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BIOMARKERS IN VASCULAR SURGERY: PREDICTING GRAFT FAILURE AND RESTENOSIS

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ABSTRACT

Vascular diseases are a major source of global morbidity and mortality, often requiring surgical intervention, but the long-term outcomes are frequently compromised by complications like graft failure and restenosis. Since traditional imaging methods often detect these issues only at an advanced stage, there is a critical need for more precise and earlier risk prediction tools. This comprehensive narrative review synthesizes existing literature on the predictive value of circulating and tissue-based biomarkers for these adverse outcomes.

The study systematically examined major electronic databases including PubMed, Scopus, and Web of Science, utilizing keywords related to vascular surgery, outcomes (e.g., graft failure, restenosis), and biomarkers. The identified biomarkers were categorized into four principal groups: inflammatory, lipid-related, genetic, and novel/emerging markers.

The review found that elevated levels of inflammatory markers—such as high-sensitivity C-reactive protein (hs-CRP) and various interleukins (IL-6, IL-1β, TNF-α, IL-18, IL-33)—are strongly associated with an increased risk of graft failure and restenosis. Conversely, anti-inflammatory interleukins like IL-10 and IL-19 were found to correlate with a reduced risk. Furthermore, an unfavorable lipid profile (high LDL, low HDL, or an elevated LDL/HDL ratio) was consistently linked to a higher incidence of these complications. The review also highlights the promising potential of genetic markers, such as specific single nucleotide polymorphisms (SNPs), and novel biomarkers like non-coding RNAs in developing personalized treatment strategies.

The findings suggest that incorporating biomarker panels into routine clinical practice could significantly enhance preoperative risk stratification, enabling tailored perioperative therapy and more effective postoperative surveillance. By allowing for the early detection of biological evidence of graft compromise, this precision-medicine model has the potential to substantially improve long-term patient outcomes in vascular surgery.

KEYWORDS

Biomarkers, Vascular Surgery, Peripheral Artery Disease (PAD), Inflammatory Markers, Vascular Graft Failure, C-Reactive Protein (CRP)

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Introduction.

The leading cause of global morbidity and mortality, vascular diseases such as peripheral artery disease and aneurysms, represent a significant challenge for modern medicine. A strong association exists between traditional cardiovascular risk factors, such as advanced age, smoking, and diabetes, and an increased risk of vascular diseases(Aday & Matsushita, 2021). Surgical intervention is often necessary for these conditions, with procedures such as bypass grafting being crucial for restoring proper blood flow and enhancing patient quality of life. The long-term outcomes of these interventions are frequently compromised by serious complications, even with substantial advances in surgical techniques and postoperative care(Jawitz et al., 2020).

These complications, namely graft failure and restenosis (the re-narrowing of the vessel), are a significant clinical problem following vascular procedures because they lead to the need for reinterventions, increase patient morbidity, and enhance healthcare costs(Jones et al., 2013). The detection of these problems at an advanced stage by traditional postoperative monitoring methods, which rely on imaging studies, highlights the urgent need to develop more precise and earlier risk prediction methods(Lane et al., 2011).

Circulating or tissue-based biomarkers, which reflect inflammatory processes, tissue remodeling, and endothelial dysfunction, are hypothesized to be a valuable tool for the early identification of high-risk patients, thereby allowing the non-invasive monitoring and prediction of biological mechanisms leading to graft failure and restenosis(Parolari et al., 2015). We estimated these markers by dividing them into sub-categories, such as inflammatory markers, lipid-related markers, genetic markers, novel and emerging biomarkers.

To categorize, review, and synthesize current knowledge on biomarkers in vascular surgery, this article not only summarizes existing discoveries but also indicates potential directions for future research. This could contribute to the development of personalized treatment strategies and the improvement of long-term outcomes.

Methodology:

This article is a comprehensive narrative synthesis of existing literature on the role of biomarkers in predicting graft failure and restenosis in vascular surgery. The methodology involves a systematic search and review process to identify, analyze, and synthesize relevant studies. A systematic literature search was conducted across major electronic databases, including PubMed, Scopus, and Web of Science. The search was performed using a combination of keywords and Medical Subject Headings (MeSH) terms to ensure a broad and inclusive retrieval of relevant studies. The search terms were grouped as follows:

Group 1 (Vascular Surgery): "vascular surgery," "bypass grafting," "endovascular," "graft patency," "arterial bypass."

