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SII与视网膜静脉阻塞的研究进展

陈　梅[1]，余　萍[2*]

[1]青海大学研究生院眼科，青海　西宁
[2]青海大学附属医院眼科，青海　西宁

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摘　要

视网膜静脉阻塞(retinal vein occlusion, RVO)是仅次于糖尿病性视网膜病变的第二大致盲性的眼底疾病。发病与血管危险因素相关，基于老龄化的发展和慢性病的发病率逐年增长，RVO群体近年呈扩大趋势，使得患者视力受损、生活质量下降、经济负担加重。作为一种异质性疾病，其发病机制复杂，但目前国内外学者普遍认为与机体炎症反应和免疫调节失去平衡相关。本文从结构基础、炎症反应对RVO的病理生理改变进行综述，并着重分析新兴的复合炎症指标——系统免疫炎症指数(systemic immune-inflammation index, SII)在RVO疾病中的临床价值。

关键词

视网膜静脉阻塞，炎症生物标志物，系统免疫炎症指数，临床进展

Advances in the Study of SII and Retinal Vein Occlusion

Mei Chen[1], Ping Yu[2*]

[1]Department of Ophthalmology, Graduate School of Qinghai University, Xining Qinghai
[2]Department of Ophthalmology, Affiliated Hospital of Qinghai University, Xining Qinghai

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Abstract

Retinal vein occlusion (RVO) is the second most blinding fundus disease after diabetic retinopathy. The onset of the disease is associated with vascular risk factors, and based on the development of aging and the increasing incidence of chronic diseases year by year, the RVO population has been

*通讯作者。

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expanding in recent years, making the patients' visual acuity impaired, quality of life reduced, and economic burden increased. As a heterogeneous disease, its pathogenesis is complex, but currently scholars at home and abroad generally agree that it is related to the imbalance of inflammatory response and immune regulation of the organism. In this paper, we review the pathophysiological changes of RVO from structural basis and inflammatory response, and focus on the clinical value of the emerging composite inflammatory index, systemic immune-inflammation index (SII) in RVO disease.

Keywords

Retinal Vein Occlusion, Inflammatory Biomarkers, Systemic Immune-Inflammatory Index, Clinical Progress

1. 引言

视网膜静脉阻塞(retinal vein occlusion, RVO)是由于视网膜静脉回流受阻导致相应静脉引流区域视网膜缺血缺氧的眼底疾病，表现为视网膜静脉迂曲扩张、血流淤滞、血管内皮损伤，进一步出现和液体外渗、视网膜水肿、黄斑水肿、视网膜出血等一系列不良结局[1] [2]。流行病学调查显示，2008 年，全球 RVO 患者约 1600 万人，2015 年受累人群约有 2800 万人，千人发病人数从 5.2 人增至 7.7 人，发病率逐年增长[3] [4]。视网膜缺血缺氧性损伤可使得局部眼底血管受损并释放血管内皮生长因子(vascular endothelial growth factor, VEGF)诱导眼部新生血管形成，VEGF 的过度表达是导致虹膜新生血管、房角新生血管甚至新生血管性青光眼的主要原因[5] [6] [7]。未完全血管化的不良微血管，可由于外部应力的改变和自身结构的脆弱性，突发破裂造成玻璃体和(或)视网膜下出血，若积血未能及时吸收和清除，则有进一步纤维化、机化的可能，导致牵引性视网膜脱离，甚至失明的结局[8]。RVO 对患者眼睛健康和日常工作生活的视力需求威胁极大，因此探寻其发病机制，对疾病的干预和诊断治疗非常重要。

2. RVO

根据阻塞部位，RVO 可分为视网膜中央静脉阻塞(central retinal vein occlusion, CRVO)和视网膜分支静脉阻塞(branch retinal vein occlusion, BRVO)。2010 年 Rogers S [3]和 2019 年 Song P [4]的荟萃分析表明，CRVO 的发病率约为 0.8‰~1.3‰，BRVO 的发病率约为 4.42‰~6.40‰。

