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The Impact of Interleukin-6 on the Severity of Coronary Artery Disease and the Prognosis of Patients with Acute Coronary Syndrome

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ABSTRACT

Acute coronary syndromes (ACS) represent a significant public health problem which is affecting an increasingly younger population. The management of these conditions becomes increasingly difficult, considering that their long-term evolution is accompanied by multiple complications. In this context, numerous studies have been conducted to identify new prognostic markers whose use can aid in patient stratification and understanding of their progression. Given its role in the atherosclerotic process, interleukin (IL)-6, a pro-inflammatory cytokine with pleiotropic effects in the body, has been the subject of numerous studies and it has been correlated with the severity of coronary artery disease and the prognosis of patients with ACS. It appears to be involved in the extent of myocardial damage, the development of ischemia-reperfusion injury, the onset of heart failure, recurrent myocardial infarction and increased cardiovascular mortality. However, studies have not been able to establish a cutoff value at which therapeutic intervention should be intensified to prevent adverse events and further investigation is needed; for this reason, its use in current practice is limited. This biomarker offers multiple applications, ranging from predicting the development of ACS, assessing the complexity of coronary artery disease, and stratifying post-infarction patients. Furthermore, it represents an attractive therapeutic target for reducing cardiovascular events; however, additional studies are needed to determine the degree of inhibition, the timing of initiation and the duration of therapy to avoid interfering with healing.

Keywords: interleukin-6, inflammation, acute coronary syndromes, prognosis, severity of coronary artery disease.

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INTRODUCTION

Acute coronary syndromes (ACS) represent a wide range of manifestations of myocardial ischemia caused by coronary artery obstruction and are responsible for approximately one in three deaths in people over the age of 35. They are classified into three phenotypes: unstable angina (UA), ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI) (1-3). The outcome for these patients is often unpredictable and is associated with various clinical and laboratory findings. Among these, inflammation is a predictor that is becoming increasingly studied, as it is associated with numerous complications (4, 5). The inflammation in ACS is of the sterile type, triggered by endogenous signals at the time of cellular injury. This subsequently activates innate and adaptive immune pathways, which mobilize leukocytes, macrophages and stimulate the secretion of pro- and anti-inflammatory cytokines. The goal is to heal the injury, but excess inflammation leads to the extension of myocardial lesions and adverse remodelling (5, 6). Interleukin (IL)-6 is a pro-inflammatory cytokine involved in the pathophysiology of cardiovascular diseases, and there is evidence of its contribution to the onset of myocardial infarction. It is mainly produced by macrophages and T cells and acts at the cellular level by modulating their proliferation, differentiation, and survival (7). In recent studies, elevated levels of this cytokine following a heart attack have been associated with reduced overall cardiac function due to cardiac remodelling, as well as with the

TABLE 1.
Key evidence connecting IL-6 to post-ACS prognosis and the severity of coronary artery disease (9, 24, 30-32, 39, 40)

First author, year, study		Subjects	Conclusion
Yang et al, 2021, meta-analysis	Kamińska et al, 2018	93	IL-6 is associated with mortality, MACE and greater disease severity in ACS
	Novo et al, 2015	33	
	Wang et al, 2014	60	
	García-Salas et al, 2014	212	
	Liu et al, 2013	40	
	Nishida et al, 2011	121	
Li et al, 2021, meta-analysis	Bennermo et al, 2004	208	IL-6 is associated with mortality, MACE, larger infarct size and reduced ejection fraction in ACS
	Chen et al, 2014	1896	
	Fan et al, 2011	263	
	Fanola et al, 2017	4939	
	Garcia-Salas et al, 2014	212	
	Hartford et al, 2007	757	
	Koukkunen et al, 2001	263	
	Lopez-Cuenca et al, 2013	216	
	Ritschel et al, 2016	989	
	Thomas et al, 2019	16400	
	Wang et al, 2019	287	
	Zairis et al, 2007	934	
	Zamani et al, 2013	2925	
Gager et al, 2020		322	IL-6 is associated with long-term cardiovascular mortality
Groot et al, 2019		369	IL-6 is associated with decreased cardiac function and larger infarct size in STEMI
Ul Ain et al, 2023		43	Mean levels of IL-6 are higher in ACS patients than in the control group
De Paula Da Silva et al, 2022		91	Mean levels of IL-6 are higher in ACS patients than in the control group, IL-6 is associated with TIMI score in UA
Ling et al, 2021		346	IL-6 is associated with SYNTAX and SYNTAX II scores in ACS patients

