REVIEW

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Systematic review and meta – analysis of the frequency and re-classification trends of pediatric inflammatory bowel disease - unclassified

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ABSTRACT – Background – The term inflammatory bowel disease-unclassified (IBDU) is used when an individual has chronic colitis but cannot be subtyped into ulcerative colitis (UC) or Crohn's disease (CD) on the basis of the clinical, endoscopic, imaging and histopathological features. On follow-up a proportion of patients with IBDU are re-classified as CD or UC. There has been considerable variability in the frequency and reclassification rates of pediatric IBDU in published literature. **Methods –** PubMed and Scopus and were searched for publications related to Pediatric Inflammatory Bowel Disease (PIBD) published between Jan,2014 and July,2021. Two reviewers independently searched and selected studies reporting the frequency of IBDU and/or their re-classification. The pooled prevalence was expressed as proportion and 95%CI. Meta-analysis was performed using the inverse variance heterogeneity model. **Results –** A total of 2750 studies were identified through a systematic search of which 27 studies were included in this systematic review. The overall pooled frequency of IBDU (n=16064) was found to be 7.1% (95%CI 5.8–8.5%). There was no variation in IBDU frequency by geographical location. Seven studies (n=5880) were included in the IBDU re-classification analysis. Overall, 50% (95%CI 41–60%) children with IBDU were re-classified on follow-up. Amongst these 32.7% (95% 21–44%) were re-classified to UC and 17% (95%CI 12–22%) were re-classified to CD. **Conclusion –** IBDU comprises 7.1% of PIBD at initial diagnosis. Half of these children are re-classified into UC or CD on follow-up with a higher likelihood of re-classification to UC as compared to CD.

Keywords – Inflammatory bowel disease; unclassified; pediatric inflammatory bowel disease; crohns disease; ulcerative colitis.

INTRODUCTION

Pediatric inflammatory bowel disease (PIBD) denotes a group of disorders characterized by chronic intestinal inflammation and it includes Crohn disease (CD), ulcerative colitis (UC), and inflammatory bowel disease unclassified (IBDU). The term IBDU is used when an individual has chronic colitis but cannot be subtyped into UC or CD on the basis of the clinical, endoscopic, imaging and histopathological features because of the presence of overlapping findings. On clinical follow-up, a proportion of these patients with IBDU are re-classified into UC or CD while others maintain their IBDU diagnosis as they are transitioned to adult healthcare services.

There has been considerable variability in the frequency of pediatric IBDU in published literature. The reason for this variation is that for a long time IBDU continued to be a poorly defined entity with no standard diagnostic criteria. In 2009, Prenzel et al. had carried out a meta-analysis of the frequency of IBDU and found that it constituted 12.7% of PIBD[1]. However, most of the studies included in their analysis did not clearly define how IBDU was diagnosed. In recent years attempts have been made to standardise the definition of IBDU with the development and validation of the revised Porto criteria in 2014 and the PIBD-classes algorithm in 2017[2,3]. Hence there is a need for an updated analysis which includes studies that take into account these diagnostic criteria.

There is also a considerable discordance in the trend of the reporting of IBDU reclassification rates in literature. It is not clear that what proportion of patients with an initial diagnosis of IBDU are re-classified to CD or UC on follow-up.

We aimed to carry out this meta–analysis to 1) Determine the frequency of IBDU 2) Determine the proportion of children with IBDU who undergo subsequent re-classification.

METHODS

Search strategy

A literature search was carried out systematically with no language restrictions using the electronic databases – PubMed and Scopus for keywords related to the inclusion criteria. There were no restrictions on the language. Studies published in the year 2014 and beyond were included in the search. The year 2014 was chosen as the starting point because that is the year the revised Porto criteria were published.

Search words used were as follows:

Pubmed - ("inflammatory bowel diseases") AND ("Pediatrics"[Mesh] OR "Child" [Mesh] OR "Child, Preschool"

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[Mesh] OR "Infant" [Mesh] OR "Adolescent" [Mesh]).

Scopus - (KEY ("inflammatory bowel disease") AND KEY ("Pediatric" OR "Children").

Subsequently the references of the includes studies were reviewed for more eligible articles.

Last search for articles was performed on 31st July 2021.

All observational studies on PIBD which included >50 patients were included. The following criteria were considered while selecting the studies:

- We selected studies when the diagnosis of CD, UC and IBDU was diagnosed using established criteria (Porto/revised Porto criteria or on similar lines) and included endoscopy, histology and radiology.
- For IBDU frequency the diagnosis of the initial presentation was used.
- Only studies in which all consecutive patients of PIBD presenting to the centre/centres from where the data was obtained were included.
- Certain publications included study populations with a considerable overlap with children enrolled in other studies. In such situations the most recent and/or largest study was chosen to avoid any duplication. We did not include data from the EUROKIDS registry and pediatric IBD Porto group as we included data from individual centres which had been published separately (some more recently).
- For the IBDU re-classification study only studies with a minimum follow-up duration of 12 months were included.

Data extraction

Two reviewers independently extracted data using a predetermined criterion. The following data was extracted from each study: Total number of children with IBD, Number of children with CD, UC and IBDU in each study and re-classification trend of children with IBDU. Any discrepancy in data extraction was resolved by mutual discussion.

Quality assessment

The quality of the studies included was evaluated by the AXIS tool. The risk of bias was assessed through 20 questions that evaluated the study's research design and validity of the results. Individual questions were assessed as yes (Y), no (N) or unclear (D).

Statistical analysis

The inverse variance heterogeneity model was used for ascertaining the summary effect in this meta-analysis. The pooled prevalence was expressed as proportion and 95%CI. The data was presented in a forest plot. Heterogeneity between studies was assessed using I^2 values. I^2 values of more than 75% would indicate high heterogeneity. A p value of less than 0.05 was considered indicative of statistically significant heterogeneity. We performed a sensitivity analyses in which we excluded each study individually to determine the effect on the test of heterogeneity and the overall pooled prevalence. Poor quality and outlier studies were considered for exclusion in sensitivity analysis. Small study effects, which may be due to a publication bias, was assessed using the Luis Furuya Kanamori (LFK) index and DOI plot. A value of LFK index <1 is indicative of no symmetry, between one and two indicates minor symmetry and more than two is indicative of major asymmetry. Meta-analysis was performed using MetaXL software v5.3 software (EpiGear International, Sunrise Beach, Australia).

RESULTS

The search strategy yielded a total of articles of which 27 studies were included in the final review (FIGURE 1).

Twenty–six studies were included in the IBDU frequency analysis, while seven studies were included in the IBDU re-classification analysis. The characteristics of the included studies has been described in TABLE 1.