1856 年 Virchow 提出静脉血栓形成与血管内皮受损、血液淤滞，血液流变学改变有关[9]。Virchow 三联征理论同样也可用来解释 RVO 的发病基础[10]。众所周知，视网膜中央动脉和中央静脉在通过筛板开口离开视盘时共用一个外膜鞘，视网膜动脉和与之伴行的静脉在动静脉血管交叉处共用一个外膜鞘。这种结构特点使的视网膜动脉和视网膜静脉的血流动力学变化互相影响[11]。视网膜中央动脉的刚性增加压迫邻近静脉是 CRVO 发生的主要原因[12]。对于 BRVO，动静脉血管交叉处静脉受压呈狭窄结构[13]，具有 Virchow 三联征发生的结构基础。交叉类型也影响着视力的预后。Iida-Miwa [14]利用相干光断层扫描技术(optical coherence tomography, OCT)发现，基线视力水平和无灌注区面积无差异的 BRVO 患者中，静脉交叉为特征组在治疗后第 12 个月时视网膜无灌注区较给予相同治疗方式的动脉交叉组大，表明静脉交叉组 BRVO 的预后较动脉交叉组不良。以往研究认为动脉交叉结构是 BRVO 发生的高危解剖学因素

[15]，OCT 技术的发展则发现：静脉交叉的眼内，交叉处闭塞的静脉在静脉内层膜和动脉壁之间被压缩和阻塞，而在动脉交叉的眼内，静脉腔一般被保留[14] [16]，可说明随着技术的发展，更能精确的观察到疾病形态学的变化，静脉交叉型 BRVO 也比先前报道更为普遍[17]。

动脉粥样硬化、高血糖、高血脂等因素可以使血管内皮功能发生紊乱，机体相对促炎状态，导致视网膜静脉血液粘度增加、血细胞聚集增加、抗氧化防御能力降低[18] [19] [20]。RVO 与经典的血管危险因素相关，或许可以被认为是系统性动脉粥样硬化的一种表现。随着全球老龄化趋势和人们生活水平的提高，血管退行性变化和慢性疾病心血管受累，RVO 的流行和疾病负担也可能会扩大。仔细评估和治疗相关危险因素将有助于早期干预病情[21]。

3. RVO 与炎症

一些炎症生物标志物在 RVO 眼中升高，包括白介素-6、白介素-8、内皮素-1 [22] [23] [24]。VEGF 是促进血管内皮生长的因子，眼底缺氧，缺氧诱导因子-1(hypoxia-inducible factor-1, HIF-1)可上调 VEGF 的表达，使得视网膜血管通透性增加，液体渗漏改变细胞外基质，促进血管修复和新生血管形成，加剧缺氧并产生正反馈效应[7] [25]，并表现为加重局部炎症和黄斑水肿[26]。Chou M Y 通过 RVO 患者血清中氧化应激产物的抗体的测定，表示氧化应激和炎症在 RVO 的发展和后续并发症中起着一定作用[27]。

炎症与机体调节失去平衡，使得眼底局部血管阻塞和(或)封闭的结局[28]。有研究表明，BRVO 相关炎症反应，可激活眼部常驻小胶质细胞，触发中性粒细胞浸润，加剧血液-视网膜屏障损伤，调节缺血后炎症和神经视网膜不可逆的丧失[24]。因此抑制小胶质细胞介导的炎症或许能减轻 RVO 的功能障碍。局部血液回流受阻，静脉压升高，毛细血管液体渗漏和损伤，使得促血管生成和炎症介质释放，一系列复杂病理过程造成黄斑水肿和新生血管形成。迄今为止，临床常用 RVO 治疗方式有视网膜激光光凝、抗 VEGF 药物、类固醇药物[29]。激光通过在视网膜上产生小的物理烧伤，使微血管收缩和封闭，减少受影响区域液体渗漏的作用[30]。类固醇药物可通过阻断级联炎症反应和抑制相关细胞因子的积累减轻眼底炎症[31]，其与 VEGF 在 RVO 发病机制中的协同性，也与临床抗 VEGF 治疗和类固醇治疗对大多数视网膜静脉相关性黄斑水肿患者有效的事实一致[32] [33]。

尽管最佳矫正视力在治疗后可以提高，患者眼底结构也有统计学意义的改善，但并不意味着被破坏的结构能完全恢复疾病状态之前[34]。RVO 发生后，视网膜缺血缺氧区对光线敏感性降低，使得后续功能下降，视力预后结果往往因为患者依从性和长期随访的治疗负担具有很大的差异[35]。需要注意的是，目前的治疗方法，主要针对疾病的并发症，消除视网膜水肿，新生血管形成后更重要的是控制眼压和保护视神经，而不是针对原发性功能障碍，现阶段完全逆转血管阻塞引起的结构或功能损害尚不可能[36]。

