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Original Article

The Role of Inflammatory Biomarkers in Predicting in-Stent Restenosis

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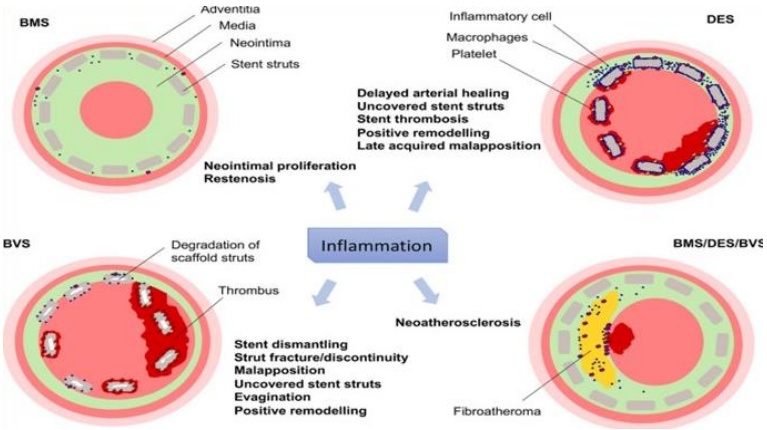
ABSTRACT

The present study aimed to assess the role of inflammatory markers including erythrocyte sedimentation rate (ESR), highly sensitive C-reactive protein (hs-CRP), neutrophils to lymphocytes ratio (NLR), and platelet-to-lymphocyte ratio (PLR) in predicting ISR. This retrospective case-control study was conducted on 818 consecutive patients suffering acute coronary syndrome and underwent coronary stenting and referred to Rajaie Cardiovascular Medical and Research Center due to being suspicion to ISR. By referring to patients' clinical records as well as accessing their angiographic movie via the Cath lab computer system, patients who had ISR over a two-year period were identified from other patients who did not have re-stenosis. Overall, 19.1% were diagnosed to have ISR within a two-year following-up. However, there was no difference in NLR and PLR across the two ISR (+) and ISR (-) groups. In ISR group, the serum levels of ESR and CRP were significantly higher in smokers versus non-smokers, in diabetics versus non-diabetics, and also in those with chronic kidney disease as compared with those without kidney involvement. The levels of inflammatory indices of ESR and CRP were positively associated with the length of stent and negatively associated with the diameter of stent. Assessing the levels of ESR and CRP can successfully predict ISR in the patients initially undergoing coronary stenting. Such predicting role may be influenced by the interfering role of some cardiovascular risk factors such as smoking, diabetes mellitus, and chronic renal failure.

GRAPHICAL ABSTRACT



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Introduction

Inflammatory responses play an important role in the progression and instability of atherosclerosis and cardiovascular disease [1,2]. The development of neointimal proliferation due to inflammation is the leading cause of stent re-stenosis [3]. Among the various inflammatory indicators, the types and number of white blood cells are associated with the likelihood of cardiovascular risk profiles [4,5] (Figure 1).

