

健脾解毒优化方对结直肠癌患者化疗毒副作用及肠道菌群的影响：一项前瞻性对照研究

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[摘要] **目的:** 结直肠癌(colorectal carcinoma, CRC)患者在接受化疗过程中常出现胃肠道反应、体重下降和骨髓抑制等不良反应, 影响治疗的连续性和患者的功能状态。肠道菌群失衡与CRC进展、化疗相关不良反应及患者对化疗的反应有关。本研究旨在观察健脾解毒优化方(Jianpi Jiedu optimized formula, JPJDYHF)辅助化疗治疗III~IV期CRC患者的临床效果、安全性及其对肠道菌群结构的影响。**方法:** 前瞻性纳入121例原发性III~IV期CRC患者, 按患者意愿分为联合组(JPJDYHF联合化疗)与对照组(单纯化疗)。对照组接受中国临床肿瘤学会(Chinese Society of Clinical Oncology, CSCO)指南推荐的一线化疗方案, 联合组在此基础上分阶段口服JPJDYHF1号方和2号方。剔除脱落病例后, 对完成6个化疗周期的113例患者, 以年龄、性别、TNM分期、化疗方案等9项基线变量构建倾向评分匹配(propensity score matching, PSM)模型, 采用1:1最邻近匹配(卡钳值0.25)筛选出60例患者(每组30例)进行统计分析。记录首周期至第2周期的化疗通过情况; 于各化疗周期结束时评估客观缓解率(objective response rate, ORR)、疾病控制率(disease control rate, DCR)、Karnofsky功能状态(Karnofsky Performance Status, KPS)评分、中医证候积分及化疗相关不良反应(胃肠道反应、体重减轻、骨髓抑制); 检测化疗前后血清癌胚抗原(carcinoembryonic antigen, CEA)与糖类抗原19-9(carbohydrate antigen 19-9, CA19-9)水平及肝肾功能。于6个化疗周期结束后, 采集粪便样本, 提取总DNA, 针对16S核糖体RNA(16S ribosomal RNA, 16S rRNA)基因V3~V4区进行高通量测序, 评估Alpha与Beta多样性, 采用线性判别分析效应量(linear discriminant analysis effect size, LEfSe)筛选差异菌群, 并采用基于未观测状态重建的群落系统发育调查2(Phylogenetic Investigation of Communities by Reconstruction of Unobserved States 2, PICRUST2)和同源蛋白簇(Clusters of Orthologous Groups, COG)数据库进行功能预测。**结果:** 经PSM后, 2组基线特征均衡。临床疗效方面, 联合组化疗通过情况优于对照组, ORR(46.67% vs 16.67%)和DCR(90.00% vs 73.33%)均更高(均 $P<0.05$)。联合组的中医证候疗效总有效率达73.3%, 高于对照组的30.0%($P<0.05$)。第3周期和第6周期时, 联合组的KPS评分均高于对照组(均 $P<0.05$)。安全性与不良反应方面, 第6周期结束时联合组的胃肠道反应严重程度、体重下降程度及骨髓抑制发生情况均较对照组改善(均 $P<0.05$), 且2组肝肾功能指标变化的差异均无统计学意义(均 $P>0.05$)。血清学指标方面, 第5、6周期结束时联合组的CEA水平低于对照组, 且下降率更高(均 $P<0.05$), 但CA19-9水平和下降率的差异均无统计学意义(均 $P>0.05$)。肠道菌群分析显示, 2组Alpha多样性无差异($P>0.05$), 而Beta多样性存在显著分离($P<0.05$)。LEfSe分析表明, 联合组拟杆菌门(Bacteroidota)、梭杆菌门(Fusobacteriota)及弯曲杆菌门(Campylobacterota)的相对丰度下降; 属水平上, 拟杆菌属(*Bacteroides*)、副拟杆菌属(*Parabacteroides*)和促癌相关梭杆菌属(*Fusobacterium*)的相对丰度下降, 而产短链脂肪酸的布劳特氏菌属(*Blautia*)、瘤胃球菌科-UCG-014(*Ruminococcaceae*-UCG-014)的相对丰度升高(均 $P<0.05$)。COG功能预测显示, 联合组肠道菌群中, 脂质转运与代谢、细胞壁/膜/包膜生物发生相关通路下调, 而信号转导功能激活。**结论:** 针对III~IV期CRC患者, JPJDYHF辅助化疗可提高其化疗耐受性与近期客观疗效, 减轻骨髓抑制和胃肠道不良反应, 促进肿瘤标志物CEA水平降低, 改善患者整体功能状态。其机制可能与重塑肠道微生态结构有关, 通过降低*Fusobacterium*等耐药相关菌群丰度、富集产短链脂肪酸菌群, 进而调节脂质代谢与信号转导通路。未来可结合多组学技术及多中心大样本队列, 进一步阐明肠道菌群代谢物在宿主免疫调节与化疗增效中的具体分子靶点。

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[关键词] 结直肠癌; 健脾解毒优化方; 肠道菌群; 倾向评分匹配; 减毒增效; 16S rRNA 基因测序

Effects of Jianpi Jiedu optimized formula on chemotherapy-related toxicities and gut microbiota in patients with colorectal carcinoma: A prospective controlled study

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ABSTRACT

Objective: Patients with colorectal carcinoma (CRC) frequently experience adverse effects during chemotherapy, including gastrointestinal reactions, weight loss, and myelosuppression, which may compromise treatment continuity and functional status. Gut microbiota dysbiosis has been associated with CRC progression, chemotherapy-related adverse effects, and treatment response. This study aims to evaluate the clinical efficacy and safety of Jianpi Jiedu optimized formula (JPJDYHF) as an adjunct to chemotherapy in patients with stage III-IV CRC and to investigate its effects on gut microbiota composition.

Methods: A total of 121 patients with primary stage III-IV CRC were prospectively enrolled and allocated, according to patient preference, to a combination group (JPJDYHF plus chemotherapy) or a control group (chemotherapy alone). The control group received first-line chemotherapy regimens recommended by the Chinese Society of Clinical Oncology (CSCO) guidelines, whereas the combination group additionally received JPJDYHF Formula No. 1 and Formula No. 2 orally in a stage-specific manner. After exclusion of dropouts, 113 patients who completed 6 chemotherapy cycles were included in propensity score matching (PSM) based on 9 baseline variables, including age, sex, TNM stage, and chemotherapy regimen. Using 1:1 nearest-neighbor matching with a caliper of 0.25, 60 patients were selected for statistical analysis, with 30 patients in each group. The ability to proceed with chemotherapy from the first to the second cycle was recorded. At the end of each chemotherapy cycle, the objective response rate (ORR), disease control rate (DCR), Karnofsky Performance Status (KPS) score, traditional Chinese medicine (TCM) syndrome score, and chemotherapy-related adverse effects, including gastrointestinal reactions, weight loss, and myelosuppression, were assessed. Serum carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), and liver and renal function indices were measured before and after chemotherapy. After completion of six chemotherapy cycles, fecal samples were collected and total DNA was extracted. High-throughput sequencing targeting the V3-V4 region of the 16S ribosomal RNA (16S rRNA) gene was performed. Alpha and beta diversity were evaluated, and differentially abundant taxa were identified using linear discriminant analysis effect size (LEfSe). Functional profiles were predicted using Phylogenetic Investigation of Communities by

Reconstruction of Unobserved States 2 (PICRUSt2) and the Clusters of Orthologous Groups (COG) database.