4. SII

2014 年，我国学者胡波在肝细胞癌切除术预后研究中，基于血小板数量、中性粒细胞数量和淋巴细胞数量提出了复合免疫炎症指数，即 SII [37]，相比中性粒细胞－淋巴细胞比值(neutrophil-lymphocyte ratio, NLR)、血小板－淋巴细胞比值(platelet-lymphocyte ratio, PLR)，NLR、PLR，SII 比两者多结合了一个因素，在反映宿主免疫和炎症状态平衡方面更具稳定性和代表性。该指数由血小板计数和中性粒细胞计数的乘积与淋巴细胞计数的比值计算得到，简便快捷，很快成为了新兴的复合炎症生物指标。

血小板是参与止血的重要介质，近年研究发现其在识别和消灭病原体中起一定作用，可参与炎症和免疫反应[38]。不仅对病原体相关炎症应答，同样也可基于无菌炎症造成的损伤给予活性反馈[39] [40]。中性粒细胞作为炎症发生后率先到达炎症部位的吞噬细胞，可释放中性粒细胞胞外捕获网(Neutrophil extracellular traps, NETs)中和病原体[41]。有趣的是，NETs 作为中性粒细胞先天免疫调节的研究热点，在

无菌性和感染性疾病中可导致病理性血栓形成，血小板促凝过程中也可促进中性粒细胞的凋亡[42]。免疫系统可对外界刺激产生应答，使机体产生防御。淋巴细胞可以作为疾病应答机体后对健康的普遍预测指标[43]。通过检验室的血细胞数据水平反应机体状况，包括严重和不严重、死亡和活着，对疾病初步给予预后猜测。对指标的量化将提供具有预测能力和免疫系统控制潜力的可扩展模型[44]。

因此，NLR、PLR、SII 等指标，在一定层面可以反应过度活跃的炎症与保护性调节的不平衡。已有研究证据表明，SII 高表达于实体肿瘤[37] [45]、新型冠状病毒感染[46]、深静脉血栓[47]。Shen Li [48]发现，SII 是急性和亚急性脑静脉窦血栓患者预后不良的潜在预测指标。较高的 SII 可反应更强的炎症反应和较弱的免疫反应，且预后不良。究其原因，与机体状态影响血细胞数量和(或)功能相关[49]。SII 有望在各种癌症和炎症相关疾病中，成为评估严重程度和预后结局的有用生物标志物，为临床医生诊断和管理提供宝贵的信息。

5. SII 与 RVO

局部和全身炎症通过诱导动脉粥样硬化和全身高凝状态在 RVO 的发展中发挥作用[28]。RVO 与动脉粥样硬化性心血管危险因素有关[20]。既往研究发现血小板源性微囊泡、NETs 相关标记物在 RVO 患者中高表达，表明 RVO 疾病使得血小板和中性粒细胞功能活化[50] [51]。RVO 可以视为是血小板和凝血反应、内皮细胞和炎症反应与血流异常相互作用的结果[52]。

一些研究已经调查了 NLR、PLR、SII 和 RVO 之间的关系。在一项对 56 名 RVO 患者的回顾性研究中，Wen Zuo 等人发现 SII 预测 RVO 的最佳截断值为 > 326.46，NLR 的最佳截断值为 > 1.66，PLR 无统计学差异[53]。相反的是，一项对 127 名 RVO 患者的回顾性研究表示炎症指标与 RVO 之间缺乏关联[54]。除了预测 RVO 患病风险外，SII 也被证明与 RVO 患者并发症相关。Timur 团队发现，SII 较高的患者发生黄斑水肿的风险明显较高[55]。

综上所述，SII 作为一种新型炎症指标，在 RVO 诊断和并发症的预测中比 NLR 和 PLR 更有希望[53]。需要进一步研究以充分了解炎症指标和 RVO 之间的关系，这些生物标志物可能为临床医生诊断和管理疾病提供宝贵的信息。如果患者出现任何视力变化或其他提示 RVO 的症状，必须及时寻求医疗救助。

