Advances in Clinical Medicine 临床医学进展, 2022, 12(12), 11555-11568
Published Online December 2022 in Hans. http://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2022.12121666

Hans汉斯

炎症性肠病中的银屑病：一项系统评价与荟萃分析

李　露[1]，陈钰琪[1]，张传栋[1]，潘文胜[2*]

[1]青岛大学医学院，山东　青岛
[2]浙江省人民医院，浙江　杭州

收稿日期：2022年11月21日；录用日期：2022年12月15日；发布日期：2022年12月26日

摘　要

背景：银屑病是炎症性肠病最常见的免疫介导的皮肤表现。目前关于共存的银屑病对炎症性肠病自然史的影响的数据很少且相互矛盾。本研究旨在确定炎症性肠病患者中银屑病的临床特征和相关风险因素。方法：对电子数据库(PubMed和Embase)进行了搜索，从开始到2022年3月12日，以确定报告炎症性肠病患者中银屑病的研究。从纳入的研究中提取了相关数据，包括无法进行荟萃分析的数据。采用随机和固定效应模型来总结临床信息。本研究遵循流行病学观察研究的Meta分析指南。结果：这项荟萃分析包括34项研究。在累计453,917名IBD患者中，总共有9487例银屑病患者。斑块状银屑病占总数的60.4% (95% CI 0.544~0.665)。50.7%的银屑病患者(95% CI 0.489~0.525)发生在被诊断为炎症性肠病之前。在荟萃分析中，银屑病与女性(RR = 1.145, 95% CI 1.110~1.180)、克罗恩病(RR = 1.128, 95% CI 1.056~1.205)、吸烟者(RR = 1.280, 95% CI 1.130~1.450)、其他肠外表现(RR = 1.907, 95% CI 1.588~2.290)和IBD相关手术史(RR = 2.083, 95% CI 1.203~3.607)有关。结论：大约一半的银屑病在炎症性肠病诊断前出现，抗肿瘤坏死因子治疗诱发的矛盾性银屑病不是停药的指征。临床医生应针对这一特殊人群制定个性化的治疗方案。

关键词

银屑病，炎症性肠病，肠外表现，抗肿瘤坏死因子

Psoriasis in Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis

Lu Li[1], Yuqi Chen[1], Chuandong Zhang[1], Wensheng Pan[2*]

[1]Medical College, Qingdao University, Qingdao Shandong
[2]Zhejiang Provincial People's Hospital, Hangzhou Zhejiang

[*]通讯作者。

文章引用: 李露, 陈钰琪, 张传栋, 潘文胜. 炎症性肠病中的银屑病: 一项系统评价与荟萃分析[J]. 临床医学进展, 2022, 12(12): 11555-11568. DOI: 10.12677/acm.2022.12121666

Received: Nov. 21st, 2022; accepted: Dec. 15th, 2022; published: Dec. 26th, 2022

Abstract

Background: Psoriasis is the most common immune-mediated cutaneous manifestation of inflammatory bowel disease. The current data on the impact of coexistent psoriasis on natural history of inflammatory bowel diseases are scarce and contradictory. This study aimed to identify the clinical features and associated risk factors of psoriasis in patients with inflammatory bowel disease. Methods: The search of electronic databases (PubMed and Embase) was conducted from inception to March 12, 2022 to identify studies reporting psoriasis among inflammatory bowel disease patients. We extracted relevant data from included studies, including data not able to be meta-analysis. Random and fixed effect models were used to summarize clinical information. This study followed meta-analysis of Observational Studies in Epidemiology guidelines. Results: This meta-analysis included 34 studies. In total, there were 9487 cases of psoriasis in the cumulative 453,917 IBD patients. Plaque psoriasis accounted for 60.4% of the total (95% CI 0.544~0.665). 50.7% of patients with psoriasis (95% CI 0.489~0.525) occurred before they were diagnosed with inflammatory bowel disease. In meta-analysis, psoriasis was associated with female (RR = 1.145, 95% CI 1.110~1.180), Crohn's disease (RR = 1.128, 95% CI 1.056~1.205), smokers (RR = 1.280, 95% CI 1.130~1.450), other extraintestinal manifestations (RR = 1.907, 95% CI 1.588~2.290), and IBD-related surgery history (RR = 2.083, 95% CI 1.203~3.607). Conclusions: About half of psoriasis appear before inflammatory bowel disease diagnosis, and gastroenterology consultation may be required when a patients with psoriasis present with intestinal symptoms. Clinicians should make personalized treatment plans for this specific population.

Keywords

Psoriasis, Inflammatory Bowel Disease, Extraintestinal Manifestations, Anti-Tumor Necrosis Factor

1. 引言

炎症性肠病(Inflammatory bowel disease, IBD)包括溃疡性结肠(Ulcerative colitis, UC)、克罗恩病(Crohn's disease, CD)和未分类的炎症性肠病，后者是一种病因不明的特发性肠道炎症性疾病。IBD 的临床表现主要是肠道症状，但其他器官也常受累，如皮肤、眼睛、关节、肝脏、胆道等[1]。由 IBD 引起的其他系统的症状被称为肠外表现(Extraintestinal manifestations, EIM)。皮肤受累是 IBD 最常见的肠外表现之一[2] [3] [4]。其皮肤表现可按病理生理学分为 4 类：1) 特异性 2) 反应性 3) 相关性 4) 治疗引起的皮损[5]。

银屑病和结节性红斑也是与 IBD 相关的最常见的皮肤病[6]。银屑病是一种慢性炎症性疾病，据世界卫生组织估计，全球有 0.09%~11.43%的人口受到影响[7]，主要症状是反复出现的红斑和鳞屑，可影响身体任何部位的皮肤。它的特点是疗程长，疗效差，容易复发[8] [9]，轻症的病例出现皮疹，而严重的病例可导致感染，甚至关节和器官损伤。

在不同的临床环境中，已经观察到银屑病和 IBD 的重合。为了阐明两者之间的关系，专家们提出了一些假说，如基因、肠道微生物群失衡、免疫反应的变化等[10] [11] [12]。一项荟萃分析报告指出，IBD 患者中银屑病的发病率为 4.2% [13]。然而，目前关于这类患者的临床过程的数据很少，而且更多的是从皮肤病学的角度而不是从胃肠病学的角度。这两种疾病(IBD 和银屑病)似乎有重叠的炎症调节途经，以前的研究表明，那些确诊为银屑病的人患 IBD 的风险增加[14] [15] [16] [17]。此外，在过去的十年中，相关的研究过于关注肿瘤坏死因子(Tumor necrosis factor, TNF)抑制剂引起的皮肤不良反应，而忽略了它们之间的原始免疫联系，并且已经做了一些尝试来阐明两者之间的双向关联。虽然个别研究表明，药物使用、家族史、性别、种族等人口学因素与银屑病有关，但目前关于 IBD 人群中银屑病的风险因素和特征的数据并不充分，且相互矛盾，现有文献未能提供明确的定义。本文通过系统评价和荟萃分析，可以更清晰地描述 IBD 患者银屑病的临床特征和相关危险因素，加深对 IBD 并发银屑病的自然史的认识。

2. 资料和方法

2.1. 材料

根据 MOOSE 指南对 IBD 患者中的银屑病表现进行了系统评价。文献检索在 PubMed 和 Embase 的英文数据库中进行，检索时间限制为从开始到 2022 年 3 月 12 日。英文检索词如下：“psoriasis”“inflammatory bowel disease”“Crohn’s disease”“ulcerative colitis”和“extraintestinal manifestations”。

2.2. 纳入和排除标准

纳入标准 1) 原始临床研究；2) IBD 患者，包括 UC 和 CD；3) 根据患者临床表现或病理活检确认的银屑病；4) 对治疗手段没有限制；5) 纳入的研究必须提供关于 IBD 患者银屑病的详细数据。

