

炎症水平相关指标与胃癌患者预后的关系

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摘要

胃癌(Gastric cancer)被定义为源自胃的原发性上皮恶性肿瘤,是一种具有多种危险因素的复杂异质性疾病。尽管在过去几十年中,GC在各个国家的发病率和死亡率总体呈下降趋势,但GC仍然是全球第五大最常见的恶性肿瘤和癌症相关死亡的第四大原因。早期胃癌的主要治疗方法是内镜切除术,非早期胃癌通过手术治疗。围手术期或辅助化疗可提高1B期或更高分期癌症患者的生存率,晚期胃癌采用序贯化疗,从一线铂类和氟嘧啶双联疗法开始。获准用于治疗胃癌的靶向疗法包括曲妥珠单抗(HER2阳性患者一线治疗)、雷莫芦单抗(抗血管生成二线治疗)和纳武利尤单抗或帕博利珠单抗(抗PD-1三线治疗)。在过去的40年中,基于氟尿嘧啶的方案仍然是辅助化疗的一线选择。然而,几项经典临床试验表明,辅助化疗组患者的总生存期仅略高于单手术组,这表明并非所有患者都能从辅助化疗中获益。这些发现强烈强调了对GC进行进一步分类、识别具有不同复发风险的患者以及确定化疗获益可能性的迫切需要。因此,如何延长胃癌患者的生存时间、提高患者的生存率是目前临床研究的重点。营养状况较差常存在于恶性肿瘤患者中,不良的营养状况可能会增加患者围术期并发症的发生率及死亡率,导致较差的预后;炎症与肿瘤常常相互作用,肿瘤诱发机体炎症加剧、炎症进一步促进肿瘤进程。目前临床上已有多种反应机体营养状况及炎症水平的指标,本文就患者的营养状况、炎症水平相关指标与胃癌患者预后的关系进行综述,为临床医生提供预测患者预后的信息,为患者制定个性化且具体的诊疗方案。

关键词

胃癌, 炎症, 预后, 免疫炎症指数

The Relationship between Inflammation Level Related Indicators and Prognosis of Gastric Cancer Patients

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Abstract

Gastric cancer, defined as a primary epithelial malignant tumor derived from the stomach, is a complex and heterogeneous disease with multiple risk factors. Despite the overall decreasing trend of GC incidence and mortality in various countries over the past decades, GC remains the fifth most common cause of malignancy and fourth cancer-related death worldwide. The main treatment for early gastric cancer is endoscopic resection. Non-early surgical gastric cancer is treated by surgery. Perioperative or adjuvant chemotherapy improves survival in patients with stage 1B or higher cancer. Advanced gastric cancer uses sequential chemotherapy, starting with first-line platinum and fluoropyrimidine bitherapy. Targeted therapies approved for the treatment of gastric cancer include trastuzumab (first-line therapy in HER2-positive patients), ramolimumab (second-line therapy), and navulizumab or pabolizumab (anti-PD-1 third-line therapy). In the past 40 years, fluorouracil-based regimens remain the first-line option for adjuvant chemotherapy. However, several classic clinical trials showed that overall survival in patients in the adjuvant chemotherapy group was only slightly higher than in the single-surgery group, suggesting that not all patients benefit from adjuvant chemotherapy. These findings strongly highlight the urgent need for further classification of GC, identification of patients with different risks of recurrence, and determining the possibility of benefit from chemotherapy. Therefore, how to prolong the survival time and improve the survival rate of GC patients is the focus of clinical research. Poor nutritional status often exists in patients with malignant tumors. Poor nutritional status may increase the incidence and mortality of perioperative complications and mortality of patients, leading to poor prognosis; inflammation and tumor often interact to induce inflammation and further promote the tumor process. At present, there are various indicators reflecting the nutritional status and inflammation level of the body in clinical practice. This paper reviews the relationship between the nutritional status and inflammation level and the prognosis of gastric cancer patients, so as to provide clinicians with information to predict the prognosis of patients, and to formulate personalized and specific diagnosis and treatment plans for patients.