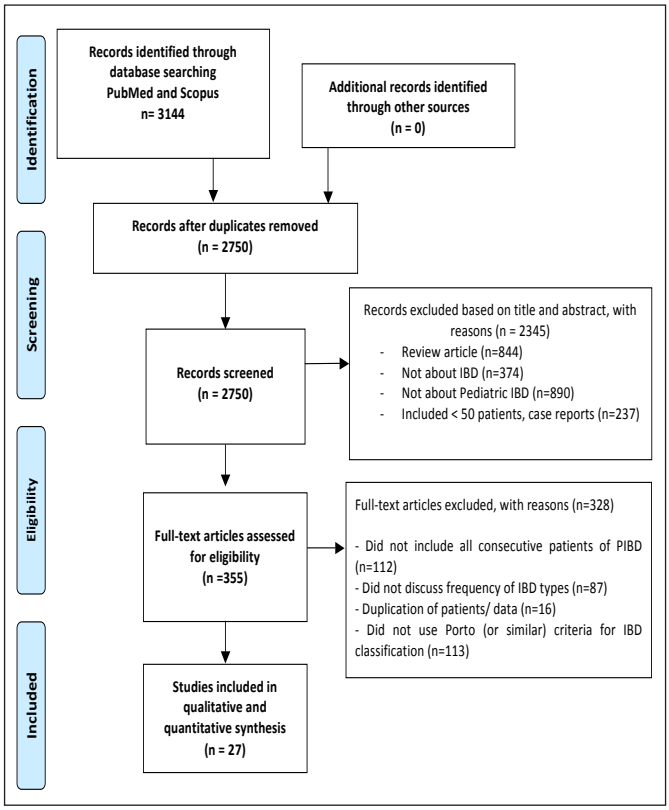

FIGURE 1. PRISMA flow diagram depicting the flow of information through different phases of the systematic review.

IBDU frequency

This analysis included a total of 26 studies comprising of 16064 children with PIBD. The data was obtained from 31 countries [Asia – six (India, China, Japan, Singapore, Israel, Saudi Arabia), North America – two (USA, Canada), South America – nine (Argentina, Mexico, Uruguay, Brazil, Bolivia, Peru, Venezuela, Nicaragua, El Salvador), Oceania – one (New Zealand), Europe – 14 (Denmark, England, Croatia, Czech, Turkey, Italy, Spain, Germany, Austria, France, Sweden, Scotland, Slovenia, Greece)]. There were no studies from Africa.

Amongst the included studies, 11 studies were conducted prospectively while the remaining 15 were a retrospective review of medical records. Seventeen studies were multi-centre studies.

The overall pooled frequency of IBDU was found to be 7% (95%CI 5–8%), I^2 – 83% (FIGURE 2). The heterogeneity could be reduced on a sensitivity analysis by excluding the study by Bequet et al. leading to a pooled frequency of 7.1% (95% 5.8–8.5%) (TABLE 2). The DOI plot to estimate small study effects is given in FIGURE 3.

TABLE 1. Characteristics of included studies.

Author (reference)	Study Period	IBD n	UC n (%)	CD n (%)	IBDU n (%)	IBDU age at diagnosis	IBDU gender (male)	IBDU median follow-up duration
Aloi M[7] 2014, Italy, Multicentre Prospective	2009–2013	506	245 (48.4%)	224 (44.2%)	37 (7.3%)	–		–
Jakobsen C[8] 2014, Denmark, Multicentre Retrospective	1982 onward	588	318 (54%)	244 (41.4%)	26 (4.4%)	10.9 years (9.3–14.5)	54%	4.7 years
Hradsky O[9] 2015, Czech – Prague, Single-centre Prospective	2014	106	31 (29.2%)	72 (68%)	3 (2.8%)	–	–	–
Urlep D[10] 2015, Slovenia, Multicentre Retrospective	2002–2010	279	105 (37.6%)	167 (59.8%)	7 (2.5%)	–	57%	–
Oliva-Hemker M[11] 2015, USA, Multicentre Prospective	2002–2012	1928	513 (26.6%)	1305 67.7%	110 (5.7%)	–		3.25 years
Cakir M[12] 2015, Turkey, Multicentre Retrospective	2004–2012	127	90 (70.9%)	29 22.8	8 (6.3%)	10.5±5.7 years	50%	–
Buderus S[13] 2015, Germany and Austria, Multicentre Prospective	2004–2014	958	278 (29%)	616 64.3	64 (6.7%)	11.9 years (0.4–17.6)	51.5%	–
Arcos-Machancoses JV[14] 2015, Spain, Single-centre Retrospective	2000–2012	53	19 (35.8%)	31 (58.4%)	3 (5.7%)	–	–	–
Dimakou K[15] 2015, Greece, Single-centre Retrospective	1981–2011	483	267 (55.2%)	167 (34.5%)	49 (10%)	8.9 years (4.8-13.7)	38.6%	–
Schwarz J[16] 2017, Czech – Pilsen, Multicentre Prospective	2000–2015	170	48 (28.2%)	105 (61.7%)	17 (10%)	14.1 years (2.5-17.7)	53%	–
Paul SP[17] 2017, UK, Single-centre Retrospective	2004–2011	344	119 (34.5%)	199 (58%)	26 (7.5%)	10.1 years (1.4-16.1)	64%	51(34–87) months
Lopez RN[18] 2017, New Zealand, Multicentre Retrospective	2015	212	32 (15.1%)	161 (75.9%)	19 (9%)	12.7 years (9.5–14.0)	68.4%	–
El Mouzan MI[19] 2017, Saudi, Single-centre Prospective	–	52	14 (27%)	38 (73%)	0	–	–	–
Bequet E[20] 2017, France, Multicentre Prospective	1988–2011	1412	343 (24.2%)	1032 (73.1%)	37 (2.6%)	–	–	–
Rinawi F[5] 2017, Israel, Single-centre Retrospective	1986–2013	723	188 (26%)	482 (66.6%)	53 (7.3%)	12.8 years (9.5–15.6)	56.6%	6.8 years
Ong C[21] 2018, Sinagpore, Multicentre Retrospective	1994–2015	228	69 (30.3%)	139 (61%)	20 (8.7%)	13.1 years (IQR 5.53)	45%	-
Chandradevan R[22] 2018, United States and Canada, Multicentre Prospective	2008–2012	1411	–	–	136 (9.6%)	12.51±3.64 years	57.3%	2 years
Ziade F[23] 2019, Denmark, Multicentre Retrospective	1998–2006	235	112 (47.6%)	108 (46%)	15 (6.4%)	8.6 years (3.1–13.5)	80%	–
Harris RE[24] 2019, Scotland, Single-centre Retrospective	2017–2018	229	31 (13.5%)	181 (79%)	17 (7.4%)	–	–	–
Ashton JJ[25] 2019, UK, Single-centre Prospective	1997–2017	825	272 (32.9%)	498 (60.3%)	55 (6.6%)	–	–	–
Zhang R[26] 2020, China, Single-centre Retrospective	2009–2018	87	25 (29%)	50 (57%)	12 (14%)	–	–	–
IvkoviÄ‡ L[27] 2020, Croatia, Multicentre Prospective	2016–2017	51	28 (56%)	19 (38%)	8 (15.6)	14.5 years (12.8–16.7)	75%	–
Mouratidou N[28] 2020, Sweden, Multicentre Retrospective	1990–2014	4201	2201 (52.3%)	1640 (39%)	360 (8.5%)	–	–	Range 1.3 to 27.2 years
Dhaliwal J[29] 2020, Canada, Multicentre Prospective	2014–2017	1092	316 (30%)	687 (62%)	89 (8%)	–	–	1 year
Arai K[30] 2020, Japan, Multicentre Prospective	2012–2015	243	146 (60.1%)	91 (37.4%)	6 (2.4%)	4.3±5.6 years	50%	–
Larrosa-Haro A[31] 2020, Latin America - 9 Countries, Multicentre Retrospective	2005–2016	607	475 (78.3%)	104 (17.1%)	28 (4.6%)	-		-
Srivastava A[32] 2020, India, Multicentre Ambispective	2016–2019	325	91 (28%)	212 (65.2%)	22 (6.7%)	3.3 years (IQR 2.3)	67%	-

