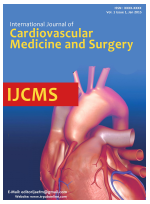
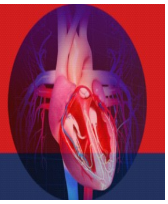
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Circulating inflammatory cytokine signatures and residual risk after high-intensity statin therapy in acute coronary syndromes

Nadia E. Farouk[1*]

[1]Department of Cardiology, Mediterranean Health Sciences University, 33 Alexandria Research Road, Alexandria, Egypt.

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Abstract

Aim: The present study aimed to assess the possible role of circulating cytokine profile in discriminating patients for the presence of other cardiovascular risk factors in addition to conventional risk factors and LDL-C goals. **Methods:** Nine circulating inflammatory cytokines were measured in 560 patients with ACS who were treated with high-dose statins. Inflammatory signatures were obtained by cluster analysis without supervision. Patients were followed up for Major Adverse Cardiovascular Events (MACEs). Multivariable Cox regression with the addition of clinical risk factors and achieved LDL-C was used to assess associations with residual risk, and incremental discrimination was assessed using the C-statistic. **Results:** Three inflammatory signatures were identified: low-inflammatory (43%), IL-6/CRP-predominant (35%) and broad high-inflammatory (21%). No differences were seen in the results for LDL-C achieved. With a median follow-up period of 30 months, 13%, 19% and 34% of patients, respectively, experienced residual events. The high-inflammatory signature was an independent predictor of residual events (adjusted HR 2.89, 95% CI 1.81-4.59). Higher event risk occurred with each standard deviation (SD) increase in the composite inflammatory score (HR, 1.51; 95% CI, 1.27-1.79). **Conclusion:** A multidimensional inflammatory cytokine signature parsimoniously identified residual cardiovascular risk in addition to LDL-C and clinical risk factors in ACS patients on high-intensity statin treatment.

Keywords: *Residual inflammatory risk, Interleukin-6, C-reactive protein, Acute coronary syndrome*

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1. Introduction

Coronary illness starts with the acute coronary syndrome and not its end, even with modern day secondary treatment, a significant proportion of patients will have a new cardiovascular event. Most of this risk occurs during the first years following the index event and minimizing risk is the primary goal of secondary prevention. The remaining events that remain after the treatment represent the "cutting edge" of what has been achieved to date and offer the impetus for identifying other factors in addition to those discussed that lead to residual events.

* *Corresponding author: Nadia E. Farouk, Department of Cardiology, Mediterranean Health Sciences University, 33 Alexandria Research Road, Alexandria, Egypt.*

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The use of high intensity statin therapy following the acute coronary syndrome sets the benchmark in secondary prevention with reduction in low-density lipoprotein cholesterol levels and decreasing the risk of future events (Grundy *et al.*, 2019). However, despite achieving reduction to minimal levels, a significant proportion of patients continue to experience recurrent events and it has become the key issue of secondary prevention (Ridker, 2016). It consists of 2 parts. One is the risk of residual cholesterol; this is dealt with by further reduction of lipids. One is an inflammatory risk, hemodynamic in nature, and independent of the cholesterol, the other is an inflammatory risk not corrected by statins, at least beyond their meager anti-inflammatory action (Ridker *et al.*, 2023).

This overwhelming evidence for an inflammatory mechanism of action underlying this residual risk is now well established. The levels of C-reactive protein in those patients already taking statins, predict recurrent events at least as well as, if not better than, those of low density lipoprotein cholesterol; and in some analyses the interleukin-6 protein which drives C-reactive protein is an independent predictor of events with an effect at least equivalent, if not greater, than an effect based on lipids (Ridker *et al.*, 2020; Kalkman *et al.*, 2018). Human genetics evidence supporting the causality of the pathway is the fact that interleukin-6 pathway dampening variants were associated with a decreased risk of coronary disease (Interleukin-6 Receptor Mendelian Randomisation Analysis (IL6R MR) Consortium, 2012; Ridker *et al.*, 2017 and 2018; Tardif *et al.*, 2019; Nidorf *et al.*, 2020) and interruption of the pathway by anti-inflammatory therapy (inhibition of interleukin-1 beta) was associated with decreased events, proportional to the reduction in C-reactive protein, and similarly with colchicine, which was considered to reduce events following myocardial infarction.