Keywords

Gastric Cancer, Inflammation, Prognosis, Immune Inflammation Index

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1. 引言

胃癌(GC)被定义为源自胃的原发性上皮恶性肿瘤,是一种具有多种危险因素的复杂异质性疾病。尽管在过去几十年中,GC在各个国家的发病率和死亡率总体呈下降趋势,但GC仍然是全球第五大最常见的恶性肿瘤和癌症相关死亡的第四大原因。尽管全球GC负担呈显著下降趋势,但在某些地区(如亚洲)仍然很严重。胃食管癌发病率和死亡率在中国所有癌症类型中排名第三,分别占全球胃癌新发病例和胃肠道相关死亡病例的近44.0%和48.6% [1]。

胃癌患者表现出“三高三低”特征,发病率高、转移率高、死亡率高,早期诊断率低、根治性切除率低、5年生存率低[2]。胃癌病例可分为早期胃癌和晚期胃癌。早期胃癌局限于黏膜或黏膜下层,无论病变的大小和是否存在淋巴结转移。超出黏膜下层侵入胃肌肉层的癌症是中胃癌,而浸润到浆膜下层或浆膜下层

到附近器官或转移的肿瘤是晚期胃癌。晚期胃癌包括中度和晚期肿瘤。肿瘤的分期决定了治疗效果和治疗策略。例如，早期胃癌患者先行根治性手术后再进行化疗，术后5年生存率为90%；因此，早期胃癌的治疗效果是可以接受的。然而，由于缺乏早期胃癌的特异性体征，检出率较低，因此，大多数患者(>70%)发展为晚期疾病。有些患者甚至失去了接受手术切除的机会。晚期胃癌也可能存在转移潜力，因此整体预后较差。近年来，为改善胃癌患者的预后进行了大量研究，新辅助化疗、放疗和分子靶向治疗已成为有效的方法。

1994年，Mai等人[3]报告了24例晚期胃癌患者，这些患者接受了5-氟尿嘧啶(5-FU) + 表柔比星 + 丝裂霉素(FAM)或mtx/5-FU化疗方案。82%的患者恶性腹水消失，68%的患者行根治性切除术，术后中位生存时间为14个月。1997年，Crookes等人[4]报告了56例晚期胃癌患者，术前接受5-FU + 亚叶酸钙 + 顺铂(FLP)化疗。总共有40名患者接受了根治性切除术。完全缓解5例，降至I期12例，降至II期13例。然而，新辅助化疗可以提高R0切除率并减少肿瘤分期，但对长期生存率没有明显优势[5][6][7]。此外，有关抗血管生成的靶向治疗已被纳入各种肿瘤的治疗方案，包括卵巢癌。血管内皮生长因子及其受体的相关通路得到了极大的探索，该通路已被证实在恶性腹水、肿瘤进展中发挥了重要作用，通过使用单克隆抗体作用于血管内皮生长因子或其受体来阻断此通路已被广泛应用于临床，代表药物为贝伐珠单抗[8]。贝伐珠单抗是一种重组人源化单克隆抗体，通过抑制VEGF起作用[9]。贝伐珠单抗与VEGF联合阻断VEGFR的活化，从而抑制肿瘤血管生成。Shah等人[10]。评估贝伐珠单抗和伊立替康联合顺铂治疗晚期胃癌的有效性。47例未经治疗的转移性胃癌或胃食管交界处癌患者中，有效率为65%，中位生存时间为12.3个月。最终组织学证据显示总缓解率高达75%。免疫疗法是一种新型的抗癌疗法，它使用免疫肿瘤疫苗或抗肿瘤抗体来激活人体自身的免疫系统来对抗癌症[11]。免疫系统可用于通过免疫监视来识别和清除恶性肿瘤，以抑制肿瘤的发展[12]。通过免疫检测点涉及的抑制信号通路抑制T细胞活性是肿瘤细胞逃避宿主主导的免疫识别和杀伤的重要机制。因此，靶向免疫细胞表面抗原的免疫调节抗体阻断免疫抑制信号，增强免疫细胞活性，代表了肿瘤治疗的新方向。PD-1可与PD-L1和PD-L2结合，抑制肿瘤微环境、肿瘤特异性T细胞功能和免疫监视功能，促进肿瘤细胞生长。

GC是一个严重的公共卫生问题，预防是降低死亡率的关键。对于GC风险较高的患者，可以考虑使用可用的筛查测试，例如血清标志物或内窥镜检查。对癌前病变的监测和仔细的内镜检查可以改善早期GC的预防和检测。发现早期病变的主要障碍是全球缺乏对GC的系统筛查测试。探寻无创安全、灵敏有效的早期筛查手段仍然是现在难以攻克的难点之一。想要改善胃癌患者的预后、显著提高患者的总体生存率，早期发现、首次就诊时全面评估、适当的支持治疗等都是重要的影响因素。

