**Association Between Inflammatory Cytokines and Long Term Adverse Outcomes in Acute Coronary Syndrome: A Systemic Review**

**Keywords:** Acute coronary syndrome, Major adverse cardiovascular events, Inflammatory Cytokines, Adverse events, Myocardial oxygen demand, Acute myocardial ischemia

**ABSTRACT**

Acute Coronary Syndrome (ACS) is a term that comprises all clinical syndromes compatible with acute myocardial ischemia causing from an imbalance between myocardial oxygen demand and supply. It was stated that the inflammatory cytokines are involved within the pathophysiology of Acute Coronary Syndrome and which is associated with major adverse cardiovascular events (MACE). We analyse the reviews including the studies involving the power of multiple cytokines to predict major adverse cardiovascular events in ACS patients with follow up of minimum one year. The main intention of this article is to produce a review which explains the association between inflammatory cytokines and long term adverse outcomes in acute coronary syndrome.
INTRODUCTION

In worldwide mortality rate Cardiovascular diseases are the primary causes, and also 50% of those deaths are associated with ACS\textsuperscript{[1,2]}. Thus it is related to important morbidity and monetary burden, as admission to hospital happens in 20% of ACS patients inside one year\textsuperscript{[1,2,3]}. Inflammation plays an important role not solely within the progression of hardening of the arteries, however additionally in mediating removal of death tissue following infarction and in shaping the repair processes that area unit essential for resolution of the acute myocardial infarction\textsuperscript{[4,5]}. For this reason, there has been hefty interest in measurement markers of inflammation in ACS and their price in predicting major adverse viscous events (MACE) like death, perennial infarction, tubing occlusion, coronary failure and perennial angina\textsuperscript{[6,7]}.

The most wide studied biomarker of inflammation is CRP, whereas varied studies have identified in associate to degree of association between CRP and MACE, the connection isn't sufficiently prophetical for activity of CRP to be counseled by current tips\textsuperscript{[7,8]}. An outsized variety of studies have additionally examined the connection between current levels of individual cytokines measured when the onset of ACS and MACE, thus the actual fact that cytokines have an additional direct relationship with coronary artery disease than CRP\textsuperscript{[9,10]}. Therefore, cytokines is also higher markers to analyse than CRP.

Inflammation may be a complicated network response of multiple totally different cell sorts to associate degree injury like AMI, that involves associate degree altered expression of cell surface markers and secretion of an outsized numbers of cytokines and chemokines. Therefore, it is probably that activity of a non-specific single marker to characterise “inflammation” during this complicated setting to associate degree over-simplified approach. A chronic cohort study found assessment of multiple inflammatory biomarkers to be a stronger predictor of the semi-permanent risk of adverse events when put next to at least one marker approach\textsuperscript{[11]}. This has additionally been according in alternative state like body part cancer and carcinoma.

Therefore, this systematic review aims to analyse whether or not, in an exceedingly population of ACS patients with multiple cytokines measured, characterisation of inflammation victimisation combined cytokines analyses as hostile one marker approach was superior for predicting MACE.
METHODS

Search Strategy:

The necessary articles for the review were collected using online publications via PubMed, NCBI, Medline, Medscape, Embase, Embase classic. The data collected from medline is from a time period of 2001 to 2021 written in English, and the other online data collection sites are also used during this time period. Various keywords were used to collect the detailed data such as: myocardial infraction, ST segment elevation angina, ST segment elevation myocardial infarction, non ST segment elevation myocardial infarction, cytokines inflammation, long term adverse effects.

In this review, the full text of the related publications were obtained and analysed in order not to miss any relevant articles. Titles and abstracts are also reviewed, and the review is prepared based on the full analysis.

INCLUSION AND EXCLUSION CRITERIA

Inclusion Criteria:

The data in which blood samples collected within 7 days of symptom onset and analysed, inflammatory cytokines and chemokines were measured which included with MACE and one year of follow up should be done[1].

Exclusion Criteria:

Studies conducted via in vitro were excluded; in vitro studies refers to the studies of biological properties that are done in test tube rather than in humans or animals[1]. Recent MI, ischemic cerebrovascular stroke, within the last 3 months of treatment, recent acute infectious diseases, acute immunological diseases where excluded[12,13,14,15,16].