排除标准 1) 包括综述、荟萃分析、会议摘要、短篇通讯、评论、信件、病例报告、病例系列报告、未发表的和非英语写作的研究；2) 计数与其他皮肤病(湿疹等)混杂，且未明确说明受试者的数据；3) 与作者联系后仍无法获得的数据。

2.3. 研究选择

在第一阶段，两位作者独立检查标题和摘要，评估成功通过第二阶段的论文，并选择符合纳入标准的论文进行数据提取。数据由两位作者独立提取，资深作者修改并确定所有最终的分歧。对于同一机构或数据库来源的纳入时间重叠的研究，我们只纳入时间跨度最长的文章以避免数据重复。当文章中含有尚未报道的潜在相关数据时，我们曾试图通过电子邮件与作者联系，但无法获得进一步的信息。

2.4. 数据提取和质量评估

只包括 IBD 人群。从每个研究中提取的信息包括。1) 识别细节：引文数据(作者，出版年份，研究时期)，研究类型，人群(国家，年龄组)。2) 流行病学特征：样本量、患者来源、IBD 病例数、性别。3) 临床特征：疾病类型，结果(银屑病患者的数量)。所有提取的数据都由共同作者反复核对以确保其准确性。采用纽卡斯尔－渥太华量表(NOS)进行质量评估，对于横断面研究采用改编版本。通过人群选择、可比性、暴露评价对研究质量进行评价，满分为 10 分，得分 ≥ 7 分为高质量研究，4~6 分为中等质量研究，<4 分为低质量研究。

2.5. 统计分析

数据处理使用 Stata 17.0 软件(Stata Corporation, Texas)。我们使用固定效应模型，使用 Freeman-Tukey 双弧线转换法，评估银屑病的表型和发病时间在诊断 IBD 之前/之后的比例。用风险比(RR)和 95%置信区

间(95% CI)描述相关的风险因素。通过 Cochrane Q 和 I^2 检验异质性。$I^2 > 50\%$认为研究之间存在异质性，并使用随机效应模型进行分析。$I^2 \leq 50\%$表示同质性良好，采用固定效应模型进行分析。$P < 0.05$ 被认为具有统计学意义。为了消除 TNF 抑制剂的影响，亚组分析包括免疫相关组和矛盾反应组。通过逐一排除研究来探索异质性和敏感性分析的来源，以检查我们结果的稳定性。使用漏斗图和 Egger's 检验来获取出版偏倚。

3. 结果

3.1. 文献检索结果

初步筛选 PubMed 中有 1785 篇文章，Embase 中有 3369 篇文章。通过标题和摘要筛选 173 项研究进行全文评估后，我们纳入了 34 篇文章，包括队列研究、病例对照研究和横断面研究。在累计的 453,917 名 IBD 患者中，共有 9487 例银屑病患者[18]-[51]。其中，12 项研究是关于 TNF 抑制剂诱导的银屑病的观察性研究[40]-[51]。研究特点见表 1。

Table 1. Characteristics of studies reporting psoriasis in IBD
表 1. IBD 中银屑病的研究特点。

Author	Year	Location	Study type	Population	Number of IBD	Psoriasis patients	Newcastle-Ottawa score
Hammer *et al.* [18]	1968	England	Case-control	NA	243	5	5
Yates *et al.* [19]	1982	England	Case-control	Mixed	204	18	5
Lakatos *et al.* [20]	2003	Hungary	Cohort	Mixed	873	4	7
Bernstein *et al.* [21]	2005	Canada	Cohort	Mixed	8060	749	6
Weng *et al.* [22]	2007	USA	Cross-sectional	Mixed	12,601	242	5
Bardella *et al.* [23]	2008	Italy	Cross-sectional	Mixed	180	3	6
Yüksel *et al.* [24]	2009	Turkey	Cohort	Mixed	352	11	5
Ciccacci *et al.* [25]	2013	Italy	Cohort	NA	467	21	7
Vavricka *et al.* [26]	2015	Switzerland	Cohort	Mixed	1249	10	8
Singh *et al.* [27]	2015	India	Cohort	Mixed	1652	7	6
Lolli *et al.* [28]	2015	Italy	Case-control	Mixed	251	62	8
Card *et al.* [29]	2016	England	Cohort	Mixed	56,097	2856	7
Kim *et al.* [30]	2016	Korea	Cross-sectional	Mixed	40,843	636	6
Karmiris *et al.* [31]	2016	Greece	Cohort	Adult	1860	51	7
Halling *et al.* [32]	2017	Denmark	Cross-sectional	Mixed	47,325	378	5
Vide *et al.* [33]	2018	Portugal	Cohort	Mixed	342	24	7
Napolitano *et al.* [34]	2019	Italy	Cohort	NA	200	32	5
Yehuda *et al.* [35]	2019	Israel	Cohort	Mixed	12,625	614	7
Ghersin *et al.* [36]	2020	Israel	Cohort	Adolescents	2372	36	5
Edigin *et al.* [37]	2021	USA	Cross-sectional	Mixed	184,120	2255	7
Koumaki *et al.* [38]	2021	Greece	Cohort	Mixed	806	30	7

Continued

JO *et al.* [39]	2021	Korea	Cross-sectional	Mixed	64,837	929	6
Tillack *et al.* [40]	2014	Germany	Cohort	Adult	434	21	6
George *et al.* [41]	2015	USA	Cohort	Mixed	521	18	6
Fréling *et al.* [42]	2015	France	Cohort	Adult	583	59	6
Pugliese *et al.* [43]	2015	England	Cohort	NA	1384	33	7
Guerra *et al.* [44]	2016	Spain	Case-control	Mixed	7415	125	7
Protic *et al.* [45]	2016	Switzerland	Cohort	NA	752	34	7
Peer *et al.* [46]	2017	Australia	Cohort	Adult	270	10	6
Sridhar *et al.* [47]	2018	USA	Cohort	Children	409	33	7
Weizman *et al.* [48]	2018	Canada	Cohort	NA	676	72	7
Andrad *et al.* [49]	2018	Portugal	Cohort	Mixed	732	39	6
Courbette *et al.* [50]	2019	France	Cohort	Children	147	20	5
Buckley *et al.* [51]	2021	USA	Cohort	Children	3035	50	6

3.2. 银屑病的表型和发病时间

本研究包括的两组受试者是有银屑病和无银屑病的 IBD 患者。因此，只用单臂荟萃分析法分析了银屑病的表型和发病时间。七项研究报告了 IBD 患者银屑病的表型。斑块状银屑病占 60.4% (95% CI 0.544 −0.665, P < 0.001) [见图 1]。四项研究报告了这两种疾病的发病顺序。令人惊讶的是，50.7%的银屑病患者(95% CI 0.489~0.525, P < 0.001)发生在被诊断为炎症性肠病之前[见图 2]。