Group 2 (Outcomes): "graft failure," "restenosis," "reocclusion," "neointimal hyperplasia," "limb salvage," "patency rate."

Group 3 (Biomarkers): "biomarker," "serum marker," "genetic marker," "inflammatory marker," "oxidative stress," "circulating marker," "microRNA."

The search strategy combined terms from each group using Boolean operators (AND, OR) to identify articles that discussed biomarkers in the context of vascular surgery outcomes. The search was limited to articles published in English, with no date restrictions applied to capture a complete historical perspective on the topic. The synthesis of the extracted data was performed through a narrative approach. The identified biomarkers were categorized into distinct groups to provide a structured overview. Within each category, the physiological role of the biomarkers and their reported associations with vascular surgery outcomes were discussed. This method facilitated a qualitative summary of the evidence, highlighting key findings, consensus points, and areas of ongoing debate and future research.

Key Biomarker Categories:

1. Inflammatory Markers

C-reactive protein (CRP)

CRP is the most widely utilized marker of inflammation. It is consistently observed among studies that CRP levels are elevated immediately after surgical intervention, with a peak at one week and a gradual decrease until one month post-surgery(Wahlgren et al., 2006). However, evidence indicates that patients who experience restenosis do not reach pre-operative levels of CRP, suggesting its correlation with a higher risk of adverse effects after surgery, such as restenosis(Lian et al., 2021).

A 2021 meta-analysis by Di et al. demonstrated an approximately 10% increased risk of adverse effects in patients with higher baseline CRP. This study defined adverse effects as: restenosis, target vessel revascularization, disease progression, reintervention, amputation, or a combination of those(Di et al., 2021).

Additionally, a 2020 study by Guo et al. explored the connection between high-sensitivity CRP (hs-CRP) and restenosis at 6 months. While baseline hs-CRP does not indicate a risk of restenosis, a 24-hour post-interventional level is an independent risk factor for restenosis(Guo et al., 2020).

An emerging area of research is the CRP-albumin ratio (CAR), which is slowly gaining popularity as a more sensitive marker of inflammation and in-stent restenosis. In their 2020 study, Calik et al. suggested a CAR value greater than 0.29 as an optimal threshold for predicting restenosis. CAR seems to be an effective and easily available marker of systemic inflammation (CRP as a positive acute phase reactant and albumin as a negative)(Calik et al., 2020).

Interleukins

The role of interleukins as a significant factor in both atherosclerosis and restenosis has garnered considerable attention over the years.

IL-1 beta

A 1995 in vitro study by Wang et al. established a link between IL-1-beta and the inflammatory response leading to atherosclerosis(Wang et al., 1995). Subsequently, Shimokawa et al. conducted an animal study, discovering a stenosis in the coronary arteries exposed to IL-1 beta(Shimokawa et al., 1996). Another animal

study by Chamberlain et al. uncovered an elevation of IL-1 beta levels following percutaneous transluminal coronary angioplasty (PTCA)(Chamberlain et al., 1999).

In his editorial, Oemar concluded that, in combination, these results may suggest that IL-1 beta may be a potential marker of restenosis(Oemar, 1999). However, the impact of IL-1 on restenosis is severely understudied.

Additionally, the CANTOS study proved that Canakinumab, an anti-IL-1 beta antibody, can significantly lower the rate of recurrent cardiovascular events(Ridker et al., 2017), making IL-1 beta not only a potential marker but also an already effective therapy target.

IL-6

Another proinflammatory cytokine, crucial in the restenosis process, is IL-6. It is a pleiotropic interleukin linked to the generation of acute-phase proteins, inflammation, antigen-specific immune responses, hematopoiesis, apoptosis, differentiation, and cellular metabolism(Uciechowski & Dempke, 2020).

An experiment conducted by Guo et al. indicates that both baseline and 24-hour postinterventional IL-6 levels are indicators of restenosis at six months (Guo et al., 2020).

IL-6 serves as a particularly valuable biomarker, as its levels can be easily accessed by clinicians, in contrast to many other cytokines.

