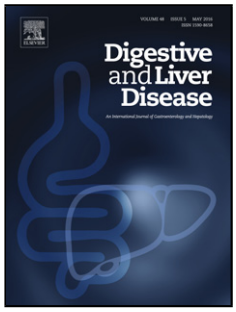


Title: Economic burden of diverticular disease: an observational analysis based on real world data from an italian region

Authors: F.S. Mennini, P. Sciattella, A. Marcellusi, B. Toraldo, M. Koch

PII: S1590-8658(17)30901-5
DOI: http://dx.doi.org/doi:10.1016/j.dld.2017.05.024
Reference: YDLD 3471

To appear in: *Digestive and Liver Disease*

Received date: 8-2-2017
Revised date: 18-5-2017
Accepted date: 30-5-2017

Please cite this article as: Mennini FS, Sciattella P, Marcellusi A, Toraldo B, Koch M.Economic burden of diverticular disease: an observational analysis based on real world data from an italian region.*Digestive and Liver Disease* http://dx.doi.org/10.1016/j.dld.2017.05.024

ECONOMIC BURDEN OF DIVERTICULAR DISEASE: AN OBSERVATIONAL ANALYSIS BASED ON REAL WORLD DATA FROM AN ITALIAN REGION

Mennini FS[1, 2], Sciattella P[1], Marcellusi A[3], Toraldo B[4], Koch M[5]

[1] Economic Evaluation and HTA (CEIS- EEHTA) - IGF Department, Faculty of Economics, University of Rome "Tor Vergata", Italy.

[2] Institute for Leadership and Management in Health - Kingston University London, London, UK

[3] National Research Council (CNR), Institute for Research on Population and Social Policies (IRPPS), Rome, Italy

[4] Alfa Wassermann Italia

[5] Complex Unit of Gastroenterology and Hepatology, San Filippo Neri Hospital, Rome

Corresponding author: Maurizio Koch

Institute: San Filippo Neri Hospital, Complex Unit of Gastroenterology and Hepatology Rome

Address: Via G. Martinotti, 20

Postal code: 00135 Rome - Italy

Tel: +39336539640

E-mail: kochmaurizio@gmail.com

Abstract

Introduction: Diverticular disease (DD), a herniation of the colonic mucosa through the muscle layer, covers a wide variety of conditions associated with the presence of diverticula in the colon. The most serious form is an acute episode of diverticulitis, which can lead to hospitalization and surgery with various types of consequences. The main aim of this study is to evaluate the

economic burden of hospitalizations arising from acute episodes of diverticulitis using data from the administrative databases used in the Marche region in Italy and, as a secondary objective of this real-world data analysis, to study patient outcome variables following initial hospitalization for diverticulitis.

Method: A deterministic linkage was performed at individual user level between the different administrative sources of the Marche region through anonymous ID number for a period of analysis between 1 January 2008 and 31 December 2014. We enrolled all patients with at least one hospitalization for “diverticulitis of the colon without mention of haemorrhage” (ICD-9-CM code 562.11) or “diverticulitis of the colon with haemorrhage” (ICD-9-CM code 562.13) as primary or secondary diagnosis. For each patient we assessed the cost of hospitalization, of medicines and of specialist services considering a time-scale of one year or cohort analysis 365 days after first admission.

Results: The total number of residents in the Marche region who had at least one hospitalization for diverticulitis in the period 2008-2014 was 2,987 (427 patients a year, corresponding to about 35 patients per 100,000 adult residents); the total number of admissions was 3,453 (just over 490 a year). The direct healthcare costs incurred by the Marche region for episodes of diverticulitis in 2008-2014 amounted to approximately €11.4 million (€1.6 million a year), of which €10.9 million (95.5%) for the hospitalizations, € 246,000 (2.1%) for pharmaceutical treatment and € 270,000 (2.4%) for specialist outpatient services. The average annual cost per patient was €3,826, of which €3,653 was for hospitalization, while pharmaceutical expenditure and specialist services accounted for €83 and €90, respectively. The cohort of patients undergoing a first admission for diverticulitis between 2010 and 2013 was made up of 1,729 people (54.4% women, mean age 68.9 years), of whom 1,500 (86.8%) did not undergo surgery while in hospital. Hospital mortality, recorded only for the over-65 age class, averaged 1.2%; for patients not receiving surgery during the initial hospitalization it was 0.5%, reaching 5.2% in patients undergoing surgery. The percentage of patients with one or more readmissions for diverticulitis within a year of the first was on average 7.8% and in 48% of cases this resulted in surgery.

