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Mast Cells in Irritable Bowel Syndrome: A Systematic Review

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ABSTRACT

Background & Aims: As mast cells (MC) serve as a link between mucosal immune activity and the nervous system, it is likely they also play a role in the pathogenesis of irritable bowel syndrome (IBS). This connection might be an important factor in the development of IBS-related symptoms.
Method: This overview comprises 36 case-control studies published from 2000 to 2018 that investigated MC in bowel biopsies of IBS patients and controls. The studies were selected from PubMed, EMBASE, Central, SemanticScholar by an electronic search, performed using RISMed R package.
Results: Significantly increased mucosal MC counts/or density in IBS patients compared to controls was observed in 30 studies. Five studies reported no differences and only one of the studies found a decreased amount of MC in an IBS patient. Furthermore, 15 studies made a statement regarding the correlation between the amount of MC and IBS associated symptoms. A significant positive correlation between MC count and IBS-associated symptoms was found in six investigations. A negative correlation was not reported.
Conclusion: The results support the idea that MC are involved in IBS pathophysiology as key players in the interplay between psychological factors and the frequency and severity of IBS symptoms.

Key words: mast cells – irritable bowel syndrome – functional gastrointestinal disorder – visceral hypersensitivity.

Abbreviations: BDI: becks depression inventory; BDQ: bowel disease questionnaire; DGBIs: disorders of gut-brain interaction; FBDS: functional bowel disease score; FIS: fatigue impact scale; GI: gastrointestinal; HADS: hospital anxiety and depression scale; 5-HT: 5-hydroxytryptamine; IBS: irritable bowel syndrome; IBS-C: constipation-predominant IBS; IBS-D: diarrhea-predominant IBS; MC: mast cells; PAR: protease activated receptor; PPAR: peroxisome proliferator-activated receptor; SF-36: short form 36; STAI: state-trait anxiety inventor.

INTRODUCTION

Irritable bowel syndrome (IBS) has a global prevalence of 11.2% and is one of the most common diagnoses in gastroenterology [1]. IBS pertains to "Disorders of Gut-Brain Interaction (DGBIs)" and is a multifactorial disease that is mainly characterized by abdominal pain along with constipation, diarrhea and flatulence. Numerous published articles reported an impaired health-related quality of life in patients with IBS or in those that suffer from IBS-related symptoms [2–6]. The pathophysiology of IBS is poorly understood and is currently thought to represent a complex interplay among gut microbiota, mucosal immune system, impaired mucosal barrier function, visceral hypersensitivity, gut motility, alterations in the gut-brain axis and overall psychosocial factors [7–12]. A recent meta-analysis found post-traumatic stress to be a significant risk factor for IBS supporting a complex biopsychosocial view of IBS [12].

The intestinal mucosa is a decisive factor in humans suffering from IBS and is part of an intricate enteric immune system that comprises a large diversity of immune cells. In response to parasites, viruses and food, the enteric immune system is possibly highly sensitized which in turn may lead to the activation of the inflammatory cascade. In IBS patients, an increasing occurrence of immune cells in lamina propria compared to healthy controls has been reported. Moreover, they showed significantly reduced levels of an endogenous peroxisome proliferator-activated receptor (PPAR) -α agonist,

fatty acid amide with anti-inflammatory properties and oleoylethanolamide [13]. Key immune cells such as mast cells (MC) together with their mediators seem to play an important role in the etiological mechanism and the pathophysiology of the syndrome as MCs are associated with multiple intestinal functions.

Irritable bowel syndrome is characterized by recurrent and chronic abdominal pain, constipation, diarrhea, and flatulence. Moreover, patients struggle with depression or anxiety and might have a limited quality of life [2–6].

Therefore, we reviewed 36 case-control studies that investigated the number of MC on the basis of biopsy specimens from different bowel segments in IBS patients. Some of the included papers focus on the correlation between mucosal changes and symptoms.

METHODS

Thirty-six case-control studies [14–49] published from 2000 to 2018 were selected from PubMed, EMBASE, Central, SemanticScholar by an electronic search. A literature search strategy was developed using terms related to IBS and mast cells (see Supplemental Material). Search was performed using RISMed R package. The screening and selection process is described in a PRISMA flow chart with inclusion and exclusion criteria (Fig. 1).

RESULTS

Thirty-six case-control studies that covered a total of 1906 IBS patients and a total of 681 healthy controls were reviewed. Table I provides an overview of these studies. Mast cells numbers/or density in IBS patients compared to healthy controls were significantly increased ($p < 0.05$) in the majority of the studies (30 out of 36 case-control studies with 1067 IBS patients and 528 healthy controls in total). No significant difference in MC number was found between patients with IBS and controls in four studies [37, 39, 40, 45]. Only one of the studies reported a decreased amount of MC in IBS patient [35]. An increased number of MC was most frequent in diarrhea-predominant IBS (IBS-D) subjects followed by constipation-predominant IBS (IBS-C) subjects.