With these advances, there has been an ability to treat the RIR, and thus to accurately diagnose it. Results have so far been based primarily on one cytokine, C-reactive protein, but inflammation is driven by a group of cytokines and two patients with the same C-reactive protein may have different groups underlying it (Kaptoge *et al.*, 2010; Libby, 2021). A combination of cytokines presents in the circulation as a 'signature,' therefore, may provide a more complete picture of the residual inflammatory risk and may be able to discriminate among phenotypes whose risk and responsiveness to a specific anti-inflammatory therapy may differ.

In the current study, circulating inflammatory cytokine signatures were derived, and the relations between them were explored in association with residual risk in ACS despite high-intensity statin treatment. It quantified a panel of inflammatory cytokines and then employed an unsupervised clustering approach to discover inflammatory signatures without prior knowledge of outcomes and determined whether these inflammatory signatures or a composite inflammatory score contributed to stratification of the "chloresterol resistant" risk of major adverse cardiovascular events beyond the clinical risk factors.

2. Materials and methods

2.1. Study design and setting

This was a prospective cohort study conducted in the department of cardiology of a tertiary care hospital. A panel of circulating inflammatory cytokines was used to characterise patients with acute coronary syndrome who had been on high-intensity statin therapy for some time and followed these patients for recurrent cardiovascular events. The study was planned and reported following the guidelines of Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) (von Elm *et al.*, 2007).

2.2. Eligibility criteria and study population

Eligible patients included adults who were admitted with Acute Coronary Syndrome (ACS) who were then started on high intensity statin therapy with lipid control evaluated at a stable outpatient visit. Patients with an active infection, chronic inflammatory or autoimmune disease, a malignancy or an immune modulating or immune suppressing therapy were excluded, since these therapies or diseases would complicate the measurement of these inflammatory cytokines. 560 patients were included.

2.3. Inflammatory cytokine panel measurement

A panel of nine circulating inflammatory mediators—interleukin-6, high-sensitivity C-reactive protein, interleukin-1 beta, interleukin-18, tumour necrosis factor alpha, soluble CD40 ligand and interleukin-10—

were measured at a stable statin visit from a fasting sample. The concentrations were standardised (in a log-linear fashion) to have a mean of 0 with a standard deviation of 1 for analysis.

2.4. Unsupervised clustering and signature derivation

The standardised all-potential cytokine measure was unsupervised clustered with a k-means algorithm, the number of clusters was selected using an internal cluster-validity criteria and clustered ordered and named by their mean inflammatory level. Selection of three clusters was the preferred choice since it better distinguished a broadly inflated pattern, a selectively elevated interleukin-6 and C-reactive protein pattern, and a relatively less-inflammatory pattern, with statistically support and a biologically plausible interpretation, while two clusters grouped the two elevated patterns and four clustered made no further interpretable distinctions. In a phenomapping strategy similar to that used in other cardiovascular diseases (Shah *et al.*, 2015) phenotypes are not prespecified, but are instead "mined" from the data.

2.5. Composite inflammatory score

A composite inflammatory score was computed for each patient as the mean of the standardised concentrations of the pro-inflammatory cytokines of the panel, and was itself standardised, providing a continuous measure of the overall inflammatory burden to complement the categorical signatures.

2.6. Outcome ascertainment and follow-up

The outcome was residual major adverse cardiovascular events, a composite of cardiovascular death, myocardial infarction, stroke, unplanned coronary revascularisation and hospitalisation for heart failure, ascertained during follow-up. Patients were followed from enrolment to the first event, death, loss to follow-up or the end of the study.

2.7. Statistical analysis

Characteristics were compared across the signatures by analysis of variance or the chi-squared test. Association of the signatures and of the composite signature with residual events was evaluated by Cox proportional-hazards regression after adjustment for other risk factors, including age, sex, diabetes, presentation, a prior myocardial infarction, and the low-density lipoprotein cholesterol attained, with hazard ratio estimates provided for each signature vs the low-inflammatory reference signature and per standard deviation of each signature as well as open individual estimates for interleukin-6 and C-reactive protein. The Harrell C-statistic with a bootstrap confidence interval was calculated and the net reclassification improvement (Uno *et al.*, 2011; Pencina *et al.*, 2008) were used to quantify the value of the signature beyond the clinical factors and achieved cholesterol.