Results: After PSM, baseline characteristics were well balanced between the two groups. In terms of clinical efficacy, the combination group showed better chemotherapy continuation than the control group and had higher ORR (46.67% vs 16.67%) and DCR (90.00% vs 73.33%) (both $P<0.05$). The overall response rate for TCM syndromes was 73.3% in the combination group, significantly higher than 30.0% in the control group ($P<0.05$). At cycles 3 and 6, KPS scores were higher in the combination group than in the control group (both $P<0.05$). Regarding safety and adverse effects, by the end of cycle 6, the combination group showed less severe gastrointestinal reactions, less weight loss, and less myelosuppression than the control group (all $P<0.05$), whereas changes in liver and renal function indices did not differ significantly between the groups (all $P>0.05$). For serum biomarkers, CEA levels were lower and the reduction rate was greater in the combination group at the end of cycles 5 and 6 (all $P<0.05$), whereas no significant between-group differences were observed in CA19-9 levels or reduction rates (all $P>0.05$). Gut microbiota analysis showed no significant difference in alpha diversity between the 2 groups ($P>0.05$), whereas beta diversity showed significant separation ($P<0.05$). LEfSe analysis indicated decreased relative abundances of Bacteroidota, Fusobacteriota, and Campylobacterota in the combination group. At the genus level, the relative abundances of Bacteroides, Parabacteroides, and cancer-associated genus Fusobacterium were reduced, whereas the relative abundances of the short-chain fatty acid-producing genera Blautia and Ruminococcaceae-UCG-014 were increased (all $P<0.05$). COG-based functional prediction showed downregulation of pathways related to lipid transport and metabolism and cell wall/membrane/envelope biogenesis, together with activation of signal transduction functions, in the gut microbiota of the combination group.

Conclusion: In patients with stage III – IV CRC, adjunctive JPJDYHF may improve chemotherapy tolerance and short-term objective response, reduce myelosuppression and gastrointestinal adverse effects, promote reductions in serum CEA levels, and improve overall functional status. These effects may be related to remodeling of the gut microbial ecosystem, including reduced abundance of drug resistance-associated taxa such as Fusobacterium and enrichment of short-chain fatty acid-producing bacteria, thereby modulating lipid metabolism and signal transduction pathways. Future studies integrating multi-omics approaches with large multicenter cohorts are warranted to further clarify the specific molecular targets through which gut microbiota-derived metabolites regulate host immunity and enhance chemotherapy efficacy.

KEY WORDS

colorectal carcinoma; Jianpi Jiedu optimized formula; gut microbiota; propensity score matching; toxicity reduction and efficacy enhancement; 16S rRNA gene sequencing

结直肠癌(colorectal carcinoma, CRC)是全球常见恶性肿瘤之一,近年来发病呈现年轻化趋势^[1]。尽管筛查与诊疗水平不断提高,仍有相当比例患者在确诊时已属中晚期,这些患者预后较差^[2]。对于III~IV期CRC患者,化疗仍是综合治疗的重要组成部分^[3]。然而,化疗相关不良反应常导致治疗耐受性降

低、依从性降低及生活质量下降,并已成为影响临床获益的重要因素^[4]。因此,如何在保证抗肿瘤疗效的同时降低化疗毒性,是CRC综合治疗中亟待解决的问题。

中医药在肿瘤辅助治疗中具有“减毒增效”的潜在价值。健脾解毒优化方(Jianpi Jiedu optimized

formula, JPJDYHF)基于“脾虚毒聚”理论,由临床经验方加减优化而成,长期用于CRC患者的辨证治疗^[5-7]。前期研究^[8-11]表明,该方联合化疗可改善患者临床状态,并可能通过调控肿瘤相关信号通路抑制肿瘤进展、逆转化疗耐药。但其在真实临床情境下的综合疗效及相关机制仍有待进一步明确。本前瞻性研究探讨JPJDYHF辅助化疗对CRC患者的临床疗效,并采用倾向评分匹配(propensity score matching, PSM)减少选择偏倚^[12]。鉴于CRC的发生、发展及化疗相关不良反应均与肠道微生态失衡密切相关^[13],本研究进一步利用16S核糖体RNA(16S ribosomal RNA, 16S rRNA)基因测序技术分析患者肠道菌群结构变化,从肠道微生态角度观察JPJDYHF辅助化疗后的菌群变化特征,同时纳入癌胚抗原(carcinoembryonic antigen, CEA)和糖类抗原19-9(carbohydrate antigen 19-9, CA19-9)等血清肿瘤标志物,补充评价JPJDYHF辅助化疗的临床效应,为阐释该方减轻化疗不良反应、提高临床获益的潜在机制提供线索。

1 资料与方法

1.1 伦理声明

本研究已获得中南大学湘雅二医院伦理委员会的批准[审批号:(2023)伦审(临研)第(K049)号],并在国际传统医学临床试验注册平台上完成注册(注册号:ITMCTR2025002443)。

1.2 对象

纳入2023年10月至2024年10月中南大学湘雅二医院中医科、肿瘤科收治的原发性III~IV期CRC患者共121例。所有患者均经组织病理学确诊,TNM分期依据中国临床肿瘤学会(Chinese Society of Clinical Oncology, CSCO)常见恶性肿瘤诊疗指南^[14]。纳入标准:Karnofsky功能状态(Karnofsky Performance Status, KPS)评分 ≥ 60 ,预计生存期 > 3 个月,自愿参加研究并签署知情同意书。排除标准:合并其他严重系统性疾病或免疫系统疾病,近1个月内使用免疫相关药物,妊娠或哺乳期,合并严重精神或认知障碍,对研究药物过敏,近4周内参加过其他临床试验,或依从性差、无法配合完成研究者。

1.3 研究设计

1.3.1 样本量计算方法

本研究为前瞻性、非随机对照研究,参考《临床流行病学:临床科研设计、测量与评价》第五版^[15]

中的样本量估算公式 $n = \left[u_{\frac{\alpha}{2}} \sqrt{2\bar{p}(1-\bar{p})} + u_{\beta} \sqrt{p_e(1-p_e) + p_c(1-p_c)} \right]^2 / (p_e - p_c)^2$ 。公式中, $u_{\frac{\alpha}{2}}$ 为显著性水平 α 对应的标准正态偏倚; u_{β} 为检验效能 $1-\beta$ 对应的标准正态偏倚; p_e 与 p_c 分别为联合组与对照组预期的临床有效率; $\bar{p}$ 为2组预期率的平均值,即 $\bar{p} = (p_e + p_c)/2$,依据以往研究^[16-17]的方法并结合本研究预期差异确定 p_e 和 p_c 。代入公式计算得出每组所需样本量为30例,本研究共分为2组,因此共计60例。

1.3.2 分组及PSM

本研究共初筛纳入121例符合标准的患者,根据患者意愿将其分配至联合组(JPJDYHF联合化疗)或对照组(单纯化疗)。剔除脱落病例后,共113例(联合组32例,对照组81例),完成6个化疗周期。为控制组间可能影响结局变量的潜在混杂因素,对完成6个化疗周期且资料完整的113例患者,基于其基线变量构建了以年龄、性别、原发部位、TNM分期、分化程度、基础疾病、手术史、靶向治疗及化疗方案为基线变量的PSM模型。采用R 4.4.0软件MatchIt包进行1:1最邻近匹配,卡钳值设为0.25,最终筛选出60例患者(每组各30例)进入最终的临床疗效与结局分析(图1)。

