Advances in Clinical Medicine 临床医学进展, 2024, 14(2), 3142-3149
Published Online February 2024 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2024.142445

Hans汉斯

系统性免疫炎症指数与动脉粥样硬化的相关性研究进展

尼格尔·艾白都拉，郑颖颖*

新疆医科大学第一附属医院心力衰竭科，新疆 乌鲁木齐

收稿日期：2024年1月21日；录用日期：2024年2月14日；发布日期：2024年2月21日

摘　要

近年来，心脑血管疾病的发生率呈持续升高趋势，成为中国人口死亡的重要原因。动脉粥样硬化作为心脑血管疾病的病理生理基础，加强对于动脉粥样硬化的防治对于降低心脑血管疾病的发病率有重要的意义。炎症在动脉粥样硬化发生发展过程中起着关键作用，系统性免疫炎症指数是一种新型的炎症预测指标，越来越多的研究发现，系统性免疫炎症指数与全身各大动脉粥样硬化的发生有相关性，本文对系统性免疫炎症指数与动脉粥样硬化的相关性进行综述，为动脉粥样硬化的防治提供新思路。

关键词

动脉粥样硬化，炎症，系统性免疫炎症指数

Research Progress on the Correlation between Systemic Immune Inflammation Index and Atherosclerosis

Nigeer Aibaidula, Yingying Zheng*

Heart Failure Department, The First Affiliated Hospital of Xinjiang Medical University, Urumqi Xinjiang

Received: Jan. 21st, 2024; accepted: Feb. 14th, 2024; published: Feb. 21st, 2024

Abstract

In recent years, the incidence of cardiovascular and cerebrovascular diseases has been continuously increasing, becoming an important cause of death in the Chinese population. Atherosclerosis is the pathophysiological basis of cardiovascular and cerebrovascular diseases. Strengthen-

*通讯作者。

文章引用：尼格尔·艾白都拉，郑颖颖. 系统性免疫炎症指数与动脉粥样硬化的相关性研究进展[J]. 临床医学进展, 2024, 14(2): 3142-3149. DOI: 10.12677/acm.2024.142445

ing the prevention and treatment of atherosclerosis is of great significance for reducing the incidence rate of cardiovascular and cerebrovascular diseases. Inflammation plays a key role in the occurrence and development of atherosclerosis. Systemic immune inflammation index is a new type of inflammation prediction index. More and more studies have found that systemic immune inflammation index is related to the occurrence of atherosclerosis in the whole body. This article reviews the correlation between systemic immune inflammation index and atherosclerosis, providing new ideas for the prevention and treatment of atherosclerosis.

Keywords

Atherosclerosis, Inflammation, Systemic Immune Inflammation Index

1. 引言

随着人口老龄化和代谢危险因素的流行，心血管疾病(cardiovascular disease, CVD)的发病率和死亡率持续增加，成为中国人口死亡的首位原因[1]。脑血管病是导致中国人口死亡的另一主要疾病，中国因脑血管病死亡的人数约占全球脑血管病死亡的 1/3 [2]。心脑血管疾病是危害人类健康的严重疾病，在中国人疾病死亡构成比中占到 40%以上，其防治一直是我国医疗卫生保障事业的重点。随着我国人口老龄化的发展，CVD 和脑血管疾病的发病率呈显著增高的趋势，常相互伴发，互为因果。目前，心脑血管疾病的治疗理念已变为从循环系统改善心脑的供血和血管的危险因素，同时减轻心、脑的病理损害，即脑心同治[3]。动脉粥样硬化(atherosclerosis, AS)是心脑血管疾病的重要病理生理基础[4]，加强对于 AS 的防治对于降低心脑血管疾病发病率有着重要的意义。AS 的发病机制尚未明确，近年来，随着人们对 AS 研究的不断深入，认为炎症在 AS 中起着重要的作用[5]，系统性免疫炎症指数(systemic immune-inflammation index, SII)作为一种新型的炎症预测指标，是结合中性粒细胞、淋巴细胞及血小板的综合性指标，即 SII = 血小板计数 × 中性粒细胞计数/淋巴细胞计数。起初，SII 被认为与癌症具有相关性[6]。随后，在心血管疾病的研究中，有学者发现高 SII 值对冠状动脉粥样硬化斑块的进展、不良发展如慢性心力衰竭伴肾功能不全以及严重冠状动脉综合征的住院和长期病程构成负面的独立威胁[7] [8] [9]。这提示 SII 在心血管疾病中起到重要的预测作用，为我们研究炎症与心血管疾病的相关性提供了关键的理论依据，AS 作为心血管疾病的重要发病基础，其发生发展与炎症的相关性也得到了一定的验证，本文对 SII 与 AS 的相关性研究进展进行概述。

2. 中性粒细胞、淋巴细胞及血小板在动脉粥样硬化中的作用

2.1. 中性粒细胞促进动脉粥样硬化的形成

中性粒细胞是人类血液细胞中含量最丰富的白细胞，已被确定为急性炎症的第一反应者。在正常情况下，中性粒细胞通过吞噬坏死细胞来阻止它们吸引更多的免疫细胞，释放介质来促进生长和血管生成，并产生分解素和保护素，从而促进分解和组织修复[10]。越来越多的证据表明，中性粒细胞在一些慢性疾病中发挥着重要作用，如动脉粥样硬化、糖尿病、非酒精性脂肪肝和自身免疫性疾病[11]。在动脉粥样硬化患者中，中性粒细胞－血小板复合物会导致肿瘤坏死因子-α 和白细胞介素-1β 水平升高，促进中性粒细