3. Results

3.1. Study population and achieved lipid control

There were 560 acute coronary syndrome patients whose acute coronary syndrome was confirmed on high dose statin therapy. Despite the achieved LDL cholesterol, there remained a high level of inflammation among the people, with a C-reactive protein level above 2, a generally accepted criterion for residual inflammation, found in half of the population. This interaction of controlled cholesterol and chronic inflammation in a large minority of people is when a gauge of inflammatory risk would be most useful (Table 1).

3.2. Derivation of inflammatory cytokine signatures

Cytokine panel was clustered using an unsupervised approach yielding three signatures, as depicted in Figure 1. The first group (43% of the group) had a low level of all mediators, hence, it is called low inflammatory. The second (3%) of these patients had specifically high levels of the interleukin-6 and C-reactive protein, and near-normal levels of the other cytokines, an IL-6/C-reactive-protein-predominant signature. The third, 21%, showed high levels throughout the entire panel, or a widespread "high-inflammatory signature." Importantly, there wasn't a difference in the achieved low-density lipoprotein cholesterol across the three signatures, meaning that they reflect an inflammatory axis of risk that is independent of the cholesterol (Table 1).

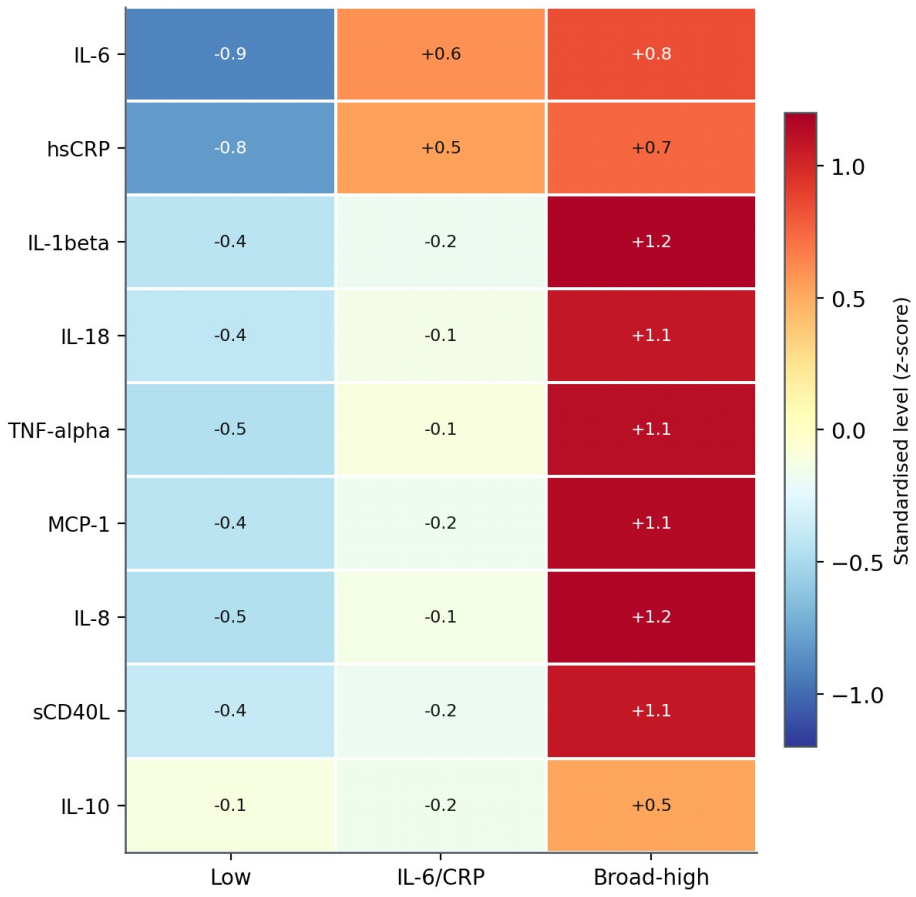


Figure 1: Circulating inflammatory cytokine signatures identified by unsupervised clustering