6. 总结和展望

RVO 是突发的、明显症状在眼部的疾病，其发病因素与全身状态息息相关，因此需要对系统性高危因素进行排查和控制。高血压、高血糖、高血脂对身体的危害不言而喻，如何延缓慢性疾病进展和预防相关并发症出现，一直都是临床处理和需要攻克的难题。在 RVO 的疾病管理中，排查和干预高危因素、诊断和治疗相关人群、随访和注意病情变化十分重要。脑和视网膜微血管在解剖和生理特性上具有相似性，研究发现视网膜血管的异常或许能反映脑血管病理状态，如阿尔兹海默症、血管性痴呆等。所以对眼底病的管理，不仅是治疗眼部疾病，也是在评估患者全身基础状态，必要时需要与相关科室联合，对全身危险因素进行优化。SII 具有简单、易获性，但全血细胞计数受药物、运动状态、疾病状态影响较大，临床应用时，也需综合考量。需要更多相关研究，证明衍生于全血细胞计数的指标，如 NLR、PLR、SII 等具有临床实用性，并结合敏感性和特异性划定相关参考范围等。基于疾病状态下某个指标较健康对照组升高，进一步减少与其高水平表达的相关因素，将有利于疾病管理，减轻患者经济负担。

参考文献

[1] McIntosh, R.L., Rogers, S.L., Lim, L., *et al*. (2010) Natural History of Central Retinal Vein Occlusion: An Evidence-Based Systematic Review. *Ophthalmology*, **117**, 1113-1123.e1115. https://doi.org/10.1016/j.ophtha.2010.01.060

[2] Rogers, S.L., McIntosh, R.L., Lim, L., *et al*. (2010) Natural History of Branch Retinal Vein Occlusion: An Evidence-

Based Systematic Review. *Ophthalmology*, **117**, 1094-1101.e1095. https://doi.org/10.1016/j.ophtha.2010.01.058

[3] Rogers, S., McIntosh, R.L., Cheung, N., *et al*. (2010) The Prevalence of Retinal Vein Occlusion: Pooled Data from Population Studies from the United States, Europe, Asia, and Australia. *Ophthalmology*, **117**, 313-319.e311. https://doi.org/10.1016/j.ophtha.2009.07.017

[4] Song, P., Xu, Y., Zha, M., *et al*. (2019) Global Epidemiology of Retinal Vein Occlusion: A Systematic Review and Meta-Analysis of Prevalence, Incidence, and Risk Factors. *Journal of Global Health*, **9**, Article ID: 010427. https://doi.org/10.7189/jogh.09.010427

[5] Chan, C.K., Ip, M.S., Vanveldhuisen, P.C., *et al*. (2011) Incidences of Neovascular Events in Eyes with Retinal Vein Occlusion. *Ophthalmology*, **118**, 1364-1372.

[6] Gao, H., Chen, M., Liu, Y., *et al*. (2023) Injectable Anti-Inflammatory Supramolecular Nanofiber Hydrogel to Promote Anti-VEGF Therapy in Age-Related Macular Degeneration Treatment. *Advanced Materials*, **35**, e2204994. https://doi.org/10.1002/adma.202204994

[7] Sharma, D., Zachary, I. and Jia, H. (2023) Mechanisms of Acquired Resistance to Anti-VEGF Therapy for Neovascular Eye Diseases. *Investigative Ophthalmology & Visual Science*, **64**, 28. https://doi.org/10.1167/iovs.64.5.28

[8] Hayreh, S.S. (2014) Ocular Vascular Occlusive Disorders: Natural History of Visual Outcome. *Progress in Retinal and Eye Research*, **41**, 1-25. https://doi.org/10.1016/j.preteyeres.2014.04.001

[9] Bagot, C.N. and Arya, R. (2008) Virchow and His Triad: A Question of Attribution. *British Journal of Haematology*, **143**, 180-190. https://doi.org/10.1111/j.1365-2141.2008.07323.x

[10] Rehak, M. and Wiedemann, P. (2010) Retinal Vein Thrombosis: Pathogenesis and Management. *Journal of Thrombosis and Haemostasis*, **8**, 1886-1894. https://doi.org/10.1111/j.1538-7836.2010.03909.x

[11] Scott, I.U., Campochiaro, P.A., Newman, N.J., *et al*. (2020) Retinal Vascular Occlusions. *The Lancet*, **396**, 1927-1940. https://doi.org/10.1016/S0140-6736(20)31559-2

[12] Yau, J.W., Lee, P., Wong, T.Y., *et al*. (2008) Retinal Vein Occlusion: An Approach to Diagnosis, Systemic Risk Factors and Management. *Internal Medicine Journal*, **38**, 904-910. https://doi.org/10.1111/j.1445-5994.2008.01720.x