胞的迁移和粘附[12]。中性粒细胞激活，即外周血白细胞中中性粒细胞弹性酶(neutrophil elastase, NE)和髓过氧化物酶(myeloperoxidase, MPO)的表达、NE 血清水平或 MPO 血浆水平，在肥胖和 2 型糖尿病(type 2 diabetes mellitus, T2DM)患者中比瘦人升高[13] [14] [15]。粒细胞集落刺激因子缺陷小鼠以高脂饮食喂养后，肝脏中性粒细胞和巨噬细胞浸润减少，缓解非酒精性脂肪肝的进展[16]。在银屑病小鼠模型中，通过输注抗 P-选择素粒细胞配体-1 抗体阻断中性粒细胞－血小板相互作用可减少咪喹莫特诱导的银屑病患者的耳厚[17]。其与动脉粥样硬化的相关性可能包括以下几方面：

中性粒细胞在动脉粥样硬化中起着关键作用，参与斑块破裂、再灌注损伤和斑块重塑[18]。其中，最主要的一种机制是中性粒细胞不断被招募到慢性炎症部位，并通过其丝氨酸蛋白酶的释放和中性粒细胞细胞外陷阱(NETs)的形成，以及其他免疫细胞的激活来推动这一过程。同时，中性粒细胞可以通过增加巨噬细胞和抗原水平来加强炎症反应；此外，中性粒细胞通过炎症介质的分泌参与急性组织损伤过程，主要通过释放前炎症细胞因子和氧自由基等活性分子触发炎症反应，还可能通过减少体内一氧化氮的利用而导致细胞内皮功能障碍以及动脉粥样硬化形成[19]。如，中性粒细胞释放花生四烯酸等生物活性物质激活炎症反应，通过氧化高密度脂蛋白胆固醇减少胆固醇的外排，导致斑块易损性增加[20]。研究发现[21]，在颈动脉粥样硬化患者中中性粒细胞计数、斑块易破裂的区域与斑块内微血管的密度呈正相关。由此表明，中性粒细胞增多可增加病变的不稳定性，并增加斑块破裂的风险。在机制上，中性粒细胞蛋白酶可以降解斑块纤维杯，并促进病变的不稳定[22]。

2.2. 淋巴细胞对动脉粥样硬化的作用

越来越多的研究表明，动脉粥样硬化是一种具有自身免疫成分的慢性炎症性疾病。淋巴细胞数量的增加被认为是动脉粥样硬化疾病的独立危险因素[23]，淋巴细胞数量的减少也被认为与风险的增加有关[24]，表明免疫系统在动脉粥样硬化的发展中的复杂作用[25]。低密度脂蛋白和载脂蛋白多肽似乎是最相关的自身抗原，它们既可以驱动动脉粥样硬化斑块中的自身免疫反应，又可以在疫苗接种状态下中具有抗动脉粥样硬化的作用[26]。

T 细胞在细胞免疫中起着关键作用，其种类包括 CD4+、CD8+、自然杀伤(NK) T 细胞和辅助 T 细胞等。大多数细胞因子是由 T 细胞分泌的。CD4+ T 细胞常见于动脉粥样硬化斑块中。大量证据表明，T 辅助性细胞 1 (TH1)具有促动脉粥样硬化的作用[26]，具体可能是通过 Th1 细胞释放 TNF-α 和 IFN-γ，发挥促动脉粥样硬化的作用[27]。而调节性 T 细胞(Treg)细胞具有抗动脉粥样硬化的作用[26]，可能的机制包括：抗炎细胞因子 TGF-β、IL-10 和 IL-35 对 Treg 细胞的抑制具有重要作用[28]。趋化因子(C-X3-C motif)受体-1 (CX3CR1)转导的-Treg 细胞的过继转移可改善对斑块的归巢，并抑制动脉粥样硬化的进展[29]。CD8+ Treg 细胞通过限制 Th1 细胞和巨噬细胞的增加，在晚期动脉粥样硬化中发挥保护作用[30]。其他 TH 细胞亚群如 TH2、TH9、TH17、TH22、滤泡辅助 T 细胞和 CD28-T 细胞以及其他 T 细胞包括 $\gamma\delta$T 细胞在内的 T 细胞亚群在动脉粥样硬化中的作用尚不清楚。此外，一些 T 细胞似乎同时具有致动脉粥样硬化和抗动脉粥样硬化的功能[26]。

B 细胞对动脉粥样硬化的影响已在许多研究中得到证实，B 细胞在动脉粥样硬化中发挥的作用与 B 细胞亚群有关。B1 细胞和边缘区 B 细胞被认为可以预防动脉粥样硬化，但滤泡 B 细胞和先天反应激活因子 B 细胞已被证明可以促进动脉粥样硬化。B 细胞的主要功能包括抗体产生、与抗原呈递 T 细胞相互作用和细胞因子的释放。所有这些功能都有可能通过多种方式影响动脉粥样硬化，并依赖于细胞环境和 B 细胞的激活状态[31]。

