

· 综述 ·

## 炎症因子在消化道肿瘤术后ERAS管理中吻合口漏的预测作用及研究进展

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**[摘要]** 近年来随着加速康复外科(enhanced recovery after surgery, ERAS)不断推广与完善,快速康复成为消化道肿瘤围手术期管理的重要内容。通过围手术期ERAS管理,患者平均住院时间明显缩短,但仍存在一些并发症(如吻合口漏等)难以早期发现,从而增加了患者再入院的风险。大量文献提出,一些炎症因子与术后吻合口漏有显著相关性,且对其发生有重要预测价值,但其在ERAS风险管控中的预测价值尚无报道。文章就炎症因子在消化道肿瘤术后ERAS管理中预测吻合口漏的研究进展进行综述,以期寻找较敏感的预测指标,指导患者安全出院。

**[关键词]** 炎症因子;消化道肿瘤;ERAS;吻合口漏

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### The role and research progress of inflammatory factors in prediction of anastomotic leakage after gastrointestinal tumor surgery within an enhanced recovery after surgery (ERAS) program

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**[Abstract]** In recent years, with the continuous promotion and improvement of enhanced recovery after surgery (ERAS), rapid recovery has become an important part of perioperative management of gastrointestinal tumors. Under the influence of ERAS, the average hospital stay of patients has been significantly shortened, but some complications (such as anastomotic leakage) are difficult to be detected early, thus increasing the risk of hospital readmission. A large number of literatures proposed that some inflammatory factors were significantly correlated with postoperative anastomotic leakage and had important predictive value in its occurrence, but its predictive value in risk management and control in ERAS has not been reported. In this paper, research progress of inflammatory factors in predicting anastomotic leakage in postoperative ERAS management of digestive tract tumors was reviewed, in order to search for more sensitive predictors to guide patients discharged safely.

**[Key words]** inflammatory factors; gastrointestinal tumors; ERAS; anastomotic leakage

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消化道肿瘤是世界上发病率和死亡率最高的肿瘤之一<sup>[1-2]</sup>,其最主要的治疗手段是根治性外科手

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术。虽然近年来手术技术在不断提高,但术后仍然存在吻合口漏的发生,且术后迟发性吻合口漏的病死率高达18%<sup>[3]</sup>。目前术后吻合口漏的诊断主要依靠临床表现及影像学检查,确诊漏的发生往往在术后第5~7天,早期发现较为困难<sup>[4]</sup>。

近年来,随着医学进步,加速康复外科(enhanced recovery after surgery, ERAS)得到不断完善

和推广,目前已被广泛应用于胃肠道手术的围手术期管理中<sup>[5]</sup>。与传统围手术期管理相比,它可缩短住院时间,减少医疗费用,减轻术后应激反应,减少并发症,促进术后胃肠功能恢复<sup>[6]</sup>。但是患者在早期出院的同时,吻合口漏这一潜在风险仍然无法规避,且目前临床缺乏有效的预测手段。因此有必要寻找敏感的炎性指标,预测可能存在这些安全隐患的患者。本文就消化道肿瘤术后ERAS管理中炎性因子对于吻合口漏的预测作用进行综述,以期寻找敏感的预测指标,指导患者安全出院,减少再入院的风险。

### 1 C-反应蛋白(C-reactive protein,CRP)

1930年,法国科学家Tillett和Francis首次在急性大叶性肺炎患者血清中发现了CRP。它是肝细胞合成的一种急性时相蛋白,在正常人体内含量极低,但当人体组织受到损伤、感染及肿瘤侵犯时,其血液中的含量可快速上升,短期内即可升高数倍甚至数百倍,并且不受性别、年龄、贫血、高球蛋白血症等因素的影响,所以成为临床上最常用的炎性指标之一。

研究发现围手术期ERAS的应用能够有效降低结肠癌术后第1天至第3天(postoperative day 1-3, POD1-3)CRP水平,且在腹腔镜手术后减少更明显<sup>[7]</sup>。而在发生并发症的患者中,POD1-3的CRP水平显著升高。越来越多研究发现CRP可作为消化道肿瘤术后并发症的潜在预测指标。Welsch等<sup>[8]</sup>研究发现,结直肠癌患者自POD2起,吻合口漏组的平均血清CRP水平显著高于非吻合口漏组,且吻合口漏组患者的血清CRP水平一直高于正常值。由此提出,术后早期血清CRP的持续升高可预测结直肠癌术后吻合口漏的发生,其中POD3血清CRP水平具有更高的灵敏度(80.0%)和特异度(81.0%),其截断值为140 mg/L。Shishido等<sup>[9]</sup>研究了CRP与胃癌术后并发症的关系,结果显示POD3血清CRP>177 mg/L对术后并发症的预测灵敏度为66.0%,特异度为84.0%。Kim等<sup>[10]</sup>通过类似研究也提出了CRP是胃癌术后并发症可靠的预测指标,POD4是最佳预测时间,其截断值为168 mg/L。吕泽坚等<sup>[11]</sup>运用ERAS管理流程对455例腹腔镜直肠癌根治术患者进行研究与分析,发现术后第3天CRP具有较高的灵敏度(79.3%)和特异度(92.3%),该截断值为80.09 mg/L,明显低于上述研究,这是否与推行ERAS有关,还有待进一步研究。

