· 脑卒中专题 ·

衍生血小板相关比值与缺血性脑卒中预后相关性的研究进展

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DOI: 10.3969/j.issn.1009-6574.2023.05.004

【摘要】 缺血性脑卒中是卒中常见的类型, 具有高复发率、高致残率的特点, 已成为患者死亡和残疾的主要原因之一。血小板在缺血性脑卒中发病机制中扮演着重要角色。近年来研究发现血小板相关比值在预测缺血性脑卒中的预后和转归方面具有重要的临床价值。现就平均血小板体积与血小板(MPV/PC)比值、血小板与淋巴细胞比值(PLR)、平均血小板体积与淋巴细胞比值(MPVLR)、血小板与中性粒细胞比值(PNR)、红细胞分布宽度与血小板比值(RPR)等衍生血小板相关比值与缺血性脑卒中预后相关性的研究进展进行综述。

【关键词】 缺血性脑卒中; 血小板; 比值; 预后; 综述

Research progress on the correlation between derived platelet-related ratios and prognosis of ischemic stroke

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【Abstract】 Ischemic stroke is the common type of stroke, with the characteristics of high recurrence rate and high disability, and has become one of the main causes of death and disability. Platelet plays an important role in the pathogenesis of ischemic stroke. In recent years, studies have found that platelet related ratio has important clinical value in predicting the prognosis and outcome of ischemic stroke. In this review, we summarize the recent development of prognostic relevance between derived platelet-related ratios and ischemic stroke, such as the mean platelet volume-to-platelet count (MPV/PC) ratio, platelet-to-lymphocyte ratio (PLR), mean platelet volume-to-lymphocyte ratio (MPVLR), platelet-to-neutrophil ratio (PNR), red blood cell distribution width-to-platelet ratio (RPR).

【Key words】 Ischemic stroke; Blood platelets; Ratio; Prognosis; Review

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(收稿日期: 2022-11-26)
(本文编辑: 赵金鑫)

缺血性脑卒中(ischemic stroke, IS)在全世界引起了广泛的健康问题,由疾病导致的后遗症及治疗费用给社会和家庭带来了巨大的经济负担[1]。目前,静脉溶栓治疗是恢复急性IS患者脑血流最重要的措施之一,但仍有部分患者行静脉溶栓治疗后病情进一步恶化[2]。因此,早期识别和评估疾病预后是目前面临的一个重要问题。影像学技术是评估急性IS患者预后的重要手段,血清学在这方面的应用也越来越多。近年来,国内外研究者将血小板相关参数与外周血细胞以比值方式组合,如平均血小板体积与血小板(MPV/PC)、血小板与淋巴细胞比值(PLR)、平均血小板体积与淋巴细胞比值(MPVLR)、血小板与中性粒细胞比值(PNR)、红细胞分布宽度与血小板比值(RPR)等,在预测心脑血管疾病预后方面具有重大价值[3-5]。所以,若能有效预测急性IS患者预后和转归,对早期制定治疗策略和改善预后将有重要意义。

一、血小板和IS

IS与动脉粥样硬化、血栓形成和神经炎症等多种病理生理过程密切相关。血小板在这些病理生理过程中起着关键作用。当血管内膜损伤时,血小板首先被内膜损伤部位暴露的胶原蛋白激活而活化[6]。然后,血小板表面的膜糖蛋白(GPIb)通过与血管性血友病因子(von Willebrand Factor, vWF)结合并介导血小板黏附,从而促进血小板与内膜损伤部位的黏附[7]。血小板黏附后会释放各种活性物质,将进一步加重内皮细胞损伤。这将致使血浆中的各种脂蛋白容易大量地沉积在内膜。同时,损伤的内皮细胞会分泌多种生长因子,如单核细胞趋化蛋白1(monocyte chemotactic protein-1, MCP-1)、血小板源性生长因子(platelet derived growth factor, PDGF)等,从而激活血管中膜平滑肌细胞迁入内膜[8]。这种平滑肌细胞表面含有脂蛋白受体,可以与低密度脂蛋白和极低密度脂蛋白相结合而成为泡沫细胞,致使内膜不断增厚、变硬和形成斑块,最后导致动脉粥样硬化的发展[9]。因此,在IS治疗中,早期抑制血小板黏附与活化至关重要。