综上，不同的淋巴细胞亚群有不同的特性，T 细胞与 B 细胞在动脉粥样硬化中的作用仍需进一步研究。

2.3. 血小板对动脉粥样硬化的作用

有研究表明，血小板计数异常增高可释放大量炎性因子，从而对中性粒细胞等其他细胞产生刺激作用，并进一步促进炎性因子的大量分泌。血小板可被视为与白细胞结合的特异性炎症标志物，进而影响这些细胞参与炎性反应过程[32]。血小板是动脉粥样硬化炎症相关表现的中心。除了对免疫细胞浸润的影响外，血小板还通过清除受体修饰、结合和内吞低密度脂蛋白，促进巨噬细胞泡沫细胞的形成来调节胆固醇细胞的代谢[33]。血小板释放的血小板活化因子(PAF)可诱导整合素介导内皮细胞与白细胞或血小板之间的牢固粘附[34]。由活化血小板产生的血小板来源的细胞外囊泡(PEV)可触发动脉粥样硬化的起始[35]。消融血小板凋亡可减少糖尿病小鼠的动脉粥样硬化，通过阻止血小板－单核细胞的相互作用和随后的单核细胞活化，形成更稳定的斑块[36]。目前抗炎治疗的进展已经确定了血栓形成继发于血小板活化的炎症介质作用[37]。因此，血小板在动脉粥样硬化的发生发展中也起到了重要作用。

3. SII 与动脉粥样硬化

近期有学者提出了一种新型的预测指标，命名为系统免疫炎症指数(SII)。SII 利用中性粒细胞、淋巴细胞和血小板，能够更好地反映患者机体的炎症和免疫状态[38]。最初 SII 的风险预测能力在肿瘤学领域被证实，高水平 SII 与肺癌患者不良预后具有强相关性[39]，相对于中性粒细胞/淋巴细胞比率、血小板/淋巴细胞比率，具有更高的预测效能[40]。有研究显示[41]，SII 与冠心病(coronary artery disease, CAD)患者冠状动脉病变程度呈正相关，这提示 SII 可以在一定程度上可以作为动脉粥样硬化的预测因子。

3.1. SII 与颈动脉粥样硬化

颈动脉粥样硬化(carotid atherosclerosis, CAS)作为全身动脉粥样硬化中的一部分，临床常将其作为反映全身动脉粥样硬化性疾病形成和演变的指标[42]。炎症、氧化应激在 CAS 中具有核心作用，颈动脉病变常表现为颈动脉内膜－中层厚度(carotid intima-media thickness, CIMT)增厚和颈动脉粥样斑块。CIMT 与 CAD 的严重程度相关，对致死性和非致死性心血管不良事件具有预测价值。CIMT 增加与动脉斑块形成、冠状动脉粥样硬化程度及心脑血管疾病终点事件直接相关[43]。研究发现，SII 在高血压患者颈动脉内膜中层厚度较高的患者中显著升高，支持 SII 与高血压患者的亚临床动脉粥样硬化、内皮功能障碍以及由此导致的不良临床结局相关[44]。卒中在世界范围内具有显著的发病率和死亡率，颈动脉粥样硬化导致大约 10%~20%的缺血性中风[45]。SII 被认为是一种可以预测急性缺血性卒中患者预后不良的新指标[46]，为了预防卒中，高危患者一直在接受颈动脉支架植入术[47]。Shuji Morikawa 等[48]纳入 129 例接受颈动脉支架植入术的患者，根据他们的SII水平进行分类，调查了长期主要心脑血管不良事件(MACCE)、住院和长期卒中发生率，以及全因死亡，发现 SII 作为一种新颖的替代指标和综合性系统性炎症标志物，在接受颈动脉支架植入术患者的长期随访期间是卒中和主要心脑血管不良事件(major adverse cardiac and cerebrovascular events, MACCE)的独立预测因子。此外，SII 被发现是比 CRP 更有用的长期 MACCE 预测指标。Yi Yang 等[49]的研究显示，在大动脉粥样硬化引起的前循环急性缺血性脑卒中的中国患者中，尤其是动脉源性栓塞和原位血栓形成，其全身免疫炎症指数越高，发生出血转化的风险越大。综上，患者的常规血液检查可以为临床诊疗提供重要的预后信息，但该结论仍需更多的研究进一步论证。

3.2. SII 与冠状动脉粥样硬化

冠状动脉粥样硬化是动脉粥样硬化最常见的类型，也是 CAD 最主要的原因。冠状动脉粥样硬化会导致冠脉与心肌之间的血液供需失衡，当不能满足心肌的大量氧耗时，便会引起短暂的心绞痛甚至心肌梗死的发生。随着生活水平的提高，CAD 发病率逐年增长[50]，并有年轻化的趋势，因此，国内外学者对