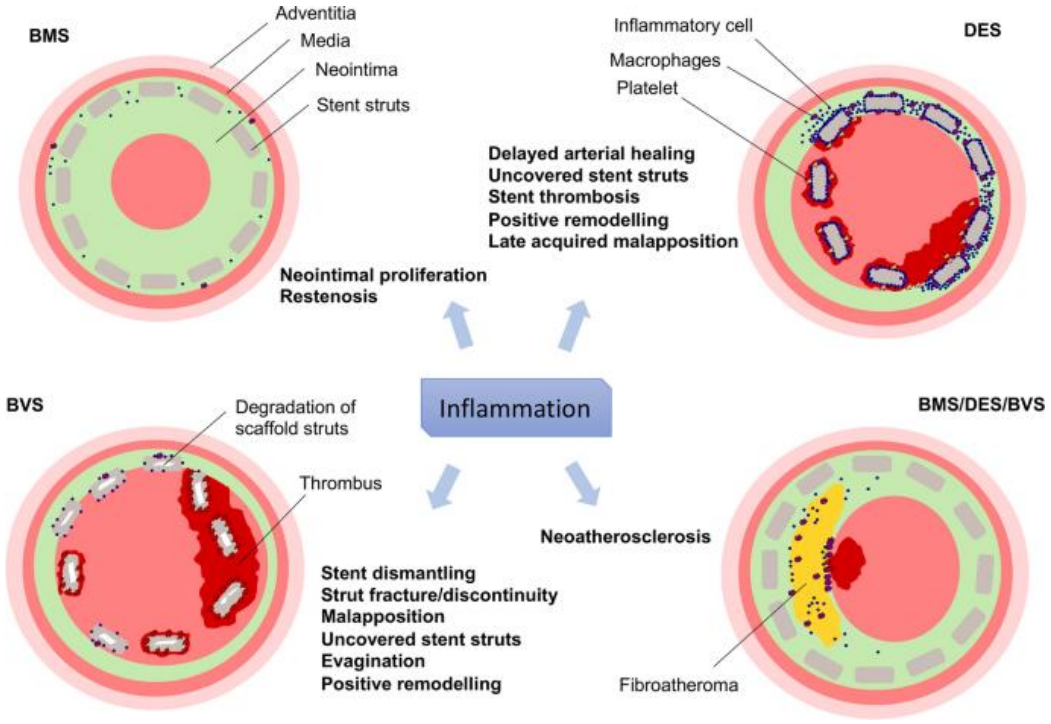

Figure 1: Inflammation as a determinant of healing response after coronary stent implantation

Chronic inflammation is now increasingly at the center of research [6-9]. A recent study identified differences in inflammatory markers between new subtypes of diabetes. But what does this information mean for the future? Complications that increase with age, such as cardiovascular disease, kidney damage, or dementia, are common consequences of type 2 diabetes. In addition to metabolic disorders, chronic inflammatory reactions are important causes of these complications. Common inflammatory cytokines, which are the body's response to chronic inflammation, can have many effects on various organs. One consequence of this is that the body no longer responds adequately to insulin. A new analysis in the German Diabetes Study (GDS) was conducted at the German Diabetes Center (DDZ) to examine differences between subtypes of diabetes in terms of inflammatory biomarkers [10-12]. Biomarkers are markers that are present in the blood or in tissues and other parts of the body and are measured to check for certain changes in the body, such as inflammation [13-15]. In the present study, 74 biomarkers covering a wide range of inflammatory processes were measured in more than 400 individuals [16-18]. The results of these studies showed that new subtypes of diabetes show a number of specific differences in inflammatory markers that can help better predict the risk of diabetes-related complications. The German Diabetes Study (GDS) had previously identified five subgroups of diabetes with different periods: Severe autoimmune diabetes (SAID), severe insulin deficiency diabetes (SIDD), and severe insulin-resistant diabetes (SIRD), moderate obesity-related diabetes (MOD) and age-related moderate diabetes (MARD) [19-21]. The present study showed that these subgroups differ not only in age and metabolic

characteristics, but also in biomarkers of inflammation [22-25]. Given the vital role of inflammatory processes in diabetes-related complications, these differences may also be related to the severity of the clinical course of diabetes [26]. "It is interesting that this study, with the help of the above biomarkers, was able to identify early disorders in people with diabetes who have recently been diagnosed with the disease," said Professor Michael Rodin, scientific director and board member of the DDZ. Therefore, with the help of these biomarkers, the consequences of diabetes can be identified earlier than before. As a result, these findings could make early treatment possible in any of the subtypes of diabetes [27-29]. This highlights the importance of overweight and obesity, which are particularly relevant to inflammation and insulin resistance. On the other hand, the SIDD subgroup, which is mainly characterized by insulin deficiency, had the lowest level of biomarkers. "This association between high levels of inflammatory markers and severe insulin resistance indicates a significant contribution to inflammatory processes in the SIRD subgroup," said Dr. Christine Herder, chair of the DDZ Inflammation Working Group. It will take several years for us to use these findings to formulate specific recommendations for the treatment of diabetes, but the results of this study are very important for understanding and understanding the complications of diabetes. Further studies are needed to investigate the extent to which differences in the characteristics of inflammation-related biomarkers can explain the differences between diabetes subtypes in terms of the risk of diabetes-related complications [30-32].