血小板在血栓形成的过程中极其重要。首先,血小板黏附于内膜损伤后暴露的胶原进而激活,接着释放含纤维蛋白原、Ⅴ因子等的α颗粒和含二磷酸腺苷(ADP)、Ca^{2+}、5-HT等的δ颗粒以及颗粒内的物质[10]。然后,ADP、5-HT和血小板产生的血栓素A2使血管中血小板相互黏集,形成血小板黏集堆。与此同时,血管内膜损伤后激活内源性凝血途径,损伤的内皮细胞释放组织因子,激活凝血因子Ⅶ,启动外源性凝血途径[11]。最后,凝血途径中的凝血酶不仅能够与血小板表面的受体结合,使血小板黏集堆进一步增大,还能将纤维蛋白原变成纤维蛋白。这将导致血小板相互交织,变成不可逆的血小板血栓[12]。

在动脉血管壁炎性过程中,血小板、白细胞和内皮细胞之间的相互作用至关重要。血管内膜损伤后,内膜下组织暴露,激活血小板在功能失调的内膜上不断黏附、聚集和释放各种活性物质[10]。一方面,血小板通过自身α颗粒膜上的P选择素与白细胞表面的P选择素糖蛋白配体(P-selectin glycoprotein ligand 1, PSGL-1)结合以介导白细胞募集,诱导整合素的活化,使白细胞黏附于内皮细胞[13]。另一方面,损伤的内皮细胞会表达血小板黏附分子,如P选择素、血管性血友病因子,后者与血小板表面的P选择素结合,致使更多的血小板黏附于血管内皮[14]。这种由血小板、白细胞和内皮细胞之间相互作用而引发的炎性反应,将贯穿动脉粥样硬化发生、进展的全过程。

二、平均血小板体积/血小板计数(MPV/PC)比值和IS

1. MPV和PC:血小板参数可以评估血小板活性,包括PC、MPV和血小板分布宽度(platelet distribution width, PDW)等,通过价廉快捷的血常规即可获得。PC是单位体积血液中所含的血小板数目,反映血小板活化程度的指标之一。既往研究表明,较高和较低水平的PC与IS严重程度相关,并且对患者的预后具有预测价值[15]。目前研究发现,将PC与某些炎性指标组合可能比单独使用PC在评估IS预后方面更有价值[16-17]。所以,血小板相关比值似乎更有研究价值。

MPV是反映血小板大小和活性的参数,与PC呈负相关,研究已明确MPV升高与血小板活化标志物相关,如血小板因子4和血栓素A2的聚集和释放[18]。有研究表明较大的血小板密度更大,含有更多的分泌颗粒,与正常血小板相比,较大的血小板能够引发更多黏附分子表达[19]。而且,血小板在ADP的刺激下,聚集会更快,更容易诱发血栓形成和栓塞,增加心血管事件风险[20]。这表明MPV可能与IS的严重程度呈正相关。另外,MPV也被认为是心房颤动中血栓形成风险的标志物,较高的MPV与心房颤动患者急性IS的发生显著相关[21]。然而,MPV在预测IS患者预后方面的价值仍存在争议。尽管一些研究表明高MPV与IS患者严重程度、不良预后

和死亡率相关[22-23]，但其他研究并没有发现这种关联[24-25]。造成这种差异的原因可能是研究对象不同或MPV水平受到抗血小板药物的影响，因此，应尽量避免影响MPV水平的因素。

