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文献综述 REVIEW

炎性生物标志物在克罗恩病诊断与疾病评估中的作用

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Role of biomarkers in diagnosis and evaluation of disease activity of Crohn's disease

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Abstract

Crohn's disease (CD) is a group of chronic, relapsing inflammatory gastrointestinal diseases with unknown etiology. The goals of treatment are to induce the transition from active stage into inactive stage and to maintain remission. Therefore, it is important to diagnose and assess disease activity in patients with CD. Recently, noninvasive markers for intestinal inflammation have been wildly adopted in clinical practice in order to differentiate CD from other diseases, to grade inflammation, to assess the response to therapy, and to demonstrate recurrent inflammation after medical or surgically-induced remission. Fecal and serum calprotectins are among the best-studied noninvasive biomarkers of inflammation in CD which have attracted clinicians' attention. This paper gives an overview of the clinical implications of biomarkers for diagnosing and monitoring disease activity of CD.

Key Words: Crohn's disease; Biomarkers; Diagnosis; Disease activity; Evaluation

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摘要

克罗恩病(Crohn's disease, CD)是炎症性肠病的主要临床表型之一, 慢性、反复发作性是其临床特征表现, 治疗目的在于诱导疾病由活动期进入缓解期, 并维持疾病长期缓解. 因此, 做好疾病的诊断与活动性评估有重要

背景资料
近十年来克罗恩病(Crohn's disease, CD)在我国呈逐步增长趋势, 已然成为消化系统常见疾病. 对CD进行及时诊断与正确活动性及严重程度评估有利于全面评估病情和估计预后, 制定治疗方案.

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研发前沿
非侵入性、方便快速、准确有效及可重复性强的炎性生物标志物为CD诊断与治疗提供方便. 目前, 炎性生物标志物作为反映肠道炎症的标志物已被广泛研究, 其中一些标志物已初具特色, 但仍未广泛投入临床使用.

意义. 随着非侵入性炎性生物标志物在CD诊断、临床疾病活动评估及药物或手术治疗后疾病复发监测中的应用研究, 炎性生物标志物尤其是血及粪钙卫蛋白在CD中的应用价值已引起人们的关注. 本文对现有非侵入性炎性生物标志物在CD诊断、分型、疾病活动监测及复发预测等方面的应用及临床意义作一总结概括.

关键词: 克罗恩病; 炎性生物标志物; 诊断; 疾病活动; 评估

核心提要: 本文将对现有非侵入性炎性生物标志物在克罗恩病(Crohn's disease, CD)诊断、疾病活动监测等方面的应用及临床意义作一综述, 拟为临床医生正确认识CD及优化治疗方案提供有益指导.

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0 引言

克罗恩病(Crohn's disease, CD)为炎症性肠病主要临床表型之一, 慢性、反复发作性是其临床特征表现. CD活动指数(CD activity index, CDAI)是临床上常用评估CD活动及疾病严重程度的指标之一, 然而这种主要基于症状的评分无法准确反映肠道炎症程度. 内镜及影像学技术是评估CD活动性较客观的指标, 但内镜为有创检查, 且检查前需肠道准备, 患者不易接受. 小肠CT造影及小肠核磁检查需注射造影剂, 且小肠CT造影有放射性, 在临床应用中受到限制[1-3]. 多项研究显示除血清C-反应蛋白(C-reactive protein, CRP)外, 血及粪钙卫蛋白(fecal calprotectin, FC)等非侵入性炎性生物标志物可用于疾病诊断、疾病活动及严重程度评估、疾病预后的预测及疗效评估, 从而指导CD临床诊治. 本文将对现有用于CD诊断、疾病活动及疗效评估的非侵入性炎性生物标志物作一综述.

1 用于CD诊断、分型及疾病行为预测的血生物标志物

1.1 病原体相关抗体

1.1.1 病原体相关抗体与CD诊断的建立: 有研究显示CD患者血抗酿酒酵母菌抗体(anti-Saccharomyces cerevisiae antibody, ASCA)-IgG及-IgA水平较健康对照者增高, 当ASCA阳性且核周型抗中性粒细胞胞浆抗体(perinuclear anti-neutrophil cytoplasmic antibodies, p-ANCA)阴性时诊断CD的敏感性为54.6%, 特异性达92.8%[4]. 当ASCA及p-ANCA均阴性时, 联合抗大肠杆菌外膜蛋白C抗体(antibody to *Escherichia Coli* outer membrane porin, anti-OmpC)可提高ASCA及p-ANCA阴性CD患者的诊断率[5]. 另有研究提示胰腺自身抗体(antibodies against exocrine pancreatic tissue, PAB)是诊断CD的特异性指标, PAB联合ASCA或抗多聚糖抗体可提高CD诊断[6]. 抗多聚糖抗体家族除上述的ASCA-IgG, ASCA-IgA外, 还包括抗乙糖苷昆布糖抗体(anti-laminaribioside carbohydrate IgG antibodies, ALCA)、抗乙糖苷壳糖抗体(anti-chitobioside carbohydrate IgA antibodies, ACCA)及抗乙糖苷甘露醇抗体(anti-mannobioside carbohydrate IgG antibodies, AMCA)等, 上述抗体滴度CD患者高于溃疡性结肠炎(ulcerative colitis, UC)患者, 提示可用于CD的鉴别诊断. 虽然ASCA、ALCA、ACCA及AMCA用于CD诊断特异性高, 但其敏感性低, ALCA为上述四者中敏感性最高, 但仅达52.8%[7,8].