于冠状动脉粥样硬化做了大量研究，炎症机制在冠状动脉粥样硬化中的作用也逐渐展露。国内的一项回顾性横断面研究连续纳入 6046 例 CAD 患者作为研究对象，收集临床资料及冠状动脉血管成像结果，Gensini 评分定量评估冠状动脉狭窄程度。根据 Gensini 评分三分位数分为：低值组(<11 分，2011 例)、中值组(11~38 分，2018 例)和高值组(>38 分，2017 例)，评估 SII 与 Gensini 评分的相关性，结果显示经控制性别等混杂因素后，CAD 患者的 SII 与 Gensini 评分呈显著独立正相关[41]。一项研究对接受冠状动脉造影和经皮冠状动脉介入治疗(PCI)的非 ST 段抬高型心肌梗死(NSTEMI)患者的全身免疫炎症指数(SII)与冠状动脉血栓负担的关系进行了探讨，结果显示 SII 评分的增加是接受 PCI 的 NSTEMI 患者大量冠状动脉血栓负担的独立预测因子。在一项纳入 5602 例慢性冠状动脉综合征 PCI 术后的队列研究中，高 SII (>694.3)可显著增加心源性死亡风险[51]。这些研究为日后 SII 作为预防心血管疾病筛查指标提供了重要循证学证据。

3.3. SII 与下肢动脉粥样硬化

下肢动脉硬化闭塞症(arteriosclerosis obliterans, ASO)是动脉粥样硬化最常见的表现之一，表现为下肢动脉狭窄或闭塞引发的缺血性病变。严重影响患者的生活质量及身体功能。近年来，受我国人口老龄化影响，ASO 的发病率持续上升，尤其在 70 岁及以上的老年人中高达 15%~20% [52]。这种疾病导致下肢血流减少，限制了腿部肌肉的能量和氧气供应，从而影响其功能和质量，进一步可能引发肌少症这种骨骼肌疾病[53] [54]。肌少症是一种进行性且全身性疾病，以肌肉质量和功能的快速丧失为特点，可能导致患者跌倒、肌肉功能下降及死亡[55]。聂璐等[56]的研究纳入 251 例 ASO 患者。依据第三腰椎腰大肌指数(PMI)将患者分为肌少症组和非肌少症组。并收集患者一般资料和血液指标，结果显示肌少症组 ASO 患者 SII 水平明显高于非肌少症组，SII 是 ASO 患者肌少症的独立危险因素。外周动脉疾病(peripheral arterial disease, PAD)的特点是在下肢动脉中存在动脉粥样硬化斑块。糖尿病(diabetes mellitus, DM)是 PAD 发生的关键危险因素，也是 PAD 患者下肢截肢和死亡的独立预测因子[57] [58] [59]。有证据表明，中性粒细胞与淋巴细胞比值(NLR)、血小板与淋巴细胞比值(PLR)可预测糖尿病患者并发症的发生[60] [61] [62]。除此之外，最近的一项研究显示，炎症标志物，如 NLR、单核细胞与淋巴细胞比值(MLR)、PLR 和 SII 在常规医疗实践中价格便宜且易于收集，可作为糖尿病多发神经病变患者亚临床动脉粥样硬化的预测因子，在 T2DM 患者和 PAD 患者的随访中发挥关键作用[63]。

4. 结论

综上，SII 评估动脉粥样硬化的价值是值得肯定的，且 SII 易从入院常规检查中获得，具有经济、有效的特点，有助于潜在动脉粥样硬化患者的筛查，其在临床上的应用具有相当广阔的前景。但是目前开展的相关研究中纳入的样本量有限，且人群特点各不相同，其结论仍需在多中心大规模的临床研究中进一步验证。

参考文献

[1] 马丽媛, 王增武, 樊静, 胡盛寿. 《中国心血管健康与疾病报告 2021》关于中国高血压流行和防治现状[J]. 中国全科医学, 2022, 25(30): 3715-3720.

[2] 中国心血管健康与疾病报告(2019)节选二: 脑血管病[J]. 心脑血管病防治, 2020, 20(6): 544-552.

[3] 心脑血管疾病的防治进入脑心同治时代[J]. 中华医学信息导报, 2022, 37(14): 17.

[4] Berry, J.D., Liu, K., Folsom, A.R., Lewis, C.E., Carr, J.J., Polak, J.F., Shea, S., Sidney, S., O'Leary, D.H., Chan, C. and Lloyd-Jones, D.M. (2009) Prevalence and Progression of Subclinical Atherosclerosis in Younger Adults with Low Short-Term but High Lifetime Estimated Risk for Cardiovascular Disease: The Coronary Artery Risk Development in Young Adults Study and Multi-Ethnic Study of Atherosclerosis. *Circulation*, **119**, 382-389.

https://doi.org/10.1161/CIRCULATIONAHA.108.800235

[5] Libby, P., Ridker, P.M. and Hansson, G.K., Leducq Transatlantic Network on Atherothrombosis (2009) Inflammation in Atherosclerosis: From Pathophysiology to Practice. *Journal of the American College of Cardiology*, **54**, 2129-2138. https://doi.org/10.1016/j.jacc.2009.09.009

[6] Nøst, T.H., Alcala, K., Urbarova, I., Byrne, K.S., Guida, F., Sandanger, T.M. and Johansson, M. (2021) Systemic Inflammation Markers and Cancer Incidence in the UK Biobank. *European Journal of Epidemiology*, **36**, 841-848. https://doi.org/10.1007/s10654-021-00752-6