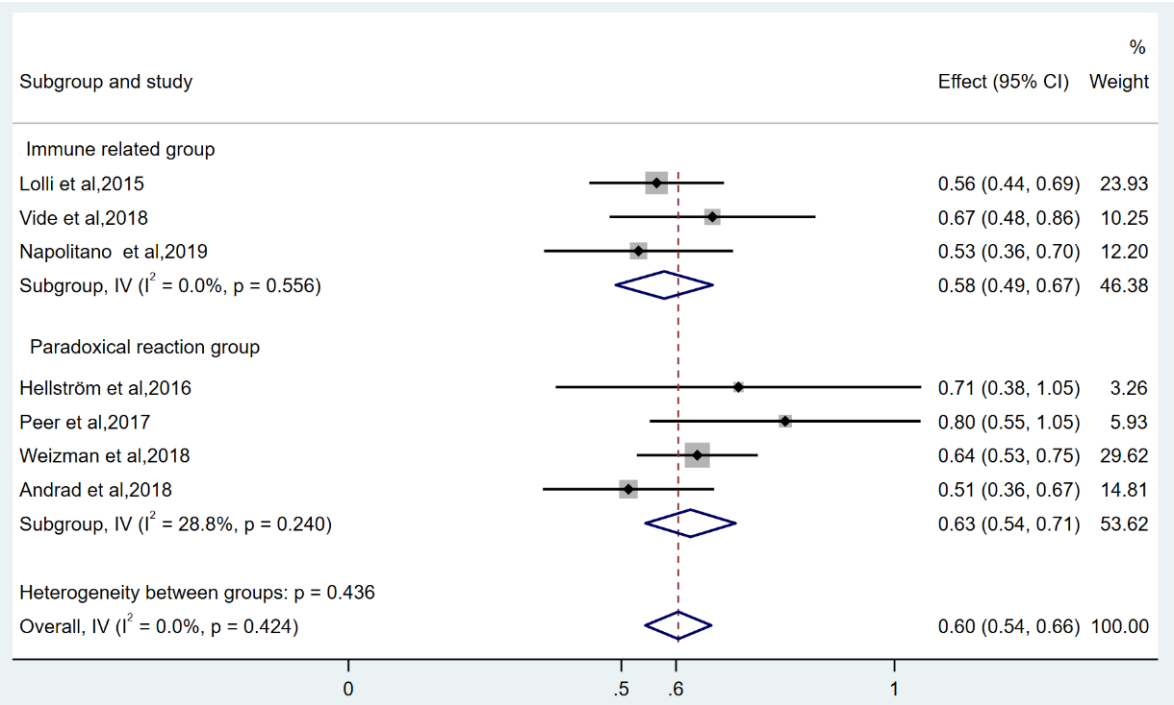

Figure 1. Forest plots of proportion of plaque psoriasis in IBD
图 1. IBD 中斑块状银屑病比例的森林图

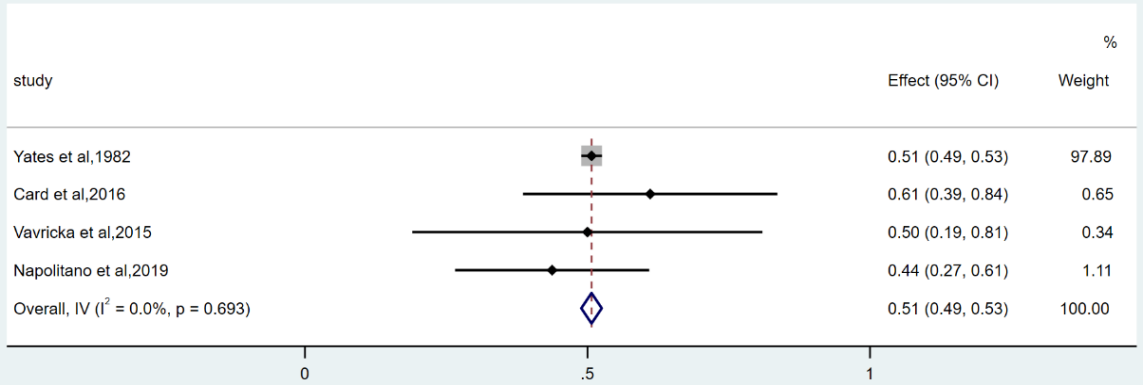

Figure 2. Forest plots of proportion of psoriasis that occurs earlier than the diagnosis of IBD
图 2. 早于 IBD 诊断发生的银屑病比例的森林图

3.3. 女性和克罗恩病

女性的相对风险高于男性(RR = 1.145, 95% CI 1.110~1.180, P < 0.001) [见图 3]。结果包括：RR(I) = 1.128 (95% CI 1.091~1.166, P < 0.001)，RR(P) = 1.275 (95% CI 1.173~1.387, P < 0.001)。

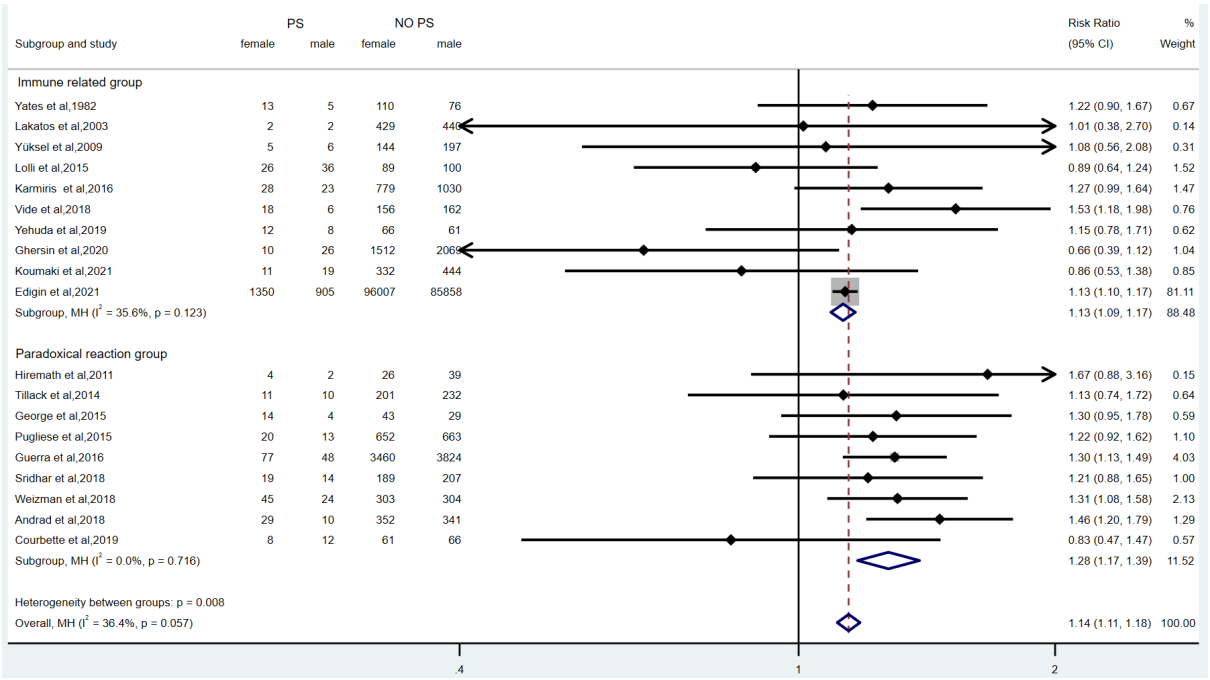

Figure 3. Forest plots represent correlation between different gender groups
图 3. 不同性别组之间的相关性的森林图

与溃疡性结肠炎相比，克罗恩病与银屑病的相对风险增加有关(RR = 1.128, 95% CI 1.056~1.205, P < 0.001) [见图 4]。同时分为 2 个亚组：RR(I) = 1.122 (95% CI 1.022~1.231, P = 0.016)，RR(P) = 1.153 (95% CI 1.062~1.251, P = 0.001)。

按研究年份、国家和研究类型进行了亚组分析，没有明显的异质性原因。逐一排除的研究表明，Bernstein 等人的研究[30]，Protic 等人的研究[51]和 Halling 等人的研究[21]是异质性的主要来源。我们推测，地理区域、环境和案例识别似乎导致了研究之间的异质性。