Conclusions: Our study is the first analysis in Italy to use real-world data to measure the financial impact of Diverticular Disease. Assuming that the diagnostic and therapeutic behaviour identified in the Marche region could be representative of the situation nationwide, the estimated annual number of hospitalizations in Italy for acute episodes of diverticulitis is 19,000. The total amount of economic resources needed to treat patients suffering from acute episodes of diverticulitis is estimated at €63.5 million a year.

Introduction

Diverticular Disease (DD) covers a wide variety of conditions associated with the presence of diverticula in the colon (herniation of the colonic mucosa through the muscle layer). Of these,

the most serious condition is an acute episode of diverticulitis that, depending on its severity, can lead to hospitalization, surgery and may even result in the patient's death.

Traditionally, three factors are associated with the pathogenesis of DD: age, diet and bowel motility. In recent years, this list has expanded to six with the addition of genetic factors, intestinal innervation and microbiota.

The incidence of diverticula is correlated with increasing age: Peery et al.'s study shows 16% of subjects are under the age of 40 rising to over 63% among the over 70s (1).

Alterations of the connective tissue, such as greater cross-linking of collagen fibrils or altered expression of matrix metalloproteinases, may help to increase the onset of diverticula with age (2).

DD has also been correlated with Western lifestyle and lack of physical activity (3).

Focus on DD is increasing exponentially, as reflected also in the number of publications devoted to it.

Most diverticulosis cases remain asymptomatic for life: only about 4% of patients with an endoscopic diagnosis of diverticulosis develop diverticulitis (4). Of these patients, around 15-30% undergo a relapse and about 15% develop complications. Admissions for diagnosis code diverticulitis without haemorrhage (562.11) are very much on the increase: in the USA alone, the increase in the admissions rate was +21% compared to 2003, with a hospital mortality rate of 0.5% (5).

Over the years, different ways of reducing the risk of occurrence and recurrence of diverticulitis have been explored, with the most promising ones including the use of non-absorbable antibiotics. Prevention of acute episodes of diverticulitis as well as improvements to DD patient management should reduce the number of hospitalizations and, consequently, the direct costs arising from DD-related complications. An evidence-based review on the natural history of DD and the role of treatment has just been published (6).

In the United States, according to data in the literature, annual costs of diverticular disease are between 2.2 and 2.6 billion dollars, making it the fifth most costly gastrointestinal disorder in terms of direct and indirect costs (5).

Despite the significant epidemiological burden, in Italy there are currently no financial evaluations available on a representative sample of the population regarding the costs of diverticular disease and its complications.

The aim of this study is to evaluate the financial impact generated by complications of Diverticular Disease using real-world data from the Marche region's administrative database and to quantify the patient outcome variables in the period following the index admission for diverticulitis.

Data source and methods

Data source

Admissions for diverticulitis were selected from the Marche region's Hospital Information System, which records all admissions to accredited public and private hospitals in the region. The discharge records include the patient's demographic (gender, age, education, residence) and clinical information, the diagnosis and the main and secondary procedures (5 fields) as set out in the International Classification of Diseases (ICD-9-CM).

Drug prescriptions were extracted from the Marche Region's Pharmaceutical Prescription Information System, containing all prescriptions sent to municipal and private pharmacies within the region and reimbursed by the Italian National Health Service.

Specialist outpatient care was selected from the Marche Region's Specialist Service Information System, containing all outpatient appointments for diagnostic and therapeutic services in the region.

A deterministic linkage was performed at individual user level between the different administrative sources through anonymous ID number for a period of analysis between 1 January 2008 and 31 December 2014.

Methods

Prevalent cases of diverticulitis per year were identified by selecting all persons residing in the Marche region with at least one admission for "diverticulitis of the colon without mention of haemorrhage" (ICD-9-CM code 562.11) or "diverticulitis of the colon with haemorrhage" (ICD-9-CM code 562.13) as primary diagnosis, or else as secondary diagnosis where, however, the main diagnosis was one of the diverticulitis-related diagnoses (see Annex).