[7] Candemir, M., Kiziltunç, E., Nurkoç, S. and Şahinarslan, A. (2021) Relationship between Systemic Immune-Inflammation Index (SII) and the Severity of Stable Coronary Artery Disease. *Angiology*, **72**, 575-581. https://doi.org/10.1177/0003319720987743

[8] Wang, Z., Qin, Z., Yuan, R., Guo, J., Xu, S., Lv, Y., Xu, Y., Lu, Y., Gao, J., Yu, F., Tang, L., Zhang, L., Bai, J., Cui, X., Zhang, J. and Tang, J. (2023) Systemic Immune-Inflammation Index as a Prognostic Marker for Advanced Chronic Heart Failure with Renal Dysfunction. *ESC Heart Failure Journal*, **10**, 478-491. https://doi.org/10.1002/ehf2.14217

[9] Altunova, M., Karakayalı, M., Kahraman, S., Avcı, Y., Demirci, G., Sevinç, S., Yazan, S., Şahin, A. and Ertürk, M. (2023) Systemic Immune-Inflammatory Index Is Associated with Residual SYNTAX Score in Patients with ST-Segment Elevation Myocardial Infarction. *The Anatolian Journal of Cardiology*, **27**, 472-478. https://doi.org/10.14744/AnatolJCardiol.2023.3074

[10] Xiao, Y., Cheng, Y., Liu, W.J., Liu, K., Wang, Y., Xu, F., Wang, D.M. and Yang, Y. (2023) Effects of Neutrophil Fate on Inflammation. *Inflammation Research*, **72**, 2237-2248. https://doi.org/10.1007/s00011-023-01811-2

[11] Herrero-Cervera, A., Soehnlein, O. and Kenne, E. (2022) Neutrophils in Chronic Inflammatory Diseases. *Cellular & Molecular Immunology*, **19**, 177-191. https://doi.org/10.1038/s41423-021-00832-3

[12] Liang, X., Xiu, C., Liu, M., Lin, C., Chen, H., Bao, R., Yang, S. and Yu, J. (2019) Platelet-Neutrophil Interaction Aggravates Vascular Inflammation and Promotes the Progression of Atherosclerosis by Activating the TLR4/NF-κB Pathway. *Journal of Cellular Biochemistry*, **120**, 5612-5619. https://doi.org/10.1002/jcb.27844

[13] Ali, M., Jasmin, S., Fariduddin, M., Alam, S.M.K., Arslan, M.I. and Biswas, S.K. (2018) Neutrophil Elastase and Myeloperoxidase MRNA Expression in Overweight and Obese Subjects. *Molecular Biology Reports*, **45**, 1245-1252. https://doi.org/10.1007/s11033-018-4279-4

[14] Nijhuis, J., Rensen, S.S., Slaats, Y., Van Dielen, F.M., Buurman, W.A. and Greve, J.W. (2009) Neutrophil Activation in Morbid Obesity, Chronic Activation of Acute Inflammation. *Obesity* (*Silver Spring*), **17**, 2014-2018. https://doi.org/10.1038/oby.2009.113

[15] Wiersma, J.J., Meuwese, M.C., Van Miert, J.N., Kastelein, A., Tijssen, J.G., Piek, J.J. and Trip, M.D. (2008) Diabetes Mellitus Type 2 Is Associated with Higher Levels of Myeloperoxidase. *Medical Science Monitor*, **14**, CR406-10.

[16] Zhang, Y., Zhou, X., Liu, P., Chen, X., Zhang, J., Zhang, H., Li, S., Chen, Y., Song, X., Wang, J., Zeng, H., Zhang, X., Tang, C., Yu, C., Li, Y. and Xu, C. (2021) GCSF Deficiency Attenuates Nonalcoholic Fatty Liver Disease through Regulating GCSFR-SOCS3-JAK-STAT3 Pathway and Immune Cells Infiltration. *American Journal of Physiology-Gastrointestinal and Liver Physiology*, **320**, G531-G542. https://doi.org/10.1152/ajpgi.00342.2020

[17] Kommoss, K.S., Bieler, T., Ringen, J., Lehmann, A., Mihalceanu, S., Hobohm, L., Keller, K., Brand, A., Fischer, B., Kramer, D., Wild, J., Waisman, A., Enk, A., Schäkel, K., Heikenwälder, M. and Karbach, S. (2024) A Simple Tool for Evaluation of Inflammation in Psoriasis: Neutrophil-to-Lymphocyte and Platelet-to-Lymphocyte Ratio as Markers in Psoriasis Patients and Related Murine Models of Psoriasis-Like Skin Disease. *Journal of Molecular Medicine*, **102**, 247-255. https://doi.org/10.1007/s00109-023-02406-4

[18] Zhang, X., Kang, Z., Yin, D. and Gao, J. (2023) Role of Neutrophils in Different Stages of Atherosclerosis. *Innate Immunity*, **29**, 97-109. https://doi.org/10.1177/17534259231189195

[19] Shafqat, A., Khan, J.A., Alkachem, A.Y., Sabur, H., Alkattan, K., Yaqinuddin, A. and Sing, G.K. (2023) How Neutrophils Shape the Immune Response: Reassessing Their Multifaceted Role in Health and Disease. *International Journal of Molecular Sciences*, **24**, Article 17583. https://doi.org/10.3390/ijms242417583

[20] 范骎, 陶蓉, 张瑞岩, 等. 炎症反应在易损斑块中的作用及其机制研究进展[J]. 中国动脉硬化杂志, 2019, 27(4): 301-306.