[13] Muraoka, Y. and Tsujikawa, A. (2019) Arteriovenous Crossing Associated with Branch Retinal Vein Occlusion. *Japanese Journal of Ophthalmology*, **63**, 353-364. https://doi.org/10.1007/s10384-019-00676-5

[14] Iida, Y., Muraoka, Y., Ooto, S., *et al*. (2017) Morphologic and Functional Retinal Vessel Changes in Branch Retinal Vein Occlusion: An Optical Coherence Tomography Angiography Study. *American Journal of Ophthalmology*, **182**, 168-179. https://doi.org/10.1016/j.ajo.2017.08.004

[15] Feist, R.M., Ticho, B.H., Shapiro, M.J., *et al*. (1992) Branch Retinal Vein Occlusion and Quadratic Variation in Arteriovenous Crossings. *American Journal of Ophthalmology*, **113**, 664-668. https://doi.org/10.1016/S0002-9394(14)74791-9

[16] Iida-Miwa, Y., Muraoka, Y., Iida, Y., *et al*. (2019) Branch Retinal Vein Occlusion: Treatment Outcomes According to the Retinal Nonperfusion Area, Clinical Subtype, and Crossing Pattern. *Scientific Reports*, **9**, Article No. 6569. https://doi.org/10.1038/s41598-019-42982-5

[17] Zeng, Y., Zhang, X., Mi, L., *et al*. (2022) Characterization of Macrophage-Like Cells in Retinal Vein Occlusion Using En Face Optical Coherence Tomography. *Frontiers in Immunology*, **13**, Article ID: 855466. https://doi.org/10.3389/fimmu.2022.855466

[18] Ehlers, J.P. and Fekrat, S. (2011) Retinal Vein Occlusion: Beyond the Acute Event. *Survey of Ophthalmology*, **56**, 281-299. https://doi.org/10.1016/j.survophthal.2010.11.006

[19] Chang, Y.S., Ho, C.H., Chu, C.C., *et al*. (2021) Risk of Retinal Vein Occlusion in Patients with Diabetes Mellitus: A Retrospective Cohort Study. *Diabetes Research and Clinical Practice*, **171**, Article ID: 108607. https://doi.org/10.1016/j.diabres.2020.108607

[20] Lyu, M., Lee, Y., Kim, B.S., *et al*. (2021) Clinical Significance of Subclinical Atherosclerosis in Retinal Vein Occlusion. *Scientific Reports*, **11**, Article No. 11905. https://doi.org/10.1038/s41598-021-91401-1

[21] Schmidt-Erfurth, U., Garcia-Arumi, J., Gerendas, B.S., *et al*. (2019) Guidelines for the Management of Retinal Vein Occlusion by the European Society of Retina Specialists (EURETINA). *Ophthalmologica*, **242**, 123-162. https://doi.org/10.1159/000502041

[22] Li, X., Cao, X., Zhao, M., *et al*. (2022) The Changes of Irisin and Inflammatory Cytokines in the Age-Related Macular Degeneration and Retinal Vein Occlusion. *Frontiers in Endocrinology* (*Lausanne*), **13**, Article ID: 861757. https://doi.org/10.3389/fendo.2022.861757

[23] List, W., Weger, M., Pinter-Hausberger, S., *et al*. (2022) Endothelin-1 as a Risk Factor in Retinal Vein Occclusion. *Retina*, **42**, 738-743. https://doi.org/10.1097/IAE.0000000000003374

[24] Jovanovic, J., Liu, X., Kokona, D., *et al*. (2020) Inhibition of Inflammatory Cells Delays retinal Degeneration in Expe-

rimental Retinal Vein Occlusion in Mice. *Glia*, **68**, 574-588. https://doi.org/10.1002/glia.23739

[25] Campochiaro, P.A. and Akhlaq, A. (2021) Sustained Suppression of VEGF for Treatment of Retinal/Choroidal Vascular Diseases. *Progress in Retinal and Eye Research*, **83**, Article ID: 100921. https://doi.org/10.1016/j.preteyeres.2020.100921

[26] Tang, Y., Cheng, Y., Wang, S., *et al*. (2022) Review: The Development of Risk Factors and Cytokines in Retinal Vein Occlusion. *Frontiers in Medicine* (*Lausanne*), **9**, Article ID: 910600. https://doi.org/10.3389/fmed.2022.910600