For these subjects, we identified all prescriptions of intestinal antibiotics (ATC A07AA), intestinal anti-inflammatory drugs (ATC A07EC) and metronidazole (ATC J01XD01; P01AB01) as well as all specialist outpatient services (see Annex) correlated with the disease which took place during the calendar year of admission.

The annual cost of diverticulitis was estimated by assigning a value to each admission based on the Marche region's tariff for hospital services in force during the year of discharge, the cost of drugs was estimated using the regional reimbursement price current at the time of dispensing and outpatient specialist care was calculated using the current regional price in the year of provision of the service.

Longitudinal analysis was performed by identifying the cohort of patients admitted for diverticulitis in the three-year period from 2010-2013 with no prior admissions for diverticulitis in the previous two years. If a patient had more than one admission during these three years, their first admission was selected as the index admission (Figure 1).

Subjects were stratified by surgical procedure (large intestine, small intestine or rectal resection) during the index admission; the procedure was identified using the DRG attributed on discharge (see supplementary table s2).

Only subjects of legal age living in the Marche region at the time of index admission were considered.

All enrolled subjects, once discharged from the index admission, were followed for one year, and all subjects requiring re-admission and/or surgery for diverticulitis during follow-up have been identified. Annual costs were thus estimated taking into account the cost of the index admission and any possible subsequent admissions occurring during the year of observation.

Results

The total number of subjects resident in the Marche region who had at least one hospitalization for diverticulitis in the period 2008-2014 was 2,987 (427 patients a year, corresponding to 35 per 100,000 adult residents) whereas the total number of admissions was 3,453 (just over 490 a year).

The number of hospitals of Marche region from which data have been collected is 44. The number of admissions for each hospital varied from 1 to 218.

On average, 75% of patients received at least one drug prescription, from a list of drugs related to diverticular disease and granted by the national health service (see supplementary table s3) in the year of admission. In the same year, 66% benefited from one of the specialist outpatient services, selected as possibly related to diverticular disease (the list of granted services is presented in supplementary table s4).

The healthcare costs covered by the Marche region for episodes of diverticulitis between 2008 and 2014 was calculated as €11.4 million (approx. €1.6 million a year), of which €10.9 million (95.5%) for the hospitalizations, including drugs prescribed during the admission, € 246,000 (2.1%) for outpatient pharmaceutical treatment related to diverticular disease, and € 270,000 (2.4%) for specialist outpatient services (see methodology section).

The average annual cost per patient with at least one hospital admission was €3,826, of which €3,653 for hospitalization, while regional pharmaceutical assistance and specialist services accounted for €83 and €90, respectively.

The cohort of patients undergoing a first admission for diverticulitis between 2010 and 2013 was made up of a total of 1,729 people (54.4% women, mean age 68.9 years), of whom 1,500 (86.8%) did not undergo surgery during the index admission. During the index admission, no statistically significant differences were found regarding gender (p value 0.4445) and age (p value 0.9748) between those undergoing surgery and those not.

Hospital mortality, recorded only in the over 65 age group, was 1.2%; fairly obvious differences emerged between patients whose index admission involved no surgery (0.5% mortality) and those who underwent surgery during the index admission (mortality 5.2%). Among patients submitted to surgery in the index admission (229 or 13,2%), open or laparoscopic surgery have been performed in 201 (87,8%) and in 28 (12,2%). Mortality in the first admission affected 11 patients (5,5%) operated with the open technique, against 1 (3,6%) operated in laparoscopy.

The percentage of patients with one or more readmissions for diverticulitis in the year after the first was on average 7.8% and in 48% of these cases the re-admission resulted in surgery.

Ten of patients (5%) who underwent open surgery had a second admission and 4 (2%) had another intervention within 1 year, in front of 0 (0)% of patients operated initially in laparoscopy. No attempt is allowed to identify statistical inference, due to the low volume of laparoscopic surgery.

Ileostomy or colostomy were performed in 56 (27,9%) of operated patients with the open approach, and only in 2 (7,1%) submitted to laparoscopy. Only 4 out 58 (6,9%) underwent new surgery for re-anastomosis in 1 year.