2. MPV/PC比值：Azab等[26]提出应将MPV与PC解释为一个比值，而不是独立参数，并回顾性研究619例非ST段抬高型心肌梗死患者中MPV/PC与死亡率的相关性，发现入院时高MPV/PC与4年死亡率相关，且优于单独的MPV。此后，MPV/PC受到国内外研究者们广泛的关注。近年来，MPV/PC与IS预后的研究仍存在争议。Quan等[27]通过随访出院后90 d mRS评分将IS患者预后分为良好和不良组，通过多变量Logistic的回归分析显示，较高的MPV/PC是大动脉粥样硬化性卒中患者90 d预后的独立预测因子（*OR*=1.083，*P*＜0.001）。而另一项研究表明，MPV/PC不是IS患者90 d预后的独立预测因素（*OR*=1.18，*P*=0.062）[28]。造成这种结果的原因可能与治疗方式、样本量有关，后一项研究对象为静脉溶栓患者，样本量较小。最新的一项关于MPV/PC与接受机械血栓切除术（MT）IS患者预后的研究中，Chen等[4]发现预后不良的患者中基线MPV/PC水平较高，高MPV/PC与入院时NIHSS评分呈正相关（*P*=0.013）。此外，Zhu等[29]研究还发现，非瓣膜性心房颤动卒中患者的MPV/PC明显高于大动脉粥样硬化型患者，表明MPV/PC可能是心房颤动患者IS风险的预测因子。因此，MPV/PC水平的升高可作为评估IS患者严重程度及不良预后的指标。

三、血小板/淋巴细胞比值（PLR）和IS

1. 血小板和淋巴细胞：神经炎症在IS的发病机制中起着至关重要的作用[30]。淋巴细胞被认为是IS炎性级联反应的关键调节剂，对缺血后脑损伤具有双重作用。当CD4、非Treg T、CD8、和γδT等细胞浸润脑实质时，将进一步加重脑组织损伤[31-32]。而Treg T细胞是缺血后脑损伤的必需神经保护因子，由其产生的双调素可抑制具有神经毒性的星形胶质细胞增生，从而促进缺血性脑损伤的神经功能恢复[33]。因此，淋巴细胞计数降低可能与卒中后不良结局相关。将血小板和淋巴细胞以比值形式组合，能更好地反映出血栓形成和神经炎症的严重程度。

2. PLR：是一个新型炎性标志物，由Smith等[34]提出，研究其与CA19-9的相关性。既往研究表明PLR在多种疾病的诊断和预后方面具有预测价值[35-36]。近年来，PLR与IS患者预后相关性受到了越来越多的研究者关注。Altintas等[37]回顾性研究57例接受机械取栓治疗的IS患者，发现高PLR与第30、90天的mRS评分呈正相关（*P*=0.004和*P*=0.014），低PLR患者具有更好的功能结局（mRS≤2分）。这种结果在其他研究中也被证实[38-39]。此外，PLR还与静脉溶栓及常规非静脉溶栓治疗的IS患者预后相关。Gong等[5]研究表明，溶栓前PLR水平可能与溶栓后早期神经功能恶化有关（*P*＜0.05），通过多变量Logistic回归分析发现，高PLR是溶栓后神经功能恶化的独立预测因素（*OR*=1.013，*P*=0.001）。Chen等[40]纳入448例非静脉溶栓治疗的IS患者发现，不良预后组患者PLR值较高（*P*＜0.001）。通过多变量Cox回归分析发现高PLR与不良预后显著相关（*OR*=3.54，*P*＜0.001）。而一项关于PLR与IS患者预后的Meta研究表明，PLR可能不是预测IS患者功能结局的预测因子（*OR*=1.00，*P*=0.30）[41]。另外，PLR还与心房颤动患者的血栓形成风险相关，高PLR水平可能会增加心房颤动患者发生血栓栓塞及脑卒中的风险[42]。同时，PLR也能预测心源性脑栓塞的早期神经系统恶化。Cong等[43]研究发现，入院时较高的PLR与非瓣膜心房颤动引起的心源性脑栓塞的早期神经系统恶化独立相关。综上表明，PLR有望成为预测IS患者预后的生物学标志物，但仍需进一步研究来验证。

四、平均血小板体积/淋巴细胞比值（MPVLR）和IS

PLR成为炎症和血栓形成相关的新型预后标志物后，Hudzik等[44]2016年首次提出了MPVLR，通过纳入523例接受经皮冠状动脉介入治疗（percutaneous coronary intervention，PCI）的ST段抬高型心肌梗死患者，回顾性研究MPVLR与疾病预后的相关性。结果发现高MPVLR水平患者的血管造影特征较差，血栓负荷较高，在ROC曲线分析中，还发现MPVLR在预测患者长期死亡率方面优于PLR。Chen等[3]首次纳入241例接受静脉溶栓急性IS患者，通过前瞻性研究MPVLR与IS功能结局的关系。研究结果显示，入院时和溶栓后18～24 h的MPVLR均与功能结局不良独立相关（*OR*=3.141，*P*=0.003和*OR*=6.555，*P*＜0.001），并且MPVLR对IS功能结局的预测价值优于PLR。另一项研究表明，与预后良好组相比，IS患者MPVLR显著增高，危重患者有着更高水平的MPVLR[45]。所以，MPVLR可能是评估IS患者预后潜在的预测指标。

