Title: COVID-19 in Children with Inflammatory Bowel Disease: A Systematic Review Study

Short Title: IBD and COVID-19

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Abstract

Background and objectives: Considering the chronic immunosuppression in inflammatory bowel disease (IBD) patients, it is necessary to evaluate the course of COVID-19 in these patients. Studies have shown various results in adult IBD patients. The aim of this study was to find out the course of this infection in pediatric IBD patients.

Methods: This was a systematic review study according to the PRISMA 2020 guideline. Scopus, PubMed, and the Web of Science were searched with a combination of "COVID-19" AND "IBD" or synonyms until October 16, 2021. Studies that have the outcomes of COVID-19 infection in patients less than 19 years of age were selected. Name of author, country, study duration and type, IBD type and drugs, and COVID-19 outcomes were extracted.

Results: From the initially retrieved 2215 articles, finally 16 articles were eligible. Totally, data from 1040 pediatric IBD patients were reported. Twenty-four patients were hospitalized, 5 patients developed Multisystem inflammatory Syndrome in children, and others had a mild disease course and were outpatient. Steroid use, severe IBD activity, and comorbidities were shown to increase disease severity and risk of hospitalization.

Conclusions: COVID-19 is a benign and self-limited disease in pediatric IBD patients. Comorbidities, steroid use, and severe IBD activity affect the patients' outcomes.

Key words: Corona virus disease 2019, Inflammatory bowel disease, SARS-CoV-2, Pediatrics

Introduction

In December 2019, the first case of pneumonia with the novel beta-corona virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was observed in Wuhan, China. The disease then spread rapidly around the world and turned to a pandemic in March 2020 [1]. The course of the disease caused by SARS-CoV-2, named as coronavirus disease 2019 (COVID-19) can range from an asymptomatic or mild infection to a severe and fatal disease and may have a variety of signs and symptoms related to different body organs [1].

Research has shown that patients with chronic diseases such as diabetes and chronic heart, lung and kidney diseases and the elderly are at greater risk for development of severe complications following infection with SARS-CoV-2 [2]. The cause of more severe disease in these people than healthy individuals has been attributed to cytokine storm formation, which is an excessive and inappropriate response of the immune system to the virus [3].

Patients with inflammatory bowel diseases (IBDs) including Crohn's disease (CD) and ulcerative colitis (UC) are believed to be at increased risk of opportunistic bacterial or viral infections due to chronic immune modulator and immunosuppressive treatments and therefore, chronic immunosuppression [2, 4]. In the meantime, it is important to assess whether these patients are at risk for more severe cases of the disease caused by the novel coronavirus [1, 5, 6].

According to the literature, taking immunosuppressive drugs has not been associated with increased severity of COVID-19 [7]. However, IBD patients may be at increased risk of COVID-19 severity following increased cytokine production or angiotensin converting enzyme (ACE-2), the receptor for SARS-CoV-2 on the host cells overexpression [8].

Since the beginning of this pandemic, many efforts have been made by various research teams to answer this question. For example, the Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease database (SECURE-IBD) is an international registry of IBD patients infected with SARS-CoV-2. European society for pediatric gastroenterology, hepatology, and nutrition also has created the COVID-19 database for IBD patients with SARS-CoV-2. The data obtained from this registry so far have shown that the risk of being infected with this virus or developing severe complications following the infection in IBD patients is not higher than in the general population. While having other comorbidities, advanced age, and steroid use can increase the risk of complications from the virus [9]. However, there is still not enough information in the literature to give a definitive answer to this question [6]. In addition, most studies in this field have been performed on adult patients and few studies have been performed on children. Accordingly, in the present study, we intend to conduct a systematic literature review to collect data on the course of COVID-19 infection in children with IBD.

Methods

Search strategy and databases

This was a systematic review study based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 guideline. The research question and PICO of this systematic review was as follows;

P: children with IBD and COVID-19 infection

I: IBD treatments

C: children with COVID-19 and without IBD

O: COVID-19 outcome

The search was based on the keywords listed in Table 1 through Scopus, PubMed, and the Web of Science databases until October 16, 2021. The search strategy in each database is listed in Table 1.

Inclusion and exclusion criteria

All English language original articles and meeting abstracts of any type including case reports, case series, cross –sectional, cohort, and case-control were included in the present systematic review study. The study population included patients with COVID-19 infection and IBD who were less than 19 years old. In this study, all studies that examined the course of COVID-19 infection in patients with IBD less than 19 years old were included. Unrelated studies, reviews, duplicates, and low-quality studies were excluded from the review process.

