Digestive and Liver Disease 51 (2019) 1270–1274

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Alimentary Tract

Prevalence and incidence of inflammatory bowel disease in two Italian islands, Sicily and Sardinia: A report based on health information systems

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ARTICLE INFO

Article history:
Received 4 February 2019
Accepted 7 May 2019
Available online 5 June 2019

Keywords:
Crohn's disease
Epidemiology
Health information systems
Incidence
Prevalence
Ulcerative colitis

ABSTRACT

Background: Few epidemiological data about inflammatory bowel disease (IBD) in Italy are available.
Aims: To estimate IBD prevalence and incidence in two Italian regions – Sicily and Sardinia – using regional health information systems.
Methods: Data from hospital discharges and disease-specific payment exemptions register were retrieved and underwent record-linkage procedures. Standardized prevalence and incidence were calculated as rates per 100,000 inhabitants.
Results: In Sicily, during the year 2013, the overall IBD incidence rate was 27 per 100,000 inhabitants, while the incidence rate of Crohn's disease (CD) was 16 for males and 13 for females, and the incidence of ulcerative colitis (UC) was 15 and 11 for males and females, respectively. At the date of December 31st, 2013, the standardized prevalence rate of IBD was estimated at 300 cases per 100,000 inhabitants. In Sardinia, during the period 2008–2010, the average IBD incidence rate per 100,000 was 15, with an incidence rate of 5 per 100,000 for CD, and 10 per 100,000 for UC, while the standardized prevalence rate of IBD was estimated at 187 cases per 100,000 inhabitants.
Conclusions: The particularly high incidence of CD in Sicily, and the marked difference of IBD occurrence between the two islands deserve future investigations.
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1. Introduction

Inflammatory bowel diseases (IBD), a term encompassing both Crohn's disease (CD) and ulcerative colitis (UC), are chronic, relapsing, inflammatory disorders of the gastrointestinal tract affecting mainly the young and middle-aged [1,2]. The management of these diseases is arduous, as inflammation often persists even in the absence of gastrointestinal symptoms [3], and this may lead to progressive bowel damage and complications requiring hospitalization or surgery. At the same time, impaired bowel function ultimately leads to impaired quality of life and disability with a considerable burden not only for patients [4], but also for the healthcare systems, especially if we consider the chronicity of the condition and the fact that life expectancy is not significantly modified by such diseases [5]. As a consequence, epidemiological data on IBD are crucial to estimating their burden on the healthcare systems and, ultimately, to plan a proper resource allocation [6].

The incidence and prevalence of IBD are increasing worldwide: from a few cases observed at the beginning of the last century to the current estimates of 2.4 million patients in Europe [7–10]. Nonetheless, epidemiological data about IBD in Italy are limited, mostly because a national register – ideally, the most precise tool to assess incidence and prevalence of any disease – has never been implemented, and most of the available studies are quite outdated [11]. A new European epidemiological study conducted among 17

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https://doi.org/10.1016/j.dld.2019.05.017
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countries estimated an overall incidence of 10.5 per 100,000 inhabitants per year in Italy — a low to medium rate of new IBD diagnoses compared to that reported for other European countries [9]. Recent Italian studies highlighted higher rates of IBD occurrence among the Italian territory, including a report from the Lazio region [12], a population-based IBD registry in the area of Forlì, northeast Italy [13], and an epidemiological study performed in the Republic of San Marino [14]. Anyway, it should be noted that a comparison between these studies and the aforementioned European survey may be not affordable, since sources of data and the methodologies employed were different.

On these premises, the aim of this study was to estimate IBD prevalence and incidence in two Italian regions – Sardinia and Sicily – using health information systems. Additionally, we assessed the active mobility (i.e. the health services provided in the territory of competence to patients incoming from other regions) and passive mobility (i.e. the health services provided to patients moving outside their territory of competence) among the two regions.

2. Materials and methods

2.1. Data sources (administrative data)

Data for this study were obtained from administrative databases of Sicily and Sardinia. Both regions (population of approximately 5,100,000 and 1,600,000 inhabitants, respectively) are included in the Italian National Health System (INHS), which provides universal health insurance for residents, including free-of-charge coverage for general practitioner assistance and hospital services. The INHS also provides free drugs and specialist cares to all patients who are suffering from chronic diseases whose diagnosis was certified by a specialist and recorded in the disease-specific payment exemptions register (DPER).

