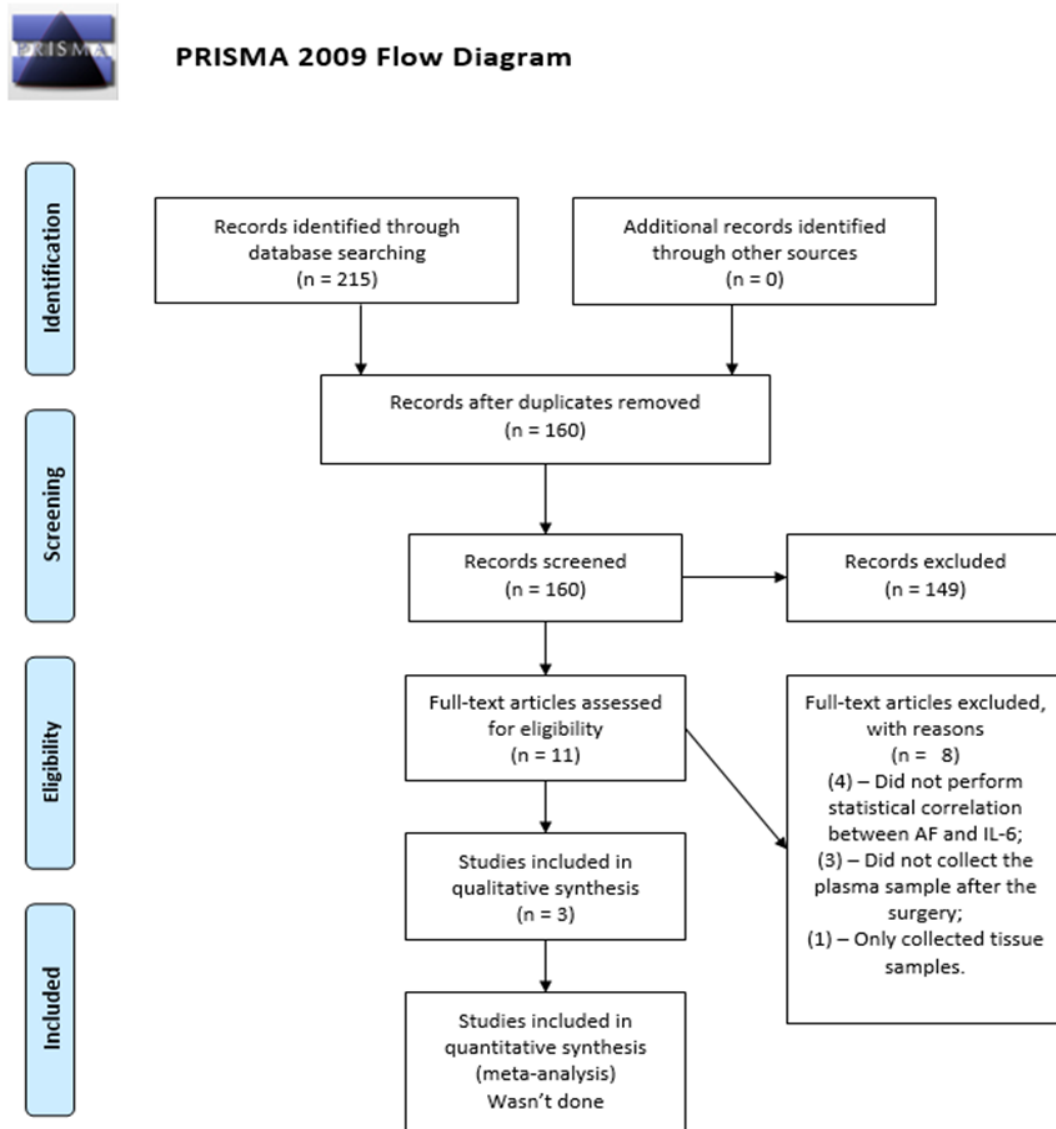


Figure 1 . Flowchart of studies selection.