IBD: inflammatory bowel disease; UC: ulcerative colitis; CD: Crohns disease; IBDU: inflammatory bowel disease – unclassified.

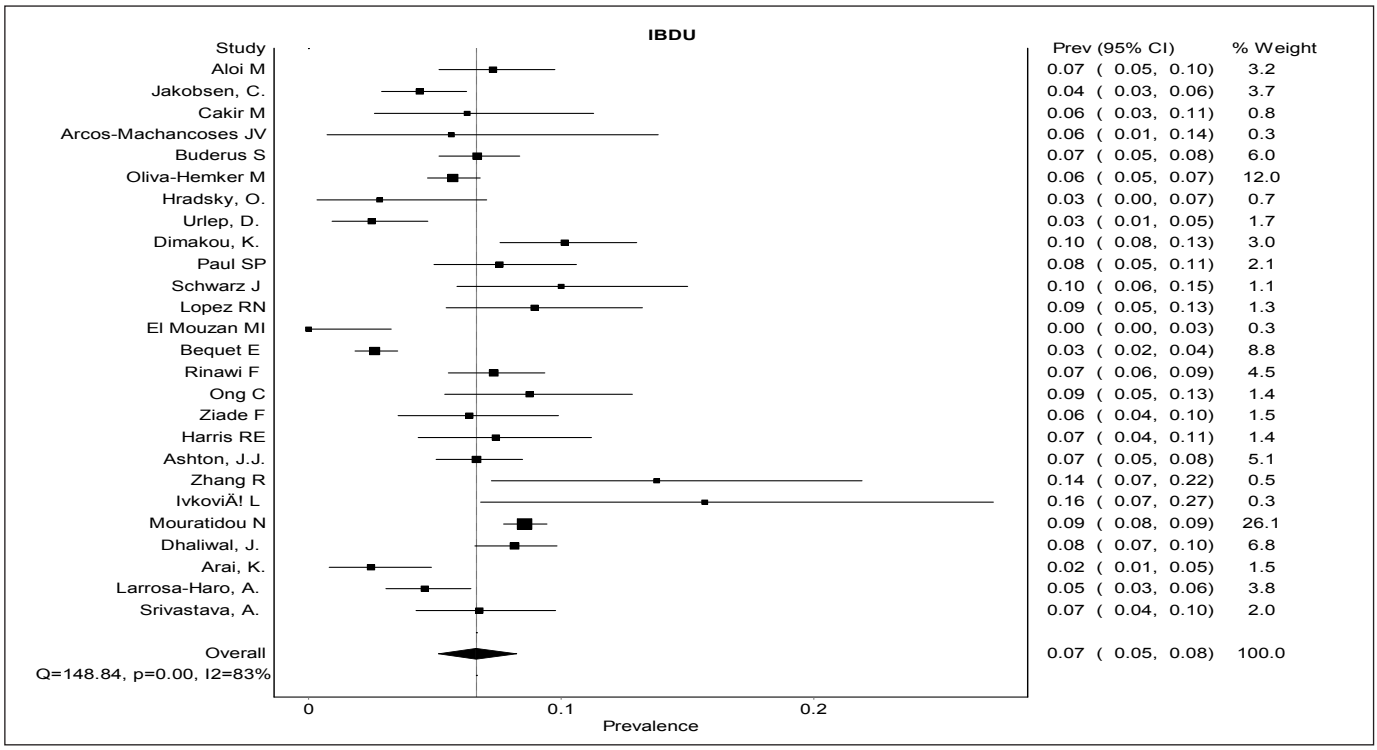

FIGURE 2. Overall frequency of inflammatory bowel disease – unclassified.
IBDU: inflammatory bowel disease – unclassified.

TABLE 2. Sensitivity analysis – inflammatory bowel disease – unclassified frequency.

Excluded study	Pooled prevalence	LCI 95%	HCI 95%	Cochran Q	*P*	I^2	I^2 LCI 95%	I^2 HCI 95%
Aloi M	0.066	0.050	0.083	148.401	0.000	83.828	77.182	88.538
Jakobsen C	0.067	0.052	0.084	143.393	0.000	83.263	76.306	88.177
Cakir M	0.067	0.051	0.083	148.840	0.000	83.875	77.255	88.568
Arcos-Machancoses JV	0.067	0.051	0.083	148.836	0.000	83.875	77.255	88.568
Buderus S	0.066	0.050	0.084	148.832	0.000	83.874	77.254	88.568
Oliva-Hemker M	0.068	0.051	0.086	145.589	0.000	83.515	76.698	88.338
Hradsky O.	0.067	0.052	0.083	146.127	0.000	83.576	76.792	88.377
Urlep D.	0.067	0.052	0.083	138.216	0.000	82.636	75.330	87.778
Dimakou K.	0.066	0.050	0.082	140.526	0.000	82.921	75.774	87.960
Paul SP	0.066	0.051	0.083	148.284	0.000	83.815	77.162	88.530
Schwarz J	0.066	0.051	0.082	145.958	0.000	83.557	76.762	88.365
Lopez RN	0.066	0.051	0.082	146.983	0.000	83.672	76.940	88.438
El Mouzan MI	0.067	0.052	0.083	141.069	0.000	82.987	75.877	88.002
Bequet E	0.071	0.058	0.085	90.188	0.000	73.389	60.513	82.066
Rinawi F	0.066	0.050	0.083	148.215	0.000	83.807	77.150	88.525
Ong C	0.066	0.051	0.083	147.134	0.000	83.688	76.966	88.449
Ziade F	0.067	0.051	0.083	148.837	0.000	83.875	77.255	88.568
Harris RE	0.066	0.051	0.083	148.521	0.000	83.841	77.202	88.546
Ashton JJ	0.066	0.050	0.084	148.834	0.000	83.875	77.254	88.568
Zhang R	0.066	0.051	0.082	143.304	0.000	83.252	76.289	88.171
IvkoviÄ! L	0.066	0.051	0.082	143.867	0.000	83.318	76.391	88.212
Mouratidou N	0.060	0.048	0.073	118.827	0.000	79.803	70.869	85.996
Dhaliwal J	0.065	0.049	0.083	144.823	0.000	83.428	76.562	88.283
Arai K	0.067	0.052	0.083	139.513	0.000	82.797	75.581	87.881
Larrosa-Haro A	0.067	0.052	0.084	144.232	0.000	83.360	76.457	88.239
Srivastava A	0.066	0.051	0.083	148.808	0.000	83.872	77.250	88.566