The temporal span considered for the identification of IBD patients goes from January 1st, 2004 to December 31st, 2013 for Sicily, and from January 1st, 2001 to December 31st, 2010 for Sardinia. More in details, our analysis used record-linkage procedures of the following Sicilian and Sardinian administrative databases:

- Hospital Information System (HIS) in the decade 2001–2010 for Sardinia and 2004–2013 for Sicily. The identification of IBD patients was performed by extracting the ICD9-CM diagnosis codes of 555. xx (CD), 556. xx (UC) as the principal or secondary diagnosis in hospital discharge cards.
- DPER, updated on December 31st, 2015. IBD patients were selected with the following exemption code: 009. Specific code for CD was 009.555, and specific code for UC was 009.556, but they were very rarely indicated (only the code 009 was generally reported), so the cumulative IBD prevalence has been finally calculated.
- Regional patients registry with integration of cancellations for death or transfer.

All subjects identified by the HIS or DPER before January 1st, 2003 (for Sicily) and January 1st, 2001 (for Sardinia) were excluded, as well as those identified by a single hospitalization with a 555.xx or 556.xx code reported only as a secondary diagnosis, with no evidence in the discharge letter of an IBD-related diagnosis or any procedure code associated with IBD (see Supplementary file 1).

2.2. Case definition criteria

2.2.1. Prevalent cases

Prevalence rates per 100,000 were calculated using as numerator the number of IBD patients that were alive at the prevalence day (December 31st, 2013 for Sicily, and December 31st, 2010 for Sardinia), and identified from the HIS between January 1st, 2001 and December 31st, 2010 for Sardinia, and from January 1st, 2004 to December 31st, 2013 for Sicily, or from the DPER in the same period of time. The populations of residents in the two regions which were alive on January 1st, 2011 in Sardinia, and January 1st, 2014 in Sicily were used as denominator (source: ISTAT data, 2011). Rates were standardized by age and gender (reference: European standard population). If a same subject was initially reported among the prevalent cases for both CD and UC, the last temporal data was taken into consideration, so that any patient was included only among UC or CD cases and never among both diseases.

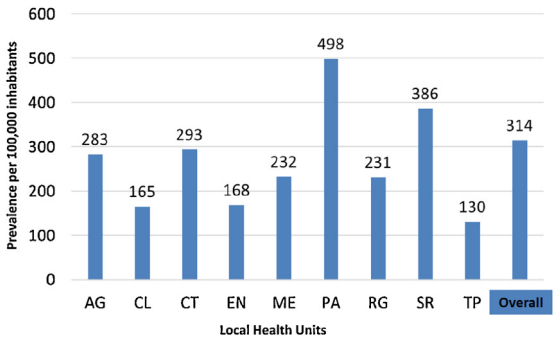

Fig. 1. Prevalence of IBD-specific exemptions in Sicily across the Local Health Units (AG: Agrigento; CL: Caltanissetta; CT: Catania; EN: Enna; ME: Messina; PA: Palermo; RG: Ragusa; SR: Siracusa; TP: Trapani).

2.2.2. Incident cases

Incident cases for Sicily were defined as the new IBD cases captured by the HIS or the DPER between January 1st and December 31st, 2013. For Sardinia, incidence was estimated only from HIS data, as a record for the historicizing of the exemptions was lacking during the time frame taken into account. In particular, the incidence rate was obtained making an average of the incident cases observed over the last available three-year period (2008–2010). Therefore, the estimated incidence in Sicily is comprehensive of hospital and DPER data, while the incidence of IBD in Sardinia is based on hospital data only. Rates were standardized by age and gender (reference: European standard population).

3. Results

3.1. Disease-specific exemptions

A total of 16,014 disease-specific exemptions in Sicily and 3230 in Sardinia were identified through the respective regional DPERs at the date of December 31st, 2015. The corresponding prevalence per 100,000 inhabitants was 314 cases in Sicily and 193 cases in Sardinia (national average: 267 cases per 100,000 inhabitants — data from the epidemiological observatories of the Regional Health Departments). Figs. 1 and 2 show the prevalence of the disease-specific exemptions across the Local Health Units in Sicily and Sardinia, respectively.