RESULTS

During the research, 143 studies were found on PubMed, 45 on Cochrane, and 27 on LILACS in May 2019, resulting in 215 studies. After removal of duplicates, 160 articles were selected after screening titles and abstracts. Eleven studies were selected for full text reading and future analysis, as presented in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram (Figure 1) (10–21).

Among the 11 studies, four did not perform a statistical correlation between AF and IL-6, three studies did not assess plasma levels of IL-6 after the surgery, and one study did not collect plasma samples. Therefore, three studies with a total of 346 patients fulfilled the eligibility and exclusion criteria and were used in this systematic review (13,18,19).

In 2006, Ishida et al. performed coronary bypass grafting in 39 patients, of whom 28 (71.1%) were male and 11

(28.3%) were female. The mean age of patients who developed AF was 70 ± 6.4 years and those who did not were 60 ± 8.8 years. 24 patients (61.5%) were hypertensive, and 24 (61.5%) were diabetic. Ishida et al. collected the plasma sample after anastomosis before protamine infusion, 3 and 6 hours after the procedure, and daily until the day 4. This plasma was centrifuged immediately ($3000 \times g$ for 5 min) and stored at -80°C . Thereafter, IL-6 levels were detected using enzyme-

linked immunosorbent assays (R&D Systems, Minneapolis, MN, USA). The follow-up period was 7 days, and 11 (28.2%) patients developed AF during this period. The IL-6 levels at both 3 and 6 h after the procedure were statistically significant, with 3 h being used in this review ($p=0.0047$). IL-6's plasma levels after 3 h were 360 ± 143 pg/mL in patients who developed AF and 230 ± 94 pg/mL in those who did not (13), as seen in table 1.

Table 1. Demographic Characteristics of the Sample.

First Author	Year	Patients number	Male (%)	Mean age of no AF patients	Mean age of AF patients	Diabetes - (%)	Hypertension - (%)
Keiichi Ishida	2006	39	28(71,7)	$60 \pm 8,8$	$70 \pm 6,4$	24(61,5)	24 (61,5)
Mias Pretorium	2007	253	166(65,6)	$56,9 \pm 10$	$66,1 \pm 1,6$	66(26,1)	198(78,2)
Shervin Ziabakhsh-Tabari	2008	54	30(51,5)	$57,2 \pm 9,0$	$51,4 \pm 10,7$	14(25,9)	14(25,9)

In 2007, Pretorius et al. selected 253 patients for coronary artery bypass grafting, of which 166 (65.6%) were male and 87 (34.4%) were female. The mean age of those who developed AF was 66.1 ± 1.6 years and 56.9 ± 1.0 years for patients without AF. Sixty-six patients had diabetes and 198 (78.2%) had hypertension as a comorbidity. Plasma samples were collected in vacutainer tubes with 0.105 mol/L sodium citrate (BD Vacutainer Systems) immediately after extracorporeal circulation disconnection. Samples were then centrifuged at 0°C for 20 min and stored at -70°C . These samples were analyzed using multiplex LINCOplex Biomarker Immunoassays (LINCO Research, Inc). Follow-up was performed for 14 days, and 67 (26.5%) developed AF, while 186 (73.5%) did not. The mean IL-6 level in AF patients was 380.6 ± 151.1 pg/mL and that in the healthy group was 178 ± 16.9 pg/mL ($p=0.019$) (18).

In 2008, Ziabakhsh-Tabari et al. conducted a study that included 54 patients (30 men [55.5%] and 24 women [44.4%]). The mean age of patients who developed AF and those who did not was 51.45 ± 10.74 years and 57.28

± 9.04 years, respectively. Fourteen (25.9%) patients were hypertensive, and 14 (25.9%) were diabetic. Plasma sample collection occurred 2 days after the procedure and was analyzed using ELISA; however, the study did not state which kit was used. Follow-up was conducted for 5 days and during this time 11 patients (20.4%) developed AF, with a mean IL-6 level of 65.4 ± 21.01 pg/mL, whilst 43 (79.6%) did not, with a mean IL-6 level of 38.2 ± 32 pg/mL. This difference was statistically significant ($P=0.004$) (19).

