

炎症指标在肝癌中的研究进展

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摘 要

炎症细胞协调的肿瘤微环境是肝癌过程中不可或缺的, 可以促进增殖, 存活和迁移。相关研究表明, 癌症的发生与炎症存在密切的关系, 释放细胞因子并调节人体的免疫系统, 因此找寻能够在早期诊断、准确评估肝癌预后的指标具有重要价值。目前, 炎症指标与肝癌的研究较多, 本文通过RDW、NLR、PLR及控制营养状态(CONUT)评分标志物等进行综述。

关键词

肝癌, 炎症, 预后

Research Progress of Preoperative Immune Nutrition Score and Prognosis of Malignant Tumor

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Abstract

The tumor microenvironment coordinated by inflammatory cells is indispensable in the process

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of liver cancer, promoting proliferation, survival and migration. Relevant studies have shown that the occurrence of cancer is closely related to inflammation, releasing cytokines and regulating the body's immune system. Therefore, it is of great value to find indicators that can be used for early diagnosis and accurate evaluation of the prognosis of liver cancer. At present, there are many studies on inflammation indicators and liver cancer. This article reviews RDW, NLR, PLR and CONUT score markers.

Keywords

Liver Cancer, Inflammation, Prognosis

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1. 引言

肝癌, 是全世界范围内常见的消化系统恶性肿瘤, 在我国尤其高发, 发病率及死亡率均居高位, 是第 4 位的常见恶性肿瘤和第 2 位的肿瘤致死病因[1]。在超过 80% 的患者中, 肝细胞癌发生在肝硬变的不利环境中, 最常与慢性乙型或丙型病毒性肝炎有关, 目前手术和移植仍然是治疗肝细胞癌的根本方法[2]。然而, 接受潜在根治性肝切除的患者的长期预后仍然很差, 报道的 5 年生存率从 26% 到 60% 不等[3] [4] [5]。尽管有治疗意图的切除, 但临床过程是不同的, 复发在很高比例的病例中发生[6], 所以寻求能够在早期诊断及高效的反映肝癌预后的指标具有重要的意义。由 Virchow 假设癌症的起源在慢性炎症部位, 部分基于他的假设, 即某些类别的刺激物, 连同它们引起的组织损伤和随之而来的炎症, 会增强细胞增殖[7]。炎症细胞协调的肿瘤微环境是肿瘤过程中不可或缺的参与者, 可以促进增殖, 存活和迁移。相关研究表明, 癌症的发生与炎症存在密切的关系, 释放细胞因子并调节人体的免疫系统[8]。因此, 炎症指标在评估肝癌预后中可能具有临床价值。常用于监测肝癌预后的指标[9]有甲胎蛋白(alpha-fetoprotein, AFP)、异常凝血酶原(des-gamma-carboxy prothrombin, DCP)等临床标志物。目前, 炎症指标与肝癌的研究较多, 本文通过 RDW、NLR 及控制营养状态(CONUT)评分标志物等进行综述。

2. 细胞分布宽度(Red Blood Cell Distribution Width, RDW)

RDW 是衡量红细胞大小变化范围的指标变化, 它与机体炎症、营养不良状态密切相关。RDW 以往被广泛应用于贫血相关疾病的临床鉴别诊断。然而, 越来越多的证据表明, 高 RDW 与肝病的风险密切相关[10]。近年来 RDW 在恶性肿瘤诊断中的应用备受关注, 一项荟萃分析[11]指出, RDW 升高是癌症患者预后的不利预测因素, 相关研究主要集中在子宫内膜癌、肺癌、肝癌等方面。肝脏病变会造成红细胞系统异常, 出现不同程度的贫血, 其原因可能是铁剂、叶酸及维生素 B12 吸收不良, 肝脏储备功能下降, 叶酸缺乏导致营养性巨幼红细胞性贫血[12]; 铁的缺乏可导致红细胞体积异质性改变, 肝癌时可能叶酸的缺乏大于铁的缺乏, 故 MCV 增大, RDW 改变。中晚期肝癌铁剂、叶酸及维生素 B12 的缺乏更严重, 故 RDW 的改变更明显, 随肝功能的损害程度愈重, RDW 改变愈明显[13]。Zhao [14]等在一项回顾性研究发现, 肝癌根治术患者术前 RDW 升高, 术后生存率低, 其可能是肝癌患者的独立预后因素。并有证据指出, Howell [15]等研究发现, RDW 与索拉非尼治疗晚期肝癌患者术后的生存率具有相关性, 在 Cox 比例风险分析(n = 175)中, RDW (HR 1.234, 95% CI 1.115~1.290, p < 0.0001), 是接受索拉非尼的患者生存