The studies focusing on the correlation between IBS symptoms and MC number/or density used a subset of different questionnaires (Table I). Nine surveys [14, 21, 23, 25, 33, 35, 42, 43, 46] noted no correlation between IBS symptoms and MC number. None of the included studies showed a negative correlation between MC numbers and IBS-related symptoms. Six studies [18, 19, 26, 29, 41, 44] found a significant positive correlation between the MC number and IBS associated symptoms. A positive correlation between increased MC activation and stool frequencies ($p < 0.001$), as well as with stress levels ($p < 0.005$) in IBS-D patients was found in the

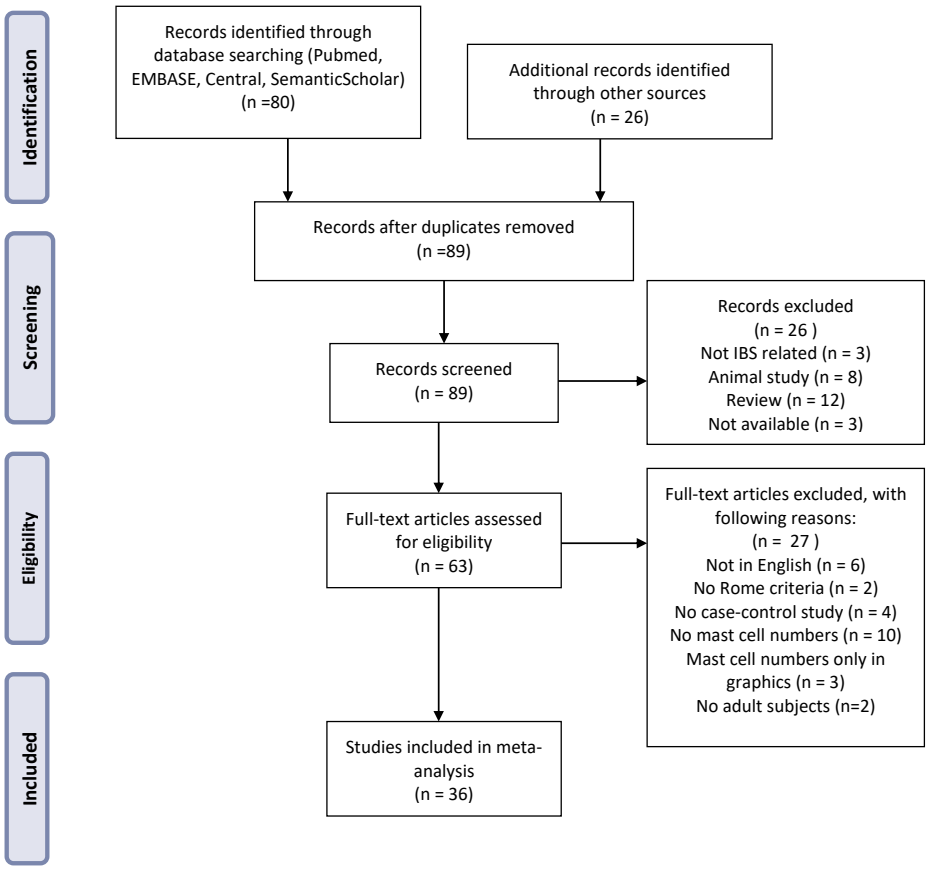

Fig. 1. PRISMA flowchart of literature search

Table I. Characteristics and results of studies

Reference Year	Country	Diagnostic criteria	IBS:HC	Gender (F:M)	Age (mean)	Side of biopsy	MC count	Findings*	Questionnaire	Correlation**
O'Sullivan et al. [14] 2000	Ireland	Rome	14:7 2 C, 8 D, 4 M	IBS 12:2 HC 5:2	IBS: 42.0 (28-65) HC: 29.0 (31-57)	CA, AC, DC, RC	IBS: 0.8 ± 1.0 /mm^2 (CA) HC: 0.4 ± 0.7 /mm^2 (CA)	Increased $p < 0.05$ (CA)	BDQ	0
Dunlop et al. [15] 2003	UK	Rome II	75:34 23 PI 52 Non-PI	IBS 53:22 HC 19:17	IBS: 39.2 HC: 45.3 ± 3.3	RC	PI: 41.9 ± 3.0 /hpf Non-PI: 53.0 ± 2.7 / HC: 45.9 ± 2.8 /hpf	Increased $p = 0.017$	n.s	n.a
Dunlop et al. [16] 2003	UK	Rome I	56:34 28 PI 28 Non-PI	PI 17:11 Non-PI: 17:11 HC 17:17	PI: 47.3 ± 2.0 Non-PI: 48.2 ± 2.6 HC: 50.3 ± 3.7	RC	PI: 49.8 ± 4.0 /hpf Non-PI: 53.5 ± 2.3 / hpf HC: 44.7 ± 2.8 /hpf	No difference ($p = 0.13$)	n.s	n.a
Park et al. [17] 2003	Korea	Rome II	14:14 14 D	IBS 8:6 HC 8:6	IBS: 47.6 ± 3.8 HC: 48.8 ± 3.9	CA, RC	IBS: 262.7 ± 35.5 /mm^2 (CA) HC: 165.1 ± 25.3 /mm^2 (CA) IBS: 184.1 ± 27.0 /mm^2 (RC) HC: 124.6 ± 10.7 /mm^2 (RC)	Increased $p \leq 0.05$ (CA, RC)	n.s	n.a