Among index-admission patients not undergoing surgery, the raw percentage of re-admissions at one year is 8.2%, and would seem to be inversely proportional to age ($OR_{40\text{-}64 \text{ vs } <40}$=0.75 p=0.424 and $OR_{65+ \text{ vs } <40}$=0.41 p=0.010). Approximately 50% of re-admissions involved surgical procedures and the percentage of repeat surgical procedures at one year is 1.8%; again there is a inverse relationship with age ($OR_{40\text{-}64 \text{ vs } <40}$=0.53 p=0.105 e $OR_{65+ \text{ vs } <40}$=0.17 p=0.001).

Within a year of index admission, patients undergoing surgery had a lower percentage of readmissions (4.6%) and repeat surgical procedures (1.8%) compared to those treated non-operatively (8.2% readmissions and 4.0% surgical procedures, respectively).

The average annual cost per patient was €3,403.43, depending largely on the surgical procedure: patients treated non-operatively during the index admission cost on average €2,472.99, rising to €9,498.03 for subjects who underwent a surgical procedure during the index admission.

The financial weight of surgery can also be seen by focusing on the cost of re-admissions: subjects treated non-operatively during the index admission have a greater chance of being re-admitted for surgery over the next 12 months (8.2% Table 2) than patients who underwent a surgical procedure during the index admission (4.6% Table 2). This has an impact on costs at one year for readmissions: €5,585.58 for the first cluster and €3,516.37 for the second.

DISCUSSION

Diverticulosis is very common in Western countries, and its prevalence increases with age. Most diverticulosis cases remain asymptomatic for life: only about 4% of patients with an endoscopic diagnosis of diverticulosis develop diverticulitis (5).

However, admissions for diagnosis code diverticulitis without haemorrhage (562.11) are very much on the increase: in the USA alone, the increase in the admissions rate was +21% compared to 2003, with a total aggregate cost of between $2.2 and $2.6 billion and a hospital mortality rate of 0.5% (5).

Two very large multicentre studies (7, 8) suggest that relapse after diverticulitis is not very severe. Broderick-Villa (8) reports on the history of 2,366 patients hospitalized for diverticulitis and treated non-operatively in the Kaiser system. At a median follow-up of 8.9 years, diverticulitis had recurred in 13.3% of patients and only 3.9% had a second relapse. The risk of subsequent relapse increased to 29% among patients who had a first relapse.

Binda's Italian study (7) reports on a follow-up of 320 patients treated with antibiotics in 17 hospitals after discharge for diverticulitis. In a comparable follow-up period (10.7 years), 25% of patients had symptoms requiring re-admission. The risk of surgery rose to 17%. In the analysis corrected for risk factors, the risk of recurrence was highest among patients under age 50 and among those with 3 previous episodes of diverticulitis. Many studies on recurrence argue that the risk is concentrated in the first 2 years of follow-up. Binda et al (7), however, suggest that this figure remains almost constant throughout the follow-up period.

The data in this study can be summarized as follows:

a) the incidence of admissions for diverticulitis remained stable from 2008 to 2010, and increased from 2011 to 2014 (+12% in 2014 v. 2008); caution should be used in evaluating this finding, since a change in medical approach (e.g. defensive medicine) could be the cause;

b) within one year from the first episode of diverticulitis, the incidence of re-admission for diverticulitis was 8.2% in patients treated non-operatively (Table 2). However, recurrence at one year can occur even in patients undergoing surgery (4.6%, Table 2) demonstrating that the role of surgery should always be carefully evaluated. It should be noted that these figures are subject to bias with regard to the definition of recurrence (recurrences recorded are limited to those requiring re-admission);

c) during the observation period, no cases of patients suffering from a second relapse were recorded;

d) acute episodes of diverticulitis involve a risk of mortality in patients over the age of 65 (1.2%).

The clinical evolution of the index admission is summarized in Figure 2.

From a financial standpoint, we estimate that the average annual cost per patient is over €3,400. The average cost is significantly affected by the performance or otherwise of a surgical procedure during the index admission; patients treated non-operatively during the index admission cost an annual average of about €2,470, whereas patients with surgery cost around 4 times that, at €9,490.

These data are consistent with the literature.

