

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	<p>Our study is observational, retrospective-prospective in nature, based on respondents evaluated and treated at the University Clinical Centre Tuzla.</p> <p>The largest gap in the epidemiological picture of IBD relates to developing countries, such as those in eastern Europe. The heterogeneity of results among the few available epidemiological studies concerning eastern Europe is intriguing. Thus, we aimed to perform a follow-up review of IBD epidemiology in the Tuzla Canton of Bosnia-Herzegovina during a 10-year period (2009–2019). Trends in the incidence and prevalence of IBD in Tuzla Canton are similar to eastern European averages. Heterogeneity between the results of studies within geographically close and demographically similar areas was observed.</p>
Introduction		
Background/rationale	2	<p>Our previous studies on the epidemiology of inflammatory bowel disease in Tuzla canton predicted an increase in incidence, which in our study objectifies an increase in the incidence of Crohn's disease but not ulcerative colitis, a trend similar to the epidemiological picture of inflammatory bowel disease in most Western societies. as mentioned above, the heterogeneity of epidemiological parameters within the geographical area of Southeast Europe imposes the need to conduct a study.</p> <p>The results of the research are significant, especially if we take into account the lack of epidemiological studies of this type in the Balkans and Southeast Europe, and which will certainly contribute to the development of the global picture of the epidemiology of inflammatory bowel disease. Such research aims to determine the amount and scope of material and technical resources necessary for planning the diagnosis and treatment of patients with inflammatory bowel disease, which is of great importance for planning the health system in the future. The research will serve as a kind of base from which we gain insight into the prevalence of the disease in our population, but also influence the level of awareness about the disease among the population. Certainly, the research will also serve as an adequate basis for future research on this topic, both locally and globally.</p>
Objectives	3	
Methods		
Study design	4	Study is observational, retrospective-prospective in its nature.
Setting	5	<p>We prospectively evaluated both IBD inpatients and outpatients residing in Tuzla Canton, in northeast Bosnia-Herzegovina, between 1 January 2009 and 31 December 2019, at the Department of Gastroenterology and Hepatology, University Clinical Centre Tuzla. Both adult and paediatric patients were included in the study.</p> <p>We prospectively evaluated both IBD inpatients and outpatients residing in Tuzla Canton, in northeast Bosnia-Herzegovina, between 1 January 2009 and 31 December 2019, at the Department of Gastroenterology and Hepatology, University Clinical Centre Tuzla. Both adult and paediatric patients were included in the study.</p>
Participants	6	<p>Since all our patients had undergone proximal and distal endoscopic evaluations at the hospital endoscopy unit, we used the hospital's database as a primary data source, alongside an additional cross-relational search of the database. The study included only patients with a definitive diagnosis; those with an uncertain diagnosis or without permanent residency in Tuzla Canton were excluded from the study.</p>
Variables	7	<p>Patients were grouped by IBD type, phenotype, age and gender. As ulcerative colitis (UC) is categorized according to endoscopic findings relating to the disease localization, it was divided into proctitis, left-sided colitis and extensive colitis. Crohn's disease (CD) was categorized according to the Montreal classification. Indeterminate colitis (IC) was diagnosed in those patients for whom endoscopic, radiological and pathohistological evaluation could not confirm either of the two main forms of IBD.</p>
Data sources/	8*	the hospital's database as a primary data source, alongside an additional cross-relational search of the database
Bias	9	The statistical level of 95% ($p < 0.05$) was considered significant for all statistical tests.