上述研究说明POD1-4 CRP水平有助于术后吻合口漏的早期诊断。实施ERAS后CRP水平虽然较传统方式有所下降,但CRP水平如果持续升高,临床上应尽早查明原因,必要时可结合影像学检查排除吻合口漏。

同时应当注意的是,CRP水平会受到某些术前因素的影响,如肿瘤分期和患者营养状况,并且在临床上也缺乏一个公认的截断值,所以作为单一指标难以充分发挥其评估价值。Ge等<sup>[12]</sup>发现将CRP与血清白蛋白(albumin, ALB)比值预测结直肠癌术后吻合口漏比单独运用CRP的准确性更高。提示选取多项敏感指标进行组合和综合评估,可能对吻合口漏的预测有更大的临床意义。

### 2 降钙素原(procalcitonin,PCT)

PCT是一种半衰期较短的炎性指标,由甲状腺滤泡细胞分泌,在人体中含量较低,很难被检测出来。当机体受到严重细菌感染或多脏器功能衰竭(multiple organ dysfunction syndrome, MODS)时可由多种器官的组织细胞产生,血液中含量极速升高,而非感染性炎症PCT水平不会升高,故临床上常用它对术后感染的严重程度进行评估。与传统的炎性指标(如CRP、白细胞计数)相比,PCT是一种更早、更灵敏可靠的标志物,可作为腹部手术后感染性并发症的早期预测指标<sup>[13]</sup>。

Oberhofer等<sup>[14]</sup>对79例择期结直肠手术患者进行前瞻性观察研究,检测术前及POD1-5的炎性指标。结果表明,PCT预测感染性并发症的最佳时间为POD2-3,其截断值为1.34 μg/L,并且连续测量PCT水平并不能提高术后感染性并发症的检出率。Giaccaglia等<sup>[15]</sup>对108例行择期结直肠手术的患者进行研究分析,POD3、POD5时吻合口漏组的血清PCT水平明显高于非吻合口漏组,且具有较高的阴性预测值(96.7%)。该研究也提出,在POD3、POD5时联合监测CRP能提高诊断准确性。Muñoz等<sup>[16]</sup>对134例按ERAS流程行腹腔镜结直肠癌手术的患者进行分析显示,PCT可预测术后吻合口漏,POD3为最佳预测时间,截断值2.5 ng/mL,灵敏度85%,特异度95%,阳性预测值44%,阴性预测值99%。

尽管大量研究表明,PCT在POD3-5时对吻合口漏具有良好的预测价值,但Lagoutte等<sup>[17]</sup>提出了反驳,通过对100例实施ERAS的结直肠癌患者进行分析,10例吻合口漏患者中只有4例PCT水平明显升高,而6例PCT水平与无并发症组差异无统计学意

义,统计得出PCT与吻合口漏的相关指数仅为9.7,远低于CRP的26.1。Facy等<sup>[18]</sup>研究结果也认为PCT的预测价值不如CRP。综上所述,PCT对于消化道肿瘤术后吻合口漏的预测准确性目前仍存在争议,因此不宜作为一个单独的预测指标。

### 3 白介素(interleukin,IL)-6

IL是由体内多种细胞产生的一类细胞因子,参与信息传递、免疫应答及炎症反应。而IL-6是白介素家族中的一员,在炎症反应中起非常重要的作用,在病理状态下,它被大量分泌进入血液循环、体液及尿液中,通过与其受体结合调节机体整个内环境的稳定<sup>[19]</sup>。