Barbara et al. [18] 2004	Italy	Rome II	44:22 12 C, 12 D	IBS 31:13 HC 12:10	IBS: 41.1 (22-75) HC: 32.5 (20-71)	DC	IBS: 4.8 ± 3.2% /hpf HC: 2.4 ± 2.3 % /hpf	Increased $p < 0.001$	BDQ	+
Wang et al. [19] 2004	China	Rome II	56:12 27 PI, 29 Non PI	IBS 31:25 HC 5:7	IBS: 43.3 HC: 41.26	IL, SC, RC	PI-IBS 11.2 /hpf (IL) Non-PI IBS: 10.8 /hpf (IL) HC 6.1 /hpf (IL)	Increased $p < 0.01$ (IL)	n.s	n.a
Tunc et al. [20] 2005	Turkey	Rome I	11:5	IBS 3:8 HC 2:3	IBS: 46.4 ± 16.5 HC: 50.4 ± 18.3	CA	IBS: 39.3 ± 11.2 /hpf HC: 13.2 ± 1.9 /hpf	Increased $p \leq 0.001$	n.s	n.a
Park et al.[21] 2006	Korea	Rome II	18:15 18 D	IBS 8:10 HC 5:10	IBS: 42.6 HC: 41.4	CO, IL, RC	IBS: 47.7 ± 5.6 /hpf (CO) HC: 37.4 ± 6.2 /hpf (CO) IBS: 49.1 ± 7.4 /hpf (IL) HC: 37.9 ± 6.2 /hpf (IL) IBS: 47.8 ± 7.6 /hpf (RC) HC: 37.3 ± 6.0 /hpf (RC)	Increased $p \leq 0.01$ (CO, IL, RC)	BDI STAI	0
Barbara et al.[22] 2007	Italy	Rome II	29:15	IBS 18:11 HC 9:6	IBS 39.0 (19-70) HC 25.7 (22-30)	DC	IBS: 7.8% ± 0.6% HC: 3.0% ± 0.3%	Increased $p < 0.001$	BDQ	n.a
Guilarte et al. [23] 2007	Spain	Rome II	20:14 20 D	IBS 14:6 HC 6:8	IBS 32.8 (21-56) HC 27.9 (22-53)	JE	IBS: 34 /hpf HC: 15.3 /hpf	Increased $p < 0.001$	BDI MSRS	0
Wang et al. [24] 2007	China	Rome III	38:20 18 C, 20 D	C 9:9 D 12:8 HC 11:9	IBS-D 48.7 ± 16.6 IBS-C 41.5 ± 15.1 HC 39.9 ± 19.5	DD, JE, IL	IBS-C: 38.7 ± 9.4 / hpf (IL) IBS-D: 35.8 ± 5.5 / hpf (IL) HC: 29.8 ± 4.4 /hpf (IL)	Increased $p < 0.001$ (IL)	n.s	+
Lee et al.[25] 2008	South Korea	Rome II	42:12 5 PI, 37 Non PI, 13 C, 17 D, 7 M	PI 4:1 IBS-C 8:5 IBS-D 8:9 IBS-M 5:2 HC 5:7	PI-IBS 44.4 IBS-C 44.2 IBS-D 49.7 IBS-M 52.6 HC 50.8	RC	PI-IBS:10.6 /hpf Non-PI IBS: 8.3 /hpf IBS-C: 7.8 /hpf IBS-D: 8.8 /hpf IBS-M: 8.1 /hpf HC: 6.8 /hpf	Increased $p \leq 0.05$	HADS	0

Table I (continued)

