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Article

# Circulating Interleukin-22 in Patients with Acute Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention

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**Abstract:** Acute coronary syndrome (ACS) represents the most severe manifestation of coronary artery disease (CAD), characterized by a particularly poor prognosis. Consequently, primary percutaneous coronary intervention (PPCI) is imperative in the event of acute ST-elevation myocardial infarction (STEMI). Interleukin-22 (IL-22) may be a new CAD biomarker because it signals and regulates immune and inflammatory responses.

**Objectives:** To investigate the differences in circulating IL-22 levels between patients with STEMI undergoing PPCI and healthy controls; and to determine if these differences are associated with the culprit coronary artery, door-to-balloon time (DBT), final angiographic result, CAD classification, and the presence of diabetes mellitus (DM). **Methods:** A total of 280 participants were recruited, comprising 210 STEMI cases and 70 healthy controls. Participants underwent clinical and angiographic evaluation, and serum IL-22 levels were measured using enzyme-linked immunosorbent assay (ELISA). Data analysis was performed using the Mann-Whitney and Fisher's tests, with a  $p < 0.05$  significant. **Results:** Serum IL-22 levels were lower in cases (149.63, 84.99–294.56) than in controls (482.67, 344.33–641.00),  $p < 0.001$ . Lower IL-22 levels were associated with the right coronary artery (RCA) (144.57, 70.84–242.43; 146.00, 63.60–279.67; 191.71, 121.80–388.97),  $p = 0.033$ . IL-22 was lower with shorter DBT ( $\leq 60$  minutes, 106.00, 49.60–171.71;  $> 60$  minutes, 153.00, 88.86–313.60),  $p = 0.043$ . **Conclusions:** IL-22 levels were significantly lower in patients with STEMI compared to healthy controls.

**Keywords:** IL-22; STEMI; ACS; Atherosclerosis

## 1. Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide, with a significant impact on productivity and quality of life [1]. Atherosclerosis, a key contributor to CVD, is a chronic inflammatory disease characterized endothelial dysfunction. This dysfunction in conjunction with other pathological events, leads to the formation of atheromas [2]. This is the pathophysiological cause of coronary artery disease (CAD), which can present as chronic coronary syndrome (CCS) or acute coronary syndrome (ACS), depending on the morphology and inflammatory status of the atheromas [3]. Acute ST-elevation myocardial infarction (STEMI) accounts for 38% of ACS cases, and are associated with the highest mortality rates [4]. STEMI often exhibits with a completely occluded coronary artery, and primary percutaneous coronary intervention (PPCI) is the gold standard for reopening the vessel. Evidence demonstrated that this approach reduces mortality and enhances patient prognosis [5,6].

IL-22 belongs to the IL-10 family and plays diverse roles in regulating cell growth and differentiation, and modulating immunological and inflammatory responses [7,8]. T helper cells type 22 (Th22) are the primary IL-22 producers. IL-22 exerts its effects by binding to a heterodimeric

receptor complex composed of the primary IL-22R1 receptor and the IL-10R2 coreceptor. This binding induces intracellular signaling through the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway [7–9]. Furthermore to the cell surface IL-22 receptor complex, there is a soluble IL-22 binding protein (IL-22BP) that demonstrates higher affinity and specificity for IL-22, being an effective competitive inhibitor of IL-22 in vitro [10,11].

Interactions between IL-22 and its receptors trigger adhesion molecule production by endothelial cells, including the intercellular adhesion molecule 1 (ICAM-1) and the vascular cell adhesion molecule 1 (VCAM-1), which recruit monocytes [7,8]. IL-22 also acts in the regulation and proliferation of vascular smooth muscle cells, increasing atheroma growth [12]. These data show that IL-22 may affect atheroma development and instability because the activation of the Signal Transducer and Activator of Transcription 3 (STAT3) protein is directly related to leukocyte activation, endothelial dysfunction progression, and intensified inflammatory cascade [13]. Nonetheless, the role of IL-22 in STEMI is still unclear due to the scarce literature on this topic.