INFLAMMATORY CYTOKINES IN ACS

Ehrin.et.al performed a cohort study with 458 patients with ACS and followed up for 2yrs and thus these datas were analysed[17].
Table 1: Pathophysiological contributions of cytokines related to the various clinical data

<table>
<thead>
<tr>
<th>Cytokines</th>
<th>Strength of Clinical Data</th>
<th>Pathophysiological Contributions</th>
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<tbody>
<tr>
<td>IL-6</td>
<td>Multiple cohort</td>
<td>Induction of acute-phase response</td>
</tr>
<tr>
<td>MCP-1</td>
<td>Single cohort</td>
<td>Monocyte migration, Activation of tissue factor</td>
</tr>
<tr>
<td>TNF-α</td>
<td>Case control</td>
<td>Myocardial dysfunction and remodeling</td>
</tr>
<tr>
<td>IL-18</td>
<td>Single cohort</td>
<td>Expression of interferon-γ</td>
</tr>
<tr>
<td>IL-10</td>
<td>Single cohort</td>
<td>Anti-inflammatory</td>
</tr>
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</table>

Cytokines are the pleiotropic proteins that regulate the activity of leukocyte. Cytokines such as interleukin-1 (IL-1) and interleukin-6 (IL-6) increases the production of reactive proteins in the acute phase. The clinically implicated biomarkers of ACS are IL-6 & monocyte chemoattractant protein-1(MCP-1)\[^{17}\].

**Interleukin-6**

Interleulin-6 (IL-6) is an omnipresent protein, the presence of that is crucial for corpuscle and epithelium cell activation. IL-6 additionally promotes production of viscous acute-phase reactants, as well as CRP\[^{17}\]. IL-6 is expressed at the shoulder region of arterial sclerosis plaques and should increase plaque instability by driving expression of matrix metalloproteinases, MCP-1, and tumour tissue (TNF)-α\[^{10}\].
Figure 1: The involvement of interleukin-6 in the pathogenesis of acute coronary syndrome.

Patients with ACS have redoubled current levels of IL-6 compared with those patients who have stable angina. Among patients with unstable angina\cite{12,17,18}, a rise in IL-6 levels that occurred forty eight hours once admission compared with the admission price was related to the combined finish purpose of death, myocardial infarction (MI), or refractory angina\cite{19}. Within the Fragmin or early Revascularization throughout instability in artery disease (FRISC-II) study, elevated IL-6 (>5 ng/L) was related to higher 6 and 12 months mortality and was additive to and freelance of viscous troponin T rate. Elevated IL-6 levels conjointly known a subgroup of patients who has the benefit of mortality. These results recommend that elevated level of IL-6 could determine patients with a lot of severe index event, thus they will benefit of aggressive treatment. Currently the massive time unit variations in IL-6 levels and lack of supportive studies limit the applications of IL-6 as a biomarker in ACS.

MCP- I = monocyte chemotactic protein- I, MMPs = matrix metalloproteinases, TNF-\(\alpha\) = tumor necrosis factor-\(\alpha\), VSMC = vascular smooth muscle cell.
Elbadwy TH et.al conducted a study with 60 patients admitted with ACS and categorise them randomly to 3 groups: including group-1 for unstable angina, group 2 for STEMI with successful thrombolytic therapy and group-3 for STEMI with failed thrombolytic therapy[19,20,21,22,23]. Additionally, they added a 4th group with healthy control patients. Blood levels of CRO, cardiac troponin 1, IL-6 were analysed. Thus, by this study they analysed that atherosclerosis is currently considered as systemic inflammatory disease and Interleukin-6 is an important inflammatory cytokine. IL-6 levels were increased in group-2 and there was a positive correlation between CRP and IL-6 in group-3 patients; IL-6 levels did not correlate with troponin level in any of ACS patients[24,25,26].