2. 营养状况与胃癌

2.1. 营养不良及影响

营养是人体摄取、消化、吸收，利用食物中的营养物质，以此维持人体生命活动的一个整体的过程。有研究显示，住院患者存在营养不良时，其身体的各个器官功能都将发生减退、机能下降，从而影响全身健康状况，若患者在治疗过程中发生营养不良，其对药物的反应程度也将有所下降、住院天数也更长[13][14]。营养不良在胃癌患者中尤为常见，因为该癌症累及一个主要消化器官，并伴有抗癌治疗后的症状(如恶心、呕吐、早饱、食欲不振和吞咽困难)，导致患者摄入不足和营养吸收不良[15][16]。晚期或转移性胃癌患者经常患有营养不良，这可能会影响生活质量，增加化疗的毒性并降低总生存期。据估计，40%~80%的癌症患者在病程中会出现营养不良，由于促炎细胞因子与宿主代谢之间的复杂相互作用，营养不良可能发展为恶病质[17][18]。最终，恶病质占有癌症相关死亡的20%以上[19]。

2.2. 营养状况评价指标

想要了解患者的营养状况并加以干预，需要在治疗前评其营养状况，主要的方法包括客观测量和主观评估，临床上常应用的营养评价方法主要以下两类。

2.2.1. 人体测量法

使用人体测量的方法筛查患者营养状况，方法简单并且易于操作。常用的指标包括患者的身高、发病前体重、入院体重、身体质量指数(BMI)、上臂维度、三角肌的皮褶厚度等。其中通过 BMI 判定患者营养状况的标准为：BMI ≥ 23 为营养过剩， $18.5 \leq \text{BMI} < 23$ 为营养正常，BMI < 18.5 为营养不足。

2.2.2. 临床辅助检验法

通过对患者血清中的白蛋白、前白蛋白、总淋巴细胞、血红蛋白等的含量进行测定判定患者营养状况。目前以上的多种指标诊断患者营养不良的参考值分别为白蛋白 $< 35 \text{ g/L}$ 、前白蛋白 $< 200 \text{ mg/L}$ 、淋巴细胞 $< 1.1 \times 10^9/\text{L}$ 、血红蛋白 $< 110 \text{ g/L}$ 。

2.3. 血清白蛋白相关指标

白蛋白是一种主要的血浆蛋白，表明一个人的营养状况。该蛋白参与维持血管内肿瘤压力、清除自由基和维持类固醇激素止血[20]。先前的研究表明，低白蛋白血症是结直肠癌[21]的预后指标。胃癌患者术前低水平的血清白蛋白与术后不良的 OS 相关，表明白蛋白是胃癌的预后生物标志物。ALP 是一种广泛存在于肝脏、骨骼和肾脏等哺乳动物组织中的膜结合糖蛋白。血清 ALP 与恶性疾病中肝脏和骨转移密切相关[22] [23] [24]。

白蛋白/碱性磷酸酶比值(Albumin-to-Alkaline Phosphatase Ratio, AAPR)

碱性磷酸酶是广泛分布于人体肝脏、骨骼、胎盘、肾脏等组织，并且经过肝脏向胆外排出的一种酶，它可以使各种类型的分子(核苷酸、蛋白质和生物碱)脱磷酸化[25]。血清碱性磷酸酶也是各种癌症的独立预测因子。包括乳腺癌[26]、胃癌[27]等。由于白蛋白和 ALP 都是几种癌症的生存预后指标，Chan 等人[28]导出了白蛋白 - 碱性磷酸酶比值，将这两个参数放在一起，发现在肝细胞癌(HCC)患者中，AAPR 比单独使用白蛋白和 ALP 更好的预后指标。此后，AAPR 的预后能力在几种类型的癌症中得到验证。但 AAPR 目前在胃癌中的研究尚无，需要进一步的大样本、多中心试验验证其预测价值。

3. 炎症水平与胃癌

3.1. 炎症与肿瘤

炎症是身体对组织损伤的反应，由身体损伤、缺血性损伤(由器官供血不足引起)、感染、暴露于毒素或其他类型的创伤引起。身体的炎症反应会引起细胞变化和免疫反应，从而导致受损组织的修复和受伤组织部位的细胞增殖(生长)。如果炎症的原因持续存在或负责关闭该过程的某些控制机制失效，炎症可能会变成慢性。当这些炎症反应变成慢性反应时，会导致细胞突变和增殖，通常会创造一个有利于癌症发展的环境。