1.4 治疗处理

对照组:按照CSCO指南接受一线化疗,可选卡培他滨+奥沙利铂(capecitabine + oxaliplatin, XELOX)、亚叶酸+5-氟尿嘧啶+奥沙利铂(folinic acid+5-fluorouracil+oxaliplatin, FOLFOX)、亚叶酸+5-氟尿嘧啶+伊立替康(folinic acid+5-fluorouracil+irinotecan, FOLFIRI)等方案;符合指征者采用联合靶向治疗。

联合组:在对照组治疗方案基础上口服JPJDYHF(由1号方和2号方组成)。于每周化疗第4天开始服用1号方,连续服用5d;化疗第9天开始服用2号方,连续服用4d。每日1剂,早、晚各煎取200 mL口服(所有汤剂均由湘雅二医院中药房熬制),并对患者进行定期随访检查。1号方:黄芪12g;党参8g;白术6g;茯苓8g;陈皮6g;法半夏5g;木香5g;砂仁4g;山药10g;神曲8g;炒鸡内金6g;炒麦芽8g;柴胡5g;甘草3g。2号方:黄芪12g;党参8g;白术6g;茯苓8g;陈皮6g;山药10g;蛇舌草8g;半枝莲6g;桂枝5g;山茱萸6g;神曲8g;柴胡4g;三棱6g;莪术6g;薏苡仁10g;甘草3g。

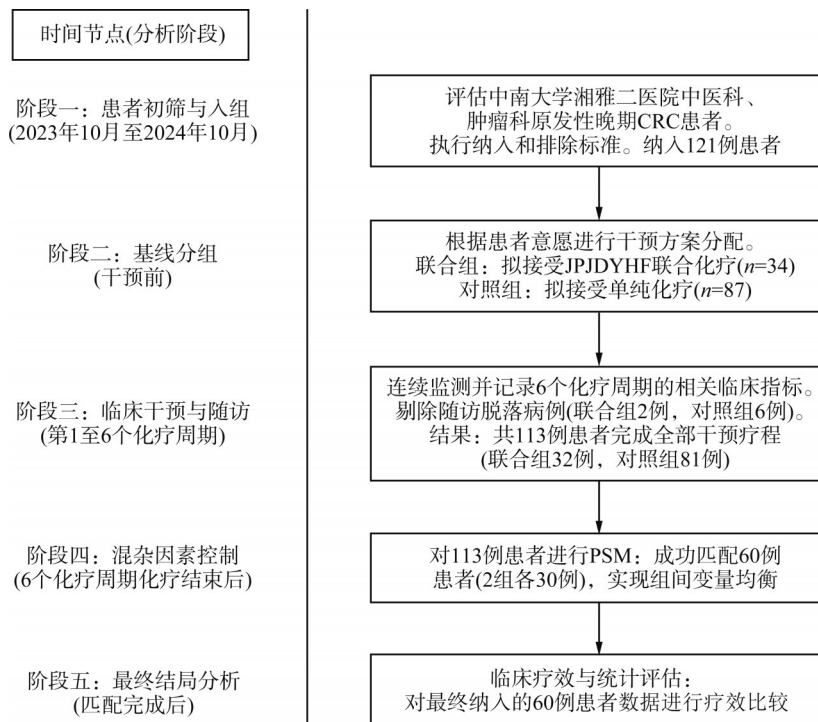


图1 实验设计流程图

Figure 1 Flowchart of study design

CRC: Colorectal carcinoma; JPJDYHF: Jianpi Jiedu optimized formula; PSM: Propensity score matching.

1.5 粪便样本采集与 16S rRNA 基因测序

于6个化疗周期结束后的第2天采集2组患者清晨空腹粪便样本，置于无菌管中， -80°C 保存。采用FastPure Stool DNA Isolation Kit(购自美国赛默飞公司)提取微生物总DNA，并检测其浓度、纯度及完整性。

以提取的DNA为模板，对细菌16S rRNA基因V3~V4区进行聚合酶链反应扩增，构建文库后在Illumina NextSeq 2000平台测序。原始数据经拆分、质控和抽平后，采用UPARSE 7.1按97%相似度进行可操作分类单元(operational taxonomic unit, OTU)聚类，利用核糖体数据库项目(Ribosomal Database Project, RDP)分类器结合SILVA数据库进行物种注释。采用基于未观测状态重建的群落系统发育调查2(Phylogenetic Investigation of Communities by Reconstruction of Unobserved States 2, PICRUSt2)进行功能预测，并基于同源蛋白簇(Clusters of Orthologous Groups, COG)数据库分析组间功能通路差异。

1.6 观察指标

主要观察指标：1)化疗通过情况。以首周期化疗开始后进入第2周期的间隔时间评价化疗通过情况，

分为好(22~<28 d)、一般(28~35 d)和差(>35 d)。2)化疗相关不良反应。每周期结束后1周内评估并记录不适症状及血常规指标，按美国国家癌症研究所不良事件通用术语标准5.0版(National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0, NCI-CTCAE v5.0)^[18]分级。骨髓抑制评级依据该周期相关指标最高等级记录。3)肠道菌群结构。基于16S rRNA基因测序分析菌群组成及丰度变化，评估JPJDYHF对肠道微生态的影响。4)肿瘤相关血清学指标。分别于化疗前基线(T0)及各化疗周期结束时(T1~T6)检测CEA、CA19-9水平，比较2组基线、T6及下降率差异，下降率按 $(T0-T6)/T0 \times 100\%$ 计算。

次要观察指标：1)KPS评分。范围为0~100分，分值越高表示患者功能状态越好，于治疗前及各化疗周期结束时进行评估。2)疾病控制率(disease control rate, DCR)。采用客观疗效评价标准完全缓解(complete response, CR)、部分缓解(partial response, PR)、疾病稳定(stable disease, SD)及疾病进展(progressive disease, PD)进行评估，计算客观缓解率(objective response rate, ORR)和DCR，公式分别为 $ORR=(CR+PR)/\text{全部病例数} \times 100\%$ ， $DCR=(CR+PR+SD)/\text{全部病例数} \times 100\%$ 。3)中医证候积分及中医

临床疗效评价。依据《中西医结合肿瘤学》及《中药新药临床研究指导原则(试行)》^[9]制订中医证候评分量表(附表1, <https://doi.org/10.57760/sciencedb.xbyxb.00200>),于治疗前及各化疗周期结束时进行评价。各证候按0(无)、2(轻)、4(中)、6(重)计分,总分36,分值越高表示中医证候程度越重。

1.7 安全性指标

于化疗前及6周期结束后采集空腹静脉血,检测丙氨酸氨基转移酶(alanine amino-transferase, ALT)、天冬氨酸氨基转移酶(aspartate amino-transferase, AST)、血尿素氮(blood urea nitrogen, BUN)及肌酐(creatinine, Cr)水平,评价联合用药安全性。