大量证据表明,围手术期ERAS管理能有效减轻患者手术应激反应,且对免疫影响较小,使术后IL-6水平低于传统方案,并在短期内恢复至正常水平<sup>[20]</sup>。若术后其水平明显升高,则提示患者可能存在并发症的风险。目前只有少数研究提出了IL-6的预测价值,这可能与其半衰期较短和检测误差大有关。Rettig等<sup>[21]</sup>研究发现,若胃癌术后第1天IL-6水平明显升高,则发生术后吻合口漏的概率也相应增加,其截断值为432 pg/mL,预测并发症的灵敏度为64%,特异度为70%。Mokart等<sup>[22]</sup>通过类似研究发现,术后第1天IL-6水平可预测未来5 d内吻合口漏的发生,截断值为310 pg/mL。

上述研究提示,与CRP和PCT相比,IL-6在POD1即可对胃肠道肿瘤术后吻合口漏进行预测,这对于ERAS管理来说意义重大,能早期发现高风险患者,及时采取干预措施,以降低其出院后发生吻合口漏的风险。但IL-6本身受到一些因素的影响,如危重患者体内含量较高、基因多态性可引起其高表达<sup>[23]</sup>等,这些往往会影响到预测的准确性。所以,IL-6难以作为一个独立的预测指标,但可与其他敏感因子联合使用,以增强预测的准确性。

### 4 炎症相关因素

#### 4.1 中性粒细胞/淋巴细胞比值(neutrophil/lymphocyte ratio, NLR)

中性粒细胞计数与淋巴细胞计数在免疫应答及炎症反应中均起着至关重要的作用。有证据表明,血液中高水平的中性粒细胞可促进肿瘤生长与转移,并且抑制抗肿瘤的免疫反应,而血液中淋巴细胞数量减少也会削弱抗肿瘤的免疫反应。因此,NLR的升高往往预示着肿瘤的进展与复发,是预后

不良的重要预测指标。

近年来针对NLR与消化道肿瘤术后并发症关系的研究也逐渐增多。Mohri等<sup>[24]</sup>研究发现术前NLR可预测胃癌术后感染性并发症及长期生存率,其截断值为3.0。Josse等<sup>[25]</sup>和Jones等<sup>[26]</sup>通过对结直肠癌患者的研究也得出类似结论,其截断值分别为2.3与4.0。而Mik等<sup>[27]</sup>报道,结直肠癌POD4 NLR水平可预测吻合口漏的发生,截断值为6.5,其灵敏度与特异度均低于CRP,且不适用于术前进行新辅助化疗的患者。但鉴于它在临床可操作性高,易于获得,因此在ERAS管理中可作为预测吻合口漏的辅助指标。

#### 4.2 血清ALB相对变化率

ALB是血浆中最主要的蛋白质,具有多种生物学效应,包括维持机体渗透压、稳定细胞生长、参与DNA的复制和全身炎症反应。血清ALB水平过低往往提示营养不良和免疫抑制,促进了肿瘤进展,增加了预后不良的风险。研究表明,术前或术后低蛋白血症是胃肠道术后感染性并发症的危险因素,尤其是手术部位感染<sup>[28]</sup>。

ALB同时也是一种急性炎症期反应蛋白,在全身炎症情况下,毛细血管通透性会增加,导致其在术后立即减少。它对手术的应激反应可能早于CRP,且在胃肠道恶性肿瘤术后2 d内可下降33%<sup>[29]</sup>,特别是在发生感染性并发症的患者中,下降更明显。Ge等<sup>[12]</sup>研究了围手术期血清ALB相对变化( $\Delta$ ALB)与腹腔镜结直肠癌术后并发症的关系,将 $\Delta$ ALB定义为(术前ALB值-POD2内ALB最低值)/术前ALB值 $\times 100\%$ ,通过ROC曲线分析得出, $\Delta$ ALB可作为预测并发症的指标,其截断值为15%。Wang等<sup>[30]</sup>通过类似研究也得出了这个结论,其截断值为17.3%。

上述研究证实了 $\Delta$ ALB有助于评估术后发生感染性并发症的风险,但有文献报道,性别、手术时间、手术方式、气孔创建、术中输血以及术中液体的使用均可影响术后ALB水平<sup>[30]</sup>,因此临床上也不宜将其单独作为预测术后感染性并发症的指标。

综上所述,ERAS通过围手术期一系列措施以达到快速康复、缩短患者住院时间的目的,但其管控过程中缺乏量化评估指标,故难以有效预测出院患者是否存在吻合口漏的潜在风险。新近文献不断提出,很多指标与术后吻合口漏有显著相关性,且对其发生有重要预测价值,尤其是CRP、PCT、IL-6、 $\Delta$ ALB、NLR敏感性高,但由于存在较多干扰因素,均不能成为独立的预测指标。鉴于其敏感性、

可操作性以及文献支持等特点,希望能进一步将几种敏感因子组成新的评估系统,以期在ERAS管控中早期预测吻合口漏的发生。

[参考文献]