Study size	10	From 1 January 2009 to 31 December 2019, 651 patients diagnosed with IBD were monitored
Quantitative variables	11	Patients were grouped by IBD type, phenotype, age and gender. As ulcerative colitis (UC) is categorized according to endoscopic findings relating to the disease localization, it was divided into proctitis, left-sided colitis and extensive colitis. Crohn's disease (CD) was categorized according to the Montreal classification. Indeterminate colitis (IC) was diagnosed in those patients for whom endoscopic, radiological and pathohistological evaluation could not confirm either of the two main forms of IBD.
Statistical methods	12	Descriptive statistical parameters were used to determine the basic characteristics of the study population. The year of diagnosis was used to calculate incidence. Incidence and prevalence calculations were performed using census data from the Statistical Office of the Federation of Bosnia and Herzegovina. Ninety-five percent confidence intervals (95% CI) for the incidence rate were calculated assuming a Poisson distribution of cases. Crude annual incidence rates for both genders were calculated based on the number of diagnosed patients and the number of inhabitants, while the average incidence rate during the observed period was calculated based on the number of years of the study. Incidence rates were standardized using standard European age groups for each of the standardized age groups. Morbidity trends from 2009 to 2019 were determined by moving three-year averages with 95% CI and by calculating annual average percentage change. The annual incidence of new cases detected per 100 distal endoscopic procedures and colonoscopies was estimated. Trends in incidence and prevalence were estimated using a linear regression model, where applicable. Prevalence estimates during the observed period were produced based on the total number of detected cases and the number of inhabitants. The statistical level of 95% ($p < 0.05$) was considered significant for all statistical tests.

Continued on next page

Results

Participants	13*	<p>From 1 January 2009 to 31 December 2019, 651 patients diagnosed with IBD were monitored (of whom 334, or 51.3%, were males, and 317, or 48.7%, were females). Of these, 346 (53.1%) had been diagnosed with UC, 292 (44.9%) with CD, and the remaining 13 (2%) with IC. In total, 440 new IBD patients were diagnosed: 240 (54.5%) with UC, 190 (43.2%) with CD and 10 (2.3%) with IC. Among the newly diagnosed, 230 (52.3%) were males, and 210 (47.7%) were females.</p>
Descriptive	14*	<p>The mean age (\pm SD) of all monitored patients was 46.2 ± 16.6 years, with a median of 47 years (25th and 75th percentile: 33 and 58 years). The mean age (\pm SD) of newly diagnosed patients was 45.26 ± 17.38 years, with a median age of 47 years (25th and 75th percentile: 30 and 59 years). The mean age of newly diagnosed patients with UC was 48.16 ± 16.31 years, with a median age of 50 years (25th and 75th percentile: 35 and 60 years), among whom the youngest patient was 15 and the oldest, 81 years old. The mean age of newly diagnosed patients with CD was 41.18 ± 18.01 years, with a median age of 40 years (25th and 75th percentile: 26 and 55 years), among whom the youngest patient was 8 and the oldest, 80 years old. In total, 27 (6.1%) newly diagnosed patients younger than 19 years of age were registered. Ulcerative colitis was diagnosed in five of these (18.5%), while CD was diagnosed in the remaining 22 (81.5%). There were slightly more males among the newly diagnosed patients than women, with a ratio of 52.3% to 47.7%. Males were more likely to suffer from both major forms of IBD. Of the new cases of UC diagnosed, 124 were male (51.7%), and 116 (48.3%) new cases were female (a ratio of 1.07:1). In total, 102 new cases of CD among the male population were registered (53.7%) and 88 (46.3%) new cases among the female population (a ratio of 1.16:1). Among the 10 new cases of IC, the gender distribution was equal.</p>
Outcome data	15*	<p>In general, no statistically significant difference in age was observed between genders at the time of diagnosis. The mean age (\pm SD) among male patients was 45.22 ± 18.01 (8–81) years, while the mean age of female patients was 45.3 ± 16.7 (11–80) years ($t = 0.046$, d.f. = 438, $p = 0.964$). A statistically significant difference in age between genders was observed among the patients diagnosed with UC. Males were older, with a mean age of 50.98 ± 18.12 (17–81) years, compared to females, with a mean age of 45.15 ± 16.05 (15–79) years ($t = 2.805$, d.f. = 238, $p = 0.005$). The same observation was true for IC. Among the patients diagnosed with CD, a statistically significant difference between genders was observed in terms of age at the time of diagnosis, and females were older than males. Thus, the average age of males was 37.53 ± 17.47 (8–76) years, while the average age of females was 45.41 ± 17.79 (11–80) years ($t = 3$, d.f. = 188, $p = 0.002$).</p>
Main results	16	<p>The mean annual crude incidence of IBD during the study was 9.01/100,000 inhabitants (95% CI 8.17–9.85), with an incidence of 9.64/100,000 inhabitants (95% CI 8.5–10.78) within the male population and 8.41/100,000 inhabitants (95% CI 7.16–9.65) within the female population, respectively. The age-standardized mean annual incidence was 8.9/100,000 inhabitants (95% CI 8.07–9.72). In general, the ratio between the incidence of individual forms (UC:CD:IC) of the disease during the study was 54.55:43.18:2.27%. The mean crude annual incidence of UC was 4.91/100,000 inhabitants per year (95% CI 4.29–5.54), with an incidence of 5.16/100,000 (95% CI 4.25–6.07) among males, and 4.68/100,000 (95% CI 3.83–5.53) among females. The age-standardized incidence for the observed period was 4.9/100,000 inhabitants per year (95% CI 4.3–5.54). The average annual incidence during the last five years of the study (2015–2019) was 4.91/100,000 inhabitants (95% CI 4–5.83). The mean crude annual incidence of CD was 3.89/100,000 inhabitants (95% CI 3.34–4.44), with a prevalence of 4.28/100,000 (95% CI 3.54–5.01) for males and 3.52/100,000 (95% CI 2.69–4.35) for females, respectively. The age-standardized incidence for the observed period was 3.76/100,000 inhabitants (95% CI 3.22–4.29). The average annual incidence for the last five years of the study was 4.05/100,000 inhabitants (95% CI 3.22–4.89). The mean crude annual incidence of IC was 0.2/100,000 inhabitants (95% CI 0.08–0.33). The mean crude annual incidence of IBD within the paediatric and adolescent population was 2.49/100,000 inhabitants (95% CI 1.55–3.43), with 0.46/100,000 inhabitants (95% CI 0.06–0.87) for UC and 2.03/100,000 inhabitants (95% CI 1.26–2.79) for CD. Overall, the highest incidence of IBD occurred within three age groups in the male population: patients between 55 and 64 years (14/100,000 inhabitants), between 25 and 34 years (10.8/100,000 inhabitants), and between 45 and 54 years (10.6/100,000 inhabitants).</p>