[21] Ionita, M.G., Van Den Borne, P., Catanzariti, L.M., *et al.* (2010) High Neutrophil Numbers in Human Carotid Atherosclerotic Plaques Are Associated with Characteristics of Rupturepronе Lesions. *Arteriosclerosis, Thrombosis, and Vascular Biology*, **30**, 1842-1848. https://doi.org/10.1161/ATVBAHA.110.209296

[22] Moreno, J.A., Ortega-Gomez, A., Delbosc, S., *et al.* (2012) *In Vitro* and *in Vivo* Evidence for the Role of Elastase Shedding of CD163 in Human Atherothrombosis. *European Heart Journal*, **33**, 252-263. https://doi.org/10.1093/eurheartj/ehr123

[23] Dworacka, M., *et al.* (2007) Pro-Atherogenic Alterations in T-Lymphocyte Subpopulations Related to Acute Hyper-

glycaemia in Type 2 Diabetic Patients. *Circulation Journal*, **71**, 962-967. https://doi.org/10.1253/circj.71.962

[24] Vakhshoori, M., Nemati, S., Sabouhi, S., Shakarami, M., Yavari, B., Emami, S.A., Bondariyan, N. and Shafie, D. (2023) Prognostic Impact of Monocyte-to-Lymphocyte Ratio in Coronary Heart Disease: A Systematic Review and Meta-Analysis. *Journal of International Medical Research*, **51**. https://doi.org/10.1177/03000605231204469

[25] Tyrrell, D.J. and Goldstein, D. R. (2021) Ageing and Atherosclerosis: Vascular Intrinsic and Extrinsic Factors and Potential Role of IL-6. *Nature Reviews Cardiology*, **18**, 58-68. https://doi.org/10.1038/s41569-020-0431-7

[26] Ryosuke, S., Holger, W. and Klaus, L. (2020) T Cell Subsets and Functions in Atherosclerosis. *Nature Reviews Cardiology*, **17**, 387-401. https://doi.org/10.1038/s41569-020-0352-5

[27] Luca, A.C., David, S.G., David, A.G., Țarcă, V., Pădureț, I.A., Mîndru, D.E., Roșu, S.T., Roșu, E.V., Adumitrăchioaiei, H., Bernic, J., Cojocaru, E. and Țarcă, E. (2023) Atherosclerosis from Newborn to Adult-Epidemiology, Pathological Aspects, and Risk Factors. *Life* (*Basel*), **13**, Article 2056. https://doi.org/10.3390/life13102056

[28] Ley, K. (2020) Role of the Adaptive Immune System in Atherosclerosis. *Biochemical Society Transactions*, **48**, 2273-2281. https://doi.org/10.1042/BST20200602

[29] Bonacina, F., *et al.* (2021) Adoptive Transfer of CX3CR1 Transduced-T Regulatory Cells Improves Homing to the Atherosclerotic Plaques and Dampens Atherosclerosis Progression. *Cardiovascular Research*, **117**, 2069-2082. https://doi.org/10.1093/cvr/cvaa264

[30] Hinkley, H., Counts, D.A., VonCanon, E. and Lacy, M. (2023) T Cells in Atherosclerosis: Key Players in the Pathogenesis of Vascular Disease. *Cells*, **12**, Article 2152. https://doi.org/10.3390/cells12172152

[31] Ma, S.D., Mussbacher, M. and Galkina, E.V (2021) Functional Role of B Cells in Atherosclerosis. *Cells*, **10**, Article 270. https://doi.org/10.3390/cells10020270

[32] Cao, J., Li, R., He, T., Zhang, L., Liu, H. and Wu, X. (2023) Role of Combined Use of Mean Platelet Volume-to-Lymphocyte Ratio and Monocyte to High-Density Lipoprotein Cholesterol Ratio in Predicting Patients with Acute Myocardial Infarction. *Journal of Cardiothoracic Surgery*, **18**, Article No. 172. https://doi.org/10.1186/s13019-023-02268-4

[33] Lordan, R., Tsoupras, A. and Zabetakis, I. (2021) Platelet Activation and Prothrombotic Mediators at the Nexus of Inflammation and Atherosclerosis: Potential Role of Antiplatelet Agents. *Blood Reviews*, **45**, Article 100694. https://doi.org/10.1016/j.blre.2020.100694

[34] Sharma, S., Tyagi, T. and Antoniak, S. (2022) Platelet in Thrombo-Inflammation: Unraveling New Therapeutic Targets. *Frontiers in Immunology*, **13**, Article 1039843. https://doi.org/10.3389/fimmu.2022.1039843

[35] Van Der Pol, E., *et al.* (2012) Classification, Functions, and Clinical Relevance of Extracellular Vesicles. *Pharmacological Reviews*, **64**, 676-705. https://doi.org/10.1124/pr.112.005983