期缩短的显著独立风险因素。因此, RDW 在用于肝癌预测预后上具有重要意义, 同时其简单快捷的获取方式, 也增加了普适性, 但需要注意的是, 在肝癌患者伴有血液及全身炎症系统等疾病时, 需鉴别引起 RDW 升高的病理因素, 确定其适用性。

3. 控制营养状态(Controlling Nutritional Status, CONUT)评分

CONUT 评分, 最早由 Ignacio [16]等提出的一项综合指标营养炎症指标。包括血清白蛋白, 总胆固醇水平和总淋巴细胞计数。CONUT 评分被广泛用于炎症性疾病、慢性心力衰竭和慢性肝病的营养评估的客观工具[17] [18] [19]。其评分标准: 血浆白蛋白(g/L) ≥ 35 、总淋巴细胞数(10^9) ≥ 1.6 、总胆固醇(mg/dl) ≥ 180 , 每项得 0 分; $30 \leq$ 血浆白蛋白(g/L) < 35 、 $1.2 \leq$ 总淋巴细胞数(10^9) < 1.6 、 $140 \leq$ 总胆固醇(mg/dl) < 180 , 每项得 1 分; $25 \leq$ 血浆白蛋白(g/L) < 30 、 $0.8 \leq$ 总淋巴细胞数(10^9) < 1.2 、 $100 \leq$ 总胆固醇(mg/dl) < 140 , 每项得 2 分; 血浆白蛋白 < 25 、总淋巴细胞数(10^9) < 0.8 、总胆固醇(mg/dl) < 100 , 每项得 3 分。CONUT 评分为上述得分总和, CONUT 评分 > 2 分营养不良。目前越来越多研究发现 CONUT 评分在恶性肿瘤[20] [21] [22] [23] [24]的预后中具有有良好的临床价值。Harimoto [25]等在一项回顾性多机构分析 2461 例接受肝细胞癌肝癌根治性肝切除术患者的研究中发现, 术前 CONUT 评分越高, 患者总生存率 OS 和无瘤生存率 RFS 越差。Li [26]等研究表明, 术后早期 CONUT 评分 ≥ 8 被确定为肝细胞癌肝癌切除术后严重并发症的危险因素, 并增加死亡率。而在肝内胆管癌中, Miyata [27]等研究则认为, 高 CONUT 评分与肝内胆管癌肝癌切除术后并发症无关。Zheng [28]等研究发现, CONUT 评分在肝内胆管癌患者根治性切除术可预测复发但不能预测生存率, 特别是在根治性手术后长期饮酒的肝内胆管癌患者中。相较于肝内胆管癌, CONUT 评分与肝细胞癌的关系更加密切, 其判断预后的价值可能越大。综上所述, 在术前 CONUT 评分升高来尽早识别及干预高危患者, 对肝癌患者术后结局具有重要临床意义。

4. 中性粒细胞与淋巴细胞比值(Neutrophil-to-Lymphocyte Ratio, NLR)