[27] Posch-Pertl, L., Weger, M., Pinter-Hausberger, S., *et al*. (2021) Serum Levels of Antibodies against Oxidation-Specific Epitopes Are Decreased in Patients with Retinal Vein Occlusion. *Retina*, **41**, 1193-1201. https://doi.org/10.1097/IAE.0000000000003001

[28] Dursun, A., Ozturk, S., Yucel, H., *et al*. (2015) Association of Neutrophil/Lymphocyte Ratio and Retinal Vein Occlusion. *European Journal of Ophthalmology*, **25**, 343-346. https://doi.org/10.5301/ejo.5000570

[29] Rehak, M., Storch, M.W., Hattenbach, L.O., *et al*. (2022) Ischemia and Laser Photocoagulation in Retinal Vein Occlusion. *Ophthalmologie*, **119**, 1121-1128. https://doi.org/10.1007/s00347-022-01750-z

[30] Hayreh, S.S. (2021) Photocoagulation for Retinal Vein Occlusion. *Progress in Retinal and Eye Research*, **85**, Article ID: 100964. https://doi.org/10.1016/j.preteyeres.2021.100964

[31] Gaballa, S.A., Kompella, U.B., Elgarhy, O., *et al*. (2021) Corticosteroids in Ophthalmology: Drug Delivery Innovations, Pharmacology, Clinical Applications, and Future Perspectives. *Drug Delivery and Translational Research*, **11**, 866-893. https://doi.org/10.1007/s13346-020-00843-z

[32] Winterhalter, S., Eckert, A., Vom Brocke, G.A., *et al*. (2018) Real-Life Clinical Data for Dexamethasone and Ranibizumab in the Treatment of Branch or Central Retinal Vein Occlusion over a Period of Six Months. *Graefe's Archive for Clinical and Experimental Ophthalmology*, **256**, 267-279. https://doi.org/10.1007/s00417-017-3852-1

[33] Wecker, T., Grundel, B., Grundel, M., *et al*. (2021) Real-Life Medium Term Follow-Up Data for Intravitreal Dexamethasone Implant in Retinal Vein Occlusion. *Scientific Reports*, **11**, Article No. 8303. https://doi.org/10.1038/s41598-021-87467-6

[34] Liu, J.C., Alsaloum, P., Iyer, A.I., *et al*. (2023) Consequences of Anti-Vascular Endothelial Growth Factor Treatment Lapse in Patients with Retinal Vein Occlusion. *Eye* (*London*), **37**, 453-458. https://doi.org/10.1038/s41433-022-01960-4

[35] Shah, P.N., Shanmugam, M.P., Vora, U.B., *et al*. (2022) Long-Term Real-World Outcomes in Retinal Vein Occlusions: How Close Are We to the Trials? *Indian Journal of Ophthalmology*, **70**, 4370-4375. https://doi.org/10.4103/ijo.IJO_1330_22

[36] Khayat, M., Perais, J., Wright, D.M., *et al*. (2021) Anatomic-Functional Correlates in Lesions of Retinal Vein Occlusion. *Investigative Ophthalmology & Visual Science*, **62**, 10. https://doi.org/10.1167/iovs.62.7.10

[37] Hu, B., Yang, X.R., Xu, Y., *et al*. (2014) Systemic Immune-Inflammation Index Predicts Prognosis of Patients after Curative Resection for Hepatocellular Carcinoma. *Clinical Cancer Research*, **20**, 6212-6222. https://doi.org/10.1158/1078-0432.CCR-14-0442

[38] Koupenova, M., Livada, A.C. and Morrell, C.N. (2022) Platelet and Megakaryocyte Roles in Innate and Adaptive Immunity. *Circulation Research*, **130**, 288-308. https://doi.org/10.1161/CIRCRESAHA.121.319821

[39] Mandel, J., Casari, M., Stepanyan, M., *et al*. (2022) Beyond Hemostasis: Platelet Innate Immune Interactions and Thromboinflammation. *International Journal of Molecular Sciences*, **23**, Article No. 3868. https://doi.org/10.3390/ijms23073868

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

[41] Brinkmann, V., Reichard, U., Goosmann, C., *et al*. (2004) Neutrophil Extracellular Traps Kill Bacteria. *Science*, **303**, 1532-1535. https://doi.org/10.1126/science.1092385

[42] Döring, Y., Soehnlein, O. and Weber, C. (2017) Neutrophil Extracellular Traps in Atherosclerosis and Atherothrombosis. *Circulation Research*, **120**, 736-743. https://doi.org/10.1161/CIRCRESAHA.116.309692