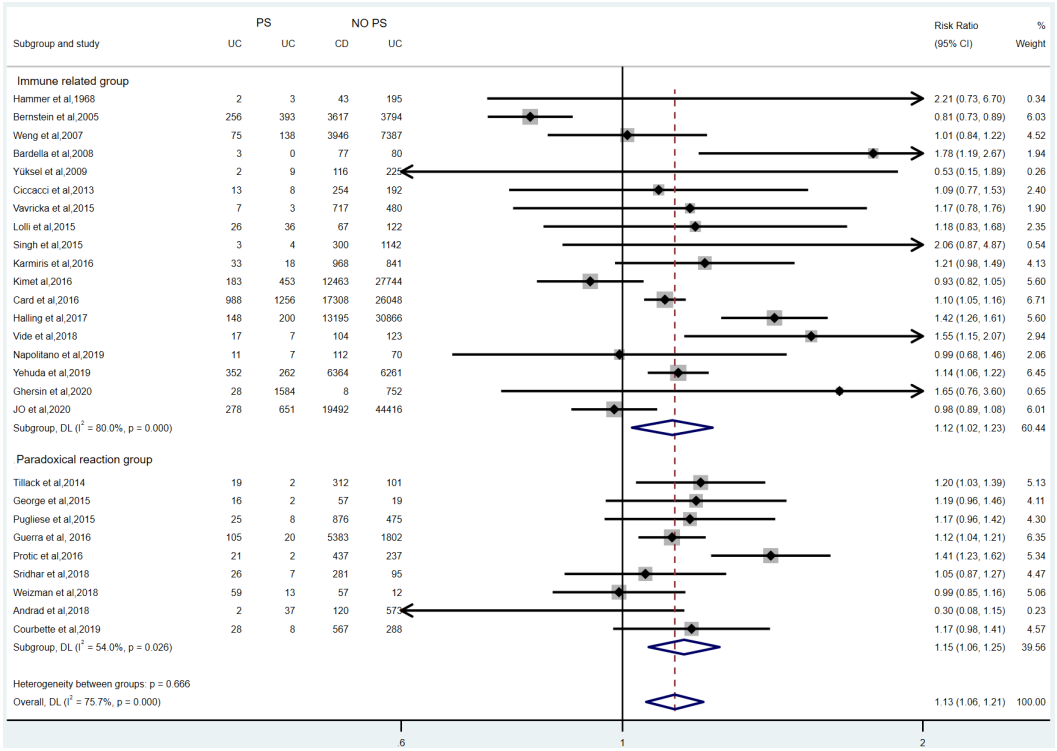

Figure 4. Forest plots represent correlation between different IBD subtype groups
图 4. 不同 IBD 亚型组之间相关性的森林图

3.4. 吸烟者、其他 EIMs 和 IBD 相关手术

吸烟者与银屑病的风险增加有关(RR = 1.280, 95% CI 1.130~1.450, P < 0.001) [见图 5]。结果包括 RR(I) = 1.058 (95% CI 0.809~1.383, P = 0.682)，RR(P) = 1.425 (95% CI 1.250~1.625, P < 0.001)。逐一排除的研究表明，Lolli 等人的研究[39]是异质性的主要来源，这可能是因为对照人群是非 IBD 患者。

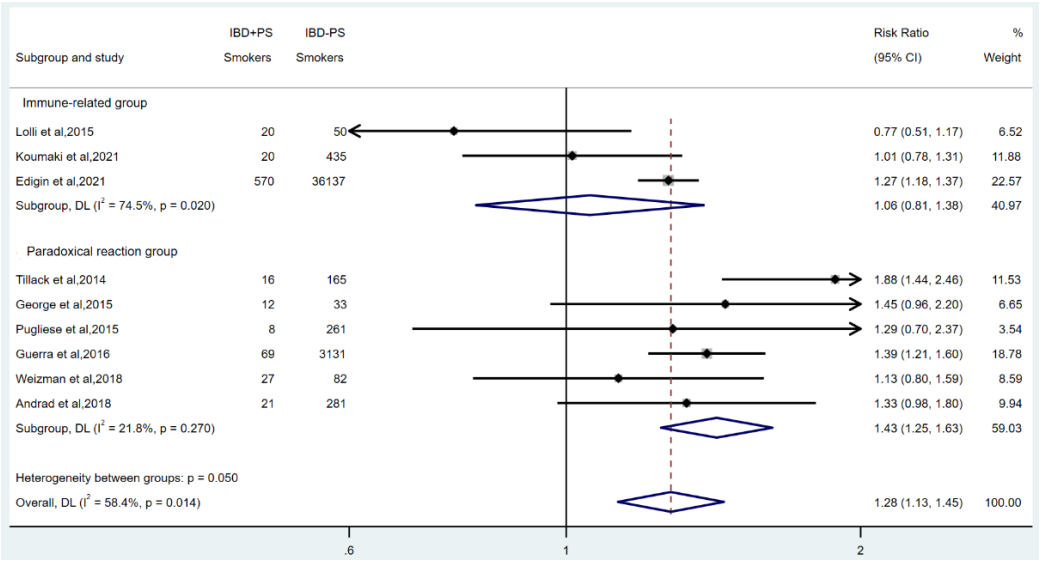

Figure 5. Forest plots represent correlation of psoriasis between smokers and non-smokers
图 5. 吸烟者和非吸烟者之间银屑病的相关性的森林图

其他 EIMs 与银屑病呈中度相关(RR = 1.907, 95% CI 1.588~2.290, P < 0.001) [见图 6]。只有两篇文章提到 IBD 相关手术史，显示与银屑病明显相关(RR = 2.083, 95% CI 1.203~3.607, P = 0.009) [见图 7]。

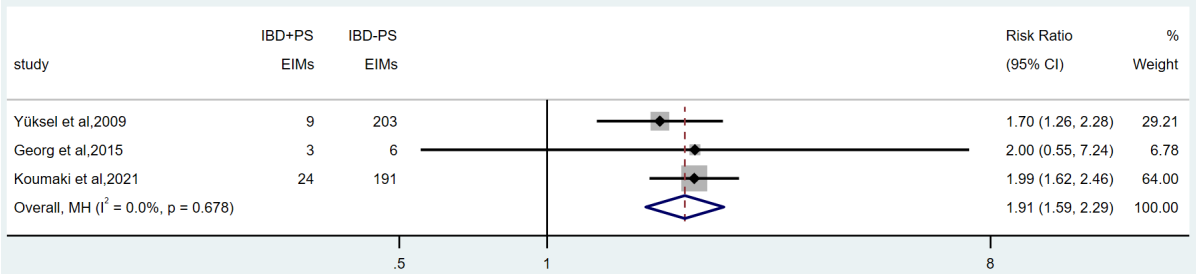

Figure 6. Forest plots of correlation of psoriasis between other EIMs
图 6. 其他 EIMs 之间的银屑病相关性的森林图

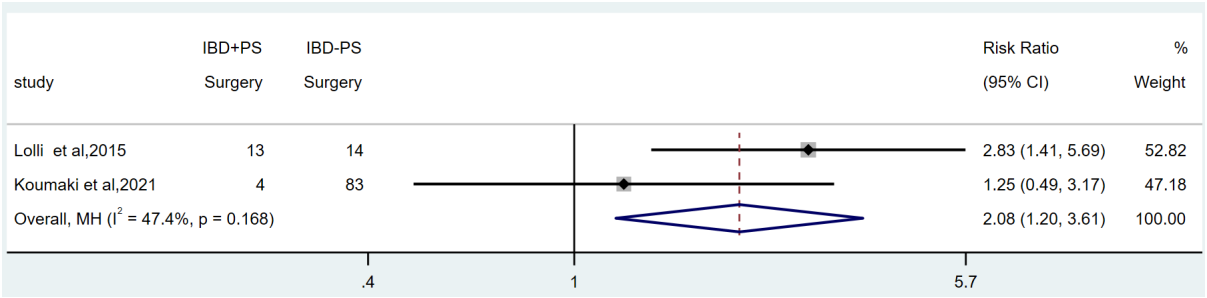

Figure 7. Forest plots of correlation of psoriasis between IBD-related surgical history
图 7. 银屑病与 IBD 相关手术史相关性的森林图