1.8 统计学处理

采用SPSS 22.0进行数据统计和分析。正态分布的计量资料以均数±标准差表示,组间比较采用独立样本 t 检验;非正态分布的计量资料以中位数(第1四分位数,第3四分位数)表示,组间比较采用Mann-Whitney U 检验。计数变量以频数(构成比或率)表示,组间比较采用卡方检验或Fisher确切概率法,PSM前后基线特征的平衡性采用标准化均差(standardized mean difference, SMD)评价,中医证候积分的纵向变

化采用重复测量方差分析。16S rRNA数据中,Alpha多样性组间比较采用Wilcoxon秩和检验;Beta多样性比较采用基于Bray-Curtis距离的主坐标分析(principal coordinate analysis, PCoA),并结合置换多元方差分析(permutational multivariate analysis of variance, PERMANOVA)检验组间差异;采用线性判别分析效应量(linear discriminant analysis effect size, LEfSe)分析筛选差异菌群,阈值设为线性判别分析(linear discriminant analysis, LDA)得分 >2 且 $P<0.05$;基于Spearman相关性分析,以 $r>0.6$ 且 $P<0.05$ 为阈值构建相关性网络。 $P<0.05$ 为差异具有统计学意义。

2 结果

2.1 基线资料比较

共121例患者初筛入组,剔除脱落病例后,113例完成6个化疗周期,其中联合组32例、对照组81例。经1:1 PSM后,最终纳入60例患者,每组30例。PSM后,2组在年龄、性别、原发部位、分化程度、TNM分期、手术史、化疗方案等基线特征方面的差异均无统计学意义(均 $P>0.05$,表1),具有可比性。

表1 2组CRC患者PSM前后的基线资料

Table 1 Baseline characteristics of patients with CRC of the 2 groups before and after PSM

变量	PSM前			统计量	P	SMD
	总体($n=113$)	对照组($n=81$)	联合组($n=32$)			
年龄/岁	57.42±11.07	57.32±10.96	57.69±11.52	$t=-0.158$	0.875	0.032
性别/[例(%)]				$\chi^2=3.148$	0.076	
女性	42(37.17)	26(32.10)	16(50.00)			0.358
男性	71(62.83)	55(67.90)	16(50.00)			-0.358
基础疾病/[例(%)]				$\chi^2=0.506$	0.477	
无	83(73.45)	61(75.31)	22(68.75)			-0.141
有	30(26.55)	20(24.69)	10(31.25)			0.141
原发部位/[例(%)]				$\chi^2=1.549$	0.461	
左半结肠	33(29.20)	21(25.93)	12(37.50)			0.239
右半结肠	46(40.71)	35(43.21)	11(34.38)			-0.186
直肠	34(30.09)	25(30.86)	9(28.12)			-0.061
分化程度/[例(%)]				$\chi^2=1.550$	0.461	
中等分化	76(67.26)	53(65.43)	23(71.88)			0.143
低分化	23(20.35)	16(19.75)	7(21.87)			0.051
高分化	14(12.39)	12(14.82)	2(6.25)			-0.354

表 1(续)

变量	PSM 前			统计量	<i>P</i>	<i>SMD</i>
	总体(<i>n</i> =113)	对照组(<i>n</i> =81)	联合组(<i>n</i> =32)			
分期/[例(%)]				$\chi^2=0.805$	0.369	
III	43(38.05)	33(40.74)	10(31.25)			-0.179
IV	70(61.95)	48(59.26)	22(68.75)			0.179
手术/[例(%)]				$\chi^2=0.003$	0.958	
否	49(43.36)	35(43.21)	14(43.75)			0.011
是	64(56.64)	46(56.79)	18(56.25)			-0.011
靶向治疗/[例(%)]				$\chi^2=3.653$	0.056	
否	55(48.67)	44(54.32)	11(34.38)			-0.420
是	58(51.33)	37(45.68)	21(65.62)			0.420
化疗方案/[例(%)]				$\chi^2=2.012$	0.366	
XELOX	50(44.25)	39(48.15)	11(34.38)			-0.281
FOLFOX	52(46.02)	34(41.98)	18(56.25)			0.288
FOLFIRI	11(9.73)	8(9.87)	3(9.37)			-0.017
变量	PSM 后			统计量	<i>P</i>	<i>SMD</i>
	总体(<i>n</i> =60)	对照组(<i>n</i> =30)	联合组(<i>n</i> =30)			
年龄/岁	58.22±10.43	58.40±9.91	58.03±11.11	<i>t</i> =0.135	0.893	-0.033
性别/[例(%)]				$\chi^2=0.617$	0.432	
女性	25(41.67)	11(36.67)	14(46.67)			0.200
男性	35(58.33)	19(63.33)	16(53.33)			-0.200
基础疾病/[例(%)]				$\chi^2=0.635$	0.426	
无	37(61.67)	17(56.67)	20(66.67)			0.212
有	23(38.33)	13(43.33)	10(33.33)			-0.212
原发部位/[例(%)]				$\chi^2=0.452$	0.798	
左半结肠	22(36.67)	11(36.67)	11(36.67)			0.000
右半结肠	24(40.00)	13(43.33)	11(36.67)			-0.138
直肠	14(23.33)	6(20.00)	8(26.66)			0.151
分化程度/[例(%)]				-	1.000	
中等分化	42(70.00)	21(70.00)	21(70.00)			0.000
低分化	15(25.00)	8(26.67)	7(23.33)			-0.079
高分化	3(5.00)	1(3.33)	2(6.67)			0.134
分期/[例(%)]				$\chi^2=0.077$	0.781	
III	19(31.67)	10(33.33)	9(30.00)			-0.073
IV	41(68.33)	20(66.67)	21(70.00)			0.073
手术/[例(%)]				$\chi^2=0.601$	0.438	
否	29(48.33)	16(53.33)	13(43.33)			-0.202
是	31(51.67)	14(46.67)	17(56.67)			0.202
靶向治疗/[例(%)]				$\chi^2=0.287$	0.592	
否	22(36.67)	12(40.00)	10(33.33)			-0.141
是	38(63.33)	18(60.00)	20(66.67)			0.141
化疗方案/[例(%)]				$\chi^2=0.625$	0.732	
XELOX	20(33.33)	9(30.00)	11(36.67)			0.141
FOLFOX	32(53.34)	16(53.33)	16(53.33)			0.000
FOLFIRI	8(13.33)	5(16.67)	3(10.00)			-0.222

计量资料采用均数±标准差表示，组间比较采用 *t* 检验。计数资料以频数(构成比或率)表示，组间比较采用卡方检验。CRC：结直肠癌；PSM：倾向评分匹配；SMD：标准化均差；XELOX：卡培他滨+奥沙利铂；FOLFOX：亚叶酸+5-氟尿嘧啶+奥沙利铂；FOLFIRI：亚叶酸+5-氟尿嘧啶+伊立替康。

2.2 临床疗效及化疗相关不良反应比较

联合组的化疗通过情况优于对照组;同时,联合组的ORR和DCR均高于对照组,差异均有统计学意义(均 $P<0.05$,表2)。

2组治疗前KPS评分比较的差异无统计学意义($P>0.05$)。化疗后,对照组的KPS评分较治疗前呈下降趋势,而联合组总体保持相对稳定。第3周期和第

6周期时,联合组的KPS评分均高于对照组(均 $P<0.05$,表2)。

第3周期时,2组胃肠道反应、体重减轻及骨髓抑制差异均无统计学意义(均 $P>0.05$);第6周期时,联合组的胃肠道反应严重程度、体重减轻及骨髓抑制均较对照组减轻,差异均有统计学意义(均 $P<0.05$,表2)。