Study selection process

At first, after removing duplicates, the articles were evaluated using the title and the abstract. This was done by two reviewers separately. Then, the full text of the remaining articles was reviewed separately by two reviewers. Unrelated items were also removed at this stage. Articles that did not include patients under 19 years of age or did not report COVID-19 outcomes in these patients were also removed from the review process. The remaining articles entered the quality assessment stage.

Quality assessment

Newcastle Ottawa Scale was used to assess the quality of the remaining studies. A score of less than 14 was considered low-quality. No studies were excluded at this stage. The methodological quality of the studies was also assessed by two independent reviewers based on Cochrane review guidelines.

Data extraction

Data were extracted from the final articles using a checklist with the following items by two independent reviewers: included author name, country, sample size, IBD type, patient IBD medications, and COVID-19 disease outcomes.

Results

From the initially retrieved 2215 articles, 1127 were duplicates. Based on the title and the abstract, 1028 articles were irrelevant or review articles and were excluded. Finally, the full text of 60 articles was read. Twenty-four articles were irrelevant. Twenty articles didn't include pediatric patients or didn't report COVID-19 outcomes in this group. Finally, 16 studies (14 articles, 2 meeting abstracts) were eligible (Figure 1).

Characteristics of the studies

Nine articles had cohort design, five were case reports, and two were cross-sectional. Totally, data from 1040 pediatric IBD patients with were reported. Regarding IBD type, 124 patients had UC, 234 had CD, 25 had IBD-unknown (IBD-U) and IBD type of the other patients was not reported. Twenty-four patients were hospitalized due to COVID-19 but there were no related deaths or severe complications and all patients recovered completely. Five patients (3 CD, 2 UC; 3 males and 2 females) developed Multisystem

Inflammatory Syndrome in Children (MIS-C). In addition to these patients, one other patient also required intensive care unit (ICU) admission due to secondary infection and disease severity. These patients were on biologics or 5-Aminosalicylic acids (5-ASA). Except for these five patients, others mainly reported mild signs and symptoms including fatigue, fever, and dry cough or were asymptomatic. In one study, it was shown that disease activity status, steroid or 5-ASA use, presence of gastrointestinal symptoms, and other comorbidities are related to hospitalization in this age group. In contrast, Tumor necrosis factor (TNF) antagonist mono therapy was associated with a lower hospitalization likelihood ratio. Another study also evaluated the relation between biologic use and symptomatic COVID-19 and there was no significant relation. Disease symptoms lasted from 4 days to 8 weeks to complete remission in a MIS-C patient (Table 2).

Discussion

According to the literature and data from SECURE-IBD registry and the COVID-19 database of the pediatric IBD Porto group of the European society for pediatric gastroenterology hepatology and nutrition, COVID-19 is a benign disease in children with IBD and disease severity and complications will not be increased in these patients compared to normal children. Symptoms of COVID-19 in pediatric IBD patients are not significantly different from the general population and mainly includes fever, fatigue, dry cough, and gastrointestinal symptoms. However, limited data show that chronic steroid therapy may increase the risk of COVID-19 severity in these patients [10-12]. In addition, studies indicate that disease activity status is related to the patients' outcomes following infection with SARS-CoV-2 [11, 13], particularly in younger individuals [14].

Patients with IBD have higher levels of ACE-2 expression. Currently, it is not clear yet whether this receptor increases the risk of COVID-19 severity or has protective roles [15, 16]. Studies also have shown a benign course of COVID-19 in immunosuppressed adults with IBD [17-19] and even protective roles of immunosuppressive agents [20]. However, one study showed a moderately increased risk of hospitalization in adult patients but not severe disease or mortality [21]. Currently, it is recommended for these patients to stop their medications except for 5-ASA when infected with this virus [16]. In children, immunosuppressive medications have not been associated with increased risk of complications from SARS-CoV-2 infection [22]. One study that evaluated the association between biologic use in children with IBD and symptomatic infection with SARS-CoV-2, found no association [23].

Preliminary reports have shown that steroid use, increasing age, and other comorbidities, increase the risk of complications following COVID-19 in adult IBD patients. Although biological therapy has been shown to be safe, thiopurine use has been shown to be accompanied by increasing adverse events [24].