3.5. 特征(蒙特利尔分类) [见表 2]

IBD 特征和银屑病之间没有明显的关联。

Table 2. No significant association between IBD characteristics and psoriasis
表 2. IBD 特征与银屑病之间无明显关联

	No. study	Risk Ratio	95% CI	P	I^2
Behavior (CD)					
B1, non-stricturing/penetrating	6	1.024	0.900~1.166	0.718	36.4
B2, stricturing	6	0.939	0.766~1.152	0.549	23.2
B3, penetrating	6	1.024	0.829~1.264	0.826	40.5
Location (CD)					
L1, ileal	6	0.987	0.823~1.184	0.888	83.1
L2, colonic	6	0.944	0.709~1.255	0.69	0
L3, ileocolonic	6	1.024	0.919~1.142	0.669	47.1
Extention (UC)					
E1, ulcerative proctitis	4	1.039	0.600~1.799	0.892	0
E2, left-sided UC	4	0.833	0.467~1.486	0.536	7.6
E3, extensive	4	1.065	0.839~1.353	0.604	10.9

3.6. 敏感性分析和发表偏倚

敏感性分析采用的是留一法，上述结果是稳定的。在本研究中，用 Stata 软件生成的漏斗图来识别是否存在发表偏倚。在各自的漏斗图和 Egger's 检验中没有发现发表偏倚的证据。

4. 讨论

有关 IBD 患者银屑病的数据很少且分散，目前这些研究在方法和人群上的差异限制了对该主题的全面评估。就“肠外表现”而言，纳入标准有很大差异。本研究纳入的大多数研究都描述了一种以上的肠外表现，一些作者只关注选定的疾病，而另一些作者则报告了“皮肤表现”，没有进一步解释银屑病。此外，在大多数研究中，银屑病诊断标准的定义尚未完全确定，而且很少提及 IBD 患者中银屑病的特定风险因素的概念。所有这些都使质量评估变得困难。尽管有这些限制，在这项荟萃分析中，女性、CD、吸烟、其他肠外表现和 IBD 相关的肠道手术史与银屑病显著相关。这些结果有助于更好地了解两者之间的关系，并指导临床决策。

首先，IBD 的延迟诊断是一个值得关注的问题，特别是在 CD 中，1/4 的患者从最初的症状发生到诊断需要 24 个月以上的时间[25]。据报道，只有 14%的肠外表现是在 IBD 诊断之前出现的，银屑病是 IBD 患者中最常见的免疫介导的 c-EIM [29] [52] [53]。根据我们的荟萃分析，超过一半的银屑病发生在 IBD 诊断之前。这一发现特别重要，因为严重的肠道损伤可能已经发生，直至疾病被诊断出来才会被发现。与其他肠外表现相比，银屑病在皮肤上更容易被发现，是对 IBD 早期诊断的警示。研究表明，银屑病可能引起相关的肠道症状，但两者之间的免疫关联顺序尚不清楚[16]。如果银屑病患者出现肠道相关症状或不明原因的体重减轻，应考虑立即就医或进行相关干预，如结肠镜检查，以免错过最佳时机。

随着生物制剂的出现，TNF 抑制剂被越来越多地用于治疗 IBD。TNF 抑制剂也被用于治疗银屑病，但在 IBD 患者中使用 TNF 抑制剂会诱发皮肤不良反应。它们之间存在着微妙的自相矛盾的关系[54]。英夫利西单抗诱导的银屑病在 2003 年被首次报道[55]。目前，银屑病已成为众所周知的 TNF 抑制剂皮肤不良事件，被称之为矛盾性银屑病。该领域的专家提出了一个共同的发病联系，并试图澄清病理机制，但实际上对此知之甚少[34]。在本研究中，为了排除药物的影响，将研究对象分为两个亚组：免疫相关组和矛盾反应组，这两组都属于 IBD 患者的银屑病，并不影响我们的研究结果。根据两个亚组，结论是相同的：女性比男性更容易患银屑病，相对于 UC，CD 的风险增加。在矛盾反应组(TNF 抑制剂治疗)中，这种关联更强。这表明，女性和 CD 是 IBD 患者发生银屑病的风险因素。这与女性更容易患自身免疫性疾病的传统观念相吻合。我们假设 CD 患者会有更严重的全身性炎症负担，导致患病的可能性增加。

吸烟是一个危险因素吗？这一点仍有争议，尽管研究证实吸烟会增加 CD 患者肠道外表现的风险，但仍缺乏针对 IBD 合并银屑病这一特定人群的专门研究。利用现有数据，有两项荟萃分析提到吸烟史是 IBD 患者在 TNF 抑制剂治疗期间患银屑病的主要风险因素[56] [57] [58]。然而，这项研究与上述两项研究的纳入标准不同。他们纳入的一些文章主要是关于抗 TNF 的皮肤不良反应，计数也与湿疹等病变混合。我们对“银屑病”进行了更严格的审查，并最终纳入了“6 + 3”篇文章。我们的荟萃分析显示了不同的结果：目前，在没有 TNF 抑制剂治疗的 IBD 患者中，吸烟不能被认为是银屑病的风险因素。有趣的是，如果将两个亚组集合起来，吸烟是 IBD 患者银屑病的一个风险因素。过去，人们认为吸烟会增强基因的表达，使银屑病的风险增加，包括 HLA-Cw6、HLA-DQA1*0201 和 CYP1A1。Nguyen 等人提出了一个悖论：在普通人群中，吸烟与 PSA 风险呈正相关，但在银屑病患者中呈负相关[59]。如果对 IBD 的特定人群做进一步研究，情况比他们描述的要复杂。事实上，有报道称吸烟会增加 CD 的风险，对 UC 有保护作用[60]。如果在 UC 和 CD 中分别分析吸烟对银屑病的影响，结果会更清楚。鉴于关于这一主题的研究很少，需要进行更多的研究。

根据我们的结果，斑块状银屑病是IBD患者中最常见的表型，如同普通人群。虽然在一些观察性研究中提到，由TNF抑制剂诱导的银屑病更为严重，但根据我们的亚组分析结果，两个亚组之间的银屑病表型没有明显差异。当然，两个亚组的受试者在年龄、发病时间、治疗史、地理、环境方面存在异质性。这一结论需要仔细考虑。IBD患者的银屑病通常较轻，TNF抑制剂诱导的银屑病不一定是停止治疗的指征，因为大多数病例可以通过外用和紫外线治疗得到有效治疗[3]。然而，如果银屑病脓疱性皮损与感染一起发展，并可能导致PsA，则应充分考虑其他治疗方案。

此外，我们发现IBD肠道手术史与银屑病之间存在适度关联。许多研究表明，维生素D的缺乏会导致银屑病患者出现更严重的炎症反应[61] [62] [63]。一项研究表明，25-羟基维生素D(25[OH]D)水平与银屑病患者的全因死亡率呈反比关系[64]。事实上，维生素D与许多自身免疫性疾病的发展呈负相关，如系统性红斑狼疮、甲状腺毒症、寻常性银屑病、风湿性多发性肌炎等[65]。手术是影响IBD患者微量营养素缺乏的一个重要因素。Schäffler等人发现，CD切除术后维生素D水平明显下降[66]。这强调了接受IBD手术的患者的易感性，以及为这一脆弱的患者群体制定术前优化策略的必要性，包括纠正贫血、营养不良管理和控制感染[67]。IBD患者可以接受适当的术前预处理和充分的营养支持。术后患者也可以考虑补充包括维生素D在内的微量元素，以减少并发症的风险。尽管如此，基础理论还不完善，目前的决策过程主要是基于临床数据。对于临床医生来说，如何为患者量身定制最佳治疗方案仍然是一个挑战。