Piche et al. [26] 2008	France	Rome II	50:21 29 C, 21 D	C 25:4 D 16:5 HC 14:7	IBS-C 51.1 IBS-D 54.5 HC 58.5	IL, CA	IBS: 9.3 /hpf IBS-C: 8.3 /hpf IBS-D: 10.2 /hpf HC: 4.0 /hpf	Increased p = 0.001 (CA)	BDI FIS	+
Bian et al. [27] 2009	China	Rome III	10:13 10 D	IBS 3:7 HC 5:8	IBS-D 34.2 HC 45.3	CO	IBS: 143.31 ± 39.93/hpf HC: 73.69 ± 59.19/hpf	Increased p = 0.004	n.s	n.a
Buhner et al. [28] 2009	Italy	Rome II	11:5 4 C, 7 D	IBS 7:4 HC 2:3	IBS 39.6 ± 17.2 HC 42.9 ± 15.8	CO	IBS: 6.6 /total lamina propria hits HC: 2.5 /total lamina propria hits	Increased p = 0.002	n.s	n.a
Cremon et al. [29] 2009	Italy	Rome II	48:24 21 C, 27 D	IBS 35:13 HC 15:9	IBS 32.0 ± 14.9 HC 41.6 ± 16.4	CO	IBS 9.7 ± 2.4 HC 4.5 ± 2.3	Increased p ≤ 0.001	BDQ	+
Walker et al. [30] 2009	Sweden	Rome II	41:48 21 C, 20 D	IBS 20:.21 HC 28:20	IBS 54 HC 53	DD	IBS-C: 255 /hpf IBS-D: 233 /hpf HC: 145 /hpf	Increased p < 0.001	ASQ	n.a
Coffier et al. [31] 2010	France	Rome II	25: 18 4 C, 13 D, 4 M	IBS 16:9 HC 9:9	IBS 44.6 ± 3.1 HC 55.2 ± 3.4	DC	IBS-D 31.2 ± 3.7 /hpf HC: 20.4 ± 2.4 /hpf	Increased p<0.05	n.s	n.a
Kim et al. [32] 2010	South Korea	Rome II	18:10	PI 2:2 Non PI 0:7 D 2:5 HC 5:5	PI-IBS 30 ± 5.1 Non-PI-IBS 51 ± 5.6 IBS-D 39 ± 10 HC 48 ± 6.9	DC, SC, RC	PI-IBS: 105.3 ± 13.33 / hpf (DC) Non-PI IBS: 52.89 ± 13.44 /hpf (DC) IBS-D: 40.86 ± 10.32 / hpf (DC) HC: 59.24 ± 12.83 /hpf (DC)	Increased p = 0.064 (DC)	n.s	n.a
Foley et al. [33] 2011	UK	Rome III	20:29 20 D	IBS 13:7 HC 18:11	IBS 41.6 ± 3.4 HC 32.3 ± 1.7	DD	IBS: 168 /mm^2 HC: 121 /mm^2	Increased p < 0.001	FBDS HADS	0
Balestra et al. [34] 2012	Italy	Rome II	37: 11 21 C, 16 D	IBS 27:10 HC 6:5	IBS 35.2 (21-70) HC 24.9 (20-30)	DC	IBS: 7.22 ± 2.54% HC: 3.56 ± 1.53%	Increased p < 0.001	BDQ	n.a
Braak et al. [35] 2012	Nether-lands	Rome II	66:20 15 C, 15 D, 36 M	IBS 49:17 HC 13:7	IBS 38.0 ± 2.0 (19-65) HC 31.0 ± 3.0 (20-61)	AC, DC, SC	IBS: 186 ± 10 (DC) HC: 370 ± 39 (DC)	Decreased p < 0.01 (DC)	GSRS HADS	0
Han et al. [36] 2012	China	Rome III	23:17 23 PI	IBS 9:14 HC 8:9	PI-IBS 36.0 (18-59) HC 39.0 (19-50)	CO	PI-IBS: : 2.832 ± 1.18 /hpf HC: 1.537 ± 0.578 /hpf	Increased p < 0.01	n.s	n.a
Kerckhoffs et al. [37] 2012	Nether-lands	Rome II	23:15 4 C, 11 D, 8 M	IBS 14:9 HC 6:9	IBS 39.5 (22-65) HC 42.1 (22-62)	SC, RC	IBS: 111.9 ± 8.5 /mm^2 (SC) HC: 94.8 ± 7.2 /mm^2 (SC) IBS: 97.1 ± 8.2 /mm^2 (RC) HC: 84.6 ± 5.0 /mm^2 (RC)	No difference (p > 0.05) (SC, RC)	n.s	
De Silva et al. [38] 2012	Sri Lanka	Rome III	49:14 49 D	IBS 13:36 HC 8:6	IBS 34 (18-59) HC 46.5 (23-56)	AC, CA, IL, RC, TC	IBS: 5.56 (3-8) /hpf (AC) HC: 2.83 (1-5)/hpf (AC) IBS: 8.87 (2-14) /hpf (CA) HC: 3.9 (2-6)/hpf (CA) IBS: 8.08 (4-20)/hpf (DC) HC: 3.5 (3-4)/hpf (DC) IBS: 15.07 (8-24)/hpf (IL) HC: 5.78 (4-8)/hpf (IL) IBS: 10.15 (7-16)/hpf (RC) HC: 4.13 (2-7)/hpf (RC)	Increased p < 0.05 (AC,CA, IL, RC)	n.s	n.a

Table I (continued)