IL-6=interleukin 6; MACE=major adverse cardiac events; ACS=acute coronary syndrome; STEMI=ST-segment elevation myocardial infarction; UA=unstable angina; TIMI=thrombolysis in myocardial infarction; SYNTAX=synergy between percutaneous coronary intervention with taxus and cardiac surgery

development of ischemia-reperfusion injury, which additionally increases mortality. Thus, IL-6 may represent a valuable parameter in estimating the prognosis of patients with acute coronary syndromes, guiding clinicians toward more intensive management of cases in terms of both follow-up and medication (8, 9). A summary of the principal associations observed between IL-6 and the angiographic and prognostic particularities of ACS patients is presented in Table 1. Considering this, new targeted anti-inflammatory therapies are emerging, providing a path toward a holistic approach to the treatment of myocardial infarction (6).

The aims of this analysis are to review existing data on the correlation between IL-6 levels and the prognosis of patients with ACS, the severity of coronary artery disease and existing and future treatment options. A literature search was conducted using the PubMed electronic database. Articles published between 2007 and 2026 were considered. The research was conducted using a combination of the following keywords: "interleukin 6", "inflammation", "acute coronary syndrome", "myocardial infarction", "prognosis", "anti-inflammatory therapy." The titles and abstracts of articles found were reviewed to determine their relevance. Subsequently, the full texts of the articles that were considered potentially relevant were analysed and those with a significant contribution to this topic were selected. The studies thus selected were analysed from a qualitative perspective and summarized.

IL-6 – From atherosclerosis to myocardial infarction

Elevated IL-6 levels were initially studied in healthy populations and were subsequently linked to long-term cardiovascular diseases, ranging from atherosclerosis-related vascular diseases to heart failure (10, 11). Atherosclerosis is considered to represent the precursor to the development of acute coronary syndromes, and inflammation appears to be involved from the earliest stages (12, 13). In addition, the level of inflammation correlates with the stability of the atherosclerotic plaque (14). Cholesterol crystals are recognized by leukocyte receptors and trigger the activation of the immune response, leading to the secretion of IL-1β and subsequently IL-6. The secretion of IL-6 alters the endothelium, promoting the secretion of nitric oxide and endothelin-1, and facilitates its interaction with platelets, transforming the vascular wall into a pro-thrombotic surface. Furthermore, its rapid increase leads to the subsequent secretion in the liver of acute-phase reactants: C-reactive protein (CRP), haptoglobin, and serum amyloid α (SAA). Increased secretion of IL-6 is thus implicated in the destabilization of atherosclerotic plaques, promoting rupture or erosion, leading to the onset of ACS (15-18). Genetic studies have shown that cytokine polymorphisms also play a significant role in determining the risk of ACS onset; specifically, the IL-6 –174G > C polymorphism is linked to the highest risk, contributing to immune imbalance and increases pro-inflammatory effects. This finding is important in terms of the opportunity to develop personalized treatments for ACS prevention, identifying patients who may benefit from more intensive treatment (1). When myocardial tissue becomes hypoxic due to coronary obstruction, inflammation occurs, accompanied by the secretion of cytokines, including IL-6, extensively studied as a prognostic marker in ACS, with good sensitivity (7, 18-21). However, it has low specificity, being influenced by numerous patient conditions, which renders it unsuitable for diagnosing ACS. Some examples of comorbidities that can increase IL-6 levels include: heart failure, type 2 diabetes mellitus, obesity, chronic kidney disease, inflammatory autoimmune diseases, chronic smoking and chronic alcoholism (20, 22). Additionally, there is a delay between the onset of angina symptoms and the elevation of inflammatory markers (22). However, some studies show a correlation between IL-6 levels and the development of classic early symptoms of ACS (23, 24). Following a heart attack, IL-6 levels rise rapidly, reaching a peak after approximately 1–2 days. Subsequently, levels begin to decline, but abnormally high values persist throughout the hospital stay, sometimes even up to 12 weeks post-infarction, without being influenced by revascularization procedures (8). There is evidence of IL-6 secretion in cardiac tissue exposed to hypoxic stress, at the viable edge of the infarct, and in revascularized areas (25). Interleukin-6 also contributes to the development of post-infarction ischemia-reperfusion injury, playing a major role in the loss of viable myocardial mass and the enlargement of the final infarct size (5, 26).