In general, a higher incidence was recorded both in the younger female age groups and in the older male age groups among patients diagnosed with UC. The highest incidence was recorded among males aged between 55 and 64: 11.2/100,000 inhabitants, and in the age group between 55 and 64 years among the female population, which was 6.9/100,000 inhabitants.

The highest incidence of CD was recorded among age groups within the male population comprising patients between 15 and 34 years: 7/100,000 inhabitants. Among the female population, the disease was most often diagnosed in patients between 45 and 54 years of age, which amounts to 5.4/100,000 inhabitants.

Based on the three-year average incidence rate, which is presented in Figure 2, the incidence of both major forms of IBD occurred fairly uniformly throughout the study. The average annual incidence percentage variation was 0.79% (95% CI 0.60–0.88) or -2.82% (95% CI (-2.67)–(-2.97)) for UC and 6.92% (95% CI 6.64–7.20) for CD. Summarizing the above, we concluded that the UC incidence trend is stable; however, the same cannot be concluded for CD, where the incidence trend is increasing.

During the study period, 24,509 distal endoscopic procedures were performed (an average of 2,228 per year). Figure 3 shows the trend of incidence per 100 colonoscopies. Any subject suspected of having IBD underwent a detailed endoscopic evaluation in the form of a gastroscopy and colonoscopy with – if the disease phenotype allowed – intubation of the terminal ileum. The incidence of IBD was 3.16/100 examinations (95% CI 2.86–3.45) or 1.72/100 examinations (95% CI 1.5–1.94) for UC and 1.36/100 examinations (95% CI 1.17–1.56) for CD.

Data from the last year of the previous study (2006) and the first year of our study (2009) were used to fill in for missing years by averaging the values of these two years.