1.1.2 病原体相关抗体与CD亚型的建立及疾病行为预测: 研究显示抗CBiR1鞭毛蛋白抗体(antibodies against bacterial flagellin, anti-CBiR1)可用于诊断CD复杂亚型, 该抗体与小肠型CD、肠穿孔、纤维狭窄等疾病行为独立相关[9]. 有学者对ASCA、anti-OmpC、anti-CBiR1及抗荧光假单胞菌CD相关蛋白抗体在预测CD并发症及手术风险方面进行研究, 发现ASCA敏感性最高, 而anti-OmpC特异性最高, 将这些抗体联合应用可提高预测价值[10]. PAB可用于CD亚型诊断, 尤其是结肠型CD的诊断, 此外, PAB与CD疾病行为(穿孔、肛周病变)及肠外表现(关节、眼部及皮肤改变)相关[6].

ALCA及AMCA与小肠型病变有关[7]. ASCA和ALCA升高的CD患者发生狭窄及穿孔风险增高, 需手术的概率增高[8].

2 用于CD疾病活动监测、复发及预后评估的血生物标志物

2.1 血清CRP、血沉

2.1.1 血清CRP、血沉与疾病活动评估: 血清CRP是机体受到炎性刺激时由肝脏合成的急性相蛋白, 是评估CD疾病活动及严重程度的一项重要指标[11]. 研究[12]证实CD活动期患者CRP较缓解期升高, 且在中重度活动期CD、回结肠型及结肠型CD患者中升高明显. CRP用于评估CD内镜下活动程度的敏感性和特异性为49%及92%. 低敏感性限制了CRP用于内镜下炎性活动程度评估[13,14]. CRP与反映疾病活动的FC、CDAI等具有较好的相关性, 有研究显示: CRP与FC及CDAI间密切相关(r_{-FC} = 0.65, r_{-CDAI} = 0.51, P<0.0001)[15]. 但研究也指出, 有25%的CD患者虽处于疾病活动期, 但CRP不升高[16].

炎症反应时血沉(erythrocyte sedimentation rate, ESR)加快. ESR在活动期CD患者较缓解期患者增高[17]. 但ESR不仅受炎症反应影响, 贫血、红细胞增多症等影响红细胞比容的疾病, ESR会升高, 甚至生理状态下ESR也会出现波动, 这些降低了其评估CD疾病活动的准确性及特异性[18].

2.1.2 血清CRP、血沉与疾病复发及预后评估: CRP可预测CD复发[15,19]. 对缓解期CD患者每6 wk进行评估, 以CRP>20 mg/L和ESR>15 mm/h来预测复发, 两者之中至少有一个阳性的患者比全阴性的患者复发风险高8倍[16]. 另有学者对英夫利昔单抗治疗14 wk后处于临床缓解的CD患者进行随访发现, 这部分患者在第22周时CRP>5 mg/L、英夫利昔谷底浓度>5.5 μg/mL及英夫利昔单抗抗体滴度>20 ng/mL提示疾病复发, 需要更换治疗方案[20]. CRP持续高表达(>45 mg/L)预示CD预后较差, 手术风险增高, 存在更为严重的临床疾病进程[16].

2.2 血小板及血小板活化因子

血小板除了维持止血功能外, 还保留了原始炎症细胞的特性, 直接或间接地参与炎症反应[21]. 研究表明活动期CD患者血小板计数(platelet count, PLT)、血小板压积(plateletcrit, PCT)升高而平均血小板体积(mean platelet volume, MPV)、血小板分布宽度(platelet distribution width, PDW)降低. PLT、PCT、MPV及PDW与CDAI显著相关(P<0.05). 在这些指标中, PCT被认为最能反映CD疾病活动. 在CRP正常的活动期CD患者中, PCT监测疾病活动的敏感性为71%, 特异性达85%[18]. 在预测疾病复发方面, 多因素分析发现, 在CRP不升高的CD患者中, CDAI评分>100且PLT>330×10^9/L提示肠道病变活动[22]. 另有研究显示在英夫利昔单抗诱导治疗第14周, MPV>10.3 fL及ΔMPV>0.4 fL预示患者维持期治疗能保持疗效并维持疾病缓解[23]. 近年研究表明血小板活化标志物可以反映CD炎症活动. 在CRP正常的CD患者中, 血小板因子-4 (platelet factor 4, PF-4)、血小板球蛋白-β(β-thromboglobulin, β-TG)与CDAI相关(r_{-PF-4} = 0.4202, P = 0.0033; $r_{-\beta-TG}$ = 0.4321, P = 0.0024). ROC曲线分析发现两者诊断活动期CD具有较好的敏感性与特异性, 可用于评估CRP正常的CD患者的疾病活动性[24].