El-Shaly et al. [39] 2013	Norway	Rome III	50:27 30 C, 20 D	IBS 42:8 HC 19:8	IBS 34 (18-62) HC 53 (20-65)	RC	IBS: 11.7 ± 0.4 /hpf HC: 10.4 ± 0.7 /hpf	No difference ($p = 0.11$)	n.s	n.a
Lee et al. [40] 2013	South Korea	Rome II	16:7 16 D	IBS 10:6 HC 3:4	IBS 54.6 (24-66) HC 49.0 (38-64)	RC	IBS: 4.71 ± 0.60 MCs/hpf HC: 4.66 ± 0.59 MCs/hpf	No difference ($p > 0.05$)	n.s	n.a
Martinéz et al. [41] 2013	Spain	Rome II	45:30 45 D	IBS 34:11 HC 16:14	IBS 36.3 (18-60) HC 33.7 (21-60)	JE	IBS: 26.2 ± 11.1 /hpf HC: 17.2 ± 8.8 /hpf	Increased $p = 0.0004$	BSF MSRS	+
Ahn et al. [42] 2014	South Korea	Rome III	83:25 83 D	IBS 37:46 HC 12:13	IBS 31.0 (25.5-45.0) HC 40.0 (32-49.5)	AC, CO, DC, RC, SC, TC	IBS: 33.3 ± 15.1 /hpf (mean of AC,CO, DC, RC, SC,TC) HC: 14.8 ± 3.6 /hpf (mean of AC,CO, DC, RC, SC,TC)	Increased $p < 0.001$ (CO)	HRQOL QOL SF-36	0
Sohn et al. [43] 2014	South Korea	Rome III	22:21 22 D	IBS 10:12 HC 10:11	IBS 50.0 ± 15.1 HC 53.4 ± 12.0	RC	IBS 9.6 ± 3.3 /hpf HC 5.7 ± 2.5 /hpf	Increased $p < 0.01$	n.s	0
Yang et al. [44] 2014	China	Rome III	78 :18 30 D 25 D (LI) 23 D (LM) 18 HC	D12:18 D (LI) 8:17 D (LI) 8:15 HC 6:12	IBS 43.4 ± 10.8 IBS (LI) 41.5 ± 11.9 IBS (LM) 44.1 ± 9.98 HC 43.6 ± 11.4	AC, SC, IL	IBS-D (LI): 9.4 /hpf (SC) HC: 6.6 /hpf (SC) IBS-D (LI): 10.2 /hpf (AC) HC: 7.0 /hpf (AC) IBS-D (LI): 11.2 /hpf (IL) HC: 7.1 /hpf (IL)	Increased $p < 0.05$ (SC, AC) $p < 0.01$ (IL)	BDQ HADS LES	+
Vicario et al. [45] 2015	Spain	Rome III	49:30 49 D	IBS 33:16 HC 11.19	IBS 35.0 (18-63) HC 29 (21-64)	JE	IBS: 71.2% HC: 12.9%	No difference ($p > 0.05$)	BDI MSRS PSS	n.a
Bednarska et al. [46] 2017	Sweden	Rome III	37:20 8 C, 8 D, 21 M	IBS 37:0 HC 20:0	IBS 31.2 (19-55) HC 29.9 (20-48)	SC	IBS: 104.0 ± 8.0 /mm^2 IBS-M: 127 ± 48 /mm^2 IBS-C: 75 ± 23/mm^2 HC: 73.7 ± 11.6 /mm^2	Increased $p < 0.05$	n.s	0
Cremon et al. [47] 2017	Italy	Rome III	44:12	Unknown	IBS 18-70 HC 37.7 ± 13.0	DC	IBS: 5.3 ± 2.7% HC: 3.2 ± 1.3%	Increased $p = 0.013$	BSF	n.a
Xu et al. [48]2017	China	Rome III	38:20 38 D	IBS 10:28 HC 8:12	IBS 30.2 ± 7.9 HC 26.80 ± 5.3	RC, SC	IBS: 10.73 ± 4.01 /mm^2 (RC,SC) HC: 5.95 ± 2.80 /mm^2 (RC, SC)	Increased $p < 0.001$ (RC, SC)	HAS HDS LES QLP SQI SSS TCSQ	n.a
Liu et al. [49] 2018	China	Rome III	42:20 42 D	IBS 15:27 HC 8:12	IBS 29.4 (22-40) HC 28.9 (20-38)	RC, SC	IBS 9.62 /mm^2 (RC, SC) HC 10.75 /mm^2 (RC, SC)	Increased $p < 0.001$ (RC, SC)	HAS HDS QOL SSS	n.a