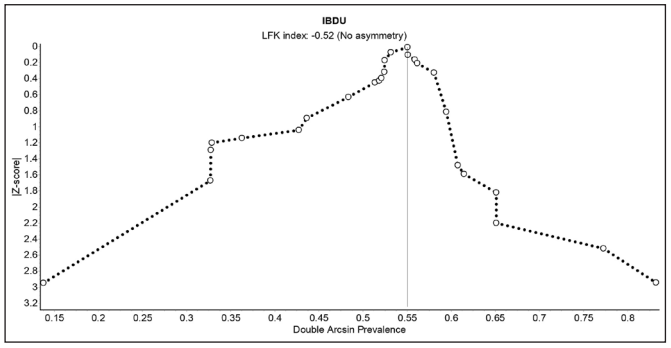

FIGURE 3. DOI Plot – IBDU frequency.
IBDU: inflammatory bowel disease – unclassified.

The frequency was significantly lower in prospectively conducted studies as compared to the retrospective ones (5.8% vs 7.6%, *P*=0.0001). There was no statistical difference between the multicentre and single–centre studies (6.6% vs 7.5%, *P*=0.09). The continent-wise pooled frequency was as follows – Asia – 6.8%, Europe – 6.9% and North America – 6.5%. (*P*=0.47) There was only one publication from South America and Oceania that was included in the analysis.

When only studies that included patients diagnosed after 2005 i.e. the publication of the Porto Criteria were included then the pooled IBDU frequency was found to be 6.5%. When only studies published after 2017 i.e. the publication of the PIBD-classes algorithm were included then the pooled IBDU frequency was found to be 7.7%.

IBDU re-classification

Seven studies comprising of 5880 patients (397 IBDU) were included in this analysis. The median follow- up duration after the diagnosis of IBDU ranged from 1 year to 6.8 years in the studies in which this data was available. Overall, 50% (95%CI 41–60%), I^2 – 67% were re-classified. Amongst these 30% (95% 18–43%), I^2 – 83% were re-classified to UC and 20% (95% 11–30%), I^2 – 77% were re-classified to Crohn's disease. (FIGURE 4 A-C).

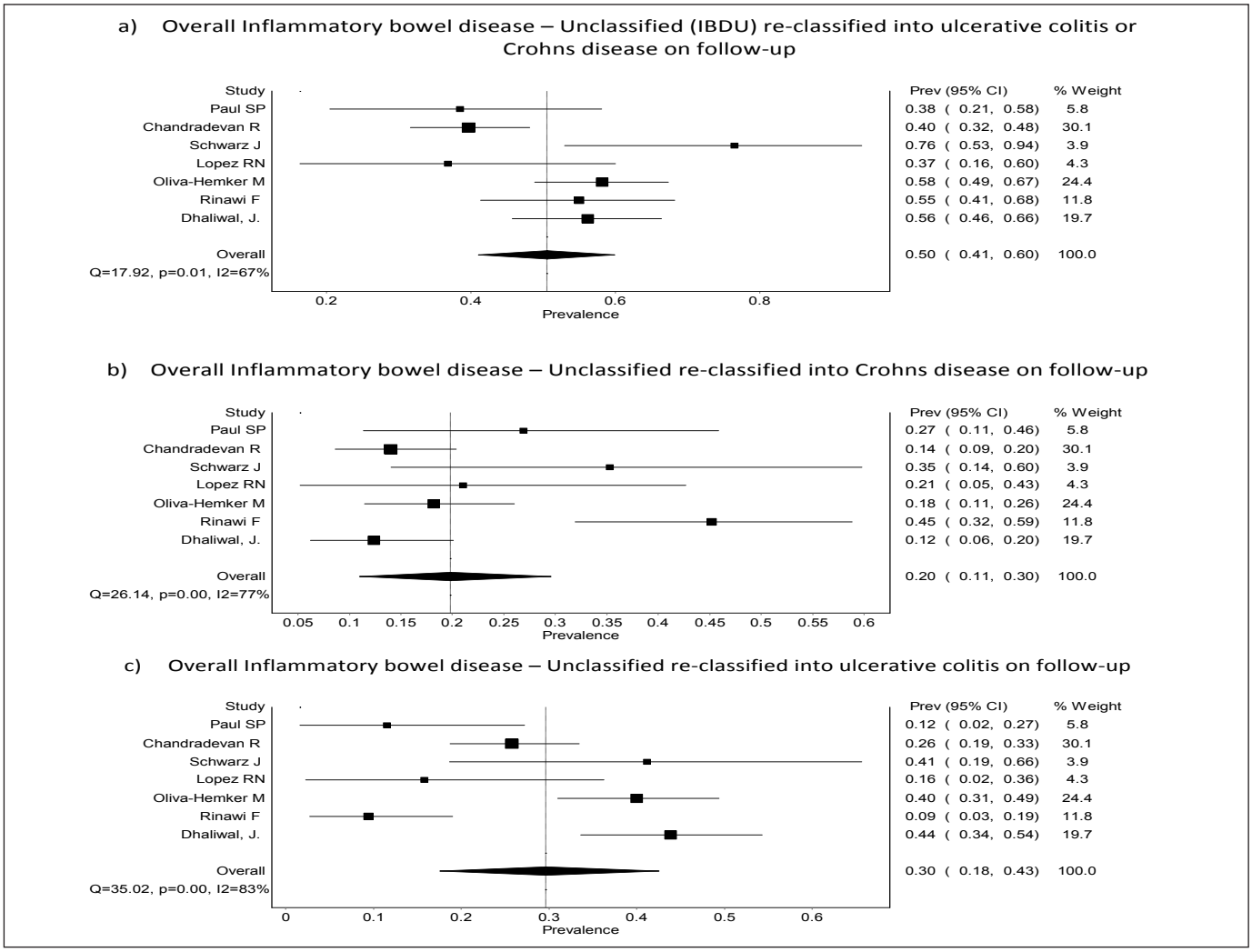

FIGURE 4. A) Proportion of children with Inflammatory Bowel Disease – Unclassified re-classified into Ulcerative colitis or Crohns disease; B) Proportion of children with Inflammatory Bowel Disease – Unclassified re-classified into Ulcerative colitis; C) Proportion of children with Inflammatory Bowel Disease – Unclassified re-classified into Crohns disease.

On sensitivity analysis, the exclusion of the study by Rinawi et al. reduced the heterogeneity. (TABLES 3 AND 4). The resulting frequency of IBDU re-classified to UC was 32.7% (95%CI 21–44%) I^2 – 74.5% and those to CD was 17% (95%CI 12–22%), I^2 – 35%. Minimal overlap in the confidence intervals in the proportion of children classified into UC or CD suggested a statistically significant difference.