Comorbidities

In the study by Ishida et al., 24 (61.5%) patients had diabetes and/or hypertension out of a total population of 39. (13). The study by Pretorius et al. had a total population of 253, with 66 (26.1%) diabetic patients and 198 (78.2%) hypertensive patients (18). Lastly, Ziabakhsh-Tabari et al. included 54 patients in their study, and 14 (25.9%) were diabetic and/or hypertensive(19). None of these studies found a correlation between AF and comorbidities (13,18,19), as seen in table. 2.

Table 2. Summary of Results from the Selected Studies.

First Author	Time of follow up after CABG	Sample collection	Number of patients	AF patients	No AF patients	IL6 in AF patients	IL6 in no AF patients	P value
Keiichi Ishida	7 days	3h	39	11 (28,2%)	28 (71,8%)	360 ± 143	230 ± 94	$p=0.0047$
Mias Pretorius	14 days	Soon after disconnection of cardiopulmonary bypass	253	67(26,5%)	186(73,5%)	$380 \pm 151,1$	$178 \pm 16,9$	$p=0,019$
Shervin Ziabakhsh	5 days	2d	54	11(20,4%)	43 (79,6%)	$65,4 \pm 21,01$	$38,2 \pm 32$	$p=0,004$

AF Incidence Rates

Ishida et al. and Pretorius et al. reported similar incidence rates of AF (28.2% and 26.5%, respectively), whilst Ziabakhsh-Tabari et al. reported a lower incidence rate of 20.4%; among the 346 patients, the mean AF incidence rate was 25.7% (13,18,19).

AF and Sex

Regarding sex, in the study by Ishida et al. the incidence of AF among female and male patients was 36.3% and

25%, respectively. However, Pretorius et al. reported an incidence rate of 28.3% and 28.9% for female and male patients, respectively. Ziabakhsh-Tabari et al. did not report separate incidence rates for the sexes; however, it was mentioned that AF patients were more likely to be female. According to the studies by Ishida et al. and Pretorius et al., there were a total of 292 patients, 194 were male (66.4%) and 55 (27.7%) of them developed

AF, and 98 (33.5%) were female, of whom 23 (23.5%) developed AF (13,18,19).

Mean age with or without AF

Ishida et al. reported that the mean age of patients who developed AF and those who did not was 70 ± 6.4 years and 60 ± 8.8 years, respectively. Meanwhile, Pretorius et al. reported a mean age of 66.1 ± 1.6 years and 56.9 ± 1.0 years for AF and healthy groups, respectively. Lastly, the study by Ziabakhsh-Tabari et al. reported a mean age of 51.45 ± 10.74 years and 57.28 ± 9.04 years for AF and healthy groups, respectively (13,18,19), as seen in table 2.

Follow-up

The patients in the study by Ishida et al. were followed up for 7 days after the surgery, while the study by Pretorius et al. included a follow-up period of 14 days. The follow-up period in the study by Ziabakhsh-Tabari et al. was 5 days after the procedure (13,18,19).

Table 2. Summary of results from the selected studies

Plasma Sample Collection

Ishida collected plasma during anesthesia induction, after anastomosis, before protamine infusion, 3 and 6 hours after the surgery, and then daily for 4 days. In the study by Pretorius, the plasma was collected immediately after extracorporeal circulation disconnection, while in the study conducted by Ziabakhsh-Tabari it was collected 2 days later (13,18,19). For example, in 2006, Ishida et al. collected the plasma sample after anastomosis before protamine infusion, 3 and 6 hours after the procedure. Nevertheless, the 3 hours sample was used for analysis. However, in 2007, Pretorius et al. study the samples were collected immediately after extracorporeal circulation disconnection. In 2008, Ziabakhsh-Tabari et al. sample collection occurred 2 days after the procedure.