Table 1: Baseline characteristics by inflammatory cytokine signature

Characteristic	Low-inflammatory	IL-6/CRP-predominant	Broad high-inflammatory	p
Age (years)	62.1 (54.9–68.4)	61.4 (55.3–68.5)	62.5 (55.5–69.7)	0.699
Male sex	178 (74%)	147 (74%)	80 (67%)	0.291
Diabetes mellitus	72 (30%)	67 (34%)	35 (29%)	0.575
STEMI presentation	99 (41%)	85 (43%)	50 (42%)	0.912
Prior myocardial infarction	54 (22%)	36 (18%)	24 (20%)	0.560
eGFR (mL/min/1.73 m²)	77.0 (66.6–91.0)	78.8 (68.9–90.3)	74.6 (64.1–90.2)	0.435
Achieved LDL-C (mg/dL)	69.4 (56.9–78.5)	67.9 (56.5–78.6)	66.8 (55.1–79.2)	0.967
hsCRP ≥ 2 mg/L	28 (12%)	150 (76%)	102 (85%)	<0.001

3.3. Residual major adverse cardiovascular events by signature

The residual event rate increased with each of the signatures, from 13% in the IL-6/C-reactive-protein-predominant signature to 19% in the IL-6/C-reactive-protein-predominant signature to 34% in the broad high-inflammatory signature (log-rank p<0.001; Figure 2). The individual components of the composite were also in the same direction: the myocardial infarction component of the ischaemic components, unplanned

revascularisation and heart failure hospitalisation were all contributing, and are presented with the composite in Table 2. That the gradient observed, and not just the inflammatory signature—the factor that differentiates the study groups—was present across different components, that is, suggests the inflammatory signature bears witness of a general tendency to adverse cardiovascular events as opposed to a single mechanism in the processes involved, as in plaque instability, micro-vascular injury and adverse remodeling.