Abbreviations: IBS: irritable bowel syndrome; HC: healthy controls; C: constipation-predominant IBS; D: diarrhea-predominant; M: mixed IBS; PI: postinfectious IBS; LI: Lactose intolerance; LD: Lactase deficiency; LM: Lactose malabsorption; F: female; M: male; hpf: High power field; AC: ascending colon; CO: colon; CA: caecum; DC: descending colon; IL: terminal ileum; JE: Jejunum; RC: rectum; SC: sigmoid colon; TC: transverse colon; * MC number of IBS compared to HC; ** Correlation between MC count and IBS symptoms; (0), no correlation; (+), positive correlation; n.a, not analyzed; n.s, not specified
Questionnaires: ASQ, Self- administered Abdominal Symptom Questionnaire; BDI, Beck Depression Inventory; BDQ, Bowel Disease Questionnaire; BSF, Bristol stool form scale; FBDS, Functional Bowel Disease Score; FIS, Fatigue Impact Scale; GSRS, Gastrointestinal Symptom Rating Scale; HAS, Hamilton Anxiety Scale; HADS, Hospital Anxiety and Depression Scale; HDS, Hamilton Depression Scale; HRQOL, Questionnaire for Health Related Quality of Life; LES, Life Event Score of Miller and Rahe; MSRS, Modified Social Readjustment Scale of Holmes & Rahe; PSQI, Pittsburgh Sleep Quality Index; PSS, Perceived Stress Scale of Cohen; QGPS, Questionnaire for the Pediatric Functional GI Disorders; QOL, Quality of Life Questionnaire; SF-36, Short Form 36; SGA, Subject's Global Assessment of Abdominal Pain and Discomfort; SSS, Symptome Severity Scale; STAI, State–Trait Anxiety Inventor; TCSQ, Trait Coping Style Questionnaire

study by Martinez et al. [41]. In 2008, Piche et al. [26] used the Becks depression inventory (BDI) to evaluate the severity of depression and the Fatigue impact scale (FIS) to find out how fatigue impacts patient's life. As a result, they reported a significant correlation between an increased MC number and both BDI scores ($r = 0.29$, $p = 0.03$) and FIS scores ($p < 0.001$)

in IBS patients. Significantly higher scores regarding anxiety in IBS patients compared to healthy controls were associated with higher MC numbers by Yang et al.[44]. Moreover, the study of Cremon et al. [29] showed that mucosal MC infiltration of IBS patients was significantly associated with abdominal bloating frequency (p=0.022) and with symptoms of dysmotility-like dyspepsia (p=0.001). Wang et al. [24] claimed that IBS associated symptoms were caused by increased MC numbers inside the bowel of patients. Furthermore, Barbara et al. [18] reported a significant positive correlation between MC in close proximity to nerves and abdominal pain or discomfort in IBS patients.

Nine studies [14, 21, 23, 25, 33, 35, 42, 43, 46] did not find a significant association between the number of MCs and IBS-related symptoms. Ahn et al. [42] performed colonoscopy in IBS-D and patients with ulcerative colitis (UC) and healthy volunteers. In this study, the Short Form 36 (SF-36) was used to assess the health-related quality of life of all participants. No positive correlation between SF-36 scores and MC number was found. However, IBS and UC patients had strong symptoms that significantly reduced their quality of life compared to controls. Even though, the MC density correlated with MC tryptase expression in all subjects, Bednarska et al. [46] reported no significant correlation between MC numbers and symptoms. Guilarte et al. [23] noted a suggestive trend, but no positive association between increased MC numbers and stress levels or depressions. In the study by Park et al. [21] no significant correlation between symptoms and MC counts was found, even though the scores of anxiety and depression which were assessed with BDI and the State–Trait Anxiety Inventor (STAI) were significantly higher in IBS patients compared to controls ($p < 0.05$). Braak et al. [35] noted a decreased number of MC and found no relation between MC counts, stress-related symptoms and the presence of visceral hypersensitivity. Moreover, Sohn et al. [43] and Foley et al. [33] did not find a significant positive correlation between numbers of MC and IBS-related symptoms.

Lee et al. [25] observed significantly higher anxiety ($p < 0.001$) and depression scores ($p< 0.05$) (evaluated with Hospital Anxiety and Depression Scale (HADS) in the IBS group compared to the control group, but did not find a significant correlation among the altered MC numbers and the HADS scores. The Functional Bowel Disease Score (FBDS) by Talley et al. [50] increased the probability of having functional bowel disease by measuring syndrome related features and the six Manning criteria. The numbers of MC in the terminal ileum were significantly increased in IBS patients compared to controls, but were not significantly correlated with the FBDS scores or Manning criteria. The IBS patients in the study of O'Sullivan et al. [14] had higher Bowel Disease Questionnaire (BDQ) scores compared to controls. However, there was no significant association observed between BDQ scores and the detected MC numbers.

Seven studies [22, 30, 34, 45, 47–49] that used a questionnaire to evaluate the patients' symptoms made no comment regarding the correlation between MC numbers and symptoms in IBS patients. Further 17 studies [15–17, 19, 20, 24, 27, 28, 31, 32, 36–40, 43, 46] did not specify the use of any symptom questionnaire. Within these studies, 15 investigations did not make a statement concerning a correlation between MC numbers and IBS-related symptoms.