在UC的扩展、CD的位置和行为方面没有明显差异。在某种程度上，这表明银屑病和炎症性肠病本身与疾病的进展关系不大。与没有银屑病的IBD患者相比，患有银屑病的IBD患者的住院时间、住院费用和二次诊断相似[38]。

荟萃分析结果表明，银屑病患者的其他肠外表现比无银屑病患者更常见。事实上，研究确实称，有一个EIM会增加出现更多EIM的可能性[68]。一些文章剖析了银屑病与其他各种系统性疾病之间的联系[69] [70]。然而，当试图根据这些肠外表现的类型和位置进行进一步的亚组分析时，由于可用的数据不多，因此受到限制。

此外，我们的研究有几个局限性：1) 首先，除吸烟外，我们没有评估任何可能导致疾病发展的环境或生活方式因素(饮酒、饮食、种族、居住在农村/城市地区或使用抗生素)。这是因为目前的数据只包含有限的诊断和临床信息。2) 尽管已经努力将这些银屑病区分为免疫介导的肠外表现或药物不良反应，但这种区分并不完全清楚，因为两者的免疫学影响也可能重叠在一起。3) 尽管一些研究提到了银屑病的结果和后续的治疗方案，但由于相关研究数量有限，随访时间短，无法对继续使用同一TNF抑制剂的患者的银屑病缓解或复发的风险因素作出结论。4) 到目前为止，很少有人尝试描述EIMs和IBD的顺序，包括银屑病。本研究收录的4篇文章中只有2篇是前瞻性队列研究，样本量不足。因此，未来有必要进行大样本量的多中心研究，以更好地描述两者的顺序和临床特征。

参考文献

[1] Thurston, R.D., *et al*. (2010) Tumor Necrosis Factor and Interferon-Gamma Down-Regulate Klotho in Mice with Colitis. *Gastroenterology*, **138**, 1384-1394.e1-2. https://doi.org/10.1053/j.gastro.2009.12.002

[2] Hernández-Tejero, M., *et al*. (2017) Prevalence, Risk Factors and Response to Treatment of Extra-Intestinal Manifestations in Patients with Inflammatory Bowel Disease. *Revista Espanola De Enfermedades Digestivas*, **109**, 627-633. https://doi.org/10.17235/reed.2017.4845/2017

[3] Jansen, F.M., *et al*. (2020) Clinical Management of the Most Common Extra-Intestinal Manifestations in Patients with Inflammatory Bowel Disease Focused on the Joints, Skin and Eyes. *United European Gastroenterology Journal*, **8**, 1031-1044. https://doi.org/10.1177/2050640620958902

[4] Pouillon, L., *et al*. (2017) Management of Patients with Inflammatory Bowel Disease and Spondyloarthritis. *Expert Review of Clinical Pharmacology*, **10**, 1363-1374. https://doi.org/10.1080/17512433.2017.1377609

[5] Greuter, T., Navarini, A. and Vavricka, S.R. (2017) Skin Manifestations of Inflammatory Bowel Disease. *Clinical Re-*

views in Allergy & Immunology, **53**, 413-427. https://doi.org/10.1007/s12016-017-8617-4

[6] Makredes, M., *et al*. (2009) The Burden of Autoimmune Disease: A Comparison of Prevalence Ratios in Patients with Psoriatic Arthritis and Psoriasis. *Journal of the American Academy of Dermatology*, **61**, 405-410. https://doi.org/10.1016/j.jaad.2009.02.015

[7] World Health Organization (2016) Global Report on Psoriasis. World Health Organization, Geneva.

[8] Alzeer, F., AlOtair, H. and Aleisa, A. (2022) Epidemiology and Cutaneous Manifestations of Psoriasis in Saudi Arabia: A Narrative Review. *Clinical*, *Cosmetic and Investigational Dermatology*, **15**, 347-355. https://doi.org/10.2147/CCID.S352654

[9] Campanati, A., *et al*. (2021) Psoriasis as an Immune-Mediated and Inflammatory Systemic Disease: From Pathophysiology to Novel Therapeutic Approaches. *Biomedicines*, **9**, Article No. 1511. https://doi.org/10.3390/biomedicines9111511

[10] De Francesco, M.A. and Caruso, A. (2022) The Gut Microbiome in Psoriasis and Crohn's Disease: Is Its Perturbation a Common Denominator for Their Pathogenesis? *Vaccines* (*Basel*), **10**, Article No. 244. https://doi.org/10.3390/vaccines10020244

[11] Hedin, C.R.H., *et al*. (2021) Inflammatory Bowel Disease and Psoriasis: Modernizing the Multidisciplinary Approach. *Journal of Internal Medicine*, **290**, 257-278. https://doi.org/10.1111/joim.13282

[12] Myers, B., *et al*. (2019) The Gut Microbiome in Psoriasis and Psoriatic Arthritis. *Best Practice & Research*: *Clinical Rheumatology*, **33**, Article ID: 101494. https://doi.org/10.1016/j.berh.2020.101494

[13] Alinaghi, F., *et al*. (2020) Global Prevalence and Bidirectional Association between Psoriasis and Inflammatory Bowel Disease—A Systematic Review and Meta-Analysis. *Journal of Crohn's and Colitis*, **14**, 351-360. https://doi.org/10.1093/ecco-jcc/jjz152

[14] Wright, S., *et al*. (2020) Real-World Risk of New-Onset Inflammatory Bowel Disease among Patients with Psoriasis Exposed to Interleukin 17 Inhibitors. *Journal of the American Academy of Dermatology*, **83**, 382-387. https://doi.org/10.1016/j.jaad.2020.04.010

[15] Yousaf, A., *et al*. (2021) Association between Psoriasis, Psoriatic Arthritis and Gastrointestinal Disease: An Exploratory Nationwide Inpatient Sample Analysis. *Wiener Klinische Wochenschrift*, **133**, 586-593. https://doi.org/10.1007/s00508-020-01740-8

[16] King, D., *et al*. (2021) The Risk of Later Diagnosis of Inflammatory Bowel Disease in Patients with Dermatological Disorders Associated with Inflammatory Bowel Disease. *Inflammatory Bowel Diseases*, **27**, 1731-1739. https://doi.org/10.1093/ibd/izaa344

[17] Lee, J.Y., *et al*. (2019) Psoriasis Increases the Risk of Concurrent Inflammatory Bowel Disease: A Population-Based Nationwide Study in Korea. *Indian Journal of Dermatology*, *Venereology and Leprology*, **85**, 145-152. https://doi.org/10.4103/ijdvl.IJDVL_875_17

[18] Card, T.R., Langan, S.M. and Chu, T.P. (2016) Extra-Gastrointestinal Manifestations of Inflammatory Bowel Disease May Be Less Common than Previously Reported. *Digestive Diseases and Sciences*, **61**, 2619-2626. https://doi.org/10.1007/s10620-016-4195-1

[19] Kim, M., *et al*. (2017) Inflammatory Bowel Disease Is Associated with an Increased Risk of Inflammatory Skin Diseases: A Population-Based Cross-Sectional Study. *Journal of the American Academy of Dermatology*, **76**, 40-48. https://doi.org/10.1016/j.jaad.2016.08.022