In the last year of the study, the prevalence of IBD was 147.44/100,000 inhabitants (95% CI 136.1–158.8): 154.48/100,000 inhabitants (95% CI 137.8–171.1) within the male population and 140.73/100,000 inhabitants (95% CI 125.2–156.2) within the female population. The age-standardized prevalence was 147.3/100,000 inhabitants (95% CI 136–158.7).

The types of individual forms of IBD according to the Montreal classification at diagnosis are presented in Tables 1 and 2. In eight patients (0.12%), a change in the previously made diagnosis was recorded.

Discussion

Until recently, scholars have considered IBD to be a disease of developed Western societies. Recent research into the global epidemiological situation confirms a stabilization of the disease's incidence in these areas, with far higher prevalence than in less developed societies, such as in eastern Europe.⁴ The GBD study observed the highest age-standardized prevalence in societies with the highest socio-demographic index (SDI).¹⁵ The study found the highest prevalence in the region of North America (422/100,000 inhabitants) and western Europe, especially the United Kingdom (449.6/100,000 inhabitants). Bosnia-Herzegovina is currently classified as a country with a high middle SDI; according to the study, the values of age-standardized prevalence do not differ significantly compared to regions and countries of a similar standard.

When it comes to neighbouring countries, the GBD study ranked Bosnia-Herzegovina among countries with an estimated age-standardized prevalence of between 100 and 120/100,000 inhabitants, which is still slightly lower than the results of our research. Among the former Yugoslavian republics, neighbouring Croatia and Slovenia lead, with an estimated prevalence of between 180 and 200/100,000 inhabitants.¹⁵ These amounts do not apply to Hungary; since the 1970s, several extensive studies have shown that Hungary hosts the highest incidence of IBD in eastern Europe.^{16, 17}

Our study recorded the highest prevalence among males over the age of 75, which is similar to the GBD study results. The highest prevalence among the female population in our study occurred among slightly younger age groups (44–54 years) than those globally.¹⁵

Paralysis of the healthcare system caused by the war in our country at the end of the last century required a longer recovery, which is certainly reflected in the volume of diagnostic tests and the results of scientific research. When compared with incidence rates from 1995–2006,^{10, 11} a stable trend can be seen in IBD incidence over the study's 10-year period. According to a study by Salkić et al. of the period between 1995 and 2006,¹¹ an average of 397 colonoscopies per year were performed, which is 3.2 times fewer than the average number of diagnostic procedures performed annually during our study. The frequency of diagnosing UC per 100 colonoscopies performed during the previous study was 3.2 times higher than now; CD was diagnosed 2.2 times more often according to the given number of procedures performed.

The incidence rate among developing countries and regions such as eastern Europe can be seen to have significantly increased when compared to previous reports.⁴ Earlier studies from developing regions have shown an increase in the incidence of CD compared to UC,¹⁸ which was (based on the average percentile annual variation) also found to be the case in our study. Conducted in 2010 among 22 European countries, the ECCO-EpiCom cohort study³ compared epidemiological differences between diseases in both western and eastern Europe, presenting the clearest and most concise epidemiological picture of IBD in eastern Europe. It showed that the annual crude incidence of IBD in eastern Europe was half that in western Europe, with an average of 8.1/100,000 inhabitants. The incidence of UC was 4.6/100,000 inhabitants in 2010, while the incidence of CD was 3.3/100,000 inhabitants, which are fairly uniform results, compared to the results presented in our study.

When it comes to the area of southeastern Europe, the epidemiological situation is – except for Greece, Croatia and Bosnia-Herzegovina⁵⁻¹¹ – poorly researched or unknown. Epidemiological studies among the paediatric population have been performed only in Slovenia.⁸ The incidence calculated during our study period is somewhat lower compared to this region. A 10-year study (2000–2010) of both major forms of IBD in Zadar county has found a trend of increasing incidence, similar to previous studies from the Tuzla Canton.^{5, 6, 10, 11} The other recent Croatian study (conducted in Split-Dalmatia county), on the other hand, observed a decline in UC incidence and stabilization of CD incidence.⁷ With the results of our study showing stabilization of UC incidence alongside an increasing trend in CD incidence, we came to the conclusion that there are significant epidemiological differences within geographically close and demographically similar areas.