表2 2组患者的治疗效果及化疗相关不良反应比较($n=30$)

Table 2 Comparison of therapeutic efficacy and adverse reactions between the 2 groups ($n=30$)

观察指标	对照组	联合组	统计量	<i>P</i>
化疗通过情况/[例(%)]				0.046
好	17(56.67)	21(70.00)		
一般	11(36.67)	9(30.00)		
差	2(6.66)	0(0.00)		
KPS评分				
治疗前	78.00±7.14	79.33±7.12	$t=0.722$	0.589
3周期	74.00±5.63	79.00±6.07	$t=3.308$	0.002
6周期	70.00±4.54	78.33±5.40	$t=6.467$	<0.001
疗效指标				
ORR/%	16.67	46.67		0.026
DCR/%	73.33	90.00		0.041
化疗相关不良反应				
胃肠道反应(严重程度)/[例(%)]				
3周期				0.083
I级	8(26.67)	9(30.00)		
II级	5(16.67)	1(3.33)		
III~IV级	2(6.67)	0(0.00)		
6周期				0.001
I级	13(43.33)	26(86.67)		
II级	12(40.00)	3(10.00)		
III~IV级	5(16.67)	1(3.33)		
体重减轻/[例(%)]				
3周期				0.254
是否发生	6(20.00)	2(6.67)		
I级	3(10.00)	1(3.33)		
II级	3(10.00)	1(3.33)		
III~IV级	0(0.00)	0(0.00)		
6周期				0.004
是否发生	30(100.00)	20(66.67)		
I级	3(10.00)	12(40.00)		
II级	15(50.00)	4(13.33)		
III~IV级	12(40.00)	4(13.33)		

表 2(续)

观察指标	对照组	联合组	<i>P</i>
骨髓抑制/[例(%)]			
3 周期			0.076
是否发生	24(80.00)	17(56.67)	
I级	11(36.67)	17(56.67)	
II级	12(40.00)	0(0.00)	
III~IV级	1(3.33)	0(0.00)	
6 周期			0.002
是否发生	30(100.00)	21(70.00)	
I级	17(56.67)	20(66.67)	
II级	12(40.00)	1(3.33)	
III~IV级	1(3.33)	0(0.00)	

计量资料以均数±标准差表示，组间比较采用 *t* 检验；计数资料以频数(构成比或率)表示，组间比较采用 Fisher 确切概率法；等级资料采用秩和检验。KPS：Karnofsky 功能状态；ORR：客观缓解率；DCR：疾病控制率。

2.3 中医证候积分比较

2 组治疗前中医证候积分比较的差异无统计学意义($P>0.05$)。重复测量方差分析显示，测量时间主效应、组别主效应及时间×组别交互效应均有统计学意义(均 $P<0.05$ ，表 3)，提示 2 组的中医证候积分随治疗进程的变化趋势存在差异。总体上，对照组证候

积分随治疗进程逐渐升高，而联合组升幅较小，提示联合组在治疗过程中证候恶化程度较轻。

中医证候疗效分析结果(表 4)显示，联合组的总有效率(显效+有效)高于对照组，差异有统计学意义($P<0.05$)，相对风险(relative risk, RR)为 2.440。

表 3 中医证候积分的方差分析

Table 3 Variance analysis for traditional Chinese medicine syndrome scores

效应类型	自由度(校正)	<i>F</i>	<i>P</i>	偏 η^2
测量时间	4.016(GG)	58.149	<0.001	0.501
测量时间×组别	4.016(GG)	4.937	0.001	0.078
组别	1	27.130	<0.001	0.319

中医证候积分采用重复测量方差分析。自由度经 Greenhouse-Geisser 校正，效应量以偏 η^2 表示。

表 4 基于中医证候积分的 2 组临床疗效比较($n=30$)

Table 4 Comparison of clinical efficacy between the 2 groups based on traditional Chinese medicine syndrome scores ($n=30$)

组别	显效/[例(%)]	有效/[例(%)]	无效/[例(%)]	显效+有效/[例(%)]	<i>P</i>	RR	OR
对照组	1(3.33)	8(26.67)	21(70.00)	9(30.00)	<0.001	2.440	6.420
联合组	7(23.33)	15(50.00)	8(26.67)	22(73.33)			

计数资料以频数(构成比)表示，组间比较采用 Fisher 确切概率法，并计算 RR 和 OR。RR：相对风险；OR：比值比。

2.4 2组患者CEA与CA19-9比较

2组化疗前的CEA与CA19-9基线水平(T0)比较的差异均无统计学意义(均 $P>0.05$),具有可比性。第6周期结束时(T6),联合组的CEA水平低于对照组,且下降率高于对照组,差异均有统计学意义(均 $P<0.05$)。2组的CA19-9在第6周期结束时(T6)的水平及

下降率方面的差异均无统计学意义(均 $P>0.05$,表5)。CEA动态变化分析结果显示,2组在T0~T4时的差异均无统计学意义(均 $P>0.05$),但至T5、T6时,联合组的CEA水平低于对照组,差异有统计学意义(均 $P<0.05$,图2A);CA19-9的各时间点比较的差异均无统计学意义(均 $P>0.05$,图2B)。

表5 2组CEA和CA19-9的基线水平、终点水平及下降率比较($n=30$)

Table 5 Comparison of baseline, endpoint, and decline rates of CEA and CA19-9 levels between the 2 groups ($n=30$)

组别	CEA/(ng·mL ⁻¹)		CEA下降率/%	CA19-9/(U·mL ⁻¹)		CA19-9下降率/%
	T0	T6		T0	T6	
联合组	6.10(4.01, 9.66)	2.75(1.62, 4.99)	44.79(26.09, 65.17)	11.00(7.47, 16.73)	10.41(8.40, 15.30)	-2.70(-6.64, 9.76)
对照组	5.92(3.46, 12.91)	3.58(2.91, 10.16)	28.55(10.91, 40.40)	11.15(8.71, 16.13)	10.94(8.53, 14.13)	4.97(-7.88, 12.50)
Z	0.353	1.981	2.130	0.394	0.230	0.812
P	0.728	0.048	0.033	0.695	0.819	0.416

偏态分布计量资料以中位数(第1四分位数,第3四分位数)表示,组间比较采用Mann-Whitney U 检验。T0:化疗前基线;T6:第6化疗周期结束时;CEA:癌胚抗原;CA19-9:糖类抗原19-9。