The DOI plot to estimate small study effects is given in FIGURE 5 A-C.

Risk of bias assessment

The risk of bias assessment of the studies included in the meta-analysis has been summarised in TABLE 5. No studies were excluded because of poor quality.

TABLE 3. Sensitivity analysis – re-classification of inflammatory bowel disease – unclassified to ulcerative colitis.

Excluded study	Pooled prevalence	LCI 95%	HCI 95%	Cochran Q	p	I^2	I^2 LCI 95%	I^2 HCI 95%
Paul SP	0.308	0.183	0.442	30.119	0.000	83.399	65.234	92.073
Chandradevan R	0.313	0.154	0.484	33.638	0.000	85.136	69.518	92.752
Schwarz J	0.292	0.165	0.428	33.876	0.000	85.240	69.772	92.793
Lopez RN	0.302	0.174	0.440	33.296	0.000	84.983	69.146	92.691
Oliva-Hemker M	0.264	0.128	0.414	28.012	0.000	82.151	62.097	91.594
Rinawi F	0.327	0.218	0.443	19.670	0.001	74.581	42.262	88.809
Dhaliwal J	0.263	0.138	0.401	25.250	0.000	80.198	57.107	90.858

TABLE 4. Sensitivity analysis – re-classification of inflammatory bowel disease – unclassified to Crohns disease.

Excluded study	Pooled prevalence	LCI 95%	HCI 95%	Cochran Q	p	I^2	I^2 LCI 95%	I^2 HCI 95%
Paul SP	0.194	0.099	0.300	25.177	0.000	80.141	56.958	90.837
Chandradevan R	0.225	0.114	0.348	21.697	0.001	76.956	48.617	89.665
Schwarz J	0.192	0.103	0.292	23.727	0.000	78.927	53.808	90.387
Lopez RN	0.197	0.102	0.304	26.063	0.000	80.816	58.696	91.090
Oliva-Hemker M	0.203	0.086	0.336	25.952	0.000	80.734	58.486	91.059
Rinawi F	0.170	0.121	0.223	7.753	0.170	35.509	0.000	74.216
Dhaliwal, J.	0.217	0.110	0.337	21.964	0.001	77.236	49.359	89.767

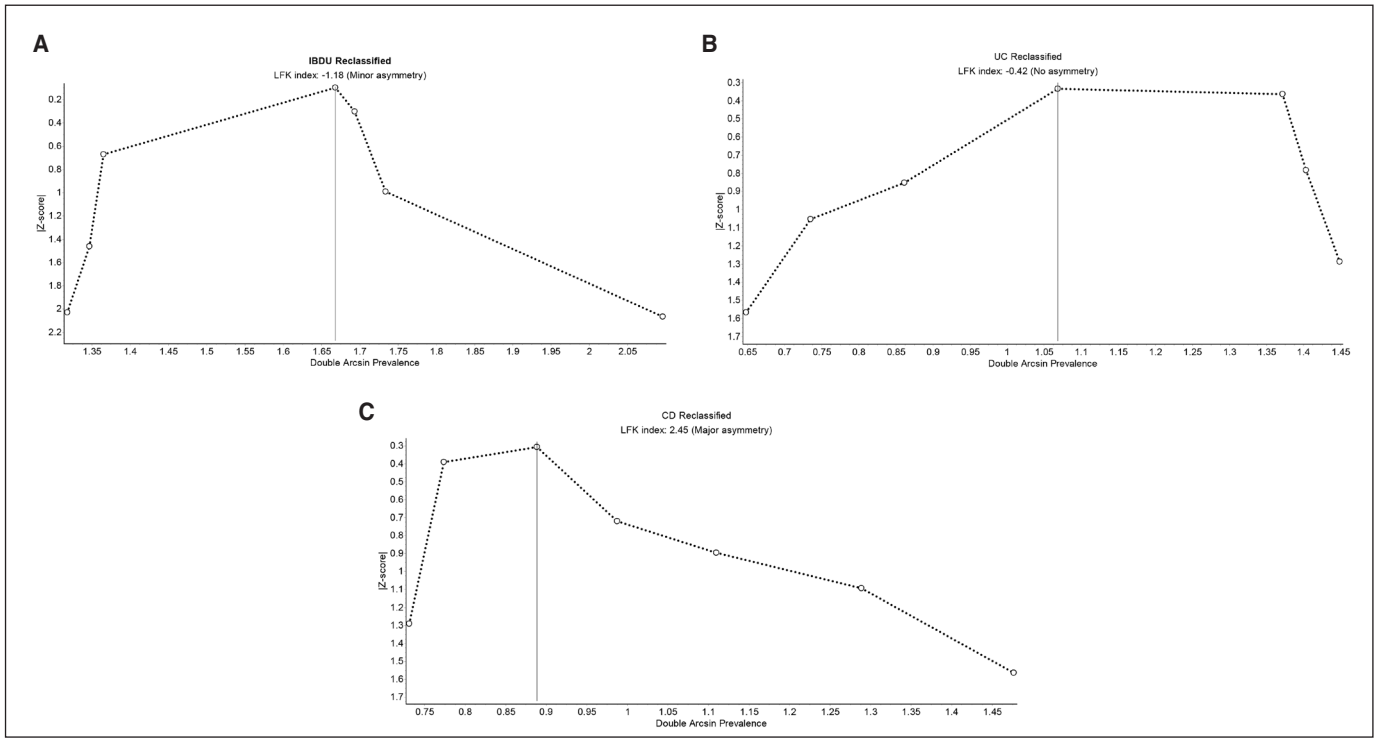

FIGURE 5. DOI plots **A)** Overall IBDU re-classified. **B)** IBDU re-classified into CD. **C)** IBDU re-classified into UC.
UC: ulcerative colitis; CD: Crohns disease; IBDU: inflammatory bowel disease – unclassified.

TABLE 5. Risk of bias assessment.