Brenner et al studied a group of pediatric IBD patients hospitalized with SARS-CoV-2 and compared them with outpatients. They concluded that presence of other comorbidities, gastrointestinal symptoms, more severe disease activity, and steroid or 5-ASA use are accompanied by a higher risk for hospitalization. Anti-TNF mono therapy was shown to reduce the risk of hospitalization. They had two patients who required ICU admission, one due to MIS-C and the other one due to disease severity and secondary infections. Both of these patients were on 5-ASA and also suffered from asthma [11].

There are several reports of MIS-C development following infection with SARS-CoV-2 in pediatric patients with IBD [25, 26]. In these cases, patient has completely recovered without any complications and has been on biologic or 5-ASA. Meredith et al reported a case of UC 10 year's old female patient with MIS-C. The patient was on 5-ASA and infliximab treatment [25]. Dolinger et al also reported

another case of CD 14 year's old male patient with MIS-C development that was successfully treated with two doses of infliximab [26]. Sweeny et al reported a 16 years old boy with no past medical history presenting with fever and gastrointestinal symptoms consistent with both new-onset IBD and MIS-C and with a hyper inflammatory state. The patient had a history of flu like disease 6 weeks prior to these symptoms. However, he had a negative nasopharyngeal swab test for SARS-CoV-2 at the time of admission. Patient had signs of IBD in endoscopy, but submucosal vasculitis was consistent with MIS-C. After receiving Intravenous immune globulin, the patient showed improvement and again the clinical condition worsened. Finally, he was successfully treated with infliximab [27]. Brenner et al reported the other case of MIS-C in a 6 years old female patient with UC and on 5-ASA who presented with respiratory failure and coagulopathy and needed ICU care and mechanical ventilation. The patient was successfully treated with corticosteroids and duration of symptoms was 19 days [11]. Other studies have reported a mild and benign course of COVID-19 in these patients. Literature reports no deaths related to infection with SARS-CoV-2 in pediatric IBD patients.

Comparing to the hospital admission rate of 33 to 66 % reported in adult IBD patients with COVID-19, Brenner et al reported a rate of 7% in children. In total, COVID-19 is generally less invasive in the pediatric population compared to adults and is usually asymptomatic [11].

Limitations

This study has several limitations. First, IBD type and medications are not reported in several included studies. Second, there is a lack of case-control studies that compare the outcomes of COVID-19 in healthy children and IBD patients. Third, we have only included English language articles.

In general, current data suggest that COVID-19 outcome in pediatric IBD patients is not significantly different from healthy children and disease activity status, steroid use, and other comorbidities affect the patients' outcome following infection with SARS-CoV-2. However, further case-control studies with larger sample size are needed to confirm these results.

Conclusion

COVID-19 is a benign and self-limited disease in pediatric IBD patients even on immunosuppressive therapy. Corticosteroids, severe IBD activity, and other comorbidities increase the risk of disease severity. Case control studies with larger sample size are needed to confirm these results.

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Table 1. Search strategy

Scopus	TITLE-ABS-KEY ((ibd) OR (inflammatory bowel disease*) OR (ulcerative colitis) OR (crohn's disease)) AND TITLE-ABS-KEY ((covid-19) OR (sars-cov-2) OR (2019 novel coronavirus disease) OR (2019 novel coronavirus infection) OR (2019-ncov disease) OR (2019-ncov infection) OR (covid-19 pandemic) OR (covid-19 pandemics) OR (covid-19 virus disease) OR (covid-19 virus infection) OR (coronavirus disease 2019) OR (coronavirus disease-19) OR (sars coronavirus 2))
PubMed	(((IBD[Title/Abstract]) OR (inflammatory bowel disease*[Title/Abstract]) OR (ulcerative colitis[Title/Abstract]) OR (crohn's disease[Title/Abstract]) OR (Inflammatory Bowel Diseases[MeSH Terms])) AND ((2019 Novel Coronavirus Disease[Title/Abstract]) AND (2019 Novel Coronavirus Infection[Title/Abstract]) AND (2019-nCoV Disease[Title/Abstract]) AND (2019-nCoV Infection[Title/Abstract]) AND (COVID-19 Pandemic[Title/Abstract]) AND (COVID-19 Pandemics[Title/Abstract]) AND (COVID-19 Virus Disease[Title/Abstract]) AND (COVID-19 Virus Infection[Title/Abstract]) AND (COVID19[Title/Abstract]) AND (Coronavirus Disease 2019[Title/Abstract]) AND (Coronavirus Disease-19[Title/Abstract]) AND (SARS Coronavirus 2[Title/Abstract]) AND (SARS-CoV-2[Title/Abstract]) OR (COVID-19[MeSH Terms])))
Web of Science	TI OR AB=(ulcerative colitis OR crohn's disease OR inflammatory bowel disease OR IBD) AND TI=(covid-19 OR sars-cov-2 OR 2019 novel coronavirus disease OR 2019 novel coronavirus infection OR 2019-ncov disease OR 2019-ncov infection OR covid-19 pandemic OR covid-19 pandemics OR covid-19 virus disease OR covid-19 virus infection OR coronavirus disease 2019 OR coronavirus disease-19 OR sars coronavirus 2)
Science Direct	(inflammatory bowel disease OR Crohn's disease OR ulcerative colitis) AND (covid-19 OR sars-cov-2 OR 2019 novel coronavirus OR 2019-ncov OR coronavirus disease 2019 OR sars coronavirus 2)