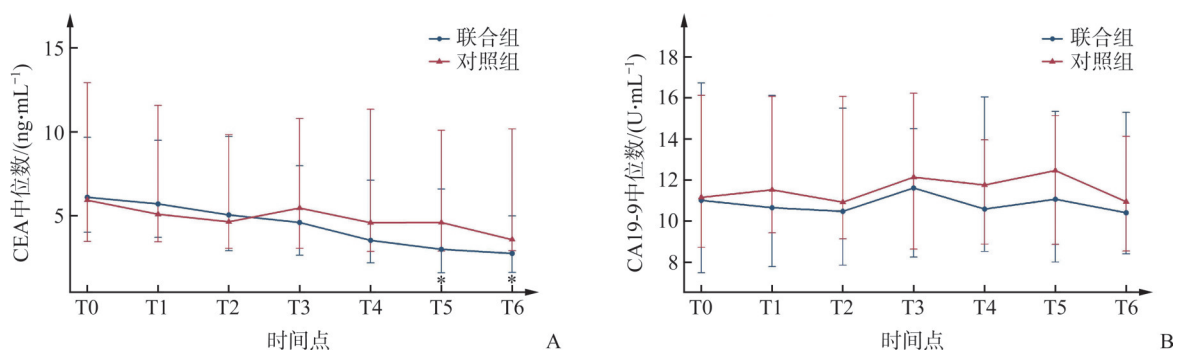


图2 2组患者CEA与CA19-9在T0至T6的变化趋势

Figure 2 Trends in CEA and CA19-9 levels from T0 to T6 in the 2 groups

A: Trends in CEA from T0 to T6 cycles. B: Trends in CA19-9 from T0 to T6 cycles. Group comparisons were performed using the Mann-Whitney U test. Error bars represent the interquartile range (from the first quartile to the third quartile). Compared with the control group at the same time point, $*P<0.05$. T0: Baseline before chemotherapy; T1: At the end of the first chemotherapy cycle; T2: At the end of the second chemotherapy cycle; T3: At the end of the third chemotherapy cycle; T4: At the end of the fourth chemotherapy cycle; T5: At the end of the fifth chemotherapy cycle; T6: At the end of the sixth chemotherapy cycle; CEA: Carcinoembryonic antigen; CA19-9: Carbohydrate antigen 19-9.

2.5 2组患者治疗前后安全性指标比较

2组治疗前ALT、AST、BUN及Cr水平比较的差异均无统计学意义(均 $P>0.05$)。治疗6个周期后,上述指标均较治疗前轻度升高,但治疗后组间比较及指标变化值比较的差异均无统计学意义(均 $P>0.05$)。化疗期间未见3级及以上肝肾功能不良事件(表6)。

2.6 JPJDYHF对化疗患者肠道菌群的影响

2.6.1 肠道菌群多样性

本研究共鉴定出282个OTUs,其中226个为2组共有(图3A)。稀释曲线在测序量达到3 000条序列时趋于平缓,且所有样本的Good's覆盖率(Good's coverage)均超过99.9%,表明测序深度充足。尽管Alpha多样性指数未见显著差异,但Beta多样性的PCoA结果显示,联合组与对照组的微生物群落结构发生了显著分离($P<0.05$,图3B)。

表6 2组患者治疗前后安全性指标比较($n=30$)Table 6 Comparison of liver and renal function indicators between the 2 groups before and after treatment ($n=30$)

组别	ALT/(U·L ⁻¹)	AST/(U·L ⁻¹)	BUN/(mmol·L ⁻¹)	Cr/(μmol·L ⁻¹)
治疗前				
对照组	25.36±10.38	24.47±7.19	5.43±1.08	73.90±15.44
联合组	26.91±10.86	24.87±7.18	5.50±1.07	74.48±15.77
<i>t</i>	0.565	0.216	0.252	0.144
<i>P</i>	0.874	0.853	0.871	0.757
治疗后				
对照组	34.56±13.17	31.3±10.59	5.97±1.26	80.11±17.57
联合组	35.42±15.13	31.63±10.88	6.02±1.29	80.62±18.39
<i>t</i>	0.235	0.119	0.152	0.110
<i>P</i>	0.848	0.828	0.869	0.740
变化值				
对照组	9.20±5.85	6.85±4.86	0.54±0.28	6.21±4.48
联合组	8.51±6.01	6.76±4.82	0.53±0.28	6.14±4.72
<i>t</i>	0.268	0.072	0.138	0.059
<i>P</i>	0.821	0.806	0.891	0.717

计量资料以均数±标准差表示，组间比较均采用独立样本 t 检验。ALT：丙氨酸氨基转移酶；AST：天冬氨酸氨基转移酶；BUN：血尿素氮；Cr：肌酐。

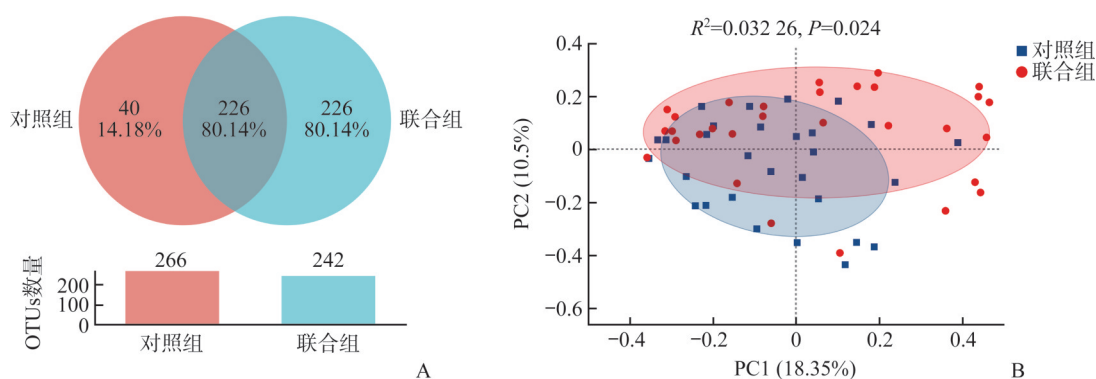


图3 2组肠道菌群的多样性分析

Figure 3 Diversity analysis of gut microbiota between the 2 groups

A: Venn diagram illustrating the shared and unique OTUs between the 2 groups. B: PCoA plot based on beta diversity, demonstrating the significant structural separation of microbial communities. OTU: Operational taxonomic unit; PCoA: Principal coordinate analysis; PC: Principal coordinate.

2.6.2 肠道菌群群落组成

在门水平上，厚壁菌门(Firmicutes)、拟杆菌门(Bacteroidota)和变形菌门(Proteobacteria)在2组中均占据主导地位，其中联合组Firmicutes的相对丰度相比对照组有所增加(图4A)。在属水平上，布劳特氏菌属(*Blautia*)、埃希氏-志贺氏菌属(*Escherichia-Shigella*)、乳杆菌属(*Lactobacillus*)、真杆菌属(*Eubacterium*)和瘤胃球菌科-UCG-014(*Ruminococcaceae*-

UCG-014)为优势菌群分类单元。LEfSe分析结果进一步提示，JPJDYHF干预后联合组的肠道菌群发生了显著的物种组成变化(图4B)。与对照组相比，联合组中Bacteroidota、梭杆菌门(*Fusobacteriota*)和弯曲杆菌门(*Campylobacterota*)以及拟杆菌属(*Bacteroides*)、副拟杆菌属(*Parabacteroides*)和梭杆菌属(*Fusobacterium*)的相对丰度显著降低，而*Blautia*和Ruminococcaceae-UCG-014的相对丰度显著升高(图4C)。