The correlation between IL-6 and the severity of coronary lesions

Elevated IL-6 levels are independently associated with coronary artery disease and the severity of ACS (24, 27, 28). Even in patients with UA, IL-6 levels were observed to be three times higher than in control patients (24, 28). This is not surprising, considering that some studies have shown elevated levels of inflammatory cytokines in patients with stable angina, but even higher levels of these biomarkers are found in patients with ACS. Nevertheless, the degree to which IL-6 increases depending on the ACS phenotype is inconsistently reported, with studies showing varying results (19, 24, 29, 30). A study comparing inflammatory marker levels in 93 patients with ACS and 30 control patients found significantly higher median levels in the ACS group, including for IL-6. However, the group with UA did not show statistically significantly higher levels than the control group, suggesting that IL-6 is associated with myocardial infarction. The differences between patients with NSTEMI and STEMI in regard to IL-6 levels were not statistically significant, but the study has the limitation of a small group of subjects (19). Another study focusing on the correlation between inflammatory markers and the Thrombolysis In Myocardial Infarction (TIMI) score in ACS also revealed that ACS patients had higher levels of inflammatory markers, including IL-6, than control patients, but without significant differences among the three subcategories (31). Regarding the degree and complexity of coronary artery disease, IL-6 showed a positive correlation with Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) and SYNTAX II scores in patients with ACS, highlighting the importance of this marker in assessing the severity of atherosclerotic disease. Consequently, IL-6 was identified as an independent predictor of an intermediate-to-high SYNTAX score and a high SYNTAX II score (32). Local evidence of inflammation in the occluded vessel, indicated by this biomarker, could explain why neither revascularization nor thrombolysis is capable of eliminating the risk of subsequent cardiovascular events (32, 33). Previous studies have shown a positive association between IL-6 and the Gensini score, which is frequently used to assess the severity of coronary artery disease (34). This correlation with the severity of atherosclerotic disease and the likelihood of its instability makes IL-6 a useful adjuvant in assessing the risk of ACS patients, potentially complementing diagnostic tests and even replacing much more sophisticated and expensive imaging methods such as optical coherence tomography (OCT), intravascular ultrasound (IVUS), or computed tomography angiography (CTA) (24, 35). Furthermore, based on imaging studies, IL-6 levels have been associated with the size of the atherosclerotic plaque (36).

The association between IL-6 levels and post-ACS prognosis

In an exploratory analysis of the Stabilization of Plaque Using Darapladib-Thrombolysis in Myocardial Infarction (SOLID-TIMI) 52 study, the correlation between IL-6 and the prognosis of patients with ACS was investigated, and it was observed that IL-6 levels were higher in certain patient groups (Caucasians, women, smokers, multivessel coronary artery disease, concomitant peripheral vascular disease, concomitant chronic kidney disease) and in patients who presented with STEMI. However, a history of myocardial infarction and hyperlipidaemia were associated with lower IL-6 levels (7). The study examined the occurrence of major cardiovascular events (MACE) (cardiovascular death, myocardial infarction, stroke), emergency coronary revascularization and death or hospitalizations due to heart failure over a 2.5-year period. It identified an association between elevated IL-6 levels at the initial presentation with myocardial infarction and the occurrence of subsequent cardiovascular events, even within the first 30 days, with a stronger association observed in patients with STEMI (7). The occurrence of new coronary events is attributed to diffuse inflammation that affects the other coronary arteries, leading to the destabilization of new atherosclerotic plaques (7, 37). On the other hand, the onset of heart failure is explained by IL-6-induced expression of matrix metalloproteinases, which leads to collagen synthesis, myocardial fibrosis, and ventricular remodelling. However, the association between IL-6 and B-type natriuretic peptide (BNP) was weak (7, 38). A meta-analysis of six studies published between 2011 and 2018 showed a positive correlation between IL-6 and high-sensitivity C-reactive protein (hsCRP) levels, as well as between IL-6 levels and the occurrence of long-term MACE, worsening the clinical status