Table 2. Studies that have reported outcomes of SARS-CoV-2 infection in pediatric IBD patients

Name of author	Country, duration	Study design	Sample size	Age of participants	IBD type	IBD Drugs	COVID-19 outcomes
Ludvigsson et al [21]	Sweden, February 1 to July 31 2020	Cohort Multicenter	608 pediatric IBD patients were followed. (Total number of COVID-19 cases?)	<18 years	NR In the age group	NR in the age group	No patients had a severe disease. Only one patient was hospitalized with COVID-19.
Brenner et al [28]	USA, Data from the SECURE-IBD registry	Cohort Multicenter	29	0-19 years	NR In the age group	NR In the age group	Three 0-9 years old IBD patients with COVID-19, all outpatient and without any complications. 26 10-19 years old IBD patients with COVID-19, 23 outpatient and 3 of them were hospitalized, without any complications.
Queiroz et al [29]	USA, Data from the SECURE-IBD registry	Cohort Multicenter	18	0-19 years old	NR in the age group	NR in the age group	Four 0-9 years old and 14 10-19 years old pediatric IBD patients with SARS-CoV-2 were reported. One patient was hospitalized but there were no deaths, ICU admissions, or other adverse outcomes.
Turner et al [30]	UK, Until March 26, 2020	Cohort multicenter	8 (From 102 sites affiliated with the pediatric Porto group	14-18	5 CD, 2 UC, 1 IBD-U	3 on biologics, 2 on biologics, thiopurines, and 5-ASA, 1 on steroids alone, 2 on 5-ASA and thiopurines	All patients experienced a mild disease, recovered completely, and were outpatient. Symptoms were as follows: Fever (n=3), cough (n=4), fatigue (n=4), rhinitis (n=1), myalgia (n=2), Anosmia and

			of ESPGHAN, no cases were reported in Korea and China.)				Ageusia (n=1), mild chest pain (n=1)
Arcangelo et al [31]	Italy, Patients who have received biological therapy from April 2012 to September 2020 for at least two months	Cohort Multicenter	4	<18 years old	2 UC 2 CD	IFX	Two patients were asymptomatic And two had a mild disease.
Spencer et al [23]	USA, May 6 2020 to November 5 2020	Retrospective observational cross-sectional, single center	26 patients had positive antibody against SARS-CoV-2	Median (IQR): 14 (11-16)	21 CD 5 UC	17 on biologics, 3 on 5-ASA, 1 on ciprofloxacin/metronidazole, and 5 on no medications	19 patients had records of their disease course, of which 68 % reported mild symptoms. 32% of them were asymptomatic. One CD male patient (male) mentioned MIS-C *there was no relation between symptomatic COVID-19 and biologic use
Sansotta et al [32]	Italy, From February 21 to May 4 2020	Cross-sectional, Multicenter	24 children with IBD and COVID-19 symptoms (one patient was positive for SARS-	Median (range): 15.2 (2-18)	11 UC 1 IBD-U 12 CD	10 on AZA, 7 on 5-ASA, 1 on ADA, 3 on IFX, 1 on CD exclusion diet, 2 on no medications	The most common symptoms were: fever (80%, n=20), cough (28%), fatigue (8%), and vomiting (4%). All patients had a mild course of the disease with no complications.