Recently, the ratio of neutrophils to lymphocytes ratio (NLRs) can be used routinely to predict further risk for cardiovascular ischemic events [6,7]. Although strong association between NLR and cardiovascular events has been observed in patients with ST-segment elevation myocardial infarction (STEMI), and even its-related death, quantitative studies have shown a link between NLR and clinical side effects in patients undergoing revascularization [33-35]. A series of studies have shown that a high NLR is an independent risk factor for the progression of atherosclerotic plaque lesions in stenotic coronary stent that results in adverse early and long-term cardiac events [36]. Moreover, increased blood platelets play an important role in the onset and progression of atherosclerosis [37]. In this regard, recent studies have revealed that the platelet-to-lymphocyte (PLR) ratio is a new inflammatory indicator and predictor of cardiovascular diseases complications [38]. In addition, high pre-procedural PLR in acute coronary syndrome group has been reported as an independent factor with high predictive power for long-term mortality [39-41]. However, the combined benefit of PLR and NLR in predicting long-term side effects in coronary artery disease (CAD) has not been adequately assessed (Figure 2).

Percutaneous coronary intervention (PCI) and especially coronary stenting led to stimulate proliferation of arterial intima-media thickness as well as synthesis of extracellular matrix, which is mediated to a large extent by inflammatory processes [42-44]. Numerous studies have shown an association between pre-procedural C-reactive protein (CRP) level and subsequent heart disease in patients treated with bare metal stent (BMS) implantation [45]; however, the duration of clinical follow-up in most relevant studies has been short. In addition, the prognostic value of CRP in predicting in-stent restenosis (ISR) remains uncertain [46]. Erythrocyte sedimentation rate (ESR) as another inflammatory marker is a simple laboratory test that is widely used in clinical setting due to high accessibility and cost-benefit [47]. ESR has been shown to be an independent predictor of coronary heart disease (CHD) [48]. Some studies have also shown its association with increased coronary atherosclerosis and its poor prognosis [49]. However, few studies to date have assessed the role of ESR levels and the risk of stent restenosis. The present study aimed to assess the role of inflammatory markers in predicting ISR (Figure 3).