中性粒细胞增多是癌症相关慢性炎症的常见特征, 中性粒细胞除了产生与肿瘤进展相关的细胞因子外, 还能抑制细胞毒性 T 细胞的活性, 促进癌细胞转移[29]。中性粒细胞增多通常伴有相对淋巴细胞减少, 代表细胞介导的适应性免疫应答显著下降, NLR 捕获了中性粒细胞增多导致的负面效果与淋巴细胞介导的适应性免疫的有益作用之间的平衡[30]。为了研究 NLR 在对实体瘤预后中的作用, Templeton [31]等人纳入了 100 项研究, 包括 40,559 名患者进行 meta 分析, 分析结果指出, NLR 与 OS (HR: 1.81, 95% CI: 1.67~1.97, $P < 0.001$)显著相关, 并指出高 NLR 与多种癌症的不良生存率有关, 如间皮瘤、胰腺癌、肝癌等。在肝脏疾病中, 慢性肝炎演变为肝硬化, 最终进展为肝癌三部曲。有证据[32]指出, 非酒精性脂肪性肝病(NAFLD)患者 NLR 与纤维化分期、非酒精性脂肪性肝病活动积分(NAS)呈显著正相关, 而慢性乙型肝炎(CHB)患者 NLR 与纤维化分期呈负相关。因此, NLR 可能与肝纤维化分期有关, 尤其是在 NAFLD 患者中。Johnson [33]等在一项前瞻性研究中发现, NLR 是肝细胞癌独立的预后因素, 但 NLR 对肝细胞癌的诊断性非常弱。目前 NLR 升高与肝癌预后相关性的机制并不明确, 有研究发现[34], 中性粒细胞在肝细胞癌中具有双重作用, 一方面, 浸润中性粒细胞可促进肿瘤微环境中的血管生成, 另一方面, 中性粒细胞中缺失增加了肝细胞癌的生长, Xu [35]等人在 13 项个体研究的一项 meta 分析得出, 移植前 NLR 升高与肝移植肝癌患者的 OS 和无病生存率密切相关, 也与血管浸润和米兰肝移植标准密切相关。但是根据目前研究的证据发现, 并没有能准确预测肝细胞癌患者预后的预测因子及评分, Hu [36]等研究发现, 甲胎蛋白(AFP)和 NLR 组合的诊断准确性最高优于单独指标, 该组合的 AUC 为 0.769, 灵敏度为 0.767, 特异性为 0.773, AFP 联合 NLR 对肝细胞癌具有一定的诊断价值。Liao [37]等研究发现, 术前 NLR > 2.31 是肝切除术后肝细胞癌中 DFS 和 OS 的不良预测指标。综上所述, NLR 在预测肝癌术后 DFS 以及 OS 具

有一定的价值。

5. 血小板与淋巴细胞比值(Platelet-to-Lymphocyte Ratio, PLR)

国内外目前研究 PLR 在评估癌症[38] [39] [40] [41]患者预后方面为该领域热点, LI [38]等在 33 项符合条件的队列研究, 包括 8215 名患者的一项 meta 分析得出, PLR 基线水平是晚期和转移性癌症患者 OS 和 PFS 的不良预后因素, 这些患者接受了手术、化疗和靶向治疗。Ma [42]等人的研究中, 高 PLR 是患者 OS 和 PFS 的独立预后危险因素, 但与血管侵犯、肿瘤部位、肿瘤分期无显著相关性。Chen [43]等人研究发现, PLR 在肝癌根治术肝转移具有相关性, 此研究共纳入 1366 例接受根治性切除的 HCC 诊断患者, 结果表明高 PLR 提示肝外转移率高。Xue [44]等观察到, 高 PLR 预示接受 TACE 的晚期肝细胞癌患者的生存率较低。PLR 与肝癌相关的分子机制并不明确, 有证据[45]指出, 相对较高的血小板分泌高水平的血管内皮生长因子(VEGF)和血小板衍生生长因子(PDGF), 它们是血管生成、细胞增殖和肿瘤转移的主要因素。因此 PLR 在肝癌各种治疗方式中均具有一定的作用, 在判断肝癌预后、复发转移等方面具有一定的价值。

6. 小结

综上所述, 肝癌患者的预后不仅与肿瘤的大小、类型及分期相关, 还和宿主免疫炎症反应有关。因此, 如结合上述炎症因子的应用能更准确预测患者的生存期并且对肝癌患者的临床诊疗具有指导意义。通过改善炎症反应提高患者预后, 及时调整肝癌患者的治疗方案。