- [1] KEHLET H, WILMORE D W. Evidence-based surgical care and the evolution of fast-track surgery[J]. *Ann Surg*, 2008,248(2):189-198
- [2] 肖亦斌,陈凇. Lgr4在胃肠道肿瘤中的研究进展[J]. *中华胃肠外科杂志*,2015,18(11):1179-1181
- [3] ALVES A, PANIS Y, TRANCART D, et al. Factors associated with clinically significant anastomotic leakage after large bowel resection: multivariate analysis of 707 patients [J]. *World J Surg*, 2002,26(4):499-502
- [4] KRARUP P M, JORGENSEN L N, ANDREASEN A H, et al. A nationwide study on anastomotic leakage after colonic cancer surgery [J]. *Colorectal Dis*, 2012, 14(10): e661-667
- [5] 俞德才,黄其根,施晓雷. 加速康复外科在肝切除围手术期的应用[J]. *南京医科大学学报(自然科学版)*, 2019,39(11):1609-1612
- [6] GRECO M, CAPRETTI G, BERETTA L, et al. Enhanced recovery program in colorectal surgery: a meta-analysis of randomized controlled trials [J]. *World J Surg*, 2014, 38(6):1531-1541
- [7] CABELLOS OLIVARES M, LABALDE MARTINEZ M, TORRALBA M, et al. C-reactive protein as a marker of the surgical stress reduction within an ERAS protocol (Enhanced Recovery After Surgery) in colorectal surgery: A prospective cohort study [J]. *J Surg Oncol*, 2018, 117(4):717-724
- [8] WELSCH T, MULLER S A, ULRICH A, et al. C-reactive protein as early predictor for infectious postoperative complications in rectal surgery [J]. *Int J Colorectal Dis*, 2007, 22(12):1499-1507
- [9] SHISHIDO Y, FUJITANI K, YAMAMOTO K, et al. C-reactive protein on postoperative day 3 as a predictor of infectious complications following gastric cancer resection [J]. *Gastric Cancer*, 2016, 19(1):293-301
- [10] KIM E Y, YIM H W, PARK C H, et al. Erratum to: C-reactive protein can be an early predictor of postoperative complications after gastrectomy for gastric cancer [J]. *Surg Endosc*, 2017, 31(1):455-454
- [11] 吕泽坚,吴德庆,蔡观福,等. C-反应蛋白预测直肠癌术后吻合口漏的临床价值[J]. *中华胃肠外科杂志*, 2018, 21(4):442-447
- [12] GE X, CAO Y, WANG H, et al. Diagnostic accuracy of the postoperative ratio of C-reactive protein to albumin for complications after colorectal surgery [J]. *World J Surg Oncol*, 2017, 15(1):15
- [13] REITH H B, MITTELKOTTER U, WAGNER R, et al. Procalcitonin (PCT) in patients with abdominal sepsis [J]. *Intensive Care Med*, 2000, 26(2):S165-169
- [14] OBERHOFER D, JURAS J, PAVICIC A M, et al. Comparison of C-reactive protein and procalcitonin as predictors of postoperative infectious complications after elective colorectal surgery [J]. *Croat Med J*, 2012, 53(6):612-619
- [15] GIACCAGLIA V, SALVI P F, CUNSOLO G V, et al. Procalcitonin, as an early biomarker of colorectal anastomotic leak, facilitates enhanced recovery after surgery [J]. *J Crit Care*, 2014, 29(4):528-532
- [16] MUÑOZ J L, ALVAREZ M O, CUQUERELLA V, et al. Procalcitonin and C-reactive protein as early markers of anastomotic leak after laparoscopic colorectal surgery within an enhanced recovery after surgery (ERAS) program [J]. *Surg Endosc*, 2018, 32(9):4003-4010
- [17] LAGOUTTE N, FACY O, RAVOIRE A, et al. C-reactive protein and procalcitonin for the early detection of anastomotic leakage after elective colorectal surgery: pilot study in 100 patients [J]. *J Visc Surg*, 2012, 149(5):e345-349
- [18] FACY O, PAQUETTE B, ORRY D, et al. Diagnostic accuracy of inflammatory markers as early predictors of infection after elective colorectal surgery: results from the IMACORS study [J]. *Ann Surg*, 2016, 263(5):961-966
- [19] 陈明祥,武正山,张信强,等. 胃癌患者血清IL-6、CA724、VEGF联合检测的临床意义[J]. *南京医科大学学报(自然科学版)*, 2013, 33(2):247-250
- [20] MARI G, CRIPPA J, COSTANZI A, et al. ERAS protocol reduces IL-6 secretion in colorectal laparoscopic surgery: results from a randomized clinical trial [J]. *Surg Laparosc Endosc Percutan Tech*, 2016, 26(6):444-448
- [21] RETTIG T C, VERWIJMEREN L, DIJKSTRA I M, et al. Postoperative interleukin-6 level and early detection of complications after elective major abdominal surgery [J]. *Ann Surg*, 2016, 263(6):1207-1212
- [22] MOKART D, MERLIN M, SANNINI A, et al. Procalcitonin, interleukin 6 and systemic inflammatory response syndrome (SIRS): early markers of postoperative sepsis after major surgery [J]. *Br J Anaesth*, 2005, 94(6):767-773
- [23] SZCZEPANIK A M, SCISLO L, SCULLY T, et al. IL-6 serum levels predict postoperative morbidity in gastric cancer patients [J]. *Gastric Cancer*, 2011, 14(3):266-273
- [24] MOHRI Y, TANAKA K, TOIYAMA Y, et al. Impact of preoperative neutrophil to lymphocyte ratio and postoperative infectious complications on survival after curative gas-