For example, a study conducted in the USA on 132 patients estimated an average cost of between $3,458 and $4,321, depending on the procedure performed (9). A similar study, conducted on 144 patients in the UK estimated an average cost of £3,143 (10), while an analysis carried out in Italy on 738 patients discharged from the Federico II University Hospital in Naples between 2004 and 2010 estimated a cost per patient amounting to €2,250, a figure which the authors regard as an underestimate as there was no emergency room in the facility (11).

It is interesting to note that in our study we found that the differences between patients undergoing surgery during the index admission and those who did not are reversed when we consider only those patients who were re-admitted once or more within one year of initial admission. In such cases, indeed, the estimated cost for patients not undergoing surgery during the index admission were over 50% higher than for those undergoing surgery, amounting to €5,500 and €3,500, respectively.

Assuming that the diagnostic and therapeutic behaviour in the Marche region could be representative of the situation nationwide, total annual expenditure in terms of direct costs for the Italian National Health Service can be estimated at over € 63 million. This figure does not include the costs for drug treatments and diagnostic procedures, not to mention the indirect costs, that in most cost-of-illness estimates make up over 50% of the costs incurred by society (12-17).

Like all analyses based on claims databases, this paper too has its limitations.

First, the analysis is based on administrative data sources which, by their very nature, were not designed to be used for epidemiological purposes, but only for accounting and billing. However, to date, there are no specific epidemiological registries for measuring diverticulitis

patients' clinical outcomes, which means that administrative sources remain the best alternative possible for tracking patients' therapeutic diagnostic process.

A second limitation of the study is the difficulty inherent in identifying which patient-related clinical variables to analyse. This means that some bias may persist linked to the severity of the disease and, more generally, to the clinical history of the patients in the analysis. In this case, the high sample size (more than 3,500 admissions covering 2,900 patients) and the stratification of subjects by age suggest that the estimates obtained are sufficiently robust.

Finally, another limitation regards estimates of patient mortality. In this case, the analysis referred only to hospital mortality, ignoring anything occurring post-discharge outside the confines of the hospital. This makes it impossible to identify deaths occurring outside the hospital environment, leading to an underestimation of patient mortality and readmission rates.

This study outlines various prospects for the future control of diverticular disease and for the incidence of diverticulitis.

While the patient's age obviously cannot be changed, more needs to be done to identify and learn about the risk factors (i.e. comorbidities, compliance and hospital stay) that can increase the likelihood of a relapse and thus of a readmission.

A better understanding of the weight of the risk factors has already highlighted some key points, in particular the use of NSAIDs and aspirin. NSAIDs, including aspirin, are now considered risk factors for diverticulitis because they cause local damage directly in the colon, compromise the integrity of the mucosa and inhibit the synthesis of prostaglandins.

Several studies have found a positive association between NSAIDs and diverticulitis. However, most of them have evaluated the concomitant use of NSAIDs and aspirin. Aspirin plays a very significant role in preventing chronic diseases, especially in the secondary prevention of cardiovascular events. It would be useful to understand the weight of aspirin alone in inducing diverticulitis, so as to help decide whether it can continue to be taken by patients with a history of diverticulitis.

Strate's study (18) suggests that using aspirin alone raises the risk of the first episode by 45% (HR 1.46, CI 95% 1.13-1.88).

However, there are no known data on the recurrence of diverticulitis. Some epidemiological assumptions, however, would suggest there is an increased diverticulitis recurrence risk in 5 out of every 100 patients over a 5-year follow-up period (95% confidence intervals from 1 to 9) (19).

While aspirin and NSAIDs are identified as risk factors for the first episode of diverticulitis, the weight of using them in those who have already had diverticulitis has yet to be directly quantified. Further research will be needed to weigh the role of aspirin and NSAIDs in these patients, taking into account that both classes of molecules are widely used and in some locations also play an increasing role in cancer prevention (20).

In this sense, further investigations into the data from this real-world study may correct the risk of using NSAIDs and aspirin in Italy.

Is there any evidence that medical treatment can reduce the risk of a first episode of diverticulitis and relapse?

From what we have found in the literature, it would very much seem that there is still rather little evidence in the therapeutic management of patients with a history of diverticulitis. This is surprising, since the direct and indirect financial costs of diverticular disease are concentrated especially in episodes of diverticulitis and management of its complications. In this regard, prospective studies with the aim of evaluating various therapies in such patients will be needed.