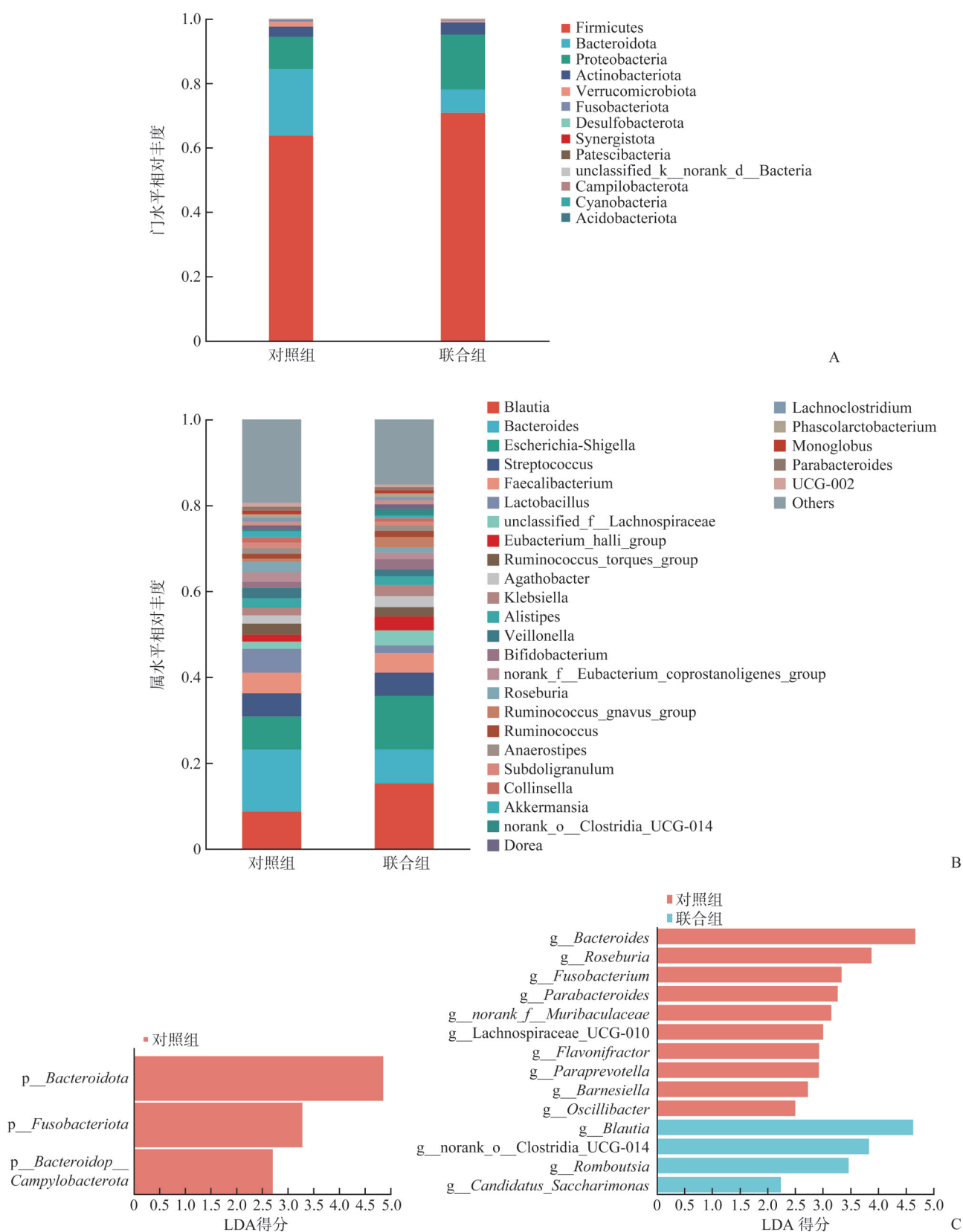


图4 干预后肠道菌群的物种组成变化与功能预测

Figure 4 Taxonomic alterations and functional prediction of gut microbiota following intervention

A: Relative abundance of microbial communities at the phylum level. B: Relative abundance of microbial communities at the genus level. C: LefSe identifying significant taxonomic shifts between the 2 groups (LDA score > 2). LefSe: Linear discriminant analysis effect size; LDA: Linear discriminant analysis.

2.6.3 肠道菌群功能预测

COG 功能预测与差异通路分析结果(图 5)显示，主要的微生物功能包括氨基酸代谢、碳水化合物代谢、转录以及复制/重组/修复。与对照组相比，联合

组的肠道菌群在脂质转运与代谢、细胞壁/膜/包膜生物发生相关通路表现出显著下调，同时信号转导功能显著激活(均 $P<0.05$)，这些功能变化可能与 CRC 相关代谢重编程及微环境改变有关。

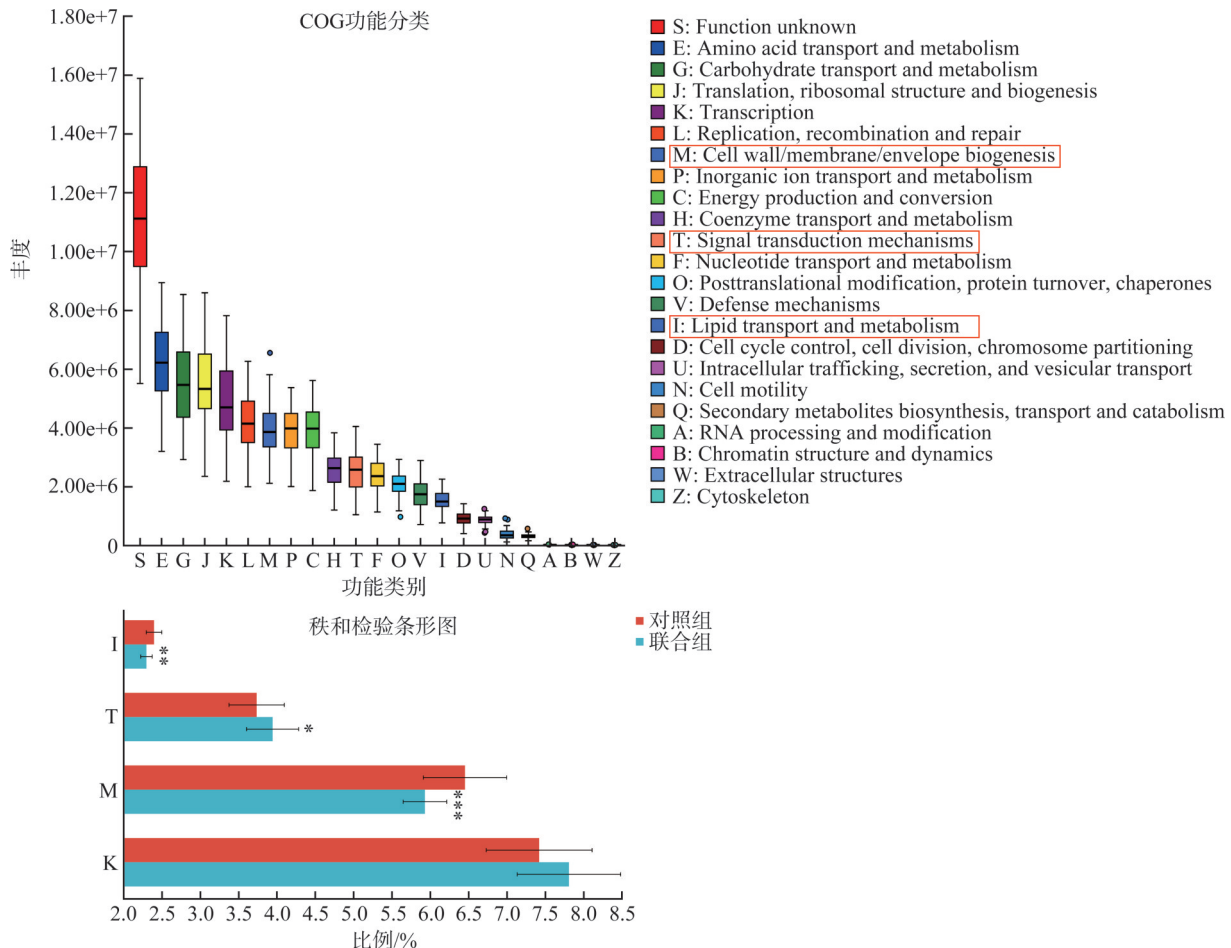


图5 基于PICRUSt2的COG功能预测与差异通路分析

Figure 5 COG functional prediction and differential pathway analysis based on PICRUSt2