Authors	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Zhang R	Y	Y	D	Y	D	Y	N	Y	Y	Y	Y	Y	D	D	Y	Y	Y	Y	N	D
Ziade F	Y	Y	N	Y	Y	Y	D	Y	Y	Y	Y	Y	D	D	Y	Y	Y	Y	N	Y
Paul SP	Y	Y	N	Y	Y	Y	D	Y	Y	Y	Y	Y	D	D	Y	Y	Y	Y	N	D
IvkoviÄ‡ L	Y	Y	D	Y	Y	Y	D	Y	Y	Y	Y	Y	D	D	Y	Y	Y	Y	N	Y
Chandradevan	Y	Y	D	Y	Y	Y	D	Y	Y	Y	Y	Y	D	D	Y	Y	Y	Y	N	Y
Schwarz J	Y	Y	N	Y	Y	Y	D	Y	Y	Y	Y	Y	D	D	Y	Y	Y	Y	N	Y
Cakir M	Y	Y	D	Y	Y	Y	D	Y	Y	Y	Y	Y	N	D	Y	Y	Y	Y	N	Y
Aloi M	Y	Y	D	Y	Y	Y	D	Y	Y	Y	Y	Y	D	D	Y	Y	Y	Y	N	Y
Arcos-Machancoses	Y	Y	D	Y	Y	Y	D	Y	Y	Y	Y	Y	D	D	Y	Y	Y	Y	N	Y
Lopez RN	Y	Y	N	Y	Y	Y	D	Y	Y	Y	Y	Y	D	D	Y	Y	Y	Y	N	Y
Buderus S	Y	Y	N	Y	Y	Y	D	Y	Y	Y	Y	Y	D	D	Y	Y	Y	Y	N	Y
El Mouzan MI	Y	Y	D	Y	Y	Y	D	Y	Y	Y	Y	Y	D	D	Y	Y	Y	Y	N	Y
Bequet E	Y	Y	N	Y	Y	Y	D	Y	Y	Y	Y	Y	D	D	Y	Y	Y	Y	N	Y
Oliva-Hemker M	Y	Y	N	Y	Y	Y	D	Y	Y	Y	Y	Y	D	D	Y	Y	Y	Y	N	Y
Rinawi F	Y	Y	D	Y	Y	Y	D	Y	Y	Y	Y	Y	D	D	Y	Y	Y	Y	N	Y
Mouratidou N	Y	Y	D	Y	Y	Y	D	Y	Y	Y	Y	Y	D	D	Y	Y	Y	Y	N	Y
Harris RE	Y	Y	D	Y	Y	Y	D	Y	Y	Y	Y	Y	D	D	Y	Y	Y	Y	N	Y
Ashton, J.J.	Y	Y	D	Y	Y	Y	D	Y	Y	Y	Y	Y	D	D	Y	Y	Y	Y	N	Y
Dhaliwal, J.	Y	Y	D	Y	Y	Y	D	Y	Y	Y	Y	Y	D	D	Y	Y	Y	Y	N	Y
Arai, K.	Y	Y	D	Y	Y	Y	D	Y	Y	Y	Y	Y	D	D	Y	Y	Y	Y	N	Y
Larrosa-Haro,	Y	Y	D	Y	Y	Y	D	Y	Y	Y	Y	D	D	D	Y	Y	Y	Y	N	Y
Srivastava, A.	Y	Y	D	Y	Y	Y	D	Y	Y	Y	Y	Y	D	D	Y	Y	Y	Y	N	Y
Jakobsen, C.	Y	Y	D	Y	Y	Y	D	Y	Y	Y	Y	Y	D	D	Y	Y	Y	Y	N	Y
Hradsky, O.	D	Y	N	Y	Y	Y	D	Y	Y	D	Y	Y	D	D	Y	Y	Y	Y	N	Y
Urlep, D.	Y	Y	N	Y	Y	Y	D	Y	Y	Y	Y	Y	D	D	Y	Y	Y	Y	N	Y
Ong C	Y	Y	D	Y	Y	Y	D	Y	Y	Y	Y	Y	D	D	Y	D	Y	Y	N	Y
Dimakou, K.	Y	Y	D	Y	Y	Y	D	Y	Y	Y	Y	Y	D	D	Y	Y	Y	Y	N	Y

Y: yes, N: no; D: unclear.

1) Were the aims/objectives of the study clear. 2) Was the study design appropriate for the stated aim(s). 3) Was the sample size justified. 4) Was the target/reference population clearly defined? (Is it clear who the research was about?) 5) Was the sample frame taken from an appropriate population base so that it closely represented the target/reference population under investigation. 6) Was the selection process likely to select subjects/participants that were representative of the target/reference population under investigation. 7) Were measures undertaken to address and categorise non-responders. 8) Were the risk factor and outcome variables measured appropriate to the aims of the study. 9) Were the risk factor and outcome variables measured correctly using instruments/measurements that had been trialled, piloted or published previously. 10) Is it clear what was used to determined statistical significance and/or precision estimates? (e.g. p-values, confidence intervals). 11) Were the methods (including statistical methods) sufficiently described to enable them to be repeated. 12) Were the basic data adequately described. 13) Does the response rate raise concerns about non-response bias. 14) If appropriate, was information about non-responders described. 15) Were the results internally consistent. 16) Were the results presented for all the analyses described in the methods. 17) Were the authors' discussions and conclusions justified by the results. 18) Were the limitations of the study discussed. 19) Were there any funding sources or conflicts of interest that may affect the authors' interpretation of the results. 20) Was ethical approval or consent of participants attained.

DISCUSSION

Our meta-analysis found that in studies published after 2014, 7.1% children with childhood onset IBD are given a label of IBDU at initial diagnosis. This has considerably decreased as compared to reports published in the early 2000s where it constituted – 13% of all PIBD[1,4]. Clearer diagnostic criteria and a more complete initial diagnostic assessment because of access to better diagnostic tools are potential reason for this occurrence. The frequency of IBDU was lower in prospectively conducted studies which is likely a reflection of a comprehensive initial assessment because of more stringent diagnostic criteria and a protocolized approach.

IBDU rates were not affected by geographical location. This indicates that even in areas with a low IBD prevalence the frequency of IBDU remains constant.

Data from our analysis also suggests that the previously held perception that IBDU is – 2 fold commoner in PIBD as compared to those with an adult-onset may not hold true. IBDU frequency in adults has remained constant over the last few decades despite the availability of better diagnostic modalities[3]. It is likely that IBDU frequency is similar in both children and adults and previously reported higher rates in children were simply a result of a higher rate of incomplete initial assessment.

It was found that on follow-up investigations 50% of children are re-classified into UC or CD. With such a high re-classification rate, it is prudent that the threshold for re-evaluating patients with IBDU with a repeat endoscopy and/or imaging should be low especially if symptoms are persistent or the follow-up clinical/laboratory parameters suggest a likelihood of CD or UC. The EUROKIDS registry which included data from 20 centres across

Europe between the years 2005–2013 found that prevalence of IBDU reduced from 7.7% to 5.6% after re-investigations during a median follow-up of 5.7 years. However, in this study only half (48%) of patients initially classified as IBDU had undergone a complete diagnostic workup. Furthermore, only a limited number of patients were completely re-evaluated (endoscopy in 54%, and a repeat radiological evaluation in 38%) on follow-up and it is conceivable that if more patients would have been re-evaluated then more might have been re-classified[4].

The overall re-classification rate observed in this study is much higher than the report by Birimberg-Schwartz et al. who have recently reported a reclassification rate of 21%[3]. A short follow-up duration (median 2.8 years) in the study by Birimber-Schwartz could be a possible reason for this occurrence. Previous pediatric studies have demonstrated a median time to reclassification of – 6 years[5].