**Monocyte Chemoattractant Protein-1**

MCP-1 is a chemokine that activates mononucleate phagocytes by promoting leukocyte endothelium binding and migration to sites of inflammation. As per the pathophysiological role in ACS, inhibition of MCP-1 communication during a mouse model of MI improved survival at four weeks and additionally improved left bodily cavity perform[12].

In the Orbofiban in patients with Unstable Coronary Syndromes (OPUS), Thrombolysis in myocardial infarction (TIMI) sixteen trial, MCP-1 level >238 pg/mL was related to hyperbolic risk of death or MI when ten months, even when adjustment for ancient risk factors[27]. Measuring of MCP-1 within the sinus blood of patients with unstable angina, an association between MCP-1 levels were demonstrated and therefore the extent of coronary hardening of the arteries as assessed by the coronary angiogram[28]. Thus, the levels of MCP-1 is primarily a surrogate for hardening of the arteries burden and thus MCP-1 remains as the promising therapeutic target with an important pathophysiological role in atherothrombosis.

**Other Cytokines**

TNF-α may be a pro-inflammatory protein involved in heart muscle pathology and transforming once ACS[27,29], within the CARE (Cholesterol And Recurrent Events) trial of patients with a recent MI, those that veteran a perennial MI or viscous death had higher levels of TNF-α at study enrollment than matched controls.

IL-18 promotes expression of interferon-γ, a intermediator of plaque progression. Administration of exogenous IL-18 markedly will increase lesion size in an exceedingly mouse model of atherosclerosis[30,31]. IL-18 mRNA is expressed at higher levels in unstable
human arteria plaques relative to stable plaques, that suggests that IL-18 conjointly mediates later events in plaque stability and ultimate disruption[31,32]. Thus in an exceedingly prospective study of patients with unstable angina, who were undergoing coronary angiography, patients with IL-18 levels within the fourth grade (>77.7 pg/mL) had a markedly redoubled risk of vas death throughout long-run follow-up; an identical association was conjointly ascertained in patients with stable angina[33,34].

Interleukin-10 is not usual in proposed ACS biomarkers. In the CAPTURE study it is identified that patients with elevated CRP and IL-10 has low risk of nonfatal MI or death when compared with patients of elevated CRP but no elevation in IL-10; thus from this study it assume that IL-10 is protective against proinflammatory cytokines in ACS[35,36].

**Long term adverse effects-ACS**

Stepinska J et.al conducted a study in 345 patients among NSTEMI and STEMI were separately studied. Thus, they analysed the time of hospital administration percutaneous coronary intervention. From the 2 year follow up it is concluded that they have increased risk of cardiovascular and bleeding problems in patients with both NSTEMI and STEMI. NSTEMI patients on oral anticoagulant experienced prolonged time of intervention, lower rates of thrombolysis in MI (TIMI) flow and prolonged hospitalization[36,37].

**MACE outcomes**

Six studies found a big association between individual cytokines and MACE, either by univariate or statistical procedure[38,39,40,41,42,44]. Four of the 5 studies that created a hazard magnitude relation (HR) for IL-6 had values higher than 1.00[38,40,41,42,44] and 3 of these HRs were statistically important, indicating that IL-6 is a risk issue for MACE[39,40,44]; there have been mixed findings for IL-10, with five hundredth of the studies showing that the biomarker was protecting for MACE. Kaski et al. found IL-18 to be a risk issue for MACE, however a similar protein had a time unit below 1.00 for death and MI alone. Thus 2 studies that assessed IL-18 found a odds magnitude relation (OR) and a time unit per unit modification higher than 1.00[38,39,40,43]. **Table-2** summarises the statistically important findings found for the clinical endpoints of the studies.
Table 2: The statistically important findings found for the clinical endpoints of the studies