参考文献

- [1] Sung, H., Ferlay, J., Siegel, R.L., *et al.* (2021) Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA: A Cancer Journal for Clinicians*, **71**, 209-249. <https://doi.org/10.3322/caac.21660>
- [2] Blum, H.E. (2005) Hepatocellular Carcinoma: Therapy and Prevention. *World Journal of Gastroenterology*, **11**, 7391-7400.
- [3] 夏永祥, 张峰, 李相成, 等. 原发性肝癌 10 966 例外科治疗分析[J]. 中华外科杂志, 2021, 59(1): 6-17.
- [4] Yin, Z., Jin, H., Ma, T., *et al.* (2018) A Meta-Analysis of Long-Term Survival Outcomes between Surgical Resection and Radiofrequency Ablation in Patients with Single Hepatocellular Carcinoma ≤ 2 cm (BCLC Very Early Stage). *International Journal of Surgery*, **56**, 61-67. <https://doi.org/10.1016/j.ijssu.2018.04.048>
- [5] Wang, L., Liu, Z., Liu, X., Zeng, Y. and Liu, J. (2017) The Hepatectomy Efficacy of Huge Hepatocellular Carcinoma and Its Risk Factors: A Meta Analysis. *Medicine*, **96**, e9226. <https://doi.org/10.1097/MD.0000000000009226>
- [6] Yamamoto, J., Kosuge, T., Takayama, T., *et al.* (1996) Recurrence of Hepatocellular Carcinoma after Surgery. *British Journal of Surgery*, **83**, 1219-1222. <https://doi.org/10.1046/j.1365-2168.1996.02342.x>
- [7] Coussens, L.M. and Werb, Z. (2002) Inflammation and Cancer. *Nature*, **420**, 860-867. <https://doi.org/10.1038/nature01322>
- [8] Del Campo, J.A., Gallego, P. and Grande, L. (2018) Role of Inflammatory Response in Liver Diseases: Therapeutic Strategies. *World Journal of Hepatology*, **10**, 1-7. <https://doi.org/10.4254/wjh.v10.i1.1>
- [9] Piñero, F., Dirchwolf, M. and Pessôa, M.G. (2020) Biomarkers in Hepatocellular Carcinoma: Diagnosis, Prognosis and Treatment Response Assessment. *Cells*, **9**, Article No. 1370. <https://doi.org/10.3390/cells9061370>
- [10] Li, X., Chen, Q., Bi, X., *et al.* (2021) Preoperatively Elevated RDW-SD and RDW-CV Predict Favorable Survival in Intrahepatic Cholangiocarcinoma Patients after Curative Resection. *BMC Surgery*, **21**, Article No. 105. <https://doi.org/10.1186/s12893-021-01094-6>
- [11] Hu, L., Li, M., Ding, Y., *et al.* (2017) Prognostic Value of RDW in Cancers: A Systematic Review and Meta-Analysis. *Oncotarget*, **8**, 16027-16035. <https://doi.org/10.18632/oncotarget.13784>
- [12] 谢荣华, 范久波. 肝病患者血液检查 4 项指标变化的临床意义[J]. 现代中西医结合杂志, 2006, 15(9): 1225-1226.
- [13] 李霞. 红细胞体积分布宽度与慢性乙型肝炎临床意义的关系[J]. 河北医药, 2012, 34(19): 2980.