Furthermore, case studies reported promising effects of an anti-IL-6 receptor antibody (Tocilizumab) in reducing the risk of restenosis in both coronary and peripheral arteries. (Leal et al., 2023; Takasaki et al., 2023).

IL-18

The results corroborate earlier research by Maffia et al., which utilized an animal model to demonstrate a significant rise in IL-18 activity following vascular injury (specifically, balloon embolectomy of the carotid artery) and subsequent neointimal proliferation. Moreover, neutralizing IL-18 resulted in diminished cell proliferation(Maffia et al., 2006), indicating promising directions for future therapeutic interventions.

IL-33

IL-33, another pro-inflammatory interleukin, has been proven to promote vascular restenosis. In a 2021 animal study, Zeng et al. induced a carotid artery injury in rats and measured IL-33 levels on days 3, 14, and 21. Compared to the placebo group (sham-operated rats), rats with carotid artery injury exhibited a higher level of IL-33. Furthermore, examination of the injured vessels showed significant narrowing, which was significantly improved by subsequent anti-IL-33 treatment(Zeng et al., 2021).

These animal model findings confirmed the 2014 Demyanets et al. results. In the study, two blood samples were drawn from patients undergoing PCI (before and 24 hours post-procedure). Patients with restenosis showed a significant increase in IL-33 upon PCI(Demyanets et al., 2014).

To our knowledge, there are presently no studies examining the role of IL-33 in vascular restenosis within peripheral arteries in humans.

Anti-inflammatory interleukins

On the contrary, anti-inflammatory interleukins like IL-10 and IL-19 are negative markers of vascular inflammation(Autieri, 2018; England & Autieri, 2012), making them potential markers and therapeutic targets for future studies. Furthermore, previously mentioned Jiang et al. research found that IL-10 higher baseline is associated with a lower risk of restenosis in patients undergoing PCI (Jiang et al., 2015).

Tumor Necrosis Factor Alpha

Scientists have extensively investigated the relationship between tumor necrosis factor alpha (TNF-alpha) and restenosis using animal models. In a 2014 study conducted by Liang et al., researchers performed carotid endarterectomy on rabbits and subsequently monitored TNF-alpha levels and instances of restenosis. They found that animals experiencing restenosis showed significantly elevated levels of TNF-alpha after the intervention (Liang et al., 2014).

In a separate 2007 study, Böse et al. examined patients undergoing stent implantation in saphenous vein aortocoronary bypass grafts. They discovered a correlation between the TNF-alpha levels measured immediately after stent implantation and the rate of restenosis observed at the five-month mark (Böse et al., 2007).

However, the findings regarding TNF-alpha and restenosis were not corroborated in patients with PAD. A 2007 study conducted by Wildgruber et al. on 32 patients with PAD found no correlation between TNF-

alpha and restenosis (Wildgruber et al., 2007). A subsequent study in 2015 by Araujo et al. reaffirmed these results; however, it's important to interpret these findings cautiously, as this research involved a relatively small sample size of just 26 patients (Araújo et al., 2015).

2. Lipid-related Markers

The lipid profile significantly impacts overall cardiovascular health. This section seeks to summarize the current understanding of the relationship between the lipid profile and vascular restenosis, while also presenting newly emerging biomarkers in this field.

High-Density Lipoprotein Cholesterol (HDL-C)

In recent years, high levels of HDL-C have been proven to lower the risk of restenosis and graft failure in many vascular beds, including cerebral, lower extremity, and coronary(Ding et al., 2021; Ryu et al., 2023; Zhu et al., 2014).

A study by Zhu et al. in 2013 established a relationship between low HDL-C levels and the failure of coronary grafts (both arterial and venous). Their findings indicated that a one standard deviation (1 SD) increase in HDL-C was associated with a significant 20.5% decrease in the risk of graft failure. Additionally, they reported that LDL-C (low-density lipoprotein cholesterol) and total cholesterol are also indicators of venous coronary graft failure. Specifically, a one-unit increase in the LDL-C to high-density lipoprotein cholesterol (HDL-C) ratio resulted in a 43% higher risk of graft failure. Similarly, a one-unit increase in the total cholesterol to HDL-C ratio correlates with a 46% increased risk of graft failure. However, the results of the arterial graft patients did not mimic those of the venous graft patients (Zhu et al., 2014).