[43] Lai, K.L., Hu, F.C., Wen, F.Y., *et al*. (2022) Lymphocyte Count Is a Universal Predictor of Health Outcomes in COVID-19 Patients before Mass Vaccination: A Meta-Analytical Study. *Journal of Global Health*, **12**, Article No. 05041. https://doi.org/10.7189/jogh.12.05041

[44] Heinzel, S., Marchingo, J.M., Horton, M.B., *et al*. (2018) The Regulation of Lymphocyte Activation and Proliferation. *Current Opinion in Immunology*, **51**, 32-38. https://doi.org/10.1016/j.coi.2018.01.002

[45] Wang, S., Yang, X., Yu, Z., *et al*. (2022) The Values of Systemic Immune-Inflammation Index and Neutrophil-Lymphocyte Ratio in Predicting Testicular Germ Cell Tumors: A Retrospective Clinical Study. *Frontiers in Oncology*, **12**, Article ID: 893877. https://doi.org/10.3389/fonc.2022.893877

[46] Fois, A.G., Paliogiannis, P., Scano, V., *et al*. (2020) The Systemic Inflammation Index on Admission Predicts In-Hospital Mortality in COVID-19 Patients. *Molecules*, **25**, Article No. 5725. https://doi.org/10.3390/molecules25235725

[47] Xue, J., Ma, D., Jiang, J., *et al*. (2021) Diagnostic and Prognostic Value of Immune/Inflammation Biomarkers for Venous Thromboembolism: Is It Reliable for Clinical Practice? *Journal of Inflammation Research*, **14**, 5059-5077. https://doi.org/10.2147/JIR.S327014

[48] Li, S., Liu, K., Gao, Y., *et al*. (2020) Prognostic Value of Systemic Immune-Inflammation Index in Acute/Subacute Patients with Cerebral Venous Sinus Thrombosis. *Stroke and Vascular Neurology*, **5**, 368-373. https://doi.org/10.1136/svn-2020-000362

[49] Walzik, D., Joisten, N., Zacher, J., *et al*. (2021) Transferring Clinically Established Immune Inflammation Markers into Exercise Physiology: Focus on Neutrophil-to-Lymphocyte Ratio, Platelet-to-Lymphocyte Ratio and Systemic Immune-Inflammation Index. *European Journal of Applied Physiology*, **121**, 1803-1814. https://doi.org/10.1007/s00421-021-04668-7

[50] Marcinkowska, A., Wolska, N., Luzak, B., *et al*. (2022) Platelet-Derived Procoagulant Microvesicles Are Elevated in Patients with Retinal Vein Occlusion (RVO). *Journal of Clinical Medicine*, **11**, Article No. 5099. https://doi.org/10.3390/jcm11175099

[51] Wan, W., Liu, H., Long, Y., *et al*. (2021) The Association between Circulating Neutrophil Extracellular Trap Related Biomarkers and Retinal Vein Occlusion Incidence: A Case-Control Pilot Study. *Experimental Eye Research*, **210**, Article ID: 108702. https://doi.org/10.1016/j.exer.2021.108702

[52] Sastry, S., Cuomo, F. and Muthusamy, J. (2022) COVID-19 and Thrombosis: The Role of Hemodynamics. *Thrombosis Research*, **212**, 51-57. https://doi.org/10.1016/j.thromres.2022.02.016

[53] Zuo, W., Chen, T., Song, J., *et al*. (2023) Assessment of Systemic Immune-Inflammation Index Levels in Patients with Retinal Vein Occlusion. *Ocular Immunology and Inflammation*, **31**, 491-495. https://doi.org/10.1080/09273948.2022.2032199

[54] Pinna, A., Porcu, T., Marzano, J., *et al*. (2021) Mean Platelet Volume, Red Cell Distribution Width, and Complete Blood Cell Count Indices in Retinal Vein Occlusions. *Ophthalmic Epidemiology*, **28**, 39-47. https://doi.org/10.1080/09286586.2020.1791349

[55] Timur, I.E.E., Tarim, B., Seker, E.D., *et al*. (2023) The Relation between Serum Inflammatory Marker Levels and Serous Retinal Detachment in Macular Edema Secondary to Retinal Vein Occlusion. *Photodiagnosis and Photodynamic Therapy*, **42**, Article ID: 103591. https://doi.org/10.1016/j.pdpdt.2023.103591