1863 年，Virchow 注意到肿瘤组织中的白细胞，并在炎症和癌症之间建立了联系。他认为，“淋巴网状浸润”反映了癌症起源于慢性炎症部位。并且炎症分子增加血管通透性、肿瘤淋巴管生成和肿瘤细胞的转移扩散，并有助于肿瘤细胞与内皮细胞的黏附和转移部位的基质侵袭。研究表明存在慢性炎症和氧自由基超载疾病的患者罹患肿瘤的风险更高，持续的炎症微环境提供了各种活性氧、生长因子和细胞因子，可以影响正常细胞内平衡的关键进程，导致基因组不稳定、诱导肿瘤发生[29]。由于炎症与肿瘤生

长密切相关，反映全身炎症水平的血清标志物可作为肿瘤临床结局和预后的预测因子。

3.2. 血清炎症标志物

3.2.1. 中性粒细胞/淋巴细胞比值(Neutrophil to Lymphocyte Ratio, NLR)

中性粒细胞可以通过释放胞外诱捕网(NETs)进而降解细胞外基质、改变血管完整性、促进血管生成等，参与肿瘤的进展和转移，亦可以通过释放中性粒细胞释放酶、促肿瘤细胞因子和趋化因子，增加肿瘤细胞的浸润[30] [31]。而淋巴细胞通过抑制肿瘤细胞增殖迁移、诱导肿瘤细胞死亡，在免疫监视及清除系统中发挥了重要的作用，淋巴细胞的减少显示了机体免疫监测系统处于功能低下状态[32]。中性粒细胞占人体循环中所有白细胞的 50%~70%，在氧化应激反应的稳态条件下平均寿命为 5.4 天[33]。目前认为它们通过产生促血管生成趋化因子和血管内皮生长因子来促进癌细胞增殖、血管形成和转移[34] [35]。外周血中的淋巴细胞目前被认为具有协同细胞毒性并发挥抑癌特性[36]。NLR 是两种细胞的绝对值之比，目前关于 NLR 在胃癌患者中价值的相关研究较多。研究表明，NLR 与 GC 的诊断有关，特别是在男性患者中。

3.2.2. 血小板/淋巴细胞比值(Platelet to Lymphocyte Ratio, PLR)

血小板作为细胞因子的重要来源，可以结合血管生成因子、TGF- β 家族蛋白等 成为生长因子的储蓄池，进而参与调节肿瘤血管生长、细胞增殖迁移和转移等重要进程[37] [38]。PLR 结合了血小板和淋巴细胞计数，是全身炎症和免疫状态的代表性指[39] [40]。越来越多的证据表明，PLR 与 GC 患者的肿瘤发展不同阶段、化疗反应和预后生存结局相关[41] [42]。多篇研究表明，PLR 升高预示着 GC 患者术后 OS 和 DFS 较差[43] [44]。Lian 等报道，低 PLR 水平与更好的临床病理学特征相关，包括浸润深度降低、淋巴结转移减少和肿瘤早期[45]。

3.2.3. 系统免疫炎症指数(Systemic Immune-Inflammation Index, SII)

在 2014 年 Hu 等学者构建了由淋巴细胞、中性粒细胞、血小板计数为基础的新型炎症水平标志物——SII，并同时表明其在预测肝癌患者预后的可行性[46]。SII 相较于 NLR、PLR 等指标，将三种炎症相关细胞整合在一起，其预测价值更高。Wang 等[47]对 448 例胃癌患者进行回顾性分析发现，与低 SII 组患者相比，高 SII 组患者的 TNM 分期明显较晚，高 SII 的胃癌患者更易发生侵袭、转移。张宇等[48]对 823 例胃癌患者研究的结果也表明，术前外周血中 SII 较高的胃癌患者 TNM 分期较晚。SII 作为临床上较易获得的炎症因子，已被广泛应用于胃癌、肝癌、结直肠癌等恶性肿瘤的预后评估[49] [50] [51]。

4. 小结

由于可靠的早期筛查手段缺乏、化疗耐药、复发率高等原因，胃癌患者仍然不能有较为理想的生存率。恶性肿瘤患者往往合并营养状况低下，这在卵巢癌患者中亦非常常见；此外，炎症相关影响也不容忽视，炎症、营养以及肿瘤之间往往是相互作用、相互影响的，多重因素导致患者机体功能下降、免疫机制受损。目前对于患者营养状况和炎症水平评估的指标日渐丰富，这些检测指标往往可得性高、花费少，可以在患者就诊时对其病情有一定的了解，并通过有效的方式在进行卵巢癌治疗予以改善一般情况，可能对患者的预后有一定的积极影响。

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