Corresponding results were presented by Ryu et al. in a 2023 paper regarding restenosis in patients with intracranial stents. The study revealed that an improvement in the LDL-C to HDL-C ratio, characterized by a significant decrease at 12 months post-procedure, was associated with a reduced risk of restenosis. Likewise, elevated levels of HDL-C over the 12 months also correlated with a reduction in the incidence of restenosis (Ryu et al., 2023).

An emerging marker in coronary restenosis is the monocyte-to-HDL ratio (MHR). Numerous studies showed that increased MHR correlates with restenosis (Ucar, 2016). In their 2016 study, Tok et al. found that pre-operative MHR over 14 had 71% sensitivity and 69% sensitivity in predicting bare metal stent restenosis (Tok et al., 2016). In subsequent years, evidence has emerged indicating that MHR significantly increases the risk of restenosis in patients with drug-eluting stents (DES) (Meng et al., 2024; Nan et al., 2020). However, to our knowledge, there have been no studies investigating the role of MHR in PAD.

Low-Density Lipoprotein (LDL) Oxidation

In 2005, Hinagata et al. conducted an animal study, injuring a common carotid artery in rats. Subsequent analysis demonstrated that neointimal hyperplasia was induced by the LOX-1 receptor, identified as an endothelial receptor for oxidized LDL (Hinagata et al., 2006). The findings from Segev et al. did not support those results. In their 2005 paper, they reported no significant difference in oxidized LDL levels—measured at 6 hours, 24 hours, 3 days, 7 days, and 1, 3, and 6 months—between patients undergoing PCI with and without restenosis (Segev et al., 2005). However, a 2006 study by Naruko et al. found that a significantly higher number of patients with elevated oxidized LDL levels at discharge experienced restenosis six months later(Naruko et al., 2006). This subject requires further analysis, including patients with PAD.

Lipoprotein (a)

Lipoprotein (a) (Lp(a)) is a marker of coronary restenosis after PCI (Qin et al., 2013), (Wu et al., 2025). However, the available data on the impact of Lp(a) on PAD regarding graft patency and restenosis is limited and inconsistent. In their 2020 paper, Golledge et al. found that participants with high serum Lp(a) were more likely to require lower limb peripheral revascularization; however, they found no association with other major cardiovascular events such as myocardial infarction, stroke, or cardiovascular death(Golledge et al., 2020).

A 2022 study by Zierfuss et al. supported Golledge's findings, indicating that there was no link between elevated Lp(a) levels and mortality in patients with PAD. This study tracked patients over five years post-revascularization, leading the authors to suggest that a longer observation timeframe could potentially yield different results(Zierfuss et al., 2022). Conversely, Marques et al. found no association of Lp(a) with restenosis after carotid endarterectomy(Marques et al., 2025). Further research is necessary to determine whether Lp(a) can serve as a useful tool for predicting adverse outcomes after PAD procedures.

3. Genetic Markers

The impact of gene polymorphism on restenosis and graft failure is understudied. Among various vascular conditions, coronary restenosis has received the most research attention. Verschuren et al. examined SNPs to determine which of them are markers of coronary restenosis after PCI; the final six included: angiotensin II receptor type 1 (AGTR), glutathione peroxidase 1 (GPX1), acetyltransferase 2B (KAT2B), matrix metallopeptidase 12 (MMP12), fibrinogen beta chain (FGB), and vitamin D receptor (VDR)(Verschuren et al., 2012).

A 2016 study by Ming et al. examined the association between heme oxygenase-1 (HO-1) gene polymorphisms and restenosis following PCI. This study found a link between allele S of the HO-1 gene and a reduced risk of restenosis compared with allele L carriers. Furthermore, in the Asian population, the risk of restenosis was significantly lower among individuals with genotype SS(Zhang et al., 2016). SNPs may lead to more personalized treatment of cardiovascular diseases; further study, including patients with PAD, is necessary.