3.2. Hospitalization rates

In Sicily, 52,097 hospitalizations with a diagnosis of IBD were recorded between 2004 and 2013. Of these, 35,906 (68.9%) reported CD or UC as primary diagnosis (Table 1). In Sardinia, there were 11,261 admissions with a diagnosis of IBD between 2001 and 2010, and 7.248 (64.3%) of these reported CD or UC as the primary diagnosis (Table 2). Considering only the hospitalizations with a primary

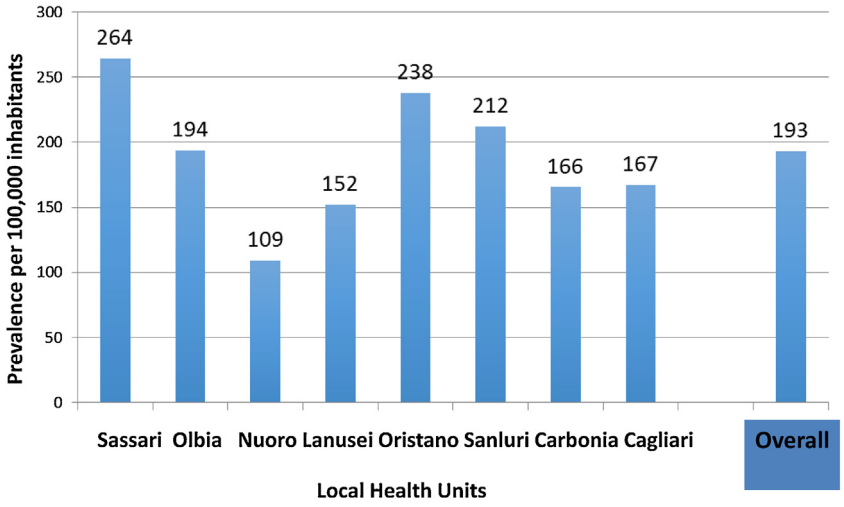

Fig. 2. Prevalence of IBD-specific exemptions in Sardinia across the Local Health Units.

Table 1
Distribution of hospitalizations in Sicily according to primary or secondary diagnosis of IBD.

Diagnosis	Rates	
	n	%
CD primary diagnosis	18,039	34.6
UC primary diagnosis	17,867	34.3
CD secondary diagnosis	6987	13.4
UC secondary diagnosis	9204	17.7
Overall	52,097	100.0

Table 2
Distribution of hospitalizations in Sardinia according to primary or secondary diagnosis of IBD.

Diagnosis	Rates	
	n	%
CD primary diagnosis	3201	28.4
UC primary diagnosis	4047	35.9
CD secondary diagnosis	1572	14.0
UC secondary diagnosis	2441	21.7
Overall	11,261	100.0

diagnosis of IBD, the overall rate of hospitalization for IBD in Sicily was 97 admissions per 100,000 for males, and 73 admissions per 100,000 for women. The sub-analysis for CD identified 49 admissions per 100,000 for males, and 37 admissions per 100,000 for females, while the sub-analysis for UC showed 48 admissions per 100,000 for males, and 36 admissions per 100,000 for females. Considering only the hospitalizations with a primary diagnosis of IBD, the overall rate of hospitalization for IBD in Sardinia amounted to 45 admissions per 100,000 inhabitants: 19 admissions per 100,000 inhabitants for CD and 26 admissions per 100,000 inhabitants for UC. The percentage of hospitalizations identified for residents was 98.7% and 96.0% in Sardinia and Sicily, respectively, with a slightly higher percentage for females in Sardinia (54.0%), and for males in Sicily (55.1%), irrespective of residence status. In both regions, the majority of hospitalizations (approximately 70%) involved patients in the age group between 18 and 64 years. Finally, considering only admissions with IBD codes as primary diagnosis, patients received medical treatments in more than 90% of cases (92.7% in Sicily and 94.3% in Sardinia), while surgical procedures were provided in only 3.6% of cases in Sicily and 3.7% of cases in Sardinia.

Table 3
Standardized (reference: European standard population) incidence and prevalence rates (per 100,000 inhabitants) of IBD in Sicily.