Finally there is the matter of elective surgery to prevent relapse. The issue is still being debated (19) and the discussion is outside the scope of this paper. However, it is evident that even from this real-world study that surgery does not exclude the risk of recurrence: 4.6% of patients operated on in the Marche Region during the index admission were re-admitted within the next 12 months following a relapse (Table 2).

In conclusion, the estimated annual number of hospitalizations in Italy for acute episodes of diverticulitis is 19,000, assuming that the diagnostic and therapeutic behaviour identified in the Marche region is representative of the situation nationwide. The total amount of direct financial resources needed to treat patients suffering from acute episodes of diverticulitis can be estimated at €63.5 million per year.

CONFLICT OF INTERESTS

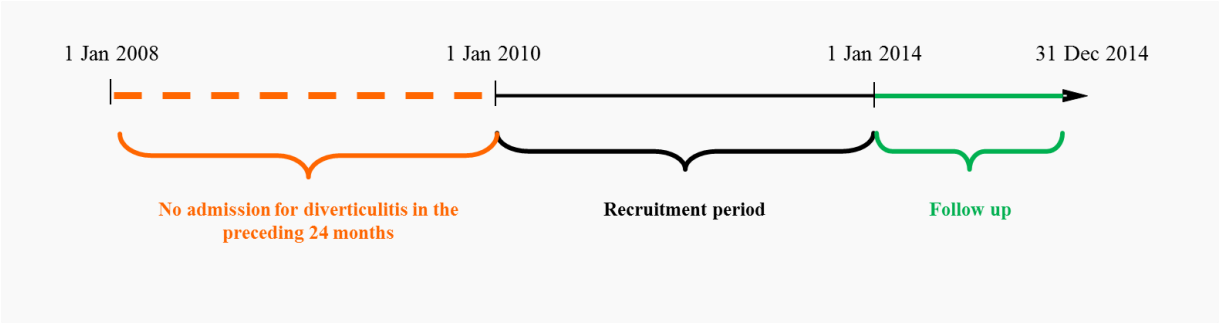
Funding

This study received an unrestricted institutional grant from the pharmaceutical company Alfa Wassermann.

1. Peery AF, Barrett PR, Park D, et al. A high-fiber diet does not protect against asymptomatic diverticulosis. Gastroenterology. 2012; 142: 266-72 e1.
2. Stumpf M, Cao W, Klinge U, et al. Increased distribution of collagen type III and reduced expression of matrix metalloproteinase 1 in patients with diverticular disease. International journal of colorectal disease. 2001; 16: 271-5.
3. Painter NS, Burkitt DP. Diverticular disease of the colon: a deficiency disease of Western civilization. Br Med J. 1971; 2: 450-4.
4. Shahedi K, Fuller G, Bolus R, et al. Long-term risk of acute diverticulitis among patients with incidental diverticulosis found during colonoscopy. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2013; 11: 1609-13.
5. Peery AF, Crockett SD, Barritt AS, et al. Burden of Gastrointestinal, Liver, and Pancreatic Diseases in the United States. Gastroenterology. 2015; 149: 1731-41 e3.
6. Koch M, Festa V, Chiesara F, et al. [Diverticular disease: towards 2020. An evidence-based approach]. Recenti progressi in medicina. 2016; 107: 309-19.
7. Binda GA, Arezzo A, Serventi A, et al. Multicentre observational study of the natural history of left-sided acute diverticulitis. The British journal of surgery. 2012; 99: 276-85.
8. Broderick-Villa G, Burchette RJ, Collins JC, et al. Hospitalization for acute diverticulitis does not mandate routine elective colectomy. Archives of surgery. 2005; 140: 576-81; discussion 81-3.
9. Senagore AJ, Duepree HJ, Delaney CP, et al. Cost structure of laparoscopic and open sigmoid colectomy for diverticular disease: similarities and differences. Dis Colon Rectum. 2002; 45: 485-90.
10. Papagrigoriadis S, Debrah S, Koreli A, et al. Impact of diverticular disease on hospital costs and activity. Colorectal Dis. 2004; 6: 81-4.
11. Aprea G, Giugliano A, Canfora A, et al. Diverticular disease hospital cost impact analysis: evaluation of testings and surgical procedures in inpatient and outpatient admissions. BMC surgery. 2012; 12 Suppl 1: S3.
12. Russo S, Viti R, Marcellusi A, et al. Direct And Indirect Costs Associated to Retinal Vascular Diseases In Italy. A Probabilistic Cost of Illness Study. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2015; 18: A418.
13. Marcellusi A, Viti R, Capone A, et al. The economic burden of HCV-induced diseases in Italy. A probabilistic cost of illness model. European review for medical and pharmacological sciences. 2015; 19: 1610-20.
14. Marcellusi A, Viti R, Mecozzi A, et al. The direct and indirect cost of diabetes in Italy: a prevalence probabilistic approach. The European journal of health economics : HEPAC : health economics in prevention and care. 2016; 17: 139-47.
15. Fabriani V, Marcellusi A, Mennini FS, et al. Cost of Illness Analysis of Duchenne Muscular Dystrophy In Italy. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2014; 17: A528.
16. Baio G, Capone A, Marcellusi A, et al. Economic burden of human papillomavirus-related diseases in Italy. PloS one. 2012; 7: e49699.
17. Patti F, Amato MP, Trojano M, et al. Multiple sclerosis in Italy: cost-of-illness study. Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology. 2011; 32: 787-94.
18. Strate LL, Liu YL, Huang ES, et al. Use of aspirin or nonsteroidal anti-inflammatory drugs increases risk for diverticulitis and diverticular bleeding. Gastroenterology. 2011; 140: 1427-33.