			CoV-2 PCR)				
Ruan et al [33]	USA	Cohort , single center	13	Pediatric IBD patients	7 CD 3 UC 3 very early onset IBD	5 on biologics, 2 on biologics and immune modulators, 2 on 5-ASA and immune modulator, 1 on biologics and steroids, 1 on immune modulator, 1 on 5-ASA, 1 on steroids and antibiotics	Six patients were asymptomatic. Seven patients had mild symptoms including: fever, fatigue, loss of smell or taste, diarrhea, abdominal pain, and dizziness.
Koletzko et al [34]	Germany, First survey From march 2020 till end of summer Second survey from November 2020 to April 2021	Cohort , multi center	90 Pediatric IBD patients were followed	Median (IQR) 15 (12-17)	44 CD 34 UC 10 IBD-u	10 on only 5-ASA, 42 on any 5-ASA, 37 on any Immune modulator, 60 on any biologics, 8 on any steroids, 74 on immune modulators, steroids, and 5-ASA, 25 on combination therapy, 3 on no medications	From the total 504 patients in the entire cohort, 90 were 6-20 years. While 41.7 % of the entire cohort reported COVID-19 related symptoms, 56.7% of them were 6-20 years. Symptoms included: fever (5.9%), chills (4.9%), infectious rhinitis (16.5%), sore throat (14.8%), dry persistent cough (5.7%), loss of smell or taste (1.6%), muscle pain (12%), headache (26.6%), fatigue (25.3%), dyspnea (3.3%), and diarrhea During the second survey, 4 children and 11 adults (8-63 years) were positive for SARS-CoV-2. None of them were hospitalized due to COVID-19 and disease course was mild and self-limited
Brenner et al [11]	USA, From March to	Cohort, multi-center	209 (from 23 countries)	≤18 years Median (IQR) 16 (14-18)	CD 138 UC 61	2 on biologics only, 4 on 5-ASA only, 3 on steroids and biologics, 3 on 5-ASA and biologics, 2 on steroid,	Hospitalization due to COVID-19: N=14 (females=9) Deaths due to COVID-19: N=0

	October 2020) Data from SECURE-IBD registry and the COVID-19 database of the pediatric IBD Porto group of the European society for pediatric gastroenterology hepatology and nutrition				IBD-U 10	biologics and 5-ASA	Mechanical ventilation needed due to MIS-C and severe disease (on 5-ASA, UC): N=2 Symptoms length: 4-21 days *Between patients hospitalized and outpatients, there were significant differences regarding disease activity, medications (including steroids and 5-ASA), presence of gastrointestinal symptoms, and other comorbidities. TNF antagonist mono therapy (without 6MP/AZA/MTX) was associated with a lower hospitalization likelihood ratio.
Arrigo et al [35]	Italy, From March 9th to May 5th 2020	Cohort, multi-center	6 COVID-19 cases in 2291 pediatric IBD patients	9-18 years	2 CD 4UC	3 on AZA, 1 on ADA, 1 on IFX, 1on 5-ASA +steroids	Except for one 18 years old patient with UC who were hospitalized but without any complications, other patients were outpatient and had a mild disease course. IBD course remained stable during the infection and no drugs were stopped. In the hospitalized patient, disease was in the remission phase, and the patient was on AZA.
Giulia et al [36]	Italy	Case report	A 17 years old CD patients	17 years old	CD	Anti-TNF-α + ADA	Patient was in CD remission. ADA was suspended due to COVID-19 infection. The patient had fever and malaise and recovered completely without

							any complications. (disease duration:2 weeks)
Abdullah et al [37]	Germany	Case report	A 18 years patient with UC	18 years old	UC	5-ASA + IFX	Patient had dry cough, mild dyspnea, abdominal and back pain and was positive for SARS-CoV-2. Patient recovered completely. (disease duration: 2 weeks)
Meredith et al [25]	UK	Case report	A 10 years old UC patient	10 years old	UC	IFX (anti-TNF-α) + 5-ASA	Patient developed pediatric Inflammatory Multisystem Syndrome temporally associated with SARS-CoV-2 Finally patient discharged without any complications and condition resolved completely within 8 weeks.
Dolinger et al [26]	USA	Case report	A 14 years old CD patient	14 years old	CD	NR	MIS-C with complete remission within 4 weeks
Sweeny et al [27]	USA	Case report	A 16 years old patient with CD	16 years old	New-onset CD		MIS-C and new-onset CD Patient recovered completely without any complications [27]

Table abbreviations: NR: not reported; CD: Crohn's disease; UC: Ulcerative colitis; IBD-U: IBD-unknown; IFX: infliximab; 5-ASA: 5-Aminosalicylic acids; AZA: Azathioprine; ADA: Adalimumb; TNF-α: Tumor necrosis factor-alpha.