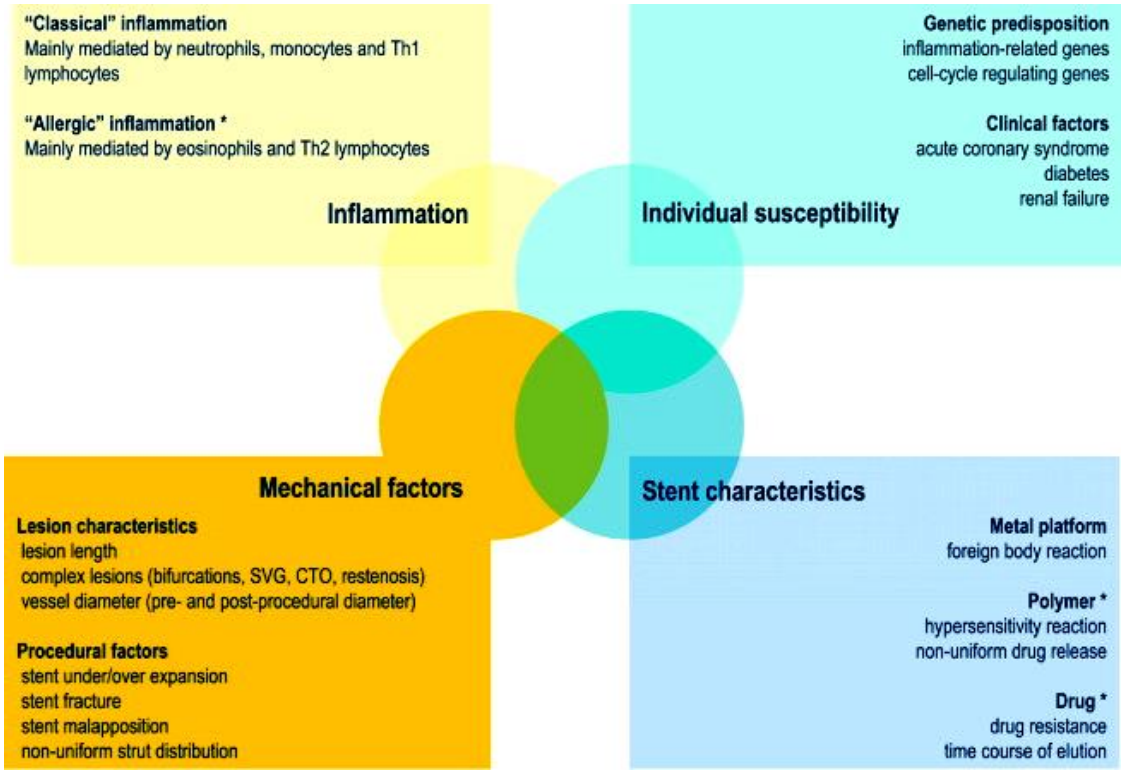

Figure 2: The evolving role of inflammatory biomarkers in risk assessment after stent implantation

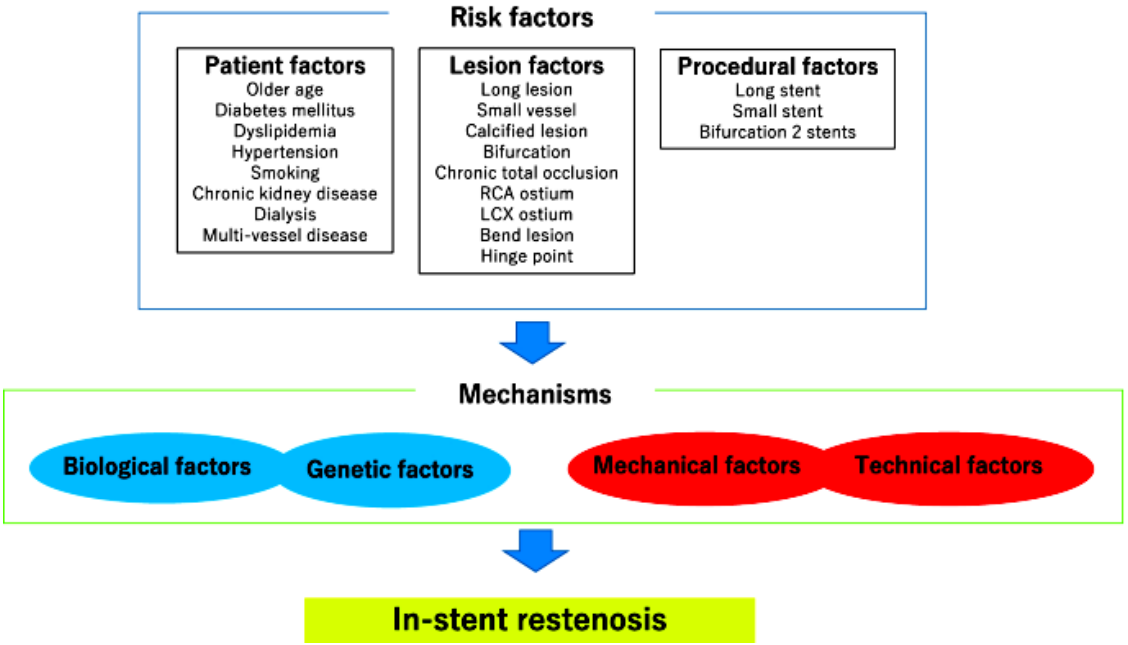

Figure 3: Mechanisms of drug-eluting stent restenosis

In the field of medical engineering, biomarkers are considered as an indicator that is usually obtained from patient samples and is measured and evaluated quantitatively or qualitatively by instruments [50]. There are various categories in the evaluation of biomarkers in terms of application and methods. A biological sample can be collected from a sick or healthy person, such as blood and urine, tissue samples, and so on. On the other hand, biomarkers can be obtained through laboratory methods and clinical tests such as blood pressure, fat and blood sugar, or imaging tests such as ECG, heart scan, echo. Biomarkers play an important role in the foundations of promising research studies as well as in clinics, from a routine diagnosis to prognosis and treatment. Ideally, biomarkers are related to different levels of disease or health

conditions, the intensity and duration of physical activity, the degree of disease and the pathogenesis process, and environmental influences and therapeutic interventions. In addition, the ideal biomarker is FDA-based:

a) Non-invasive and accessible; ideally, sampling should be done in a way that is least risky (not lethal);

b) high and special sensitivity; one of the characteristics of biomarkers is that it is a tool for diagnosis and treatment guide and a solution for treatment clinics. One of the most important characteristics of biomarkers is high and cheap sensitivity and their wide range of applications. Lack of sensitivity is one of the primary reasons for the devaluation of a biomarker; and

c) cost value; an ideal biomarker should be available everywhere.