2.3 血清钙卫蛋白

血清钙卫蛋白在CD患者中显著高于正常对照者(8892 ng/mL *vs* 1318 ng/mL, P<0.0001), 且活动期患者高于缓解期患者(19584 ng/mL *vs* 8353 ng/mL, P<0.0001). 其与CRP密切相关(r = 0.4091, P<0.0001), 与CDAI相关(r = 0.4442, P<0.0001), 但与CD内镜严重程度指数(CD endoscopic index of severity, CDEIS)无相关性. 在预测英夫利昔单抗治疗后CD疾病复发方面, 血清钙卫蛋白>5675 ng/mL与FC(>250 μg/g)及hsCRP(>5 mg/L)具有相近的价值[15].

2.4 其他血清炎性指标

研究发现活动期CD患者血清β2-微球蛋白(beta-2-microglobulin, B2-M)高于缓解期患者. B2-M与CRP及ESR有良好相关性(r_{-CRP} = 0.79, r_{-ESR} = 0.76, P = 0.001). B2-M>1.84 mg/L诊断CD活动的敏感性及特异性分别为78%和75%[25]. 另有研究发现血清降钙素原(serum procalcitonin, SPL)可反映CD活动及严重程度, 其与CRP、CDAI评分、简化CD内镜评分(Simplified Endoscopic Activity Score for CD, SES-CD)呈强相关(r_{-CRP} = 0.625, P = 0.0002; r_{-CDAI} = 0.545, P = 0.002; $r_{-SES-CD}$ = 0.797, P = 0.0006), SPL与CRP联合诊断CD活动或重度活动效能优于单用CRP[26].

相关报道

粪钙卫蛋白(fecal calprotectin, FC)是一种来源于中性粒细胞和巨噬细胞的含钙蛋白, 其表达具有组织或细胞特异性, 可作为急性炎性细胞活化的标志物. FC可反映CD患者肠道炎症程度, 与内镜下表现具有较好的一致性.

创新盘点
本文为一综述性报道, 系统介绍了炎性生物标志物在CD诊断与疾病评估中的作用, 其中重点介绍了血液及粪便标志物在CD诊断、分型、疾病活动监测及复发预测等方面中的作用.

3 用于CD疾病活动监测、复发及预后评估的血生物标志物

3.1 FC

3.1.1 FC与疾病活动评估: FC及粪S100A12(fecal S100A12, FS)同属于S100蛋白家族, 在肠道黏膜炎症时通过对钙离子的调节及与靶蛋白的相互作用起促进白细胞聚集作用. FC与CDEIS及SES-CD密切相关(r_{-CDEIS} = 0.66, P<0.001; $r_{-SES-CD}$ = 0.76; P<0.0001), 与内镜下炎症活动有较好一致性, 可有效评估CD疾病活动严重程度[27,28]. FC与磁共振小肠造影活动指数相关(r = 0.56, P<0.001), 且与用于评估手术标本病理炎症活动分级的Chiorean's评分具有较好的一致性(P<0.05)[29].

3.1.2 FC与疾病复发及预后评估: FC预测回结肠或结肠病变复发的准确性高, 但对病变仅累及小肠的患者预测复发的能力受限[30]. 小肠型CD患者FC水平显著低于回结肠或结肠型CD患者(297 μg/g±81 μg/g *vs* 1523 μg/g±97 μg/g, P<0.0001)[28]. 另外, FC可用于监测空回肠节段切除术后无症状CD患者炎症状态[14,31], 以100 μg/g为临界值判别术后内镜下缓解与复发, 敏感性95%, 特异性54%, 阳性预测值69%, 阴性预测值93%, 总体准确性77%[14]. 其预测疾病复发的准确性优于粪乳铁蛋白(fecal lactoferrin, FL)、血清CRP及CDAI评分[32]. 考虑到其阴性预测值高, FC对CD术后随访是否需行内镜检查提供有益参考[14,32]. 此外, 有研究显示FC能较好反映使用生物制剂治疗的CD患者诱导期治疗效果, 且在第14周检测FC<82 μg/g用于预测维持期治疗CD患者处临床缓解的敏感性为93%, 特异性为68%[33]. 停用生物制剂的CD患者, 当合并有贫血、高CRP及FC状态, 其复发风险显著增高[34].