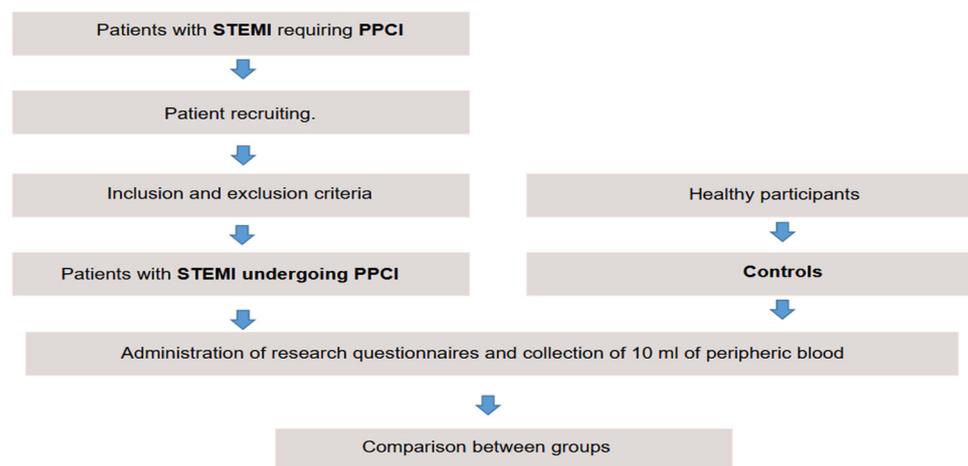
Thus, the primary objective of this study was to investigate differences in circulating IL-22 levels between patients with STEMI undergoing PPCI and healthy controls; and the secondary objectives were to compare serum IL-22 levels considering the culprit coronary artery, door-to-balloon time (DBT), final angiographic result, CAD classification, and presence of diabetes mellitus (DM).

## 2. Materials and Methods

This cross-sectional, descriptive and analytical study was conducted in a reference hospital in cardiology. A total of 210 patients with STEMI undergoing PPCI and 70 healthy controls were recruited between January 2022–August 2023.

The inclusion criteria were age  $\geq 18$  years and a clinical diagnosis of STEMI treated with PPCI. The exclusion criteria were previous or current oncologic disease, severe liver disease, blood dyscrasia, inability to respond to the questionnaire, or refusal to participate in the study. The controls were healthy volunteers  $\geq 18$  years old.

Patients meeting these criteria were invited to participate in the study. Those who accepted signed the informed consent form (Figure 1).



**Figure 1.** Study flowchart. **Source:** Prepared by the author (2022).

After admission, the participants answered a clinical questionnaire. Clinical and socioeconomic parameters were self-declared, and documented in a research-specific clinical record that was stored in a database.

The culprit vessel was defined as the coronary artery causing STEMI and undergoing PPCI. Multivessel CAD was defined as two or more obstructed vessels ( $\geq 70\%$ ); and single-vessel CAD as only one vessel affected. DBT was classified as  $> 60$  minutes or  $\leq 60$  minutes. The final coronary flow was measured according to the criteria proposed by the Thrombolysis in Myocardial Infarction

(TIMI) Study Group [14]. Angiographic success was determined by TIMI 3 final coronary flow, residual lesion < 10%, and absence of thrombi and dissections.

### 2.1. Serum IL-22 Analysis

The standard technique was used to collect 10 ml of peripheral blood for measuring IL-22 levels. This collection occurred immediately after PPCI in the patient group, and electively in the control group.

The blood was centrifuged, and the supernatant was collected and stored at -80 °C. Sandwich enzyme-linked immunosorbent assay (ELISA) quantified serum IL-22 levels using the Human IL-22 DuoSet® kit (R&D Systems Inc, USA & CAN), according to the manufacturer's recommendations. This kit has a minimum detection level of 50 pg/ml.

### 2.2. Statistical Analysis

The data included the descriptive analysis of clinical and angiographic characteristics of the patients, and the comparative analysis of serum IL-22 levels between cases and controls. Numeric parameters were analyzed by the Shapiro-Wilk normality test. Normal parameters were presented as mean and standard deviation, and non-normal parameters as median and 25th and 75th percentiles. Categorical parameters were presented as absolute values and percentages.

The Student's t-test, Mann-Whitney test, and analysis of variance (ANOVA) were used to analyze numerical parameters, depending on their normality. Categorical parameters were analyzed using the chi-square test or the Fisher's exact test. Statistical analyses were prepared by an independent statistician using the SPSS software version 23. P-values < 0.05 were considered statistically significant.

All participants were comparatively analyzed. Subsequently, the cases were divided into five subgroups, considering the culprit vessel, CAD classification, DBT, angiographic success of PPCI, and DM. These subgroups were distributed by sex, age, clinical status, and angiographic profile. IL-22 levels were also compared.

## 3. Results

The study included 280 participants, 210 cases of STEMI undergoing PPCI and 70 healthy controls. Descriptive analysis exhibited a higher prevalence of men in the case group (63.8% men, 36.2% women). The most prevalent risk factors were systemic arterial hypertension (SAH) (76.2%), smoking history (55.2%), and DM (38.1%) (Table 1).