Given the diverse effects of physical activity and inflammatory mediators, in this section we will focus on the applications and limitations of inflammatory biomarkers in order to evaluate multiple statistical communities of sports studies. Some studies have reported the benefits of physical activity in rehabilitating patients, especially heart patients. Beavars and colleagues (2018) evaluated the effects of long-term exercise (6 to 12 months) on inflammatory biomarkers in the elderly. In this study, a group of biomarkers including the cytokine-dependent interleukin family (IL-Ira-IL-2sRa-IL-6sR-IL-8I-, IL-ILsRll-, IL15) and adiponectin and TNFα were measured. They found that IL8 was the only biomarker affected by physical activity in these individuals. A similar result was observed in a study of short-term physical activity [41]. Luna and colleagues (2016) examined the stability of biomarkers in short-term exercise in middle-aged men. According to their findings, changes in exercise patterns (changes in the intensity of exercise and daily exercise) have no effect on CRP or IL6 and TNFα, and these inflammatory markers are stable and are rarely affected by exercise behaviors. Prominent recent data and information suggest that inflammatory biomarkers may be affected by strenuous physical activity. Another study (2021) reported differently. In this study, there are differences in previous studies and the author selected vo2max changes as the first efficiency and determined the changes of biomarkers (increase or decrease in the level of biomarkers) compared with various sports activities. Biomarkers evaluated in this study included IL1BIL10, IL6, TNFα, hs-CRp and soluble adhesive molecule (SICA-1) and the ratio of IL10 to TNFα in the peripheral circulation.

Material and methods

This retrospective case-control study was conducted on consecutive patients suffering acute coronary syndrome and underwent coronary stenting consecutively, who referred to Rajaie Cardiovascular Medical and Research Center due to being suspicion to ISR in 2019 and 2020. By referring to patients' clinical records as well as accessing their angiographic movie via the Cath Lab computer system, patients who had ISR over a two-year period (as the case group) were identified from other patients who did not have re-stenosis (as the control group).

Result and Dissection

Overall, 882 consecutive patients who underwent coronary intervention were initially included, of whom, incomplete data were found in 64 files that were excluded from our study and thus 818 patients were finally analyzed. Baseline characteristics of study subjects are summarized in Table 1.

Briefly, most patients (79.0%) aged higher than 50 years and more than two-third of them (68.1%) were male. Regarding underlying coronary disease, 13.3% suffered from stable angina, 43.9% from unstable angina, 24.9% from non-STEMI, and 31.2% from STEMI. According to repeated angiography report, 156 patients (19.1%) were diagnosed to have ISR within a two-year following-up. Overall, 10.8% of stents implanted sized less than 10mm, while the stent size used for 35.8% was in the range of 30 to 40mm. Regarding types of stent, drug-eluting stent (DES) was used in 56.6% and BMS in 43.4%. The results of laboratory parameters in the two groups with and without ISR are shown in Table 2.

Table 1: Baseline characteristics in patients undergoing coronary stenting

Characteristics	Frequency (%)
Age subgroups	
<30 years	8 (0.97)
30 to 50 years	163 (20.0)
> 50 years	647 (79.03)
Gender	
Male	557 (68.1)
Female	261 (31.9)
History of smoking	201 (24.6)
History of diabetes mellitus	243 (29.7)
History of kidney disease	11 (1.3)
Length of stent, mm	
<10mm	17 (10.8)
10-20 mm	39 (25.0)
20-30 mm	44 (28.2)
30-40 mm	56 (36.0)
Diameter of stent	
2 mm	11 (7.1)
2.5 mm	39 (25.0)
2.75 mm	56 (36.0)
3 mm	26 (16.7)
3.5 mm	18 (11.5)
4 mm	6 (2.7)
Type of stent	
DES	463 (56.6)
BMS	355 (43.4)