- [14] Zhao, T., Cui, L. and Li, A. (2016) The Significance of RDW in Patients with Hepatocellular Carcinoma after Radical Resection. *Cancer Biomarkers*, **16**, 507-512. <https://doi.org/10.3233/CBM-160591>
- [15] Howell, J., Pinato, D.J., Ramaswami, R., *et al.* (2017) Integration of the Cancer-Related Inflammatory Response as a Stratifying Biomarker of Survival in Hepatocellular Carcinoma Treated with Sorafenib. *Oncotarget*, **8**, 36161-36170. <https://doi.org/10.18632/oncotarget.15322>
- [16] Ignacio De Ulbarri, J., González-Madroño, A., De Villar, N.G.P., *et al.* (2005) CONUT: A Tool for Controlling Nutritional Status. First Validation in a Hospital Population. *Nutricion Hospitalaria*, **20**, 38-45.
- [17] Nakagomi, A., Kohashi, K., Morisawa, T., *et al.* (2016) Nutritional Status Is Associated with Inflammation and Predicts a Poor Outcome in Patients with Chronic Heart Failure. *Journal of Atherosclerosis and Thrombosis*, **23**, 713-727. <https://doi.org/10.5551/jat.31526>
- [18] Narumi, T., Arimoto, T., Funayama, A., *et al.* (2013) The Prognostic Importance of Objective Nutritional Indexes in Patients with Chronic Heart Failure. *Journal of Cardiology*, **62**, 307-313. <https://doi.org/10.1016/j.jicc.2013.05.007>
- [19] Yıldırım, B., Biteker, F.S., Acar, E. and Demir, A. (2020) Controlling Nutritional Status Score: A Novel Prognostic Marker for Patients with Community-Acquired Pneumonia. *Hong Kong Journal of Emergency Medicine*, **28**, 227-232. <https://doi.org/10.1177/1024907920923919>
- [20] Kuroda, D., Sawayama, H., Kurashige, J., *et al.* (2018) Controlling Nutritional Status (CONUT) Score Is a Prognostic Marker for Gastric Cancer Patients after Curative Resection. *Gastric Cancer*, **21**, 204-212. <https://doi.org/10.1007/s10120-017-0744-3>
- [21] Tokunaga, R., Sakamoto, Y., Nakagawa, S., *et al.* (2017) CONUT: A Novel Independent Predictive Score for Colorectal Cancer Patients Undergoing Potentially Curative Resection. *International Journal of Colorectal Disease*, **32**, 99-106. <https://doi.org/10.1007/s00384-016-2668-5>
- [22] Toyokawa, T., Kubo, N., Tamura, T., *et al.* (2016) The Pretreatment Controlling Nutritional Status (CONUT) Score Is an Independent Prognostic Factor in Patients with Resectable Thoracic Esophageal Squamous Cell Carcinoma: Results from a Retrospective Study. *BMC Cancer*, **16**, Article No. 722. <https://doi.org/10.1186/s12885-016-2696-0>
- [23] Takagi, K., Yagi, T., Umeda, Y., *et al.* (2017) Preoperative Controlling Nutritional Status (CONUT) Score for Assessment of Prognosis Following Hepatectomy for Hepatocellular Carcinoma. *World Journal of Surgery*, **41**, 2353-2360. <https://doi.org/10.1007/s00268-017-3985-8>
- [24] Yılmaz, A., Tekin, S.B., Bilici, M. and Yılmaz, H. (2020) The Significance of Controlling Nutritional Status (CONUT) Score as a Novel Prognostic Parameter in Small Cell Lung Cancer. *Lung*, **198**, 695-704. <https://doi.org/10.1007/s00408-020-00361-2>
- [25] Harimoto, N., Yoshizumi, T., Inokuchi, S., Itoh, S., *et al.* (2018) Prognostic Significance of Preoperative Controlling Nutritional Status (CONUT) Score in Patients Undergoing Hepatic Resection for Hepatocellular Carcinoma: A Multi-Institutional Study. *Annals of Surgical Oncology*, **25**, 3316-3323. <https://doi.org/10.1245/s10434-018-6672-6>
- [26] Li, L., Liu, C., Yang, J., *et al.* (2018) Early Postoperative Controlling Nutritional Status (CONUT) Score Is Associated with Complication III-V after Hepatectomy in Hepatocellular Carcinoma: A Retrospective Cohort Study of 1,334 Patients. *Scientific Reports*, **8**, Article No. 13406. <https://doi.org/10.1038/s41598-018-31714-w>
- [27] Miyata, T., Yamashita, Y.-I., Higashi, T., *et al.* (2018) The Prognostic Impact of Controlling Nutritional Status (CONUT) in Intrahepatic Cholangiocarcinoma Following Curative Hepatectomy: A Retrospective Single Institution Study. *World Journal of Surgery*, **42**, 1085-1091. <https://doi.org/10.1007/s00268-017-4214-1>
- [28] Zheng, Y., Wu, F., Rong, W., *et al.* (2020) Prognostic Value of the Controlling Nutritional Status (CONUT) Score in Intrahepatic Cholangiocarcinoma Patients Especially Who Had Long-Time Alcohol Consumption. *Journal of Clinical Biochemistry and Nutrition*, **67**, 323-331. <https://doi.org/10.3164/jcbrn.20-27>
- [29] Coffelt, S.B., Kersten, K., Doornebal, C.W., *et al.* (2015) IL-17-Producing $\gamma\delta$ T Cells and Neutrophils Conspire to Promote Breast Cancer Metastasis. *Nature*, **522**, 345-348. <https://doi.org/10.1038/nature14282>
- [30] Zahorec, R. (2001) Ratio of Neutrophil to Lymphocyte Counts—Rapid and Simple Parameter of Systemic Inflammation and Stress in Critically Ill. *Bratislavské Lekárske Listy*, **102**, 5-14.
- [31] Templeton, A.J., Mcnamara, M.G., Šeruga, B., *et al.* (2014) Prognostic Role of Neutrophil-to-Lymphocyte Ratio in Solid Tumors: A Systematic Review and Meta-Analysis. *Journal of the National Cancer Institute*, **106**, dju124. <https://doi.org/10.1093/jnci/dju124>
- [32] Peng Y, Li Y, He Y, *et al.* (2018) The Role of Neutrophil to Lymphocyte Ratio for the Assessment of Liver Fibrosis and Cirrhosis: A Systematic Review. *Expert Review of Gastroenterology & Hepatology*, **12**, 503-513. <https://doi.org/10.1080/17474124.2018.1463158>
- [33] Johnson, P.J., Dhanaraj, S., Berhane, S., Bonnett, L. and Ma, Y.T. (2021) The Prognostic and Diagnostic Significance of the Neutrophil-to-Lymphocyte Ratio in Hepatocellular Carcinoma: A Prospective Controlled Study. *British Journal of Cancer*, **125**, 714-716. <https://doi.org/10.1038/s41416-021-01445-3>