[36] Lee, M.K.S., *et al.* (2021) Apoptotic Ablation of Platelets Reduces Atherosclerosis in Mice with Diabetes. *Arteriosclerosis, Thrombosis, and Vascular Biology*, **41**, 1167-1178. https://doi.org/10.1161/ATVBAHA.120.315369

[37] Theofilis, P., *et al.* (2021) Inflammatory Mediators of Platelet Activation: Focus on Atherosclerosis and COVID-19. *International Journal of Molecular Sciences*, **22**, Article 11170. https://doi.org/10.3390/ijms222011170

[38] Zhang, T. and Miao, Y.C. (2023) Prognostic Evaluation of Preoperative Systemic Immune Inflammatory Index in Patients with Colorectal Cancer. *Frontiers in Oncology*, **13**, Article 1260796. https://doi.org/10.3389/fonc.2023.1260796

[39] Erasaki, F., Sugiura, T., Okamura, Y., Ito, T., Yamamoto, Y., Ashida, R., Ohgi, K. and Uesaka, K. (2021) Systemic Immune-Inflammation Index as a Prognostic Marker for Distal Cholangiocarcinoma. *Surgery Today*, **51**, 1602-1609. https://doi.org/10.1007/s00595-021-02312-7

[40] Xie, Q.K., Chen, P., Hu, W.M., Sun, P., He, W.Z., Jiang, C., Kong, P.F., Liu, S.S., Chen, H.T., Yang, Y.Z., Wang, D., Yang, L. and Xia, L.P. (2018) The Systemic Immune-Inflammation Index Is An Independent Predictor of Survival for Metastatic Colorectal Cancer and Its Association with the Lymphocytic Response to the Tumor. *Journal of Translational Medicine*, **16**, Article No. 273. https://doi.org/10.1186/s12967-018-1638-9

[41] 闵轩, 王凯阳, 宁怡, 等. 系统免疫炎症指数与冠心病患者冠状动脉病变程度的相关性研究[J]. 中国心血管杂志, 2023, 28(3): 228-233.

[42] 伍满燕, 梁文卿, 陈江天, 陈红. 颈动脉粥样硬化性疾病的诊治进展[J]. 中华老年心脑血管病杂志, 2019, 21(11): 1223-1226.

[43] Korkmaz, L., Bektas, H., Korkmaz, A.A., Agaç, M.T., Acar, Z., Erkan, H. and Celik, S. (2012) Increased Carotid Intima-Media Thickness Is Associated with Higher SYNTAX Score. *Angiology*, **63**, 386-389. https://doi.org/10.1177/0003319711419837

[44] Çırakoğlu, Ö.F. and Yılmaz, A.S. (2021) Systemic Immune-Inflammation Index Is Associated with Increased Carotid Intima-Media Thickness in Hypertensive Patients. *Clinical and Experimental Hypertension*, **43**, 565-571. https://doi.org/10.1080/10641963.2021.1916944

[45] Ismail, A., Ravipati, S., Gonzalez-Hernandez, D., Mahmood, H., Imran, A., Munoz, E.J., Naeem, S., Abdin, Z.U. and Siddiqui, H.F. (2023) Carotid Artery Stenosis: A Look into the Diagnostic and Management Strategies, and Related Complications. *Cureus*, **15**, e38794. https://doi.org/10.7759/cureus.38794

[46] Li, L.H., Chen, C.T., Chang, Y.C., Chen, Y.J., Lee, I.H. and How, C.K. (2021) Prognostic Role of Neutrophil-to-Lymphocyte Ratio, Platelet-to-Lymphocyte Ratio, and Systemic Immune Inflammation Index in Acute Ischemic Stroke: A STROBE-Compliant Retrospective Study. *Medicine* (*Baltimore*), **100**, e26354. https://doi.org/10.1097/MD.0000000000026354

[47] Munich, S.A., Cress, M.C., Krishna, C. and Levy, E.I. (2015) Indications and Therapeutic Management of Carotid Stenosis in High-Risk Patients: SAPPHIRE and Beyond. *Journal of Neurosurgical Sciences*, **59**, 63-71.

[48] Morikawa, S., Okumura, K., Inoue, N., Ogane, T., Takayama, Y. and Murohara, T. (2023) Systemic Immune-Inflammation Index as a Predictor of Prognosis after Carotid Artery Stenting Compared with C-Reactive Protein. *PLOS ONE*, **18**, e0288564. https://doi.org/10.1371/journal.pone.0288564

[49] Yang, Y., Han, Y., Sun, W. and Zhang, Y. (2023) Increased Systemic Immune-Inflammation Index Predicts Hemorrhagic Transformation in Anterior Circulation Acute Ischemic Stroke Due to Large-Artery Atherosclerotic. *International Journal of Neuroscience*, **133**, 629-635. https://doi.org/10.1080/00207454.2021.1953021

[50] Su, B., Guo, S. and Zheng, X. (2023) Transitions in Chronic Disease Mortality in China: Evidence and Implications. *China CDC Weekly*, **5**, 1131-1134. https://doi.org/10.46234/ccdcw2023.211

[51] Yang, Y.L., Wu, C.H., Hsu, P.F., Chen, S.C., Huang, S.S., Chan, W.L., Lin, S.J., Chou, C.Y., Chen, J.W., Pan, J.P., Charng, M.J., Chen, Y.H., Wu, T.C., Lu, T.M., Huang, P.H., Cheng, H.M., Huang, C.C., Sung, S.H., Lin, Y.J. and Leu, H.B. (2020) Systemic Immune-Inflammation Index (SII) Predicted Clinical Outcome in Patients with Coronary Artery Disease. *European Journal of Clinical Investigation*, **50**, e13230. https://doi.org/10.1111/eci.13230

[52] 中华医学会外科学分会血管外科学组. 下肢动脉硬化闭塞症诊治指南[J]. 中华普通外科学文献(电子版), 2016, 10(1): 1-18.