4. Novel and Emerging Biomarkers

Non-coding RNAs

Emerging markers of restenosis in both coronary and peripheral vascular systems include noncoding RNAs, such as microRNA, long noncoding RNA, small interfering RNA, circular RNA, and piwi-interacting RNA(Liu et al., 2018). The most extensive research has been conducted on microRNAs, revealing numerous molecules that either promote or inhibit restenosis(Efovi & Xiao, 2022; Gareri et al., 2016; Varela et al., 2019). Those particles, in response to injury, promote proliferation, apoptosis, migration, and differentiation of vascular smooth cells and endothelial cells(Gareri et al., 2016; Indolfi et al., 2019). While presenting each particle is beyond the scope of this study, we would like to draw attention to this new, emerging marker.

Discussion – clinical applications and future directions:

These biomarkers can assist in preoperative risk stratification by characterizing patients with an underlying pro-inflammatory or pro-atherogenic phenotype who will be at higher risk of graft failure or restenosis after vascular surgery. Higher levels of systemic inflammatory markers such as hs-CRP, IL-6, IL-1β, TNF-α, and occasionally IL-18 or IL-33 show an immune-activated status that promotes endothelial dysfunction, vascular smooth muscle cell proliferation, and neointimal hyperplasia—processes with direct correlation to restenosis and graft occlusion(Hiramoto et al., 2012; Owens et al., 2007; Yi et al., 2013). Conversely, a low concentration of the anti-inflammatory cytokine IL-10 would reflect a reduced capacity to counterbalance these deleterious responses(Ho et al., 2008), once more tending towards a poor outcome.

At the same time, an unfavorable lipid profile—elevated LDL cholesterol, reduced HDL cholesterol, or elevated LDL/HDL ratio results in accelerated atherosclerotic remodeling of the graft(Ghali et al., 2010). Their preoperative measurement allows clinicians to recognize patients at higher risk, especially when analyzed in combination with traditional predictors such as age, diabetes, current smoking status, and conduit type employed (Ridker et al., 1997) High-risk patients can be optimized by vigorous medical management, such as aggressive lipid lowering, stringent glycemic control, and selective anti-inflammatory interventions, combined with enhanced postoperative surveillance to detect early signs of graft dysfunction(Ghali et al., 2010).

Even though no single biomarker is adequate for decision-making by itself, their combination in a multivariable model can significantly augment preoperative risk stratification and aid in individualizing both intraoperative management and postoperative care(Owens et al., 2007; Yi et al., 2013). The incorporation of a biomarker panel into vascular surgical practice presents an opportunity to tailor perioperative therapy, optimizing results beyond the predictive value of standard risk factors.

A preoperative inflammatory profile with elevated IL-6, IL-1β, TNF-α, and hs-CRP (Owens et al., 2007; Yi et al., 2013) may indicate the need for enhanced anti-inflammatory modulation and early initiation or intensification of statins, given their pleiotropic effects on both lipid lowering and inflammation(Ghali et al., 2010). Patients with high LDL cholesterol and low HDL cholesterol may particularly benefit from aggressive statin therapy, possibly in combination with ezetimibe or PCSK9 inhibitors, to reduce neointimal hyperplasia and graft atherosclerosis(Hiramoto et al., 2012).

Beyond lipid reduction, biomarker-stratified antiplatelet therapy is a promising approach. Elevation of IL-18, IL-33, or hs-CRP on the day after surgery may reflect continued endothelial activation and platelet reactivity, warranting more aggressive platelet inhibition protocols or dual antiplatelet therapy in selected individuals, balanced with bleeding risk. Conversely, individuals with increased baseline IL-10 or IL-19 may

have an improved vascular healing profile, allowing for a less aggressive antiplatelet regimen without compromising graft patency(Ho et al., 2008).

Follow-up surveillance of the biomarker panel enables fine-tuning of management. Rising CRP or pro-inflammatory interleukins during follow-up can trigger early imaging or intensification of therapy, while stable or improving biomarker signatures can justify safe de-escalation of therapy. Ultimately, integration of biochemical signals with patient-specific clinical factors could lead to dynamic, adaptive treatment protocols, transforming vascular surgery from a one-size-fits-all model to a precision-medicine(Schillinger & Minar, 2005; Wang et al., 2019).