DISCUSSION

As more data are gathered on IBS, one of the most often diagnosed gastrointestinal conditions, the influence of immunocompetent cells is being uncovered [51]. It is evident that bowel habits and intestinal activity are linked to the human brain. The interplay between gut and brain might also connect the stress and emotions with bowel movements and/or abdominal pain [52–55]. Our systematic review aimed to examine the potential role of MC in IBS. Overall, the majority of the studies (30 out of 36) showed a significant increase in MC numbers in female and male patients with IBS compared to healthy controls. Despite that, four studies [37, 39, 40, 45] reported no significant difference in the MC number between IBS patients and controls. Strikingly, only one of the analyzed studies demonstrated a decrease of MC occupying the lamina propria [35]. Even though Dunlop et al. [56] reported a decline of MCs with age, other studies did not observe age-related differences.

We should mention that only a minority of the included studies had specifically aimed to study the MC counts as a factor in IBS pathology. The majority of the studies initially aimed to determine general alterations in inflammatory cells and immune activation based on the thought that low-grade inflammation is a potential factor of IBS pathology. Other studies focused on MC mediators and the evaluation of MC interaction with nerve cells. However, even though MC counts were not necessarily part of the main objectives of the investigations, the majority of the studies showed that MC counts were significantly increased in IBS patients.

Among the included studies, a significant positive correlation between the MC number and IBS-associated symptoms was found in six studies [18, 19, 26, 29, 41, 44], whereas a negative correlation was not reported.

It should be noted that the studies themselves could be limited or even biased. This may relate to the differences in the selection process of controls and the types of IBS cases recruited in the studies. Most controls were not gender- and age-matched to the IBS patients. In addition, only slightly more than half of the healthy controls were individuals selected from the general population. That means that half of the healthy controls were recruited in the clinic and that the condition of these controls could in turn influence the study outcome. Furthermore, the evaluation of symptoms via questionnaires might yield in inaccurate results. Finally, different cell count methodologies might have been an influencing factor on the findings.

Our analysis supports the assumption that IBS patients show higher numbers of MCs in the intestinal mucosa compared to healthy controls. The studies that reported a comparable MC number between IBS patients and controls had a smaller study population than all other studies (in total: 88 IBS, 52 controls vs. 842 IBS; 599 controls). The small size of the analyzed population might have influenced the results. Moreover, in most of these studies [37, 40, 45], the majority in the control group were men, whereas the other studies showed a majority of female controls. The female controls would be

a better and representative comparison group as IBS is more frequent in females [1, 57]. Therefore, studies should show an equal distribution of female and men for more representative results.

Female IBS patients represent the majority in the patient groups [58]. Several studies support sex-based differences in immune responses. On average, women have a stronger immune response than men. Autoimmune diseases are more frequent in women as estrogens enhance B-cell activities and the expression of chemokine receptors by T-cells, for instance [59–61]. In general, women are more resistant to infections, but suffer more often from allergies and autoimmune diseases. The fact that women fall ill with IBS more often than men [1, 62] might indicate the role of the immune system in the pathogenesis of this disease.

Furthermore, 16 studies evaluated MC numbers in biopsy specimens of different parts of the bowel. Four studies showed a difference in MC numbers between biopsy specimens of different bowel segments in patients with IBS [24, 32, 35, 38]. Since study designs greatly vary amongst these 16 papers, no meaningful statement of correlation can be made with respect to findings in different bowel segments.

The worldwide prevalence of IBS varies between countries and within countries. The majority of IBS patients show postprandial symptoms [63]. Negative reactions to foods containing large proportions of fat and carbohydrates are frequently reported in IBS patients [64]. Therefore, diet is probably one predictor for the development, frequency, and severity of abdominal pain as it is now evident that diet greatly impacts the microbiome and leads to microbial shifts [65]. The study of De Palma et al. [66] showed that a highly fermentable diet leads to altered microbiome compositions. This has been demonstrated in mice that were colonized with fecal microbiota from IBS patients with high urinary histamine. Moreover, those mice showed increased MC numbers. The results of our systematic review also suggest that alterations in the number of MC might play an important role in IBS pathogenesis.

The findings regarding the correlation between MC numbers and IBS-related symptoms are controversial, as the explicit statements vary greatly among these studies. The heterogeneous findings might be due to the great variety of different questionnaires used to evaluate symptoms. In addition, the data evaluated via questionnaires mostly underlie subjective criteria. How humans sense psychological stress, pain or discomfort is among other aspects shaped by cultural aspects and individual pain sensitivity. For instance, Nayak et al. [67] reported a higher pain tolerance of Indian participants compared to American participants in their study. These findings are consistent to the given prevalence scores for IBS that indicate a prevalence of > 20% in the United States of America and < 10% in India [58]. Those facts demonstrate the complexity of an objective elevation of symptoms in IBS patients.