**Table 1.** Descriptive analysis of the clinical characteristics of patients.

CLINICAL PARAMETERS	
<b>210 (100.0)</b>	<b>Total</b>
	<b>Sex</b>
134 (63.8)	Male, n (%)
76 (36.2)	Female, n (%)
	<b>SAH</b>
160 (76.2)	Yes, n (%)
	<b>DM</b>
80 (38.1)	Yes, n (%)
	<b>Smoking history</b>
116 (55.2)	Yes, n (%)

	<b>DLP</b>
54 (25.7)	Yes, n (%)
	<b>Previous AMI</b>
37 (17.6)	Yes, n (%)
	<b>Previous PPCI</b>
17 (8.1)	Yes, n (%)
	<b>Stroke</b>
8 (3.8)	Yes, n (%)
	<b>CKD</b>
7 (3.3)	Yes, n (%)

Systemic arterial hypertension (SAH), diabetes mellitus (DM), dyslipidemia (DLP), acute myocardial infarction (AMI), primary percutaneous coronary intervention (PPCI), chronic kidney disease (CKD).

In the subgroups, descriptive analysis showed that 83.3% of cases had a DBT > 60 minutes, and that the anterior descending artery (LAD) was affected in 53.8% of cases. Multivessel CAD was present in 71.4% of cases, with an angiographic success rate of 84.8% (Table 2).

Serum IL-22 levels were lower in cases (149.63, 84.99–294.56) than in controls (482.67, 344.33–641.00), with  $p < 0.001$ .

**Table 2.** Descriptive analysis of patients by subgroups.

<b>PATIENT SUBGROUPS</b>	
<b>210 (100.0)</b>	<b>Total, n (%)</b>
	<b>DBT</b>
35 (16.7)	≤ 60 minutes, n (%)
175 (83.3)	> 60 minutes, n (%)
	<b>Culprit artery</b>
37 (17.6)	CCA, n (%)
113 (53.8)	ADA, n (%)
60 (28.6)	RCA, n (%)
	<b>Angiographic success</b>
32 (15.2)	No, n (%)
178 (84.8)	Yes, n (%)
	<b>CAD classification</b>
150 (71.4)	Multivessel, n (%)
60 (28.6)	Single-vessel, n (%)

Circumflex artery (CXA), anterior descending artery (ADA), right coronary artery (RCA), coronary artery disease (CAD), diabetes mellitus (DM).

Serum IL-22 levels were compared by subgroup, according to the culprit coronary artery, CAD classification, DBT, angiographic success, and DM (Table 3).

**Table 3.** Comparison between serum IL-22 levels according to the culprit artery, CAD classification, DBT, angiographic success, and DM.

### Culprit artery

p-value	RCA (n = 60)	ADA (n = 113)	CXA (n = 37)	IL-22
p = 0.033	144.57 (70.84–242.43)	146.00 (63.60–279.67)	191.71 (121.80–388.97)	IL-22

#### CAD classification

	Single-vessel (n = 60)	Multivessel (n = 150)	IL-22
p = 0.255	153.79 (101.00–271.33)	149.23 (61.60–306.33)	IL-22

#### DBT

	> 60 minutes (n = 175)	≤ 60 minutes (n = 35)	IL-22
p = 0.043	153.00 (88.86–313.60)	106.00 (49.60–171.71)	IL-22

#### Angiographic success

	Yes (n = 178)	No (n = 32)	IL-22
p = 0.821	149.67 (84.99–281.33)	137.36 (84.13–346.33)	IL-22

#### DM

	No (n = 130)	Yes (n = 80)	IL-22
p = 0.379	151.33 (85.90–306.33)	147.80 (70.84–276.96)	IL-22

Circumflex artery (CXA), anterior descending artery (ADA), right coronary artery (RCA), interleukin-22 (IL-22), diabetes mellitus (DM).

## 4. Discussion

Herein, the results demonstrated lower circulating IL-22 in patients with STEMI undergoing PPCI than in healthy controls. In the subgroups, cases with DBT < 60 minutes and with the RCA as culprit artery had lower IL-22 levels. CAD classification, angiography success, and DM showed no influence on IL-22 levels.

Some studies indicate that high IL-22 levels have an atherogenic effect, especially in stable disease. However, it is unclear if this is a specific cause or part of an immune-inflammatory response [15,16].

Conversely, animal studies had different results. IL-22 had a protective effect against myocardial remodeling and unfavorable cardiovascular outcomes after AMI induction in rats, which may be linked to atheroma stabilization. Differently from most human studies, which evaluate CCS, that study analyzed an ACS model [17,18].

Yamamoto et al. [18] assessed the role of endogenous IL-22 in mice. That study induced AMI by ligating the left coronary artery in wild-type and IL-22 knock-out mice, with a significantly lower survival rate in IL-22 knock-out animals due to a higher rate of cardiac rupture. Tang et al. [19] assessed the effect of exogenous IL-22 in rats. They induced AMI by ADA ligation, followed by subcutaneous injection of 100 µg/kg/day of recombinant IL-22 (IL-22R) for seven days. Animals treated with IL-22R exhibited attenuated adverse ventricular remodeling and improved post-AMI cardiac function. It is noteworthy that the pharmacological inhibition of STAT3 also inhibited IL-22 [19].