Data from this meta-analysis suggests that the likelihood of re-classification of IBDU to UC is higher. Patients with IBDU should be managed on the lines of UC rather than CD. In a recent large multicentre retrospective longitudinal study of 797 pediatric IBD patients with isolated colitis comprising of 250 children with CD, 287 with UC, and 260 with IBDU it was found that the disease course of IBDU is in general mild and more in sync with UC than CD[6]. It was observed that – 17% of children with IBDU are also re-classified into CD and it is important to identify this subset early so that their treatment is not delayed. The over-liberal use of the term "backwash ileitis" should be avoided at the initial diagnosis and on follow-up a close – eye should be kept on those with a familial history of CD, hypoalbuminemia at diagnosis and the need for nutritional support during follow-up as these factors have been found to be predictors of re-classification to CD[5].

The strength of our meta-analysis is that it is updated, including all relevant studies from across the globe published before July, 2021. Most children were diagnosed in large tertiary pediatric referral centres. Only studies in which the diagnosis of IBDU was based on an accepted diagnostic criteria were included.

Limitations include the fact that none of the included studies used the recently validated PIBD-classes algorithm to classify their IBD patients as IBDU[3]. In the future there would likely be the need for an updated meta-analysis that includes patients in which this criteria have been used to identify patients with IBDU. We could not stratify the prevalence of IBDU by age-group as this data was available only in a small number of studies. There is also a variability of the follow-up duration in the studies included in the analysis and it is possible that studies with a shorter follow-up duration might have under-reported the proportion of IBDU re-classified on follow-up. A definitive attempt to reclassify (i.e. repeat assessment) all patients was not made in the studies included in the re-classification analysis. These included studies represent "real world" data where attempts to re-classify are made only when the follow-up clinical, laboratory parameters or imaging suggests a likelihood of CD or UC. There is a need for a prospective protocolized follow-up study of patients with IBDU which would give the true rate of re-classification. Another limitation was significant heterogeneity among the studies included which we tried to eliminate with a sensitivity analysis.

To conclude, IBDU comprises 7.1% of PIBD at initial diagnosis. Half of these children are re-classified into UC or CD on follow-up with a higher likelihood of re-classification to UC as compared to CD.

Authors' contribution

Bolia R: study conception and design, data acquisition, analysis and data interpretation, drafting of the manuscript, critical revision. Goel AD: data acquisition, analysis and data interpretation, critical revision.

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Bolia R, Goel AD. Revisão sistemática e meta-análise das tendências de frequência e reclassificação da doença inflamatória pediátrica intestinal – não classificadas. Arq Gastroenterol. 2022;59(4):531-39.

RESUMO – Contexto – O termo doença inflamatória intestinal não classificada (DIINC) é usado quando um indivíduo tem colite crônica, mas não pode ser sub tipificado em colite ulcerativa (UC) ou doença de Crohn (DC) com base nas características clínicas, endoscópicas, de imagem e histopatológicas. No acompanhamento, uma proporção de pacientes com DIINC são reclassificadas como DC ou UC. Houve considerável variabilidade nas taxas de frequência e reclassificação de DIINC pediátrico na literatura publicada. **Métodos** – Foram procuradas publicações no PubMed e Scopus relacionadas à doença inflamatória pediátrica intestinal publicadas entre janeiro de 2014 e julho de 2021. Dois revisores pesquisaram e selecionaram estudos independentemente relatando a frequência da DIINC e/ou sua reclassificação. A prevalência agrupada foi expressa em proporção e para IC95%. A meta-análise foi realizada utilizando o modelo de heterogeneidade de variância inversa. **Resultados** – Foram identificados 2.750 estudos por meio de uma busca sistemática, dos quais 27 estudos foram incluídos nesta revisão sistemática. A frequência total agrupada da DIINC (n=16064) foi de 7,1% (IC95% 5,8–8,5%). Não houve variação na frequência da DIINC por localização geográfica. Sete estudos (n=5880) foram incluídos na análise de reclassificação da DIINC. No geral, 50% (IC95% 41–60%) foram reclassificadas no seguimento. Entre esses 32,7% (95% 21–44%) foram reclassificados para UC e 17% (IC95%12–22%) foram reclassificados para DC. **Conclusão** – DIINC compreende 7,1% da doença inflamatória pediátrica intestinal no diagnóstico inicial. Metade dessas crianças são reclassificados em UC ou DC no seguimento com maior probabilidade de reclassificação para UC em comparação com o DC.

Palavras-chave – Doença inflamatória intestinal; não classificado; doença inflamatória intestinal pediátrica; doença de Crohn; colite ulcerativa.