Serial measurement of inflammatory and lipid biomarkers after vascular surgery provides a non-invasive method to detect early biological evidence of graft compromise before the onset of clinical symptoms. Persistently elevated or rising levels of hs-CRP, IL-6, and TNF-α in the early postoperative period have been associated with ongoing endothelial injury and neointimal proliferation, both of which precede radiographic evidence of restenosis(Owens et al., 2007; Yi et al., 2013). Similarly, postoperative peaks in IL-18 and IL-33 can indicate sustained immune activation and heightened vascular smooth muscle cell proliferation, mechanisms implicated in accelerated graft narrowing(Ho et al., 2008). In contrast, stable or rising anti-inflammatory mediators such as IL-10 can reflect favorable vessel wall remodeling and reduced risk of early graft occlusion(Hiramoto et al., 2012).

Lipid profiles also retain predictive value during the surveillance period. An increasing LDL cholesterol level or a decrease in HDL cholesterol despite treatment may indicate poor lipid control, creating a milieu favorable for atherogenesis within the graft(Ghali et al., 2010). Incorporating these biomarker trajectories into surveillance protocols can enable risk-stratified imaging schedules—patients with concerning biomarker trends may undergo earlier duplex ultrasound or CT angiography, whereas those with stable or improving profiles can follow standard intervals. This approach optimizes resource use and increases the potential for detecting subclinical graft failure at a reversible stage, reducing the need for emergency reinterventions and lowering the risk of limb loss.

Despite their promise, several limitations and challenges hinder the routine use of biomarker panels in vascular surgery. A major barrier is the absence of standardized protocols for measuring inflammatory cytokines and lipid subfractions. Variability in assay sensitivity, specimen handling, and timing of collection can yield inconsistent results, complicating inter-study comparisons and clinical application (Hiramoto et al., 2012; Owens et al., 2007). Furthermore, many reported associations between biomarkers such as hs-CRP, IL-6, or IL-18 and graft outcomes are based on relatively small, single-center cohorts, limiting generalizability and reproducibility(Yi et al., 2013). Large multicenter validation trials remain necessary before these biomarkers can be integrated into formal risk models or treatment algorithms.

Biological complexity also complicates interpretation. Inflammatory and lipid biomarkers are not specific to vascular graft pathology—they can be influenced by infection, systemic inflammatory diseases, or metabolic (Ho et al., 2008; Ridker et al., 1997). This nonspecificity may lead to unnecessary investigations or overtreatment if results are not interpreted in the appropriate clinical context.

Economic considerations present further challenges. Comprehensive biomarker panels, especially those including less common interleukins such as IL-33 or IL-19, can be costly to perform repeatedly during the perioperative period. Without clear cost-effectiveness data showing improved outcomes at reasonable expense, widespread adoption may be difficult to justify(Zeng et al., 2021). Finally, regulatory and logistical obstacles remain - each novel biomarker assay must undergo rigorous analytical validation and demonstrate clinical utility before being incorporated into guidelines. Addressing these limitations will require coordinated efforts between researchers, clinicians, and policymakers to translate biomarker-guided vascular surgery from research to standard practice(Elsaka, 2024).

Conclusions

Application of biomarkers in vascular surgery, particularly in the prognosis of transplant failure and restenosis, is a future direction in the development of personalized medicine. Research indicates that inflammatory biomarkers such as hs-CRP, IL-6, IL-1β, TNF-α, IL-18, and IL-33 are connected with poor outcomes following vascular surgery. Lipid-associated biomarkers, such as the ratio of LDL-C to HDL-C, are connected with poor outcomes. By contrast, anti-inflammatory interleukins such as IL-10 and IL-19 might indicate healthful processes in the vessel wall.

While these promising findings exist, routine clinical application of biomarker panels is slowed by a variety of complications. The most significant of these may be the absence of standardized endpoints, which

generates variable data and makes study comparison difficult. Furthermore, with few exceptions, studies have utilized small cohorts within one center, which limits the results' external validity. The non-specificity of biological is also a concern because other states of disease, including infection, will affect biomarker concentrations, requiring results to be interpreted in the appropriate clinical context.

To advance this discipline, future endeavours must be aimed at conducting large, multicenter validation studies to determine the utility of such biomarkers, especially in peripheral artery disease (PAD) patients. Overcoming these obstacles, namely economic and regulatory hurdles, will be important to advancing beyond standard treatment modalities and embracing individualized therapies that optimize outcomes and improve postoperative care.

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