Another important fact is the discovery of altered intestinal secretion in IBS patients that can be induced by MCs [68]. Decreased intestinal secretion is particularly noticeable in IBS-C, whereas patients with IBS-D show increased intestinal secretion. The involvement of MCs in these alterations have been proven in animal models of parasitic infection and food allergy [68]. The rat model in the study of Santos et al. [69] showed increased permeability triggered by stress along with mast cell activation and hyperplasia. In addition, the mice model of Groschwitz et al. [70] demonstrated a decreased permeability suggesting the involvement of MCs in the regulation of intestinal migration and architecture. These models revealed MC mediators such as chymase, histamine, stimulated water, chloride and prostaglandin D2 as the causative trigger for increased intestinal secretion [68]. Thus, the effects of proinflammatory mediators released from activated MC seem to be also of importance concerning the severity and frequency of IBS symptoms, rather than alterations in MC number. Interestingly, Barbara et al. [18] reported a correlation between MC in close proximity to nerves and abdominal pain, but no correlation between increased MC numbers or degranulated MC with abdominal pain or discomfort in IBS patients. Further investigation is required to establish how MC interact with nerve fibers to promote disease. An increase of 150% in the number of degranulating MC was found in IBS patients compared to controls [71]. MC mediators such as tryptase are proposed to initiate and raise neuronal signaling and therefore conduce visceral hypersensitivity by activating protease activated receptor (PAR)-2 [36, 71, 72]. This signaling pathway was associated with clinical IBS symptoms by Liang et al. [71]. They found a positive correlation between the expression of mast cell tryptase and levels of PAR-2, which in turn correlated with abdominal bloating and pain. In addition, some studies reported molecular alterations in serotonergic signaling mechanisms in IBS patients [33, 73]. Moreover, a significant correlation between increased MC activation, stress levels and stool parameters was noted [41]. Those findings support the assumption that MC mediators such as 5-hydroxytryptamin (5-HT) might influence GI functions including motility, sensation, and secretion. Furthermore, quantitative abnormalities in fecal microbiota in IBS patients confirm its role in pathogenesis [74] and reinforce the thought of MC mediators as predictors for IBS symptoms. This is consistent with the results of Klooker et al. [75] who showed that MC stabilizers such as ketotifen decrease abdominal pain and other IBS-associated symptoms.

Our findings are in agreement with other reports on colonic immune cells in IBS patients and controls [76–78]. Increased MC counts as well as increased $CD3^+$ T-cells, dependent on different bowel segments and IBS subtypes, were reported in the studies summarized in the analysis of Bashashati et al. [78].

CONCLUSIONS

The results of this systematic review support the involvement of MCs in IBS pathophysiology. It can be suggested that MC and especially MC mediators trigger low-grade inflammation and might be involved in the development of IBS symptoms. Future investigations should consider standardized questionnaires and recruiting well-balanced subjects of different IBS subtypes.

Conflicts of interest: None to declare.

Authors' contributions: L.K., A.S. and A.L. designed the study. L.K. and A.S. performed the electronic search. L.K., A.S. and A.L. were

involved in the acquisition and interpretation of data. L.K. wrote the paper. A.L. had primary responsibility for the final content. All authors read and approved the final version of the manuscript.

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Supplemental Material

Search Strategy

Search was performed using RISMed R package. The keywords used were**:**

Terms relating to the condition of interest: Irritable bowel syndrome, IBS

Terms relating to the collection method: Biopsy

Terms relating to the biomarker of interest: Mast cell

Terms relating to the study design: Cohort, case control, randomized controlled trials, longitudinal, and exclude animal studies; Master search string (adapted for use in individual databases as required) – Query: ((("irritable mood"[MeSH Terms] OR ("irritable"[All Fields] AND "mood"[All Fields]) OR "irritable mood"[All Fields] OR "irritable"[All Fields]) AND bowl[All Fields] AND ("syndrome"[MeSH Terms] OR "syndrome"[All Fields])) OR IBS[All Fields]) AND ("pathology"[Subheading] OR "pathology"[All Fields] OR "biopsy"[All Fields] OR "biopsy"[MeSH Terms]) AND ("mast cells"[MeSH Terms] OR ("mast"[All Fields] AND "cells"[All Fields]) OR "mast cells"[All Fields] OR ("mast"[All Fields] AND "cell"[All Fields]) OR "mast cell"[All Fields]) AND (("cohort studies"[MeSH Terms] OR ("cohort"[All Fields] AND "studies"[All Fields]) OR "cohort studies"[All Fields] OR "cohort"[All Fields]) OR ("case-control studies"[MeSH Terms] OR ("case-control"[All Fields] AND "studies"[All Fields]) OR "case-control studies"[All Fields] OR ("case"[All Fields] AND "control"[All Fields]) OR "case control"[All Fields]) OR ("random allocation"[MeSH Terms] OR ("random"[All Fields] AND "allocation"[All Fields]) OR "random allocation"[All Fields] OR "randomized"[All Fields]) OR longitudinal[All Fields] OR ("therapy"[Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields]) OR study[All Fields]) AND (("humans"[MeSH Terms] OR "humans"[All Fields] OR "human"[All Fields]) OR ("patients"[MeSH Terms] OR "patients"[All Fields] OR "patient"[All Fields])).