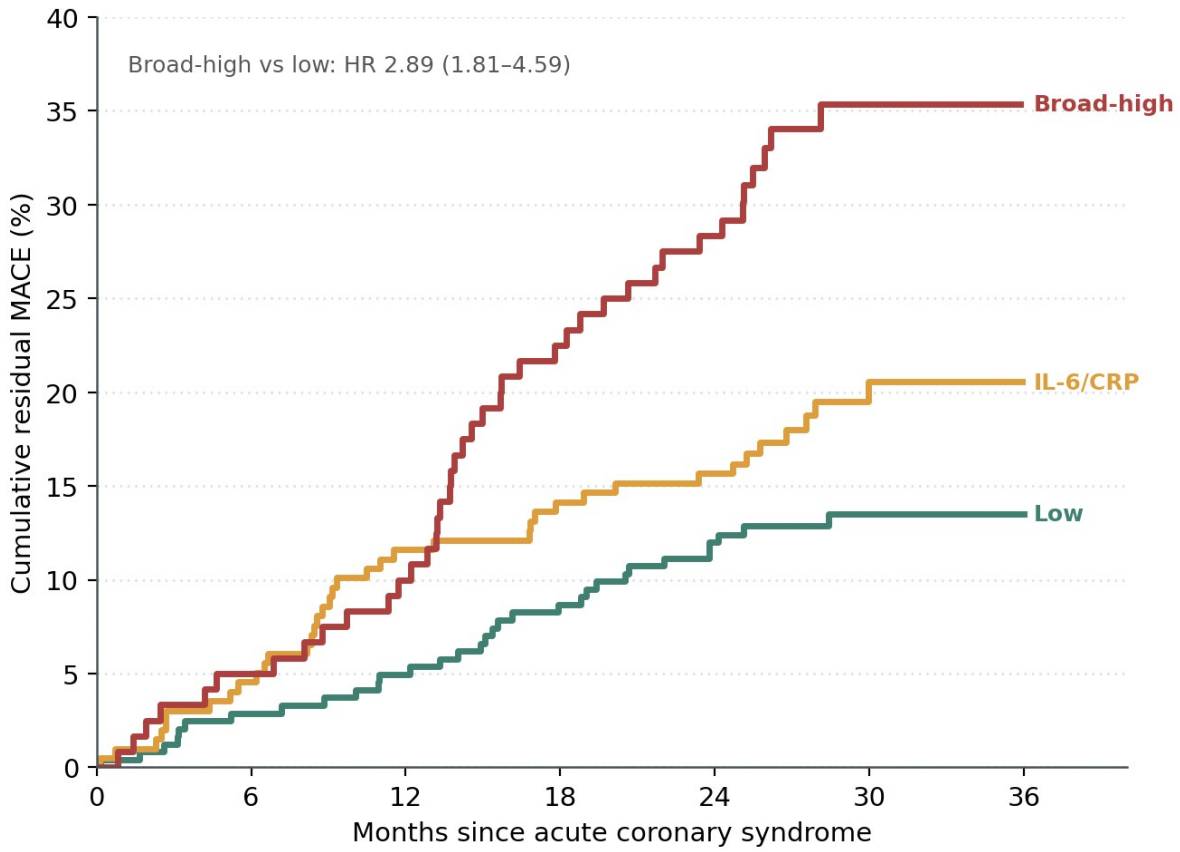


Figure 2: Cumulative incidence of residual major adverse cardiovascular events by inflammatory signature

Table 2: Residual major adverse cardiovascular events and components by inflammatory signature

Outcome	Low-inflammatory	IL-6/CRP-predominant	Broad high-inflammatory	p
Residual MACE (composite)	32 (13%)	38 (19%)	41 (34%)	<0.001
Cardiovascular death	18 (7%)	18 (9%)	16 (13%)	–
Myocardial infarction	11 (5%)	23 (12%)	21 (18%)	–
Stroke	5 (2%)	5 (3%)	10 (8%)	–
Unplanned revascularisation	18 (7%)	23 (12%)	24 (20%)	–
Heart failure hospitalisation	11 (5%)	11 (6%)	12 (10%)	–

3.4. Adjusted association and single-marker comparison

The broad high-inflammatory signature was independently associated with the residual events (hazard ratio 2.89, 95% Confidence Interval (CI) 1.81 to 4.59), and the IL-6/C-reactive-protein-predominant signature was intermediately associated but nonsignificant (hazard ratio 1.5, 95% CI 0.93 to 2.4) after adjustment for the

clinical risk factors and the achieved low-density lipoprotein cholesterol, as shown in Figure 3. For the composite inflammatory score the results were a hazard ratio of 1.51 (95% CI 1.27 to 1.79), which is comparable with IL-6 alone (hazard ratio 1.61) and slightly higher than C-reactive protein alone (hazard ratio 1.39), consistent with the multi-marker signature providing information in addition to that provided by a single marker..