[20] Koumaki, D., *et al*. (2021) Mucocutaneous Manifestations in Patients with Inflammatory Bowel Disease: A Decade Study from a Greek Cohort. *European Journal of Gastroenterology & Hepatology*, **33**, 1387-1393. https://doi.org/10.1097/MEG.0000000000002053

[21] Halling, M.L., *et al*. (2017) Patients with Inflammatory Bowel Disease Have Increased Risk of Autoimmune and Inflammatory Diseases. *World Journal of Gastroenterology*, **23**, 6137-6146. https://doi.org/10.3748/wjg.v23.i33.6137

[22] Jo, U.H., *et al*. (2021) Various Skin Manifestations Related to Inflammatory Bowel Disease: A Nationwide Cross-Sectional Study on the Korean Population. *The Journal of Dermatology*, **48**, 431-438. https://doi.org/10.1111/1346-8138.15676

[23] Karmiris, K., *et al*. (2016) Prevalence and Characteristics of Extra-Intestinal Manifestations in a Large Cohort of Greek Patients with Inflammatory Bowel Disease. *Journal of Crohn's and Colitis*, **10**, 429-436. https://doi.org/10.1093/ecco-jcc/jjv232

[24] Yates, V.M., Watkinson, G. and Kelman, A. (1982) Further Evidence for an Association between Psoriasis, Crohn's Disease and Ulcerative Colitis. *British Journal of Dermatology*, **106**, 323-330. https://doi.org/10.1111/j.1365-2133.1982.tb01731.x

[25] Vavricka, S.R., *et al*. (2015) Chronological Order of Appearance of Extraintestinal Manifestations Relative to the Time of IBD Diagnosis in the Swiss Inflammatory Bowel Disease Cohort. *Inflammatory Bowel Diseases*, **21**, 1794-1800.

https://doi.org/10.1097/MIB.0000000000000429

[26] Lakatos, L., *et al*. (2003) Association of Extraintestinal Manifestations of Inflammatory Bowel Disease in a Province of Western Hungary with Disease Phenotype: Results of a 25-Year Follow-Up Study. *World Journal of Gastroenterology*, **9**, 2300-2307. https://doi.org/10.3748/wjg.v9.i10.2300

[27] Yüksel, I., *et al*. (2009) Mucocutaneous Manifestations in Inflammatory Bowel Disease. *Inflammatory Bowel Diseases*, **15**, 546-550. https://doi.org/10.1002/ibd.20807

[28] Napolitano, M., *et al*. (2019) Psoriasis Features in Patients with Inflammatory Bowel Disease. *Open Access Macedonian Journal of Medical Sciences*, **7**, 1001-1003. https://doi.org/10.3889/oamjms.2019.161

[29] Vide, J., *et al*. (2018) Cutaneous Morbidity among Inflammatory Bowel Disease Patients: A Cohort Study. *Journal of Crohn's and Colitis*, **12**, 442-451. https://doi.org/10.1093/ecco-jcc/jjx178

[30] Bernstein, C.N., Wajda, A. and Blanchard, J.F. (2005) The Clustering of Other Chronic Inflammatory Diseases in Inflammatory Bowel Disease: A Population-Based Study. *Gastroenterology*, **129**, 827-836. https://doi.org/10.1053/j.gastro.2005.06.021

[31] Hammer, B., Ashurst, P. and Naish, J. (1968) Diseases Associated with Ulcerative Colitis and Crohn's Disease. *Gut*, **9**, 17-21. https://doi.org/10.1136/gut.9.1.17

[32] Weng, X., *et al*. (2007) Clustering of Inflammatory Bowel Disease with Immune Mediated Diseases among Members of a Northern California-Managed Care Organization. *The American Journal of Gastroenterology*, **102**, 1429-1435. https://doi.org/10.1111/j.1572-0241.2007.01215.x

[33] Bardella, M.T., *et al*. (2009) Autoimmune Disorders In Patients Affected by Celiac Sprue and Inflammatory Bowel Disease. *Annals of Medicine*, **41**, 139-143. https://doi.org/10.1080/07853890802378817

[34] Ciccacci, C., *et al*. (2013) TRAF3IP2 Gene Is Associated with Cutaneous Extraintestinal Manifestations in Inflammatory Bowel Disease. *Journal of Crohn's and Colitis*, **7**, 44-52. https://doi.org/10.1016/j.crohns.2012.02.020

[35] Singh, B., *et al*. (2015) Extraintestinal Manifestations of Inflammatory Bowel Disease and Intestinal Tuberculosis: Frequency and Relation with Disease Phenotype. *Indian Journal of Gastroenterology*, **34**, 43-50. https://doi.org/10.1007/s12664-015-0538-7

[36] Ghersin, I., *et al*. (2020) Comorbidities in Adolescents with Inflammatory Bowel Disease: Findings from a Population-Based Cohort Study. *Pediatric Research*, **87**, 1256-1262. https://doi.org/10.1038/s41390-019-0702-3

[37] Bar Yehuda, S., *et al*. (2019) The Association of Inflammatory Bowel Diseases with Autoimmune Disorders: A Report from the epi-IIRN. *Journal of Crohn's and Colitis*, **13**, 324-329. https://doi.org/10.1093/ecco-jcc/jjy166

[38] Edigin, E., *et al*. (2020) Coexisting Psoriasis Is Associated with an Increased Risk of Hospitalization for Patients with Inflammatory Bowel Disease: An Analysis of the National Inpatient Sample Database. *Journal of Investigative Medicine*, **69**, 857-862. https://doi.org/10.1136/jim-2020-001689

[39] Lolli, E., *et al*. (2015) Psoriasis Phenotype in Inflammatory Bowel Disease: A Case-Control Prospective Study. *Journal of Crohn's and Colitis*, **9**, 699-707. https://doi.org/10.1093/ecco-jcc/jjv068

[40] Sridhar, S., *et al*. (2018) Dermatological Manifestations in Pediatric Patients with Inflammatory Bowel Diseases on Anti-TNF Therapy. *Inflammatory Bowel Diseases*, **24**, 2086-2092. https://doi.org/10.1093/ibd/izy112

[41] George, L.A., *et al*. (2015) Psoriasiform Skin Lesions Are Caused by Anti-TNF Agents Used for the Treatment of Inflammatory Bowel Disease. *Digestive Diseases and Sciences*, **60**, 3424-3430. https://doi.org/10.1007/s10620-015-3763-0

[42] Peer, F.C., *et al*. (2017) Paradoxical Psoriasiform Reactions of Anti-Tumour Necrosis Factor Therapy in Inflammatory Bowel Disease Patients. *Internal Medicine Journal*, **47**, 1445-1448. https://doi.org/10.1111/imj.13637

[43] Fréling, E., *et al*. (2015) Cumulative Incidence of, Risk Factors for, and Outcome of Dermatological Complications of Anti-TNF Therapy in Inflammatory Bowel Disease: A 14-Year Experience. *The American Journal of Gastroenterology*, **110**, 1186-1196. https://doi.org/10.1038/ajg.2015.205

[44] Pugliese, D., *et al*. (2015) Paradoxical Psoriasis in a Large Cohort of Patients with Inflammatory Bowel Disease Receiving Treatment with Anti-TNF Alpha: 5-Year Follow-Up Study. *Alimentary Pharmacology & Therapeutics*, **42**, 880-888. https://doi.org/10.1111/apt.13352

[45] Weizman, A.V., *et al*. (2018) Stricturing and Fistulizing Crohn's Disease Is Associated with Anti-Tumor Necrosis Factor-Induced Psoriasis in Patients with Inflammatory Bowel Disease. *Digestive Diseases and Sciences*, **63**, 2430-2438. https://doi.org/10.1007/s10620-018-5096-2