3.2 FS FS活动期CD患者显著高于缓解期患者(1.5 mg/kg *vs* 0.7 mg/kg, P<0.01), 且病变仅累及结肠者FS水平高于回肠病变及回结肠病变患者(1.0、0.5、0.5 mg/kg; P<0.05). FS与CDAI中度相关(r = 0.401, P<0.0001), 与CRP、ESR及PLT低度相关(r_{-CRP} = 0.270; r_{-ESR} = 0.251; r_{-PLT} = 0.234; P<0.0001). 在预测疾病复发方面, 研究[35]显示, FS升高早于临床复发至少6 mo. 以0.43 mg/kg作为FS临界值, 预测复发的敏感性70%, 特异性83%. 另有研究指出, CD患者术后6 mo复查FS>10.5 μg/g提示内镜下复发(敏感性91%, 特异性81%, 阴性预测值71%)[36].

3.3 FL FL是一种在白细胞内表达的铁结合性糖蛋白, 在肠道急性炎症时表达增高. 研究[13]表明, FL可有效监测CD患者的肠道炎症情况. FL与CRP、CDAI评分及SES-CD相关(r_{-CRP} = 0.5, P<0.0001; r_{-CDAI} = 0.3, P = 0.001; $r_{-SES-CD}$ = 0.5, P<0.0001). FL以145.82 μg/mL为临界值, 预测内镜下活动的敏感性及特异性分别为42%及92%[37]. 在对静止期CD患者进行随访观察时发现, 初始FL阴性的患者中有5.5%复发, 阳性患者中有29%复发. 可见FL阳性的CD患者临床复发的风险增高[38]. 对于行手术治疗的CD患者, FL>140 μg/g亦可有效评估术后复发情况(敏感性67%, 特异性71%)[39].

3.4 粪新碟呤及粪α1-抗胰蛋白酶 研究[40,41]发现粪新碟呤(neopterin, NP)浓度在活动期CD患者中高于缓解期患者, 可用于监测疾病活动. 粪NP与反映CD临床活动的Harvey和Bradshaw标准相关(r = 0.41, P<0.001), 与反映CD内镜下活动的SES-CD相关(r = 0.47, P<0.001), 以200 pmol/g设为临界值, 预测CD内镜下活动的准确性与FC相近[40]. 研究发现粪α1-抗胰蛋白酶(fecal alpha1-antitrypsin, α1-AT)在活动期CD患者及CD术后早期复发患者中浓度升高. 粪α1-AT>120 mL/d可用于预测CD临床复发(敏感性为75%, 特异性为85%)[42,43].

3.5 其他粪炎性相关标志物 粪便中M2型丙酮酸激酶、粪溶菌酶、嗜酸粒细胞阳离子蛋白、嗜酸性粒细胞X、中性粒细胞弹性蛋白酶、基质金属蛋白酶(matrix metalloproteinases, MMP)-9及粪髓过氧化物酶均与炎症性肠病活动相关[43-45], 但缺少其与CD关系的进一步研究及更多大规模研究加以认证.

4 用于CD诊断及疾病活动评估的尿液标志物

研究[46]发现尿微量白蛋白(microalbuminuria, MAU)与CD重度活动(r = 0.797, P = 0.0002)及CD肠外症状的出现(r = 0.625, P = 0.0096)密切相关. MAU在缓解期CD患者中普遍存在, 但不能用于预测缓解期CD患者疾病复发[47]. 除此之外, MMP[48], α1-酸性糖蛋白、锌-α2-糖蛋白[49]和NP[50]认为与CD活动相关, 但相关研究较少且CD缺乏大样本研究证实.

5 结论

血液及粪便炎性标志物在CD诊断、病情评估及疾病复发预测等方面具有较好的临床应用价值. 但也存在问题, 如各研究对标志物临界值设定不一, 且结论存在不一致性, 需要多中心、大样本的临床研究进一步评估其临床应用价值.

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应用要点

本文系统介绍了各类非侵入性炎性生物标志物在CD诊断、分型、疾病活动监测及复发预测等方面的应用及临床价值, 为临床诊治提供了新的理论依据与指导.

名词解释

克罗恩病(CD): 一种慢性、反复发作的肠道非特异性炎性疾病, 好发于青年期. 腹痛、腹泻及体质量减轻是CD的常见症状, 少部分CD患者以肛周脓肿和肛周瘘管为首诊表现.

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同行评价

非侵入性生物标志物对CD的诊断及疾病活动度评估是一种无创性检查方法, 可重复性高, 可推广度高, 结果准确可靠, 在临床上有应用价值.

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