[53] Tsai, P.S., Lin, D.C., Jan, Y.T., Liu, Y.P., Wu, T.H. and Huang, S.C. (2023) Lower-Extremity Muscle Wasting in Patients with Peripheral Arterial Disease: Quantitative Measurement and Evaluation with CT. *European Radiology*, **33**, 4063-4072. https://doi.org/10.1007/s00330-022-09356-4

[54] Cruz-Jentoft, A.J. and Sayer, A.A. (2019) Sarcopenia. *The Lancet*, **393**, 2636-2646. Erratum in: Lancet. 2019 Jun 29, 393 (10191), 2590. https://doi.org/10.1016/S0140-6736(19)31138-9

[55] Cevei, M., Onofrei, R.R., Cioara, F. and Stoicanescu, D. (2020) Correlations between the Quality of Life Domains and Clinical Variables in Sarcopenic Osteoporotic Postmenopausal Women. *Journal of Clinical Medicine*, **9**, Article 441. https://doi.org/10.3390/jcm9020441

[56] 聂璐, 杨启帆, 郑维淼, 等. 系统性炎症指标对下肢动脉硬化闭塞症患者发生肌少症的预测价值[J]. 江苏大学学报(医学版), 2024, 34(1): 74-78-92. https://doi.org/10.13312/j.issn.1671-7783.y230203

[57] MAchim, A., Stanek, A., Homorodean, C., Spinu, M., Onea, H.L., Lazăr, L., Marc, M., Ruzsa, Z. and Olinic, D.M. (2022) Approaches to Peripheral Artery Disease in Diabetes: Are There Any Differences? *International Journal of Environmental Research and Public Health*, **19**, Article 9801. https://doi.org/10.3390/ijerph19169801

[58] Humphries, M.D., Brunson, A., Hedayati, N., Romano, P. and Melnkow, J. (2016) Amputation Risk in Patients with Diabetes Mellitus and Peripheral Artery Disease Using Statewide Data. *Annals of Vascular Surgery*, **30**, 123-131. https://doi.org/10.1016/j.avsg.2015.04.089

[59] Ying, A.F., Tang, T.Y., Jin, A., Chong, T.T., Hausenloy, D.J. and Koh, W.P. (2022) Diabetes and Other Vascular Risk Factors in Association with the Risk of Lower Extremity Amputation in Chronic Limb-Threatening Ischemia: A Prospective Cohort Study. *Cardiovascular Diabetology*, **21**, Article No. 7. https://doi.org/10.1186/s12933-021-01441-0

[60] Liu, N., Sheng, J., Pan, T. and Wang, Y. (2019) Neutrophil to Lymphocyte Ratio and Platelet to Lymphocyte Ratio Are Associated with Lower Extremity Vascular Lesions in Chinese Patients with Type 2 Diabetes. *Clinical Laboratory*, **65**. https://doi.org/10.7754/Clin.Lab.2018.180804

[61] Liu, Y., Wang, X., Wang, L., Chen, W., Liu, W., Ye, T., Hong, J., Zhu, H. and Shen, F. (2022) Platelet-to-Lymphocyte Ratio Predicts the Presence of Diabetic Neurogenic Bladder. *Diabetes, Metabolic Syndrome and Obesity*, **15**, 7-13. https://doi.org/10.2147/DMSO.S335957

[62] Dascalu, A.M., Georgescu, A., Costea, A.C., Tribus, L., El Youssoufi, A., Serban, D., Arsene, A.L., Stana, D., Alexandrescu, C., Cristea, B.M., Tanasescu, D., Bobirca, A., Serboiu, C., Alius, C. and Bratu, D.G. (2023) Association between Neutrophil-to-Lymphocyte Ratio (NLR) and Platelet-to-Lymphocyte Ratio (PLR) with Diabetic Retinopathy in Type 2 Diabetic Patients. *Cureus*, **15**, e48581. https://doi.org/10.7759/cureus.48581

[63] Mureşan, A.V., Tomac, A., Opriş, D.R., Bandici, B.C., Coşarcă, C.M., Covalcic, D.C., Hălmaciu, I., Akácsos-Szász, O.Z., Rădulescu, F., Lázár, K., Stoian, A. and Tilinca, M.C. (2023) Inflammatory Markers Used as Predictors of Subclinical Atherosclerosis in Patients with Diabetic Polyneuropathy. *Life* (*Basel*), **13**, Article 1861. https://doi.org/10.3390/life13091861