Diagnosis	Incidence[a]	Prevalence[b]
IBD (overall)	27	300
Males	31	336
Females	24	268
CD		
Males	16	178
Females	13	142
UC		
Males	15	158
Females	11	126

Abbreviations: CD: Crohn's disease; IBD: inflammatory bowel disease; UC: ulcerative colitis.
[a] Incidence rate of the year 2013.
[b] Prevalence rate at the date of 31st December 2013.

3.3. Active and passive mobility

Out of 35,906 hospitalizations in Sicily with a primary diagnosis of IBD between 2004 and 2013, 1713 (4.8%) were performed as active mobility, while in Sardinia 73 out of 7248 (1.0%) hospitalizations with a primary diagnosis of IBD were performed as active mobility between 2001 and 2010. In contrast, the rate of admissions for passive mobility was about 9% for both regions.

3.4. Prevalence and incidence of IBD

At the date of 31st December 2013, the standardized prevalence rate for Sicily was estimated to be 300 cases per 100,000 inhabitants: 336 cases per 100,000 (95% CI 329–344) for males, and 268 per 100,000 (95% CI 262–275) for females. Furthermore, the prevalence rate of CD was 178 cases per 100,000 (95% CI 173–184) for males, and 142 cases per 100,000 (95% CI 138–147) for females. The prevalence rate of UC was lower both in males (158 per 100,000; 95% CI 153–163) and in females (126 per 100,000; 95% CI 121–130) (Table 3). In Sicily, during the year 2013, the overall incidence of IBD was 27 per 100,000 inhabitants, 31 for males and 24 for females. The incidence rate of CD per 100,000 was 16 for males and 13 for females, while the incidence rate of UC per 100,000 was 15 and 11 for males and females, respectively.

In Sardinia, at the date of December 31st, 2010, the standardized prevalence rate was estimated to be 187 cases per 100,000 inhabitants, with a prevalence rate of 63 cases per 100,000 inhabitants for CD, and 124 cases per 100,000 inhabitants for UC (Table 4). During

Table 4
Standardized (reference: European standard population) incidence and prevalence rates (per 100,000 inhabitants) of IBD in Sardinia.

Diagnosis	Incidence[a]	Prevalence[b]
IBD (overall)	15	187
CD	5	63
UC	10	124

Abbreviations: CD: Crohn's disease; IBD: inflammatory bowel disease; UC: ulcerative colitis.

[a] Average incidence rate of years 2008 incidence rate of years 2008–2010 obtained by hospital data only.

[b] Prevalence rate at the date of 31st December 2010.

the period 2008–2010, the average IBD incidence rate per 100,000 inhabitants was 15 (95% CI: 13–18), with an incidence rate of 5 per 100,000 (95% CI: 4–6) for CD, and 10 per 100,000 (95% CI: 9–12) for UC.

4. Discussion

This study contributes to the knowledge of the epidemiology of IBD in Italy. In particular, it provides new robust insights into IBD prevalence and incidence in two Italian Regions, Sardinia and Sicily, via the extraction of data based on Health Information Systems. Overall, our recent epidemiological data showed high incidence and prevalence rates of IBD in these two regions. Even if our study was not designed to detect epidemiological trends of these diseases, these findings suggest that their occurrence could be on the rise over the last years [11].

About the mechanisms underlying the high incidences reported in our study, the use of administrative databases is certainly a plausible explanation, since this method allows the capture of an adequate number of cases. Not by chance, the incidence reported for Sicily is not very different from that recorded in the studies conducted in the region Lazio [12] and in the Forlì area [13] — studies that employed methods similar to ours. In any case, this high incidence seems to be real and not secondary to other causes such as – for example – an increased diagnostic capability, as shown for example by a recent Italian work by Cantoro et al. [15] which showed how the average diagnostic delay for IBD over the last 60 years has remained unchanged. Interestingly, in our study the occurrence rate for CD in Sicily was superior to that of UC — a finding in countertendency compared with most of the studies. However, it should be noted that this high occurrence of CD in Sicily had been already reported by a previous epidemiological study conducted in a small township in Sicily (Casteltermini) from 1979 to 2002 [16], and by a previous study conducted in the province of Palermo, where the hospital-based incidence of CD for the year 1987–1989 was 2.7 per 100,000, a rate quite similar to that observed in Northern Europe at those times [17–19].