I: Lipid transport and metabolism; T: Signal transduction mechanisms; M: Cell wall/membrane/envelope biogenesis; K: Transcription. Compared with the control group, * $P<0.05$, ** $P<0.01$, *** $P<0.001$. COG: Clusters of orthologous groups; PICRUSt2: Phylogenetic Investigation of Communities by Reconstruction of Unobserved States 2.

3 讨论

CRC是常见消化系统恶性肿瘤，对于III~IV期患者，化疗仍是综合治疗的重要组成部分^[20-22]。然而，化疗相关胃肠道反应、骨髓抑制等不良反应常影响治疗的依从性和完成度，成为限制临床获益的重要因素^[23]。因此，在维持化疗的抗肿瘤疗效的同时减轻化疗相关不良反应，已成为目前CRC综合治疗中的关键问题。既往研究^[21]提示，中医药在改善肿瘤患者整体状态、减轻化疗相关不良反应及改善治疗耐受性方面具有一定优势。本研究在采用PSM平衡基线差异后显示，JPJDYHF辅助化疗的获益不仅体

现在症状缓解，还表现为更好的化疗通过情况、更高的DCR及整体状态改善，且未增加肝肾功能负担。这提示其有助于维持治疗连续性并提升综合获益。

JPJDYHF源于临床经验方，并经长期实践加减优化^[24]。从治疗思路看，该方并非仅针对单一不适症状，而是根据化疗不同阶段患者脾胃受损、毒邪内蕴及正气耗伤等特点进行分期干预。化疗初期重在健脾理气、和胃降逆，以改善食欲不振(纳差)、恶心、腹泻等消化道反应^[25-26]；中后期则兼顾清热解毒与扶正培本，以应对持续治疗所致的耐受性降低和机体失衡^[27]。本研究中，联合组胃肠道反应减轻、体重下降幅度减少、骨髓抑制程度较轻，与上述分期

干预思路具有较好一致性。结合既往药理研究^[28-33], JPJDYHF“减毒增效”的作用基础可能与其多成分、多靶点协同调控有关,包括减轻肠黏膜损伤、调节炎症反应与氧化应激、减轻造血抑制及增强化疗敏感性等。这也提示,其临床效应并非局限于局部症状控制,而可能涉及肠黏膜屏障功能、免疫状态和耐药相关过程的综合调节。

本研究的创新点在于从肠道菌群角度观察 JPJDYHF 辅助化疗后的微生态变化。肠道是机体重要的免疫器官和屏障,聚集了大量免疫细胞,肠道菌群通过维持黏膜屏障、调控局部及全身免疫反应参与宿主稳态维持^[34-36]。对 CRC 患者而言,肠道菌群失衡不仅与肿瘤的发生、发展有关,也与化疗相关不良反应和疗效差异密切相关^[34]。此外,中药复方以口服为主要给药方式,其成分不可避免地与肠道微生物发生双向作用:一方面,菌群可参与药物代谢与活化;另一方面,药物也可反过来重塑菌群结构。因此,从肠道菌群角度探讨 JPJDYHF 的作用机制,具有一定的科学依据。

本研究的 16S rRNA 测序结果显示,联合组与对照组的微生物群落结构的 Beta 多样性差异显著,而 Alpha 多样性无显著差异,表明 JPJDYHF 可能主要用于菌群的结构性重塑,而非单纯增加菌群丰富度。具体来看,联合组中 *Blautia* 和 *Ruminococcaceae-UCG-014* 相对丰度升高,二者均可产生短链脂肪酸(short-chain fatty acid, SCFA)^[37]。SCFA 中的丁酸盐既是肠上皮细胞的主要能量来源,又能通过抑制组蛋白脱乙酰酶(histone deacetylase, HDAC)活性发挥免疫调节功能^[38]。研究^[38-39]表明,丁酸盐可进入循环系统,影响髓源性抑制细胞和调节性 T 细胞的分化与功能,从而改变肿瘤微环境的免疫状态,可能间接增强化疗药物的抗肿瘤效应。因此,本研究中上述有益菌群的富集,可能与联合组胃肠道反应较轻、化疗通过情况较好相关。

与之相对,联合组中 *Bacteroides*、*Parabacteroides* 和 *Fusobacterium* 相对丰度下降。具核梭杆菌(*Fusobacterium nucleatum*)已被证实与 CRC 进展、炎症反应及化疗耐药相关,可通过 Toll 样受体 4(Toll-like receptor 4, TLR4)/髓系分化初级反应蛋白质 88(myeloid differentiation primary response protein 88, MYD88)等通路促进肿瘤细胞存活并削弱奥沙利铂、5-氟尿嘧啶(5-fluorouracil, 5-FU)等药物敏感性^[40]。上述变化与联合组较好的化疗通过情况和 DCR 在方向上相一致,提示 JPJDYHF 可能部分通过调节与炎症、屏障损伤及耐药相关的菌群失衡状态,参与化疗减毒增效过程。

本研究的功能预测结果进一步支持了这一趋势。联合组的肠道菌群在脂质转运与代谢、细胞壁/膜/包膜生物发生^[41-43]等 COG 功能类别中相对丰度下降,而转录相关功能^[39-41]类别相对丰度升高。已有研究^[43-44]表明,肿瘤进展及宿主-微生物相互作用往往伴随代谢重编程与微环境改变。上述结果提示,JPJDYHF 的作用可能不仅体现在菌群组成变化层面,还可能通过影响菌群相关代谢功能及宿主-微生物相互作用,进而改善化疗相关不良反应并提高临床获益。结合本课题前期关于“肠道菌群-色氨酸-芳香烃受体轴”的研究基础^[45],推测 JPJDYHF 可能通过直接药理效应与微生态调节的协同作用影响宿主内环境,但其具体分子机制仍有待进一步验证。

本研究仍存在一定局限性。首先,本研究为单中心、小样本、前瞻性、非随机对照研究,尽管采用了 PSM 降低基线混杂因素影响,但仍难以完全避免选择偏倚。其次,本研究的随访时间较短,尚缺乏无进展生存期、总生存期等远期预后指标。此外,本研究对肠道菌群的分析主要基于 16S rRNA 基因测序及功能预测,缺少代谢组学和机制实验的直接支持。未来仍需开展多中心、大样本、前瞻性随机对照研究,并结合代谢组学、转录组学及功能实验,进一步阐明 JPJDYHF 辅助化疗的作用机制及其临床获益基础。

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