19. Strate LL, Peery AF, Neumann I. American Gastroenterological Association Institute Technical Review on the Management of Acute Diverticulitis. Gastroenterology. 2015; 149: 1950-76 e12.
20. Cao Y, Nishihara R, Wu K, et al. Population-wide Impact of Long-term Use of Aspirin and the Risk for Cancer. JAMA Oncol. 2016; 2: 762-9.

Figure 1 - Patient recruitment diagram - longitudinal analysis



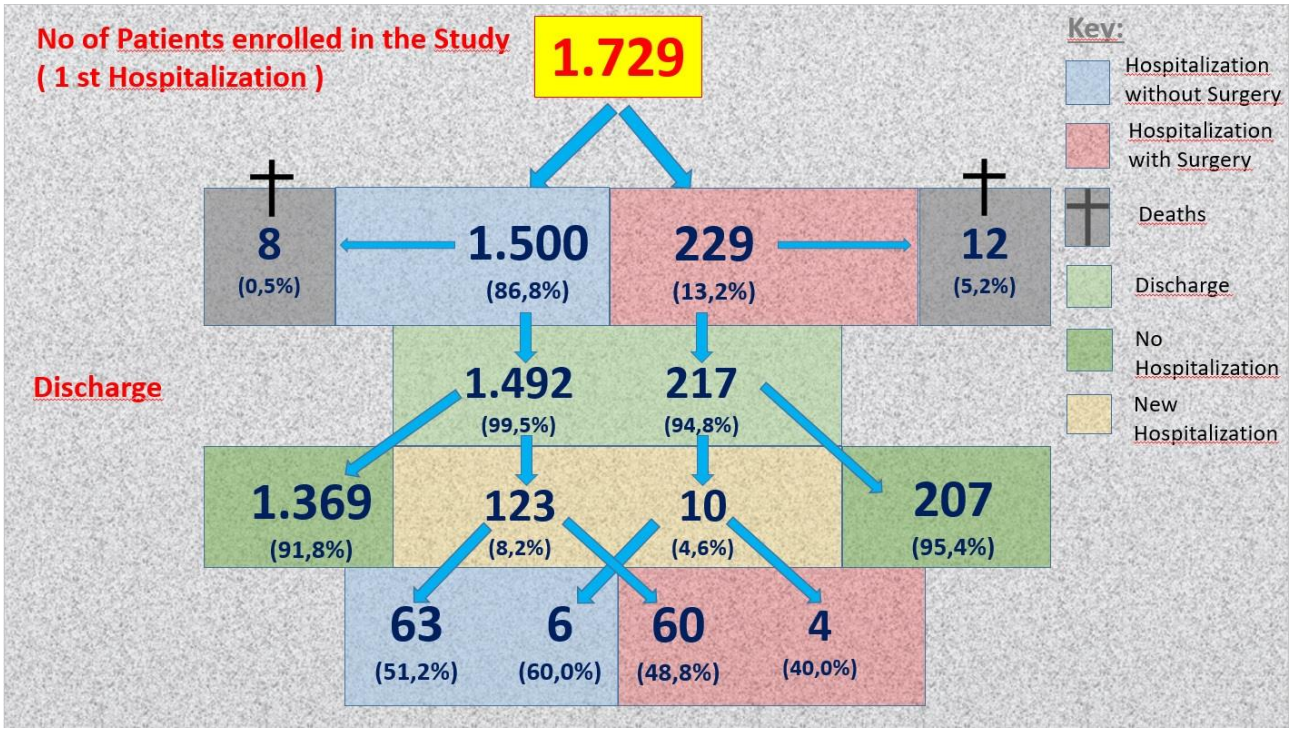


Figure 2. The clinical evolution of the index admission.

Table 1. Costs per year for patients admitted to hospital once or more for diverticulitis

Year	Subjects	Hospitalizations	Cost of Hospitalizations	Users	Cost of Drugs	Patients	Cost of Specialist Care	TOTAL
2008	435	460	€ 1,527,352	317	€ 34,639	271	€ 25,485	€ 1.587.477
2009	419	449	€ 1,422,886	306	€ 35,002	246	€ 35,213	€ 1.493.101
2010	412	438	€ 1,328,730	301	€ 31,671	236	€ 30,561	€ 1.390.962
2011	484	515	€ 1,685,063	354	€ 27,120	355	€ 46,558	€ 1.758.742
2012	494	530	€ 1,516,335	369	€ 30,926	320	€ 37,128	€ 1.584.389
2013	491	531	€ 1,686,612	385	€ 42,815	336	€ 48,416	€ 1.777.842
2014	487	530	€ 1,744,483	379	€ 43,963	322	€ 46,730	€ 1.835.176
Total	**2,987**	**3,453**	**€ 10,911,461**	**2.227**	**€ 246,136**	**1,968**	**€ 270,091**	**€ 11.427.688**

Source: Our processing of Marche regional data from 2008-2014

Table 2 Subjects with at least one admission for diverticulitis: Readmissions and subsequent surgery within one year