Table 2: Comparing study variables in the two groups with and without ISR

Item	ISR (+) (n = 156)	ISR (-) (n = 662)	P value
Serum CRP level			<0.001
≤ 6	9 (5.8%)	627 (94.7)	
> 6	147 (94.2)	35 (5.3)	
Serum hs-CRP level			<0.001
≤ 3	17 (10.9)	583 (88.0)	
> 3	138 (89.1)	57 (12.0)	
Serum ESR level (men)			<0.001
≤ 10	28 (28.0)	264 (58.0)	
> 10	72 (72.0)	193 (42.0)	
Serum ESR level (women)			<0.001
≤ 20	9 (17.0)	119 (58.0)	
> 20	47 (83.0)	86 (42.0)	
History of smoking	42 (27.0)	159 (24.0)	0.558
History of diabetes mellitus	51 (33.0)	192 (29.0)	0.508
History of kidney disease	2 (1.3)	9 (1.4)	0.941
Mean NLR	2.36±0.46	2.38±0.48	0.745
Mean PLR	1.03±0.05	1.02±0.04	0.783

Comparing inflammatory biomarkers showed significantly higher levels of ESR and CRP in patients suffering ISR as compared with non-ISR group. However, there was no difference in NLR and PLR across the two ISR (+) and ISR (-) groups.

In the next step, we analyzed the interaction between each of inflammatory biomarkers and baseline cardiovascular risk factors as well as stent characteristics in the subgroups with ISR. As summarized in Table 3, the serum levels of ESR and CRP were significantly higher in smokers versus non-smokers, in diabetics versus non-diabetics, and also in those with chronic kidney disease as compared with those without kidney involvement.

Table 3: The interaction between inflammatory biomarkers and cardiovascular risk factors as well as stent parameters

Item	CRP	hs-CRP	ESR
Smoking			
Positive	9.12	6.14	19.45
Negative	7.09	4.00	15.45
P value	0.012	<0.001	0.007
Diabetes mellitus			
Positive	9.17	7.06	28.93
Negative	8.94	5.15	19.76
P value	0.040	<0.001	0.034
Chronic kidney dis.			
Positive	9.65	5.15	44.00
Negative	7.09	4.78	22.48
P value	0.010	0.020	0.048
Stent length			
<10mm	8.28	4.89	24.173
10-20 mm	9.14	5.27	27.4201
20-30 mm	9.54	5.88	29.0182
30-40 mm	10.91	6.93	33.0176
P value	<0.001	<0.001	<0.001
Stent diameter			
2 mm	10.42	6.30	28.01
2.5 mm	10.08	5.90	27.14
2.75 mm	9.82	5.70	25.00
3 mm	8.10	5.42	24.95
3.5 mm	8.00	5.31	23.08
4 mm	7.94	4.96	22.19
P value	<0.001	<0.001	<0.001
Type of stent			
DES	8.53	5.15	24.73
BMS	10.10	5.80	26.14
P value	0.024	0.012	0.036

Also, the levels of each inflammatory indices of ESR and CRP were positively associated with the length of stent and negatively associated with the diameter of stent. In addition, the levels of ESR ($p < 0.001$) and CRP ($p < 0.001$) were significantly higher in BMS than in DES stents.

Response to vascular injury is sourced from activation of systemic inflammatory cascades triggered by invasive coronary interventions. Following injury, two major cellular events including proliferation of arterial intimal tissue and synthesis of extracellular matrix via activation of inflammatory mediators can provide the background for re-stenosis. However, the mediatory role of inflammatory mediators in induction and progression of ISR remains uncertain. Our findings could effectively show higher levels of both ESR and CRP biomarkers as the main arms of inflammatory responses and it can be judged that pre-procedural ESR and CRP levels could be accompanied by greater risk for ISR. Of course, in another analysis, we could also find the interactive effective of underlying cardiovascular risk factors including smoking, diabetes mellitus and chronic renal failure and in fact, it can be concluded that the inflammatory response can be intensified by such risk profiles.