Another relevant point arising from our data lies in the marked difference of occurrence of IBD between Sicily and Sardinia. Indeed, even if epidemiological data of Sardinia are overall less accurate than those collected for Sicily, the occurrence of both CD and UC are clearly inferior to that reported for Sicily, and this is confirmed even if we compare only the hospitalization rates of the two regions, as the incidence of IBD in Sardinia is hospital-based only. There is not an explanation for this point. We could speculate that Sardinia – a region geographically more isolated then Sicily – has selected a population less prone to develop IBD due to different genetic or environmental factors. Anyway, even if the rates of hospitalization for Sicily were double as compared with those reported for Sardinia, the percentage of IBD as primary diagnosis was quite similar between the two regions. In this line, we chose to focus on the main diagnoses of IBD because we believe that they are the one really associated with medical assistance related to IBD. Conversely, finding such codes as secondary diagnoses could be due to simple signaling of IBD as comorbidity, whereas the hospitalization was motivated by other nosological causes and/or traumatic events. Therefore, focusing only on the main diagnoses helps us understand the real cost and weight of the disease.

Other interesting findings were obtained by the analysis of active and passive mobility — data that have been rarely described in other IBD works. However, we wanted to consider also this standpoint in order to get an idea on how much the regional health systems were able to guarantee specific cares to resident patients – particularly considering that these are two islands – and how they could be attractive to non-residents. It is clear that, for geographical reasons, we could not expect high active mobility, anyway the rate of passive mobility was not high (9%) — this probably indicating an acceptable healthcare capacity for both regions.

To date, this work is one of the first studies using administrative databases to calculate the incidence and prevalence rates of IBD. In this line, the use of administrative databases has been proven to be effective to estimate the prevalence and incidence of other common chronic diseases such as diabetes or heart disease [20]. Our methodology of data search was based on the retrospective combination of hospitalization rates with the DPER in a decade (2001–2010 in Sardinia, 2004–2013 for Sicily). This modality of data analysis – although overall reliable – has also some limitations. In particular, the number of patients extracted by the DPER is probably an underestimate, because a proportion of IBD patients may have obtained the exemption not for the diagnosis of IBD, but for other diseases, age, disability, or economic status. As a consequence, IBD patients that have never been hospitalized during our temporal frame of observation and that were not entered into the specific DPER of IBD may have been missed. Obviously, the ideal way to collect reliable epidemiological data is a national registry for IBD — a tool currently not available in Italy, which could be helpful to validate our estimates. In this line, we should mention a recent population-based registry designed to calculate the incidence and prevalence of IBD in the area of Forlì (north-eastern Italy) from 1993 to 2013 [13], whose estimates for UC were overall similar to ours, while we observed higher rates for CD. Another limitation lies in the lack of other research sources which could intercept more IBD patients, particularly prescription of drugs specifically used in IBD (for instance, vedolizumab or mesalamine), or other IBD-related healthcare utilization, such as archives of therapeutic plans. Furthermore, epidemiological data of Sardinia are overall less accurate than those collected for Sicily, and the incidence of IBD in Sardinia is a hospital-based only data, thus it would be not appropriate to perform a direct comparison between the two regions, as the modality of data collection was quite different.

In conclusion, this study provides knowledge on the epidemiology of IBD in two Italian regions using administrative databases as sources. The prevalence and incidence data of our study were overall higher than those established in other epidemiological studies. Although limited by the risk of underestimating the prevalence, and waiting for a national IBD registry, analysis of administrative databases should be considered an interesting source of data to measure the health and social burden of IBD, allowing for periodic updates.

Conflict of interests

Fabio Salvatore Macaluso served as advisory board member for MSD and Biogen, and received lecture grants from MSD, AbbVie, Takeda Pharmaceuticals and Zambon. Ambrogio Orlando served as advisory board member for AbbVie, MSD, Takeda Pharmaceuticals, Janssen, Pfizer, and received lecture grants from AbbVie, MSD, Sofar, Chiesi, and Takeda Pharmaceuticals. Other authors: nothing to disclose.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.dld.2019.05.017.

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