IL-6 Levels on AF group

Ishida et al. reported the plasma levels of IL-6 during the post-operative period as 360 ± 143 pg/mL, while Pretorius et al. reported it to be 380.6 ± 151.1 pg/mL. Lastly, Ziabakhsh-Tabari et al. reported a post-operative plasma IL-6 level of 38.2 ± 32 pg/mL (13,18,19).

Bias

Ishida et al. did not use extracorporeal circulation, while Pretorius et al. and Ziabakhsh-Tabari et al. did. The follow-up time was also heterogeneous, being 5 days in the study by Ziabakhsh-Tabari et al. and 7 days in the study by Ishida et al. Lastly, the plasma sample collection times were not close (13,18,19). The studies are heterogeneous with different times for sample collection.

DISCUSSION

Two of the studies included in this review have similar AF incidence rates (Ishida and Pretorius report 28.2% and 26.5% respectively), but Ziabakhsh-Tabari et al. reported a lower incidence rate (20.4%). Incidence rate in the literature can vary, Girerd et al. reported 19.6% incidence rate in a much bigger population ($n=2,214$), and Canbazet al also found a similar number (18.3%) but with less patients ($n=71$). Kaireviciute et al., on the other hand, reported a 30% incidence rate with $n=100$, in line

with the studies by Ishida et al. and Pretorius et al. (10,12,13,15,18,19).

The levels of plasma IL-6 were considerably lower in the study by Ziabakhsh-Tabari et al. (38.2 ± 32 pg/mL), due to the short interval between the procedure and sample collection (48 h). This interval leads to a decrease in inflammation and a sequential reduction in IL-6 levels. Plasma levels of IL-6 rapidly decrease after the first 24 h (13,17). Pretorius et al. and Ishida et al. collected plasma samples closer to the procedure (right after the extracorporeal circulation disconnection and 3 h after, respectively), reporting similar levels (380.6 ± 151.1 pg/mL and 360 ± 143 pg/mL, respectively) (13,18).

Ishida et al., Pretorius et al., and Ziabakhsh-Tabari et al. followed-up their patients for different time periods (7, 14, and 5 days, respectively). The onset of AF is more likely to occur in the first 5 days postoperatively, but it can occur after a longer period, representing a potential sub-diagnosis if the follow-up time is too short (22).

Regarding diabetes and hypertension, these comorbidities were not statistically significant risk factors for AF. This is corroborated by other studies (12,15–17). Regarding sex, this study found that the mean incidence rate of AF on males was 27.7% and that on females was 23.5%. Ishida reported a 36.3% incidence rate in women, possibly due to the smaller population ($n=39$). Ishida and Pretorius found that age was a statistically significant risk factor for AF. This was also reported by Kourliourous et al., Girerd et al., and Kaireviciute et al. (12,15,16). However, Ziabakhsh-Tabari et al. reported no correlation between the two (19). Advanced age is an important factor in AF development (24).

LIMITATIONS

The main limitation of this systematic review is the number of studies available. Only three studies adequately presented the postoperative plasma level of IL-6 and its statistical correlation with AF development. In those studies, there was a difference in the sample collection time and a small population in two of them ($n=39$ and $n=54$). In addition, follow-up was only 5 days in one study and 7 days in the other. Lastly, none of the three studies detailed the AF appearance; this data would be important to correlate with IL-6 plasma concentration over time.

CONCLUSION

Although the meta-analysis results found statistical significance for IL-6 as an AF development predictor, it is considered that new studies about the object of this systematic review are necessary, and these studies should be more standardized. Preferably, it would be important for the daily measurement of IL-6 and its correlation with AF development for statistical analysis to set the best time for sample collection and cut-off value.

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AUTHORS' CONTRIBUTIONS

The participation of each author corresponds to the criteria of authorship and contributorship emphasized in the [Recommendations for the Conduct, Reporting,](#)

[Editing, and Publication of Scholarly work in Medical Journals of the International Committee of Medical Journal Editors](#). Indeed, all the authors have actively participated in the redaction, the revision of the manuscript, and provided approval for this final revised version.

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COMPETING INTERESTS

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