The population of Tuzla Canton is generally older than it was during the previous studies, which ultimately affects the results in terms of the epidemiological situation. Although the canton's population is still younger than the average European population, the subjects involved in the study are generally older than the patients analysed in the ECCO-EpiCom study.³ Despalatović et al. reported the highest incidence of UC within the 18–30 and 51–60 age groups.⁷ Their results are similar to ours and the results from a previous study from Tuzla Canton.¹¹ One can consider age structure to be a bimodal distribution of incidence. Similarities in the findings of these two studies can also be seen in relation to CD incidence, with the results showing a higher incidence of CD among the younger population.^{7, 10}

When it comes to the paediatric and adolescent population, our study recorded a significantly lower incidence of IBD than research conducted in Croatia, Slovenia and most of Europe,^{5, 8, 19} probably due to a relatively small number of colonoscopies performed in the paediatric and adolescent population in our centre.

The main forms of IBD are characterized by a relapsing and remitting course, with a tendency to change localization and phenotype over time, although the results among studies are inconsistent.²⁰⁻²³ The trend of localization change over time is more pronounced in UC than in CD. We registered a change in the localization of CD in 3.53% of patients during our study, which is significantly lower than the studies of Louis et al. and Lo et al.^{20, 21} Phenotype change was recorded in 16.47% of patients, which is close to the results conducted by Lo et al. but drastically lower than Louis et al.'s study, which observed a change in phenotype in 45.9% of patients. Considering the new modalities of CD treatment – primarily in terms of the introduction of anti-TNF therapy – the reduction in phenotype change frequency is unsurprising. Modification of the earlier diagnosis was observed far less frequently than in the IBSEN study,²⁴ in which the diagnosis of 9% of patients changed over time.

In comparison with an earlier study by Salkić et al., we observed a significantly higher incidence of proctitis at the expense of left-sided colitis. Given the significantly greater number of endoscopic procedures, our observation might have resulted from earlier detection of the disease. Interestingly, both studies detected the same incidence of extensive colitis, which was diagnosed in 16.3% of patients. The results of our study are close to the eastern European average, with a higher incidence of left-sided colitis but a lower incidence of proctitis and extensive colitis. The localization and phenotype of CD do not differ significantly between eastern and western Europe. Except for a somewhat more frequent incidence of colic and stenotic types of CD, the results of our study do not differ significantly from the (eastern) European average. The results of our study showed a higher incidence of the ileocolic form among the younger population, while the colic form was found to affect the older population more frequently (results which are analogous to previous studies).^{25, 26}

Conducted in a clinical centre, this was a hospital study and, as such, has its limitations. The University Clinical Centre Tuzla was the only institution capable of providing a comprehensive evaluation of patients with IBD in Tuzla Canton. Additionally, since all patients undergoing any form of IBD treatment must have a written recommendation for treatment in order to obtain reimbursement for the costs, any IBD patient from Tuzla Canton must eventually be evaluated in our centre. We therefore feel safe in our assumption that despite it being single-hospital-based, our study is a confident representation of the epidemiological status of IBD in our region.

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Interpretation 20 Given above

The design of our study was conceived according to a follow-up of patients over a 10-year period. Given the lack of an adequate information system from 2006 to 2009, 2009 was accepted as satisfactory for our study's beginning point. Our study is retrospective-prospective in nature, based on respondents evaluated and treated at the University Clinical Centre Tuzla, which is the only clinical centre in the region and is a meeting place for all IBD-treated patients in the region and beyond. Given that the largest gap in the epidemiological picture of IBD relates to regions and developing countries²⁷ that include Bosnia-Herzegovina, we believe that our study (along with earlier reports^{10, 11}) can serve as a template for understanding the epidemiological picture in developing countries. In future, a multicentre study of the territory of Bosnia-Herzegovina and the countries of southeastern Europe would greatly help us to understand this issue.

Generalisability 21

Other information

Funding 22 None to declare

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.