Zhang et al. [17] evaluated 26 patients with non-ST-segment elevation myocardial infarction (NSTEMI), 16 patients with unstable angina, 16 patients with stable angina, and 16 healthy controls. They reported significantly higher plasma IL-22 levels in AMI patients with NSTEMI ( $33.09 \pm 6.53$  pg/ml) than in patients with unstable angina ( $29.86 \pm 3.49$  pg/ml,  $p = 0.02$ ), patients with stable angina ( $26.96 \pm 3.09$  pg/ml,  $p < 0.001$ ), and healthy controls ( $24.16 \pm 2.46$  pg/ml,  $p < 0.001$ ).

Opposing with the study by Zhang et al. [17], this study exhibited lower IL-22 levels in patients with ACS. However, the clinical profile of our patients was also different. We analyzed STEMI cases

undergoing PCCI, while Zhang et al. [17] studied patients with NSTEMI and CCS. On the one hand, IL-22 levels may differ irrespective of total vessel occlusion or PPCI.

On the other hand, animal studies associated higher IL-22 levels with positive remodeling effects and increased survival, but the animals analyzed in those studies had no coronary reperfusion after AMI induction, which hinders comparisons with our model. The impact of coronary reperfusion on circulating IL-22 levels needs further clarification.

IL-22 is part of the IL-10 family and acts at a cellular level, mainly through the Jak/STAT pathway. It has a pro-atherogenic effect by inducing endothelial cells to produce ICAM-1 and VCAM-1 and stimulating monocyte recruitment [7,8]. STAT3 phosphorylation is induced after IL-22 binds with its receptors (IL-22R1 and IL-10R2) [8].

After activation, STAT3 translocates to the nucleus, modulating the expression of its target genes [20]. In humans, STAT3 pathway signaling directly relates to the expression of inflammatory mediators, which act in leukocyte activation and endothelial dysfunction progression [13]. In animals, blocking this pathway may be associated with improved clinical prognosis [13,19].

To summarize, IL-22 appears to have an atherogenic effect in a stable coronary disease model in humans, and patients with NSTEMI had higher serum IL-22 levels than patients with CCS and healthy controls. In AMI-induced animal models, higher IL-22 levels were associated with better survival. This study confirmed that patients with STEMI undergoing PPCI had lower circulating IL-22 levels than healthy controls.

In the case of STEMI and PPCI, acute arterial occlusion causes myocardial ischemia and necrosis, triggering an inflammatory cascade whose severity depends on the anatomical territories involved [6,15,21,22]. We found no studies in the literature on IL-22 levels in patients with STEMI undergoing PPCI.

DM is a well-known risk factor for CAD. It is associated with a pro-inflammatory status that accelerates the onset of atherosclerosis. It is also an independent predictor of worse prognosis in patients with ACS [23,24]. Despite this, IL-22 levels had no correlation with DM in this study.

The role of IL-22 in patients with DM and STEMI is not clear. However, we can infer a crosstalk between these mediators because IL-22 is part of the IL-10 family. IL-10 decreases inflammation, potentially improving the treatment of DM2 by inhibiting pro-inflammatory factors and increasing peripheral sensitivity to insulin [25]. Thus, new studies should investigate the synergism between IL-22 and IL-10 actions. Considering the lack of data on IL-22 in some subgroups of STEMI patients undergoing PPCI, future studies need to confirm our findings that patients with DBT < 60 minutes and with the RCA as culprit artery have lower IL-22 than controls.

The main limitations of this study include its single-center design, the inclusion of patients treated for STEMI with medications that can affect with IL-22 levels, the analysis of only a single IL22 dosage, and the lack of evaluation of the association between IL-22 levels and prognosis due to the low rate of clinical events after PPCI.

## 5. Conclusions

This study demonstrated that IL-22 levels were significantly lower in patients with STEMI compared to healthy controls.

Within the subgroups, patients with a door-to-balloon time (DBT) of less than 60 minutes and those with the right coronary artery (RCA) as the culprit artery exhibited lower IL-22 levels. However, CAD classification, angiography success, and the presence of diabetes mellitus (DM) did not influence serum IL-22 levels.

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**Institutional Review Board Statement:** The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Ethics Committee of Cardiology Emergency Room of Pernambuco - University of Pernambuco (protocol code 29969220500005192 – January 4, 2022) for studies involving humans.

**Informed Consent Statement:** Informed consent was obtained from all subjects involved in the study .

**Data Availability Statement:** The data generated and analyzed during this study are included in this published article and are available from the corresponding author.

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