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Combined Cytokine Analyses</th>
<th>Author</th>
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<tr>
<td>Combination of all cause death &amp; MI</td>
<td>No joint analysis conducted</td>
<td>Simon T, et al.</td>
</tr>
<tr>
<td>All-cause death</td>
<td>Punished reversion analysis showed that 32 markers and GDF-15 + TRAIL-R2 alone had ROC AUCs of 0.85.</td>
<td>Skau E, et al.</td>
</tr>
<tr>
<td>Primary endpoint: Combination of all-cause death, MI, UA, PCI, &amp; CABG</td>
<td>No joint analysis conducted</td>
<td>Kaski JC, et al.</td>
</tr>
<tr>
<td>Secondary endpoint: Combination of death &amp; MI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combination of all-cause death, MI, stroke &amp; TLR</td>
<td>No joint analysis conducted</td>
<td>Yu CW, et al.</td>
</tr>
<tr>
<td>Combination of repeated angina, MI, death, new revascularisation, &amp; HF</td>
<td>Higher rank tally (with all 27 biomarkers) was related with MACE, F = 5.07; ROC curve analysis: Score of &gt;13 cytokine levels beyond the median was a better analyst of MACE, with an AUC 0.72</td>
<td>Novo G, et al.</td>
</tr>
<tr>
<td>Combination of all-cause death &amp; HF</td>
<td>No joint analysis conducted</td>
<td>Valgimigli M, et al.</td>
</tr>
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Note: All the standards are statistically significant (p ≤ 0.05). MI - myocardial infarction, GDF-15 - growth differentiation factor 15, TRAIL-R2: tumour necrosis factor-related apoptosis-inducing ligand receptor 2, UA - unstable angina, ROC - receiver operative characteristics, AUC - area under curve, CABG - coronary artery bypass graft, PCI - percutaneous coronary intervention, TLR - target lesion revascularisation, HF - heart failure, F - analysis of variance (ANOVA) F value, IL - interleukin, OR - odds ratio
The 8 studies that conducted a statistical procedure created changes for a range of potential confounders, supported what was found to be statistically important within the univariate analysis. Three of the 8 studies that measured individual cytokines on statistical procedure found that a little of these cytokines were considerably related to MACE\[^{38,40,44}\]. Skau et al. and Chalikias et al. used many models adjusted for various teams of confounders\[^{37,41}\]. Skau et al. had 4 models: one for age and sex alone; one for ancient risk factors for MACE; one for age, sex and biomarkers together with growth differentiation factor-15 (GDF-15), and path receptor-2 (TRAIL-R2); and a final model together with ancient risk factors and therefore the hand-picked biomarkers. All four models created high space underneath the curves (AUCs) from receiver operator curves starting from 0.79 for the model adjusting for less than age and sex, to 0.88 for the model adjusting for each ancient risk factors and therefore the hand-picked biomarkers. Chalikias et al. had 4 models primarily based on: clinical factors that were important on univariate analysis, lipid-related risk factors, MACE-related risk factors and medications. Out of those 4 models, IL-10 and IL-18 separately were solely considerably related to MACE in one or 2 of those models, whereas a combined IL-18/IL-10 magnitude relation was considerably related to MACE all told models\[^{45}\].

**DISCUSSION**

In this systematic review, substantial heterogeneity was ascertained in methodology together with the cytokines and chemokine studies, temporal order of blood assortment, definition of MACE, length of follow-up, and methodology of applied math analysis. All studies had either acceptable or poor internal validity, with most giving no clear explanation behind the selection of cytokines studied and a typically poor news on the validation of cohort size. However, all those studies that did a multi-marker analysis showed a major applied math association with MACE.

**CONCLUSION**

Even though some studies have analysed important associations between individual cytokines and MACE, we tend to found mixed associations from the various studies enclosed during this review. However, a joint analysis of multiple cytokines could have more association with MACE. This review highlights some cracks within the current body of proof on the connection between inflammatory cytokines and MACE in ACS patients, showing that there is sizeable non uniformity in strategies and results, like protein choice, blood
assortment times and cohort sizes. We might suggest future studies to supply a principle for his or her protein choice and be adequately hopped-up to find a clinically important distinction in fitly outlined MACE outcomes. Various studies were needed to identify the importance of the time of blood assortment. New strongly designed prospective studies that addresses the particular insufficiencies of past studies, those may need to check whether a multi-marker approach is also a big choice. Various investigations are needed to identify that which set of markers creates associate degree ideal panel and which methodology is most correct for merging the markers.

REFERENCES


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