- [34] Arvanitakis, K., Mitroulis, I. and Germanidis, G. (2021) Tumor-Associated Neutrophils in Hepatocellular Carcinoma Pathogenesis, Prognosis, and Therapy. *Cancers*, **13**, Article No. 2899. <https://doi.org/10.3390/cancers13122899>
- [35] Xu, Z.-G., Ye, C.-J., Liu, L.-X., *et al.* (2018) The Pretransplant Neutrophil-Lymphocyte Ratio as a New Prognostic Predictor after Liver Transplantation for Hepatocellular Cancer: A Systematic Review and Meta-Analysis. *Biomarkers in Medicine*, **12**, 189-199. <https://doi.org/10.2217/bmm-2017-0307>
- [36] Hu, J., Wang, N., Yang, Y., Ma, L., Han, R., *et al.* (2018) Diagnostic Value of Alpha-Fetoprotein Combined with Neutrophil-to-Lymphocyte Ratio for Hepatocellular Carcinoma. *BMC Gastroenterology*, **18**, Article No. 186. <https://doi.org/10.1186/s12876-018-0908-6>
- [37] Liao, W., Zhang, J., Zhu, Q., *et al.* (2014) Preoperative Neutrophil-to-Lymphocyte Ratio as a New Prognostic Marker in Hepatocellular Carcinoma after Curative Resection. *Translational Oncology*, **7**, 248-255. <https://doi.org/10.1016/j.tranon.2014.02.011>
- [38] Li, B., Zhou, P., Liu, Y., *et al.* (2018) Platelet-to-Lymphocyte Ratio in Advanced Cancer: Review and Meta-Analysis. *Clinica Chimica Acta*, **483**, 48-56. <https://doi.org/10.1016/j.cca.2018.04.023>
- [39] Diem, S., Schmid, S., Krapf, M., *et al.* (2017) Neutrophil-to-Lymphocyte Ratio (NLR) and Platelet-to-Lymphocyte ratio (PLR) as Prognostic Markers in Patients with Non-Small Cell Lung Cancer (NSCLC) Treated with Nivolumab. *Lung Cancer*, **111**, 176-181. <https://doi.org/10.1016/j.lungcan.2017.07.024>
- [40] Zhang, Y., Zheng, L., Quan, L. and Du, L. (2021) Prognostic Role of Platelet-to-Lymphocyte Ratio in Oral Cancer: A Meta-Analysis. *Journal of Oral Pathology & Medicine*, **50**, 274-279. <https://doi.org/10.1111/jop.12832>
- [41] Lin, W.-F., Zhong, M.-F., Zhang, Y.-R., *et al.* (2018) Prognostic Role of Platelet-to-Lymphocyte Ratio in Hepatocellular Carcinoma with Different BCLC Stages: A Systematic Review and Meta-Analysis. *Gastroenterology Research and Practice*, **2018**, Article ID: 5670949. <https://doi.org/10.1155/2018/5670949>
- [42] Ma, W., Zhang, P., Qi, J., *et al.* (2016) Prognostic Value of Platelet to Lymphocyte Ratio in Hepatocellular Carcinoma: A Meta-Analysis. *Scientific Reports*, **6**, Article No. 35378. <https://doi.org/10.1038/srep35378>
- [43] Chen, Y., Zeng, J., Guo, P., Zeng, J. and Liu, J. (2021) Prognostic Significance of Platelet-to-Lymphocyte Ratio (PLR) in Extrahepatic Metastasis of Hepatocellular Carcinoma after Curative Resection. *Cancer Management and Research*, **13**, 1395-405. <https://doi.org/10.2147/CMAR.S290738>
- [44] Xue, T.-C., Jia, Q.-A., Ge, N.-L., *et al.* (2015) The Platelet-to-Lymphocyte Ratio Predicts Poor Survival in Patients with Huge Hepatocellular Carcinoma That Received Transarterial Chemoembolization. *Tumor Biology*, **36**, 6045-6051. <https://doi.org/10.1007/s13277-015-3281-x>
- [45] Bambace, N.M. and Holmes, C.E. (2011) The Platelet Contribution to Cancer Progression. *Journal of Thrombosis and Haemostasis*, **9**, 237-249. <https://doi.org/10.1111/j.1538-7836.2010.04131.x>