五、血小板/中性粒细胞比值(PNR)和IS

在外周白细胞中，中性粒细胞是缺血后脑损伤的重要炎性细胞。在卒中后的6～8 h，中性粒细胞开始侵入脑缺血区域，接着释放炎性介质，进而加剧脑损伤[46]。此外，中性粒细胞与血小板的相互作用会诱发血栓炎性反应，促进血栓形成[47]。因此，将血小板与中性粒细胞组合为PNR，与单一指标相比，能更好反映出血栓形成和炎症的严重程度[48]。PNR可能是潜在的预测IS预后生物学标志物。Jin等[49]观察到PNR水平是IS患者90 d预后的独立预测因子(*OR*=0.966，*P*=0.023)。而Cao等[50]纳入633例急性IS患者，发现PNR＜31.14与90 d预后独立相关，通过Kaplan-Meier生存曲线分析显示，PNR＜31.14与脑卒中患者90 d卒中复发或死亡率相关(*P*＜0.001)。另外两项研究均通过静脉溶栓后的PNR预测IS患者的预后，结果表明溶栓后24 h内PNR均与功能结局不良独立相关[51-52]。目前，其他溶栓后24 h内的血小板相关比值研究较少，且研究多局限于大动脉粥样硬化性卒中，尚没有涉及其他类型卒中。

六、红细胞分布宽度/血小板比值(RPR)和IS

红细胞分布宽度(RDW)是反映红细胞大小变异性的指标，通常用于区分贫血的病因[53]。既往研究表明，RDW升高可能反映了缺血期炎性反应和氧化应激的状态，高RDW与IS发生相关，但在预测患者临床结局方面尚且存在争议[54-55]。而将RDW与PC组合成RPR指标，可能比单一指标更具灵敏性和特异性。RPR由我国学者陈国德等[56]首次提出，用来预测慢性乙型肝炎患者的肝硬化严重程度。目前，关于RPR与IS的相关性研究相对匮乏，国内外只有少量报道，且研究对象多为大动脉粥样硬化性卒中。李丽莹等[57]研究发现，IS患者的RPR越高，脑梗死面积越大。最新一项研究表明，较高的RPR可能是预测接受MT治疗的IS患者90 d预后的独立预测因子(*OR*=1.671，*P*=0.011)。通过Kaplan-Meier生存曲线分析显示，低RPR组和高RPR组患者90 d生存率差异有统计学意义(*P*=0.026)[39]。这些研究提示了RPR在预测IS预后方面的潜在价值，并为下一步RPR与静脉溶栓患者预后的相关性研究奠定了基础。

七、总结与展望

综上所述，血小板在IS发病机制中起着不可替代的作用。通过检测血小板相关比值对血小板活性及功能进行评估，从而预测IS患者的预后和转归。目前，关于血小板相关比值与IS的研究多为单中心回顾性研究，研究对象多局限于大动脉粥样硬化性卒中，纳入的样本量小，且存在诸多混杂因素，结果可能存在一定误差。其次，在IS诊治过程中，血小板相关比值会动态变化。今后的研究可以动态检测血小板相关比值，而不仅仅是溶栓前的比值。此外，在这些血小板相关比值中，哪一个指标更具敏感及特异性，值得进一步探索。总之，从目前的研究结果来看，衍生血小板相关比值与IS预后不良相关，可能是预测IS预后潜在的生物学标志物。

利益冲突 文章所有作者共同认可文章无相关利益冲突

作者贡献声明 文章构思、设计、修订为刘倍良、王玉芬，文献调研与整理、论文撰写为刘倍良，王玉芬审校

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(收稿日期: 2022-07-19)

(本文编辑: 赵金鑫)