and prognosis of patients with ACS (24). Another meta-analysis of 13 studies published between 2001 and 2019 showed that elevated IL-6 levels in patients with ACS are associated with a 29% increase in MACE (death, heart failure, reinfarction, stroke, need for revascularization, angina, and malignant arrhythmias), a 55% increase in cardiovascular mortality, and a 50% increase in overall mortality (39). The greatest impact on MACE was observed in studies with a short follow-up period of no more than one year. Nevertheless, the meta-analysis was unable to determine a cut-off value above which IL-6 was considered abnormal, due to the heterogeneity of the values used in these studies, but it highlights the necessity of closer monitoring of those patients with higher concentrations (39). Table 2 provides an overview of the variability of IL-6 values and the evaluated endpoints. An additional study investigating the prognostic value of IL-6 for post-ACS cardiovascular mortality established a cutoff of 3.3 pg/mL and indicated that IL-6 is a stronger predictor than hsCRP, with a sensitivity of 48% and a specificity of 99% for IL-6 (40). This observation is not consistently reported in the literature (41, 42). It may be explained by the timing of sample collection in relation to the onset of ACS or inflammation, since hsCRP is secreted later in the course of the disease by the liver under the influence of IL-6 (25,40,42). Furthermore, the half-life of IL-6 is shorter than those of hsCRP (43). The risk at six years of follow-up was estimated to be 8.6 times higher in the group with elevated IL-6 levels, with a negative predictive value of 99% and a positive predictive value of 9%. No differences were observed between patients with STEMI and NSTEMI regarding the predictive power of IL-6. Most deaths occurred in the first year of follow-up (40).

IL-6 – Current and future therapeutic perspectives

Reducing IL-6 levels, as well as other inflammatory markers, through anti-inflammatory thera-

TABLE 2. Heterogeneity of IL-6 cutoff values in relation to the study endpoint – adaptation after Li *et al*, 2021 (39, 40)

Study, author, year		Endpoint	IL-6 cut-off (pg/mL)
Li et al, 2021, meta-analysis	Bennermo et al, 2004	CV death, MI	>1.48 *vs* ≤1.48
	Chen et al, 2014	CV death, MI, all-cause death, TVR, TLR, stent thrombosis	≥9 *vs* <9
	Fan et al, 2011	CV death	≥5.57 *vs* <5.57
	Fanola et al, 2017	CV death, MI, stroke, HF hospitalization	Quartiles 4 *vs* 1; median 2.02
	Garcia-Salas et al, 2014	all-cause death, recurrent ACS, non-elective revascularisation, HF hospitalization	>12.4 *vs* ≤12.4
	Hartford et al, 2007	All-cause death, HF hospitalization	Quartiles 4 *vs* 1
	Koukkunen et al, 2001	Coronary death, nonfatal MI, hospitalization for UA, revascularization	>4.49 *vs* ≤4.49
	Lopez-Cuenca et al, 2013	All-cause death, nonfatal MI, HF hospitalization	>8.24 *vs* ≤8.24
	Ritschel et al, 2016	All-cause mortality, MI, stroke, non-elective revascularization, HF hospitalization	Quartiles 4 *vs* 1; median 18.8
	Thomas et al, 2019	Cardiovascular death, MI	Quartiles 4 *vs* 1
	Wang et al, 2019	All-cause death, MI, TVR, stroke, malignant arrhythmia, HF	≥5.8 *vs* <5.8
	Zairis et al, 2007	CV death	High *vs* low; median 4.8/6.1
	Zamani et al, 2013	All-cause death, recurrent nonfatal ACS	Quartiles 4 *vs* 1
Gager et al, 2020, prospective observational study		CV mortality, nonfatal MI, nonfatal stroke	≥3.3 *vs* <3.3