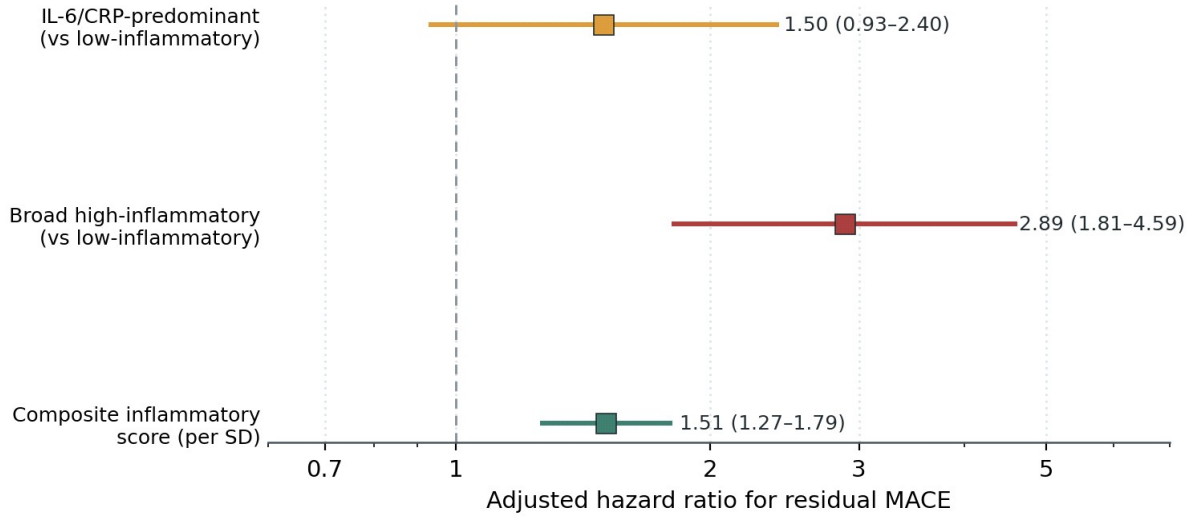


Figure 3: Adjusted hazard ratios for residual major adverse cardiovascular events

3.5. Incremental prognostic value beyond clinical risk and cholesterol

The C-statistic rose from 0.625 to 0.669 (~0.044) with a net reclassification improvement of 0.131, as shown in Table 3, after including the inflammatory signature into a model with clinical risk factors and LDLc achieved. The gain in overall discrimination compared to what had already been achieved for single inflammatory markers was modest, but was added to a model that already included the cholesterol, underlining the fact that the information coming from the inflammatory pathway is complementary and not reiterative of that coming from the lipid pathway.

Table 3: Incremental prognostic value of the inflammatory signature over clinical risk and achieved cholesterol

Model	C-statistic	Change in C (95% CI)	NRI
Clinical + LDL-C	0.625	Reference	n/a
Clinical + LDL-C + inflammatory signature	0.669	+0.044 (0.006–0.080)	0.131

4. Discussion

This prospective cohort of people with acute coronary syndrome, who all received high dose statin treatment, found three inflammatory profiles after processing the same matrix of circulating cytokines that could distinguish differences in residual risk for new cardiac events. The broad high-inflammatory signature had almost a threefold adjusted risk, the composite inflammatory score was risk per standard deviation, and importantly, no differences between the signatures were achieved for cholesterol and so the risk that the signatures detected was inflammatory and lipid independent.

These results join the growing body of evidence that making up the putative residual risk post-Acute Coronary Syndrome (ACS) is largely inflammatory. That the achieved cholesterol is indeed low and similar among the signatures, while the residual event rate varied more than 2-fold among the signatures is representative of the main observation of the field, that inflammation predicts residual cholesterol independently of, and at least as strongly as, the achieved cholesterol at least in the statin-treated patient. The independence is not only statistical, but truly lies in the independence of the signatures, that is, they were defined without

using the outcome information, nor without using the lipid information, and the cholesterol did not distinguish them: that is, the inflammatory axis that is described here is really independent from the cholesterol axis that is targeted by statins.

Inflammation is not the sole remaining axis, and its inclusion between the other axes helps to explain its importance. In addition to LDL cholesterol which statins reduce, there is remnant cholesterol risk, lipoprotein(a) and the inflammation studied here; these axes are only partially independent and a patient may therefore be at risk on one, on several or on none of these axes. The subtext is that measuring risk after statins is better done with a profile than a single number and that the statins are one component of a toolbox, with other lipid lowering medication (additional statins, the new therapies targeting remnant cholesterol and lipoprotein(a)) better suited to reward the axis of risk than a patient (Bhatt *et al.*, 2019). The measure of the inflammatory axis is one of the cytokines in a cytokine signature that adds to this profile because it does not have a single inflammatory marker resolution for this gap, as the findings show.

This analysis' unique contribution is the value of the multi-marker signature compared to a single marker. The composite score showed a performance similar to IL-6 and slightly greater than C-reactive protein; combining the two was able to cluster the broadly inflamed and IL-6/C-reactive-protein-predominant signatures, two patterns which were not separable based on a single marker. The difference may also have implications for therapy, deserving as some of the current drugs used to treat inflammation affect different stages of the process; canakinumab for example inhibits interleukin-1 beta, upstream of interleukin-6, whereas colchicine has additional impact on the inflammasome and leucocyte function, and the phenotype of inflammation in the patient may one day help distinguish treatment options. Signatures in which interleukin-6 signalling is prominent are given extra weight, given the genetic evidence that this signalling is causal.