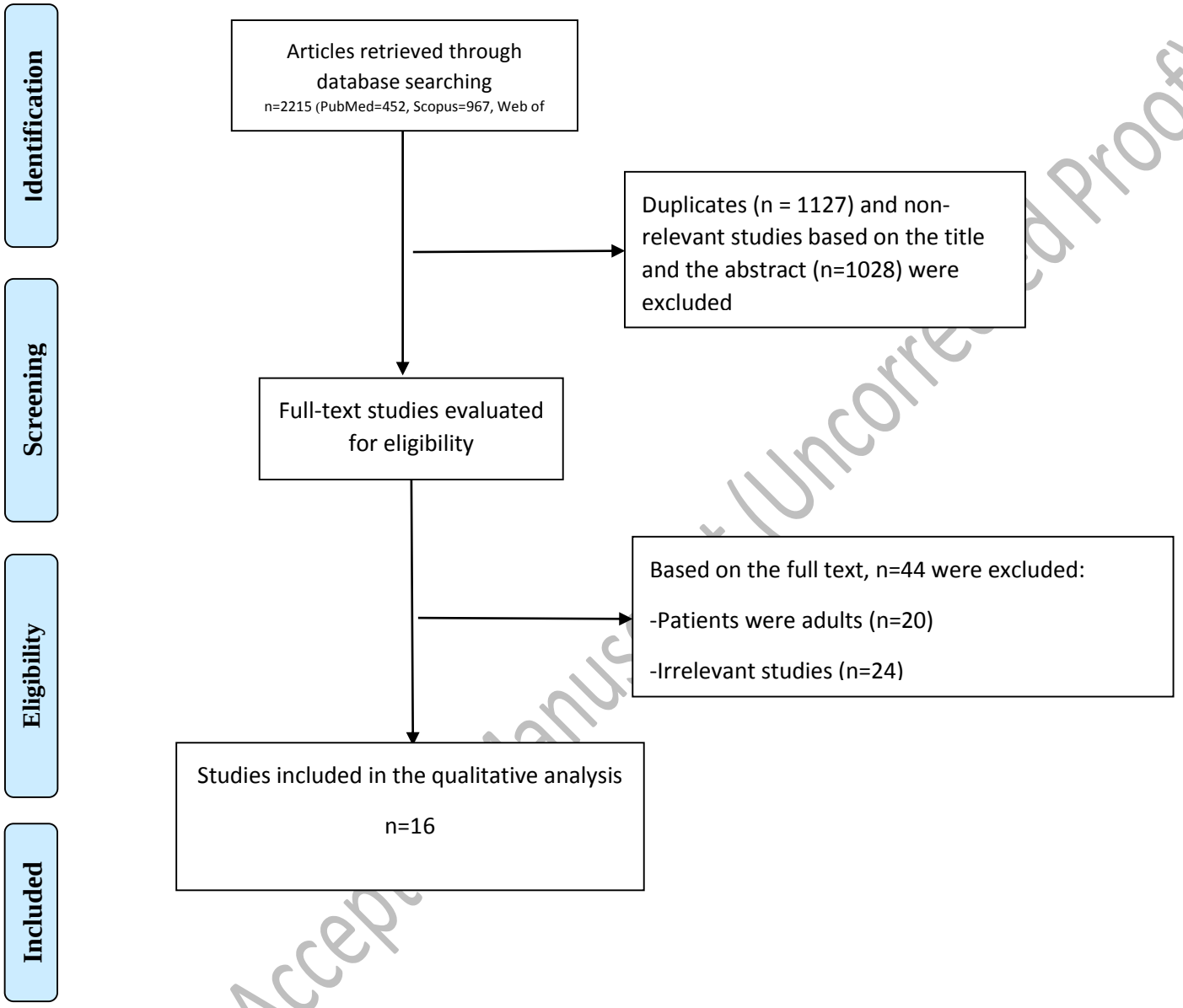

Figure 1. Study selection process