With regard to the predictive role of CRP for ISR, some recent meta-analyses attempted to test its predictive power. As shown by Li et al. [6], by reviewing nine prospective observational studies, it was found that CRP level was higher in patients who experienced ISR as compared with those without ISR; however, significant heterogeneity across the studies was highlighted. hs-CRP has a central role in progression of arterial atherosclerosis and even can effectively predict cardiovascular and cerebrovascular events in the future. In other words, according to

histological studies, the post-procedural raising this marker indicates vascular inflammatory response followed by atheromatous plaques instability and hypercoagulative status. However, according to the present results, assessing its value preoperatively can also predict ISR successfully and thus can be applied as a predicting factor for such life-threatening event. In total, post-stenting assessment of CRP level can help to early predict ISR and hence it's preventing. Regarding the role of ESR for predicting ISR, fewer studies have focused on this suggestion, but according to our observation, this marker can also powerfully predict ISR. Most studies have focused on the role of ESR in progressing arterial stenosis. As shown by Puz et al. [7], patients with internal carotid artery stenosis had significantly higher serum concentrations of ESR and CRP values than the individuals from the control group. In a study by Kang et al. [8], stent stenosis was in parallel with raising ESR and removing the stenosis was associated with reaching the level of this marker to normal range. But, the role of ESR in ISR has been refused by some other authors. As contrarily indicated by Cho et al. [9], there was no difference in the level of ESR between ISR and non-ISR subgroups. Therefore, in order to demonstrate its value for predicting ISR as well as its interaction with other cardiovascular risk profiles, we need to perform further studies.

Researchers at the Cedars-Sinai Medical Center in the United States focused on "Children's Multisystem Inflammatory Syndrome" (MIS-C), in which an inflammatory response affects several organs. This condition can occur weeks after getting Covid-19. Although most patients get better with medication, more than half of people with pediatric multisystem inflammatory syndrome in the United States are admitted to the intensive care unit, and their condition can be fatal. As of August 15, a total of 4,404 cases of pediatric multisystem inflammatory syndrome and 37 deaths have been reported. The report shows that the average age of patients was 9 years, and more than 60% of them were black or Latino children. According to reports of children with Covid-19 being admitted to the United States and many students returning to school in the fall, our understanding of the case of pediatric multisystem inflammatory syndrome is very important. The adverse effects of pediatric multisystem inflammatory syndrome, especially given race and ethnicity, are worrying. The researchers have looked at a small group of patients to identify a set of pathogenic pathways in pediatric multisystem inflammatory syndrome, as well as to identify proteins in the blood that act as biomarkers to predict the severity of the syndrome and help make treatment decisions. He continued: "The picture of pediatric multisystem inflammatory syndrome appears as an autoimmune disease in which the immune system is overactive and mistakenly attacks the organs of the body." This process may be due to extensive damage to the tissue caused by Covid-19. Children with multisystem inflammatory syndrome usually experience symptoms similar to those of a "cytokine storm," [38], which is an inflammatory reaction in patients with Covid-19 and can be fatal. These symptoms may include persistent fever and gastrointestinal, respiratory, neurological, and cardiovascular problems, including shock and inflammation of the heart muscle [39, 40], Studies by Arditi et al. (2018) show biological processes involved in pediatric multisystem inflammatory syndrome, cytokine storm, and toxic shock syndrome. Toxic shock syndrome is a rare complication of life-threatening bacterial infections. In their new study, the research team took an interdisciplinary approach and collaborated with experts from the Siders-Signai Institute and five other institutes. "We used a set of advanced techniques such as proteomics, arane sequencing, antibody analysis and immune signaling," said Van Eyk, one of the project's researchers. By combining forces, we can accelerate scientific discoveries to keep pace with the rapidly evolving Covid-19 epidemic and help raise awareness of clinical decisions. The researchers noted that their research was limited by their small scale. They looked at 69 children with and without multiple sclerosis, as well as seven children with another inflammatory disorder called Kawasaki syndrome.

Conclusion

In-Stent Restenosis after vascular interventions is the main limitation of its long-term success. Despite advances made in recent years to reduce restenosis, this problem remains a clinical challenge. As the final conclusion, both inflammatory biomarkers of ESR and CRP can predict the risk for ISR in patients initially undergoing coronary stenting. It seems that such a role can be intensified by the presence of cardiovascular risk factors especially smoking, diabetes mellitus, and chronic renal failure.

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Authors' contributions

All authors contributed toward data analysis, drafting and revising the paper and agreed to be responsible for all the aspects of this work.

Conflict of Interest

We have no conflicts of interest to disclose.

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