[46] Buckley, L.H., *et al*. (2021) Psoriasis Associated with Tumor Necrosis Factor Inhibitors in Children with Inflammatory Diseases. *Arthritis Care & Research* (*Hoboken*), **73**, 215-220. https://doi.org/10.1002/acr.24100

[47] Courbette, O., *et al*. (2019) Infliximab Paradoxical Psoriasis in a Cohort of Children with Inflammatory Bowel Disease. *Journal of Pediatric Gastroenterology and Nutrition*, **69**, 189-193. https://doi.org/10.1097/MPG.0000000000002349

[48] Andrade, P., *et al*. (2018) Anti-Tumor Necrosis Factor-α-Induced Dermatological Complications in a Large Cohort of Inflammatory Bowel Disease Patients. *Digestive Diseases and Sciences*, **63**, 746-754. https://doi.org/10.1007/s10620-018-4921-y

[49] Tillack, C., *et al*. (2014) Anti-TNF Antibody-Induced Psoriasiform Skin Lesions in Patients with Inflammatory Bowel Disease Are Characterised by Interferon-γ-Expressing Th1 Cells and IL-17A/IL-22-Expressing Th17 Cells and Respond to Anti-IL-12/IL-23 Antibody Treatment. *Gut*, **63**, 567-577. https://doi.org/10.1136/gutjnl-2012-302853

[50] Guerra, I., *et al*. (2016) Incidence, Clinical Characteristics, and Management of Psoriasis Induced by Anti-TNF Therapy in Patients with Inflammatory Bowel Disease: A Nationwide Cohort Study. *Inflammatory Bowel Diseases*, **22**, 894-901. https://doi.org/10.1097/MIB.0000000000000757

[51] Protic, M., *et al*. (2016) Development of Psoriasis in IBD Patients under TNF-Antagonist Therapy Is Associated neither with Anti-TNF-Antagonist Antibodies nor Trough Levels. *Scandinavian Journal of Gastroenterology*, **51**, 1482-1488. https://doi.org/10.1080/00365521.2016.1218541

[52] Fedor, I., Zold, E. and Barta, Z. (2021) Temporal Relationship of Extraintestinal Manifestations in Inflammatory Bowel Disease. *Journal of Clinical Medicine*, **10**, Article No. 5984. https://doi.org/10.3390/jcm10245984

[53] Park, S.K., *et al*. (2021) Extraintestinal Manifestation of Inflammatory Bowel Disease in Asian Patients: A Multinational Study. *Digestive and Liver Disease*, **53**, 196-201. https://doi.org/10.1016/j.dld.2020.06.046

[54] Al-Janabi, A. and Yiu, Z.Z.N. (2022) Biologics in Psoriasis: Updated Perspectives on Long-Term Safety and Risk Management. *Psoriasis* (*Auckl*), **12**, 1-14. https://doi.org/10.2147/PTT.S328575

[55] Baeten, D., *et al*. (2003) Systematic Safety Follow Up in a Cohort of 107 Patients with Spondyloarthropathy Treated with Infliximab: A New Perspective on the Role of Host Defence in the Pathogenesis of the Disease? *Annals of Rheumatic Diseases*, **62**, 829-834. https://doi.org/10.1136/ard.62.9.829

[56] Xie, W., *et al*. (2022) Incidence of and Risk Factors for Paradoxical Psoriasis or Psoriasiform Lesions in Inflammatory Bowel Disease Patients Receiving Anti-TNF Therapy: Systematic Review with Meta-Analysis. *Frontiers in Immunology*, **13**, Article ID: 847160. https://doi.org/10.3389/fimmu.2022.847160

[57] Ott, C., *et al*. (2014) Smoking Increases the Risk of Extraintestinal Manifestations in Crohn's Disease. *World Journal of Gastroenterology*, **20**, 12269-12276. https://doi.org/10.3748/wjg.v20.i34.12269

[58] Yang, M., *et al*. (2021) The Incidence of Psoriasis among Smokers and/or Former Smokers Inflammatory Bowel Diseases Patients Treated with Tumor Necrosis Factor Antagonist: A Systematic Review and Meta-Analysis. *Medicine* (*Baltimore*), **100**, e27510. https://doi.org/10.1097/MD.0000000000027510

[59] Nguyen, U.D.T., *et al*. (2018) Smoking Paradox in the Development of Psoriatic Arthritis among Patients with Psoriasis: A Population-Based Study. *Annals of Rheumatic Diseases*, **77**, 119-123. https://doi.org/10.1136/annrheumdis-2017-211625

[60] Mahid, S.S., *et al*. (2006) Smoking and Inflammatory Bowel Disease: A Meta-Analysis. *Mayo Clinic Proceedings*, **81**, 1462-1471. https://doi.org/10.4065/81.11.1462

[61] Prtina, A., *et al*. (2021) The Effect of Three-Month Vitamin D Supplementation on the Levels of Homocysteine Metabolism Markers and Inflammatory Cytokines in Sera of Psoriatic Patients. *Biomolecules*, **11**, Article No. 1865. https://doi.org/10.3390/biom11121865

[62] Wierzbicka, J.M., *et al*. (2021) The Effects of Vitamin D on the Expression of IL-33 and Its Receptor ST2 in Skin Cells; Potential Implication for Psoriasis. *International Journal of Molecular Sciences*, **22**, Article No. 12907. https://doi.org/10.3390/ijms222312907

[63] Chandra, R., Roesyanto-Mahadi, I.D. and Yosi, A. (2020) Pilot Study: Immunohistochemistry Expressions of Vitamin D Receptor Associated with Severity of Disease in Psoriasis Patients. *International Journal of Dermatology*, **59**, 1092-1097. https://doi.org/10.1111/ijd.15018

[64] Fu, H., *et al*. (2021) Relationship between Vitamin D Level and Mortality in Adults with Psoriasis: A Retrospective Cohort Study of NHANES Data. *Clinical Therapeutics*, **43**, e33-e38. https://doi.org/10.1016/j.clinthera.2020.11.016

[65] Murdaca, G., *et al*. (2019) Emerging Role of Vitamin D in Autoimmune Diseases: An Update on Evidence and Therapeutic Implications. *Autoimmunity Reviews*, **18**, Article ID: 102350. https://doi.org/10.1016/j.autrev.2019.102350

[66] Schäffler, H., *et al*. (2018) Clinical Factors Are Associated with Vitamin D Levels in IBD Patients: A Retrospective Analysis. *Journal of Digestive Diseases*, **19**, 24-32. https://doi.org/10.1111/1751-2980.12565

[67] Abd-El-Aziz, M.A., *et al*. (2022) Simple Clinical Screening Underestimates Malnutrition in Surgical Patients with Inflammatory Bowel Disease—An ACS NSQIP Analysis. *Nutrients*, **14**, Article No. 932. https://doi.org/10.3390/nu14050932

[68] Taleban, S., *et al*. (2016) Ocular Manifestations in Inflammatory Bowel Disease Are Associated with Other Extra-Intestinal Manifestations, Gender, and Genes Implicated in Other Immune-Related Traits. *Journal of Crohn's and*

Colitis, **10**, 43-49. https://doi.org/10.1093/ecco-jcc/jjv178

[69] Köse, B., Uzlu, D. and Erdöl, H. (2022) Psoriasis and Uveitis. *International Ophthalmology*, **42**, 2303-2310. https://doi.org/10.1007/s10792-022-02225-5

[70] Wu, J.J., *et al*. (2022) Psoriasis and Metabolic Syndrome: Implications for the Management and Treatment of Psoriasis. *The Journal of the European Academy of Dermatology and Venereology*, **36**, 797-806. https://doi.org/10.1111/jdv.18044