REFERENCES

1. Prenzel F, Uhlig HH. Frequency of indeterminate colitis in children and adults with IBD - a metaanalysis. J Crohns Colitis. 2009;3:277-81.
2. Levine A, Koletzko S, Turner D, Escher JC, Cucchiara S, de Ridder L, et al. ESPGHAN revised porto criteria for the diagnosis of inflammatory bowel disease in children and adolescents. J Pediatr Gastroenterol Nutr. 2014;58:795-806.
3. Birimberg-Schwartz L, Zucker DM, Akriv A, Cucchiara S, Cameron FL, Wilson DC, et al. Development and Validation of Diagnostic Criteria for IBD Subtypes Including IBD-unclassified in Children: a Multicentre Study From the Pediatric IBD Porto Group of ESPGHAN. J Crohn's Colitis. 2017;11:1078-84.
4. Winter DA, Karolewska-Bochenek K, Lazowska-Przeorek I, Lionetti P, Mearin ML, Chong SK, et al. Pediatric IBD-unclassified Is Less Common than Previously Reported; Results of an 8-Year Audit of the EUROKIDS Registry. Inflamm Bowel Dis. 2015;21:2145-53.
5. Rinawi F, Assa A, Eliakim R, Mozer-Glassberg Y, Nachmias Friedler V, Niv Y, et al. The natural history of pediatric-onset IBD-unclassified and prediction of Crohn's disease reclassification: a 27-year study. Scand J Gastroenterol. 2017;52:558-63.
6. Aloi M, Birimberg-Schwartz L, Buderus S, Hojsak I, Fell JM, Bronsky J, et al. Treatment Options and Outcomes of Pediatric IBDU Compared with Other IBD Subtypes: A Retrospective Multicenter Study from the IBD Porto Group of ESPGHAN. Inflamm Bowel Dis. 2016;22:1378-83.
7. Aloi M, Lionetti P, Barabino A, Guariso G, Costa S, Fontana M, et al. Phenotype and disease course of early-onset pediatric inflammatory bowel disease. Inflamm Bowel Dis. 2014;20:597-605. doi: 10.1097/01.MIB.0000442921.77945.09.
8. Jakobsen C, Cleynen I, Andersen PS, Vermeire S, Munkholm P, Paerregaard A, et al. Genetic susceptibility and genotype-phenotype association in 588 Danish children with inflammatory bowel disease. J Crohns Colitis. 2014;8:678-85. doi: 10.1016/j.crohns.2013.12.010.
9. Hradsky O, Copova I, Zarubova K, Durilova M, Nevoral J, Maminak M, et al. Seroprevalence of Epstein-Barr Virus, Cytomegalovirus, and Polyomaviruses in Children with Inflammatory Bowel Disease. Dig Dis Sci. 2015;60:3399-407.
10. Urlep D, Blagus R, Orel R. Incidence Trends and Geographical Variability of Pediatric Inflammatory Bowel Disease in Slovenia: A Nationwide Study. Biomed Res Int. 2015;2015:921730.
11. Oliva-Hemker M, Hutfless S, Al Kazzi ES, Lerer T, Mack D, LeLeiko N, et al. Clinical Presentation and Five-Year Therapeutic Management of Very Early-Onset Inflammatory Bowel Disease in a Large North American Cohort. J Pediatr. 2015;167:527-32.e1-3.
12. Cakir M, Unal F, Dinler G, Baran M, Yuksekkaya HA, Tumgor G, et al. Inflammatory bowel disease in Turkish children. World J Pediatr. 2015;11:331-7.
13. Buderus S, Scholz D, Behrens R, Classen M, De Laffolie J, Keller KM, et al. Inflammatory bowel disease in pediatric patients: Characteristics of newly diagnosed patients from the CEDATA-GPGE Registry. Dtsch Arztebl Int. 2015;112:121-7.
14. Arcos-Machancoses JV, Donat-Aliaga E, Polo-Miquel B, Masip-Simó E, Ribes-Koninckx C, Pereda-Pérez A. Retraso diagnóstico en la enfermedad inflamatoria intestinal pediátrica. Descripción y estudio de los factores de riesgo [Description and study of risk factors for the diagnostic delay of pediatric inflammatory bowel disease]. An Pediatr (Barc). 2015;82:247-54.
15. Dimakou K, Pachoula I, Panayotou I, Stefanaki K, Orfanou I, Lagona E, et al. Pediatric inflammatory bowel disease in Greece: 30-years experience of a single center. Ann Gastroenterol. 2015;28:81-6.
16. Schwarz J, Sýkora J, Cvalínová D, Pomahačová R, Klečková J, Kryl M, et al. Inflammatory bowel disease incidence in Czech children: A regional prospective study, 2000-2015. World J Gastroenterol. 2017;23:4090-4101
17. Paul SP, Sandhu BK. Long-term Outcome of Inflammatory Bowel Disease-Unclassified in Children. Indian Pediatr. 2017;54:742-5.
18. Lopez RN, Evans HM, Appleton L, Bishop J, Chin S, Mouat S, et al. Point Prevalence of Pediatric Inflammatory Bowel Disease in New Zealand in 2015: Initial Results from the PINZ Study. Inflamm Bowel Dis. 2017;23:1418-24.
19. El Mouzan MI, Al Mofarreh MA, Al Sarkhy AA, Assiri AM, Hamed YM. Pre-illness diet as risk factor in pediatric inflammatory bowel disease in Saudi Arabia. Saudi J Gastroenterol. 2017;23:287-90.
20. Bequet E, Sarter H, Fumery M, Vasseur F, Armengol-Debeir L, Pariente B, et al. Incidence and Phenotype at Diagnosis of Very-early-onset Compared with Later-onset Paediatric Inflammatory Bowel Disease: A Population-based Study [1988-2011]. J Crohns Colitis. 2017;11:519-26.
21. Ong C, Aw MM, Liwanag MJ, Quak SH, Phua KB. Rapid rise in the incidence and clinical characteristics of pediatric inflammatory bowel disease in a South-East Asian cohort in Singapore, 1994-2015. J Dig Dis. 2018;19:395-403. doi: 10.1111/1751-2980.12641.
22. Chandradevan R, Hofmekler T, Mondal K, Harun N, Venkateswaran S, Somineni HK, et al. Evolution of Pediatric Inflammatory Bowel Disease Unclassified (IBD-U): Incorporated With Serological and Gene Expression Profiles. Inflamm Bowel Dis. 2018;24:2285-90.
23. Ziade F, Rungoe C, Kallemose T, Paerregaard A, Wewer AV, Jakobsen C. Biochemical Markers, Genotype, and Inflammation in Pediatric Inflammatory Bowel Disease: A Danish Population-Based Study. Dig Dis. 2019;37:140-6.
24. Harris RE, Sim W, Sutton H, Garrick V, Curtis L, Gervais L, et al. Using a Steroid-sparing Tool in Paediatric Inflammatory Bowel Disease to Evaluate Steroid Use and Dependency. J Pediatr Gastroenterol Nutr. 2019;69:557-63.
25. Ashton JJ, Borca F, Mossotto E, Coelho T, Batra A, Afzal NA, et al. Increased prevalence of anti-TNF therapy in paediatric inflammatory bowel disease is associated with a decline in surgical resections during childhood. Aliment Pharmacol Ther. 2019;49:398-407.
26. Zhang R, Zhong XM, Gong YZ, Ma X, Zhu D, Ning HJ, et al. [Analysis of clinical characteristics and drug treatment of inflammatory bowel disease in children: a single center study]. Zhonghua Er Ke Za Zhi. 2020;58:570-5.
27. Ivković L, Hojsak I, Trivić I, Sila S, Hrabač P, Konjik V, et al. Incidence and Geographical Variability of Pediatric Inflammatory Bowel Disease in Croatia: Data From the Croatian National Registry for Children With Inflammatory Bowel Disease. Clin Pediatr (Phila). 2020;59:1182-90.
28. Mouratidou N, Malmborg P, Sachs MC, Askling J, Ekbom A, Neovius M, et al. Adult height in patients with childhood-onset inflammatory bowel disease: a nationwide population-based cohort study. Aliment Pharmacol Ther. 2020;51:789-800.
29. Dhaliwal J, Walters TD, Mack DR, Huynh HQ, Jacobson K, Otley AR, et al. Phenotypic Variation in Paediatric Inflammatory Bowel Disease by Age: A Multicentre Prospective Inception Cohort Study of the Canadian Children IBD Network. J Crohns Colitis. 2020;14:445-54.
30. Arai K, Kunisaki R, Kakuta F, Hagiwara SI, Murakoshi T, Yanagi T, et al. Phenotypic characteristics of pediatric inflammatory bowel disease in Japan: results from a multicenter registry. Intest Res. 2020;18:412-20.
31. Larrosa-Haro A, Abundis-Castro L, Contreras MB, Gallo MJ, Peña-Quintana L, Targa Ferreira CH, et al. Epidemiologic trend of pediatric inflammatory bowel disease in Latin America: The Latin American Society for Pediatric Gastroenterology, Hepatology and Nutrition (LASPGHAN) Working Group. Rev Gastroenterol Mex (Engl Ed). 2021;86:328-34.
32. Srivastava A, Sathiyasekharan M, Jagadisan B, Bolia R, Peethambaran M, Mammayil G, et al. Paediatric inflammatory bowel disease in India: a prospective multicentre study. Eur J Gastroenterol Hepatol. 2020;32:1305-11.