- trectomy for gastric cancer: a single institutional cohort study[J]. *Medicine(Baltimore)*, 2016, 95(11):e3125
- [25] JOSSE J M, CLEGHORN M C, RAMJI K M, et al. The neutrophil-to-lymphocyte ratio predicts major perioperative complications in patients undergoing colorectal surgery[J]. *Colorectal Dis*, 2016, 18(7):236-242
- [26] JONES H G, QASEM E, DILAVER N, et al. Inflammatory cell ratios predict major septic complications following rectal cancer surgery [J]. *Int J Colorectal Dis*, 2018, 33(7):857-862
- [27] MIK M, DZIKI L, BERUT M, et al. Neutrophil to lymphocyte ratio and C-reactive protein as two predictive tools of anastomotic leak in colorectal cancer open surgery [J]. *Dig Surg*, 2018, 35(1):77-84
- [28] MOGHADAMYEGHANEH Z, HWANG G, HANNA M H, et al. Even modest hypoalbuminemia affects outcomes of colorectal surgery patients[J]. *Am J Surg*, 2015, 210(2):276-284
- [29] NORBERG A, ROOYACKERS O, SEGERSVARD R, et al. Albumin kinetics in patients undergoing major abdominal surgery[J]. *PLoS One*, 2015, 10(8):e0136371
- [30] WANG Y, WANG H, JIANG J, et al. Early decrease in postoperative serum albumin predicts severe complications in patients with colorectal cancer after curative laparoscopic surgery[J]. *World J Surg Oncol*, 2018, 16(1):192
- [收稿日期] 2019-08-30

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- [41] 董杰, 邢娟, 路国涛, 等. 肠内营养对质子泵抑制剂导致的胃肠道不良反应的保护作用[J]. *南京医科大学学报(自然科学版)*, 2019, 39(1):77-83
- [42] MCDONALD E G, MILLIGAN J, FRENETTE C, et al. Continuous proton pump inhibitor therapy and the associated risk of recurrent *Clostridium difficile* infection[J]. *JAMA Intern Med*, 2015, 175(5):784-791
- [43] FREEDBERG D E, SALMASIAN H, FRIEDMAN C, et al. Proton pump inhibitors and risk for recurrent *Clostridium difficile* infection among inpatients[J]. *Am J Gastroenterol*, 2013, 108(11):1794-1801
- [44] FREEDBERG D E, LAMOUSÉ-SMITH E S, LIGHTDALE J R, et al. Use of acid suppression medication is associated with risk for *C. difficile* infection in infants and children: a population-based study[J]. *Clin Infect Dis*, 2015, 61(6):912-917
- [45] CLOONEY A G, BERNSTEIN C N, LESLIE W D, et al. A comparison of the gut microbiome between long-term users and non-users of proton pump inhibitors [J]. *Aliment Pharmacol Ther*, 2016, 43(9):974-984
- [46] LEBWOHL B, SPECHLER S J, WANG T C, et al. Use of proton pump inhibitors and subsequent risk of celiac disease[J]. *Dig Liver Dis*, 2014, 46(1):36-40
- [47] HUNGIN A P S, MITCHELL C R, WHORWELL P, et al. Systematic review: probiotics in the management of lower gastrointestinal symptoms - an updated evidence-based international consensus [J]. *Aliment Pharmacol Ther*, 2018, 47(8):1054-1070
- [收稿日期] 2019-08-08