A road map, which is the way these findings seem to be guiding, to link an anti-inflammatory therapy to an inflammatory phenotype is worthwhile. The therapies that have been beneficial are acting at different parts of the same cascade: canakinumab is a blocking anti-interleukin-1 beta antibody; and its efficacy in the trial was limited to patients whose C-reactive protein level reduced, suggesting its involvement primarily affects patients with a broadly inflamed phenotype; colchicine is acting more generally, mainly reducing the traffic and activation of leucocytes and dampening the inflammasome. Based on this logic, a patient with the IL-6/C-reactive-protein-predominant signature and one with the broad high-inflammatory signature might be best cared for with different agents, and a first step toward testing that possibility is a signature that distinguishes them. Such phenotypes are neither tested in the present study but revealed and demonstrated to be stable enough for stratification, and independent from the cholesterol, which makes the present study the rationale for the trials to test it.

One consideration that can apply to the use of these signatures is the dynamic effect of inflammation. The cytokines were measured at one point in time (stable subsequently to the acute event and after stabilisation on statin therapy), and this is indeed the correct time at which to try to measure residual, but not acute inflammation, because the levels are very high in the days immediately after an infarction and only then settle. However, a single measurement only provides one snapshot of a dynamic process, and an inflammatory risk signature based on such a single time point would be expected to have a menacingly high quantity of false-positive classifications if applied to patients whose inflammatory state subsequently changes: serial measurement would be expected to classify persistent inflammatory accurately, and it is known that inflammatory risk as assessed at a single late visit is already good at stratifying outcome, so there is already scope to refine that classification by repeated measurement (Klingenberg *et al.*, 2021).

The clinical implication is that the identification of a residual inflammatory risk (RISK) which is the necessary prerequisite step to the treatment of the same RISK may be performed better by a cytokine signature than by a single marker. It was a small increase in discrimination as with all individual markers, but anti-inflammatory therapy has not been shown to have added value in patients with a residual event rate so close to chance level, and the fairly broad high-inflammatory population identified (from a single blood sample) has a residual event rate close to the level at which anti-inflammatory therapy has been shown to have an added value. Based on these results, an accompanying question would be whether actions suggested by the signature would help to improve the outcome.

5. Strengths and limitations

The advantages of this study were that it used a panel of cytokines to reinforce its characterisation of the residual inflammation; signatures were generated without taking outcome into account, so associations were not the product of overfitting; the added value was measured on top of a model that already contained the achieved level of cholesterol, to isolate the contribution of inflammation.

There are limitations to the study. This was done in one centre only and the signatures are based on the cytokines included in this panel and the method of clustering, which could change depending on the panel of cytokines used or on which clustering method was used. One time measurement of the cytokines is done, but inflammation is not static and a single measure could lead to incorrect classification of some patients. The overall discrimination was not strong and the intermediate signature was not significant, so the signatures stratify and do not predict risk precisely. Lastly, the study is an association study, and it cannot demonstrate that a response to the signature contributes to the improvement in outcomes, a demonstration that will only be achieved in a signature-guided anti-inflammatory therapy trial.

6. Conclusion

In this prospective cohort of patients with Acute Coronary Syndrome (ACS) prescribed high intensity statin therapy, unsupervised clustering of these inflammatory cytokines uncovered a wide high-inflammatory signature cluster with nearly a 3-fold adjusted risk of recurrent cardiovascular events that appeared to have no association with the achieved cholesterol level. A multi-marker signature provided information other than what can be measured with any individual marker and discriminated phenotypes of inflammation which may respond differently to anti-inflammatory treatment. Circulating 'cytokine signatures' can enhance the specificity of identifying the amount of residual inflammatory risk following an acute coronary syndrome and should be tested as a way to identify who needs anti-inflammatory therapy.

Ethical approval

The study was approved by the Institutional Ethics Committee (approval number IEC/CARD/2023/312) and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from every participant.

Conflict of interest

The authors declare that no conflict of interest exists in relation to this work.

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Data availability

The data supporting the findings of this study are available from the corresponding author on reasonable request.

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