Surgery during index admission	Age group	Subjects 2010-2013 no. (%)	deaths during index admission no. (%)	Subjects rehospitalized within 1 year no. (%)	Subjects undergoing surgery within 1 year no. (%)
No	< 40	73 (4.2%)	0 (0%)	10 (13.7%)	8 (11%)
	40-64	462 (26.7%)	0 (0%)	54 (11.7%)	31 (6.7%)
	65 +	965 (55.8%)	8 (0.8%)	59 (6.2%)	21 (2.2%)
	Sub-total	1.500 (86.8%)	8 (0.5%)	123 (8.2%)	60 (4%)
Yes	< 40	9 (0.5%)	0 (0%)	1 (11.1%)	1 (11.1%)
	40-64	64 (3.7%)	0 (0%)	1 (1.6%)	1 (1.6%)
	65 +	156 (9%)	12 (7.7%)	8 (5.6%)	2 (1.4%)
	Sub-total	229 (13.2%)	12 (5.2%)	10 (4.6%)	4 (1.8%)
Total		**1,729**	**20 (1.2%)**	**133 (7.8%)**	**64 (3.7%)**

Source: Our processing of Marche regional data from 2008-2014

Table 3 Subjects with at least one admission for diverticulitis: Annual costs

Surgery during index admission	Age group	Subjects 2010-2013	Average cost per patient at one year	Subjects with subsequent readmissions	Average cost per patient readmitted within 1 year
No	< 40	73	€ 2,798.47	10	€ 8,854.78
	40-64	462	€ 2,291.34	54	€ 5,703.25
	65 +	965	€ 2,535.33	59	€ 4,923.78
	Sub-total	1.500	€ 2,472.99	123	€ 5,585.58
Yes	< 40	9	€ 8,836.12	1	€ 3,841.00
	40-64	64	€ 8,874.06	1	€ 5,976.00
	65 +	156	€ 9,792.20	8	€ 3,168.34
	Sub-total	229	€ 9,498.03	10	€ 3,516.37
Total		**1,729**	**€ 3,403.43**	**133**	**€ 5,430.00**

Source: Our processing of Marche regional data from 2008-2014