IL-6=interleukin 6; CV=cardiovascular; MI=myocardial infarction; TVR=target vessel revascularization; TLR=target lesion revascularization; HF=heart failure; ACS=acute coronary syndrome; UA=unstable angina

pies has become increasingly attractive with the growing evidence of inflammation's role in the prognosis of patients with ACS. However, complete inhibition of IL-6 is not a suitable solution, as it is also involved in post-infarction repair processes. This makes it difficult to reduce the cytokine to an optimal level at the right time using therapeutic methods (15, 44). Animal studies have shown that excessive levels of IL-6 can lead to cardiac hypertrophy, whereas the absence of this cytokine's action leads to cardiac dilation (45). Recent data suggest that the conventional medications administered following a cardiovascular event could also impact IL-6 concentrations. A common example is the choice of lipid-lowering therapy: statins lower this biomarker, whereas ezetimibe and PCSK9 inhibitors have no evidence to support this effect (46-48). Antiplatelet therapies have also been shown to have anti-inflammatory effects, which vary depending on the specific drug. The use of ticagrelor results in lower levels of IL-6 at one day, 7 and 30 days after percutaneous coronary intervention (PCI) compared with clopidogrel (49, 50). The most significant results regarding anti-inflammatory drugs were obtained with canakinumab and tocilizumab, which reduced IL-6 levels. However, these drugs did not provide a clear benefit for patient prognosis, as it remains unclear in which patients, at which dose, and for how long these therapies should be administered to reduce mortality and long-term cardiovascular events (6, 26, 51-54). There are also studies on the inhibition of IL-6 in the early stages of atherosclerosis to prevent cardiovascular events such as ACS. Ziltivekimab, a new monoclonal antibody, has been tested in patients with chronic kidney disease, a group in which atherosclerosis is significantly exacerbated compared to the general population. It demonstrated a significant reduction in inflammation in a dose-dependent manner. The specific reduction in atherosclerosis-related cardiovascular events is currently under investigation in ZEUS (Ziltivekimab Cardiovascular Outcomes Study) trial (55). New potential therapies are currently in preclinical trials, including the recombinant fusion protein Soluble Glycoprotein 130 Fragment crystallizable (sgp130Fc), which appears to have a much more selective inhibitory effect on IL-6. This leads to a reduction in infarct size and an improvement in ejection fraction at 28 days of follow-up (56). ❑

DISCUSSIONS AND CONCLUSIONS

IL-6 is a pro-inflammatory cytokine with multiple effects in the body which is strongly associated with the development of atherosclerosis and plaque destabilization, leading to the development of acute coronary syndromes (12-14). Additionally, IL-6 levels might be a valuable tool for estimating the severity and complexity of coronary lesions. According to imaging studies, IL-6 has been correlated with the size and instability of atherosclerotic plaques, suggesting that it might serve as an alternative to less widely available imaging methods. Thus, it might help to identify those patients who could benefit most from additional investigations. Its association with the SYNTAX, SYNTAX II and Gensini scores confirms its utility in predicting the severity of coronary artery disease, potentially influencing the time and type of intervention (24, 32, 34, 36). The onset of ACS leads to a significant increase in IL-6, a finding demonstrated in several studies, due to the triggering of inflammatory processes (19, 30, 31). However, the challenge consists in distinguishing between physiological inflammation, which leads to optimal healing, and excessive inflammation, which can have numerous adverse cardiovascular effects. This distinction is even more difficult because IL-6 levels are also influenced by other patient characteristics and pathologies (6, 7). Numerous studies have shown that elevated post-ACS IL-6 levels are associated with increased overall and cardiovascular mortality and the early onset of MACE (reinfarction, stroke, emergency revascularization, malignant arrhythmias) during the patients' evolution, as well as the development of heart failure and an increased number of hospitalizations for its management (7, 24, 39, 40). Furthermore, IL-6 has been associated with the development of ischemia-reperfusion injury, leading to an increase in the infarct size and additional loss of cardiac function (5, 26). This association with a poor prognosis makes it even more necessary to identify the cut-off point at which IL-6 levels should be considered pathologically elevated, in order to intensify treatment and patient follow-up. Based on this necessity, new therapeutic approaches can be developed, either by using exis-

ting anti-IL-6 agents or by developing new drugs (26, 51-53, 55).

Despite the limited evidence currently available regarding this therapeutic approach, the accumulated data suggest that inflammation assessed by IL-6, plays a significant role in the development and progression of atherosclerosis, as well as in the onset of ACS. Research into anti-inflammatory therapies for atherothrombotic diseases should continue from the perspective of both primary and secondary prevention. A more concrete identification of the target group with an increased residual risk despite conventional therapies, which would benefit most from a reduction in IL-6, is needed. Furthermore, determining the optimal route of administration and the doses required to exclusively inhibit adverse events without affecting reparative mechanisms are important objectives of future investigations. ❑

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