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Original Article

Determinants of Hospital Costs of Inflammatory Bowel Disease

Kamran Bagheri Lankarani[1], Sulmaz Ghahramani[1,*], Maryam Hadipour[1], Mohammad Pourhashemi[2], Ali Mahmoodi[2], Mahdi Zeraatpishe[2], Amirhossein Babaei[2,3]

[1] Health Policy Research Center, Institute of Health, Shiraz University of Medical Sciences, Shiraz, Iran
[2] Student Research Committee, Shiraz University of Medical Sciences, Shiraz, Iran
[3] Department of Otolaryngology, Khalili Hospital, Shiraz University of Medical Sciences, Shiraz, Iran

ABSTRACT

Background:
Rate of hospital admission for inflammatory bowel disease (IBD) and its related cost has an increasing trend worldwide. Iran has an increasing number of patients with IBD. In this study, we aimed to identify in-hospital costs of patients with IBD and its determinants in two tertiary hospitals in the south of Iran.

Materials and Methods:
Applying relevant ICD (International Classification of Diseases) codes, records and hospital bills of all hospitalized patients with IBD during 2013-2015 were reviewed. Annual hospitalization cost per patient, cost per hospitalization, and daily cost during hospital admissions were also estimated. Predictors of total hospital admission costs were evaluated using Stata SE .11. A significant level was set at 0.05.

Results:
158 patients with a median age of 35 years admitted to the hospitals during the study period. Most patients were female (63.3%). The median length for hospital stay (LOS) was 3 days. The total hospital cost of IBD was 843,640 International US Dollar (IUSD). Costs were more for patients with ulcerative colitis (UC) than Crohn's disease (CD). Daily cost during hospital admissions was more than 700 IUSD. Predictors for all three quartiles of total hospital cost for UC were: LOS, living status on check out, and year of study and for CD was LOS, all with $p < 0.001$.

Conclusion:
This study showed that patients with UC had higher hospital costs than patients with CD. LOS was a strong predictor for the total hospital cost of IBD. There was a time trend for increasing cost in UC. Living status on discharge strongly predicted higher total hospital costs for patients with UC. Further prospective studies with larger sample size on direct as well as the indirect cost of IBD and its determinants are strongly recommended.

Keywords: Hospital cost, Determinant, Inflammatory bowel disease, Iran

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Corresponding Author:
Sulmaz Ghahramani, MD
Health Policy Research Center, Institute of Health, Shiraz University of Medical Sciences, Building No 2, Eighth Floor, School of Medicine, Zand Avenue, 71348-45794, Shiraz, Iran
Telefax: + 98 71 32309615
E-mail: Suli.ghahraman@gmail.com

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INTRODUCTION

The incidence and prevalence of Crohn's disease (CD) and ulcerative colitis (UC), collectively known as inflammatory bowel disease (IBD), is increasing worldwide (1). The prevalence of UC in Asia and the Middle East is 4.9 to 168.3 per 100,000 and for CD is 0.88 to 67.9 per 100,000 in the same region (1). In Iran, the prevalences of UC and CD were 35.5 and 5 per 100,000, respectively in 2012 and it is stated that both the prevalence and incidence of IBDs are rising in Iran (2-4).

In Iran, UC is more prevalent than CD and IBD is slightly more prevalent in women than men (5). In CD the disease course is generally distinguished by a sequence of

flare-up episodes and remissions of varying durations, while the course of UC is characterized by flares that alternate with periods of remission. A minority of patients have continuous activity (4).

Due to the nature of IBD and its complications along with the increasing prevalence and incidence of IBD, the rate of hospital admission and its related cost is increasing worldwide (6). The cost of IBD in the US is estimated to be US$ 6.3 billion in 2004 (7). In Canada in 2012, annual direct health-care costs in over 200,000 patients with IBD were estimated more than CDN$ 1.2 billion (8). In developing nations; however, there is no available data on the cost of IBD (9). The cost is predicted to increase during the next decade (10).

Most reports indicate that the cost of CD is more than UC (11,12). Major drivers of direct medical costs of IBD are reported to be hospitalizations, surgery, ambulatory care (office visits and procedures), and medications. In other words, the cost of this illness is influenced by the rate of hospitalization, disease severity grade, and disease extent (13).

Studies on hospitalization rate showed that throughout life, a significant portion of patients with IBD may require hospital admissions. The rate of hospital admissions varies based on the type of IBD, disease severity, years from diagnosis, definition of hospitalization rate, and study region. Based on definition, the rate of hospital admissions ranged between 25% to 83% for CD and 29.4% to 41.9% For UC (14-18).

Although patients with IBD may account for a minority of patients who admitted to hospitals, their hospitalization costs could be huge and is considered as the major economic burden of IBD and the major part of direct medical costs, ranging from 49% to 80% of total healthcare costs of IBD (13,19,20). Surgery is a high-cost service in IBD especially for CD, (21,22) however, it is evident that the cost of surgery has steadily decreased over time (8,23,24). The cost of new therapies such as anti-TNF medications caused a shift in cost toward medication rather than surgery (20,25).

The importance of monitoring the hospital cost of IBD for health policy planning, recourse allocation, and cost-effectiveness studies is of utmost importance especially in countries with limited resources like Iran where epidemics of IBD are experienced. Despite its importance, there is no report on hospitalization costs of IBD in Iran. It is noteworthy to point that since 2014 Iran's health system implemented a series of reforms, called as the Health System Transformation Plan (HSTP). In the first run of this reform, copayments for hospitals affiliated to the Ministry of Health and Medical Education for inpatient services were aimed to be 10% for the residents of medium and large cities and 5% for nomadic people and residents of rural regions, and small towns (with a population less than 20,000).

In the current study, we aimed to assess the in-hospital costs of IBD over a period (2013 to 2015) and identify predictors of higher total hospital costs in hospital inpatients with IBD.

MATERIALS AND METHODS

Study population and Data collection

This retrospective study was performed in two tertiary referral hospitals affiliated to Shiraz University of Medical Sciences, which are the main referral centers for IBD in the south of Iran. This city is the center of Fars province, the largest province in the southeast, Iran with a population of 4,851,274 according to the 2016 census (https://www.amar.org.ir/english).

In this study, the records of all hospital inpatients with IBD from the first of January 2013 until the end of June 2015 with ICD (International Classification of Diseases) codes of "Crohn's disease (ICD10-K50)," and "ulcerative colitis (ICD10- K51)," were reviewed. Records were double-checked according to ICD numbers by researchers. As there was a transition in ICD coding system at the end of June 2015, the data gathering was stopped at that period. The hospitalization year was recorded according to the check-out date. In this study the diagnosis of IBD was based on the clinical, endoscopic, and/or radiological imaging along with pathological confirmation (26).

All admissions were recorded to avoid missing patients with multiple admissions. Also all records were evaluated for being relevant to the IBD disease based on admission symptoms.

Patient characteristics and Clinical data

For the study purpose, the patients' demographic and clinical information including the dates of admission and discharge, length of hospital stay (LOS) (day), status on discharge (alive/deceased), insurance status, type of disease (UC/CD), recorded

site of gastrointestinal (GI) involvement, surgical intervention, complications during hospital course, and final diagnosis were collected. Disease severity indexes at admission and at discharge naming Crohn's Disease Activity Index (CDAI) (27) for patients with CD and Mayo Score (28) for patients with UC were calculated. The Mayo scores ranged from 0 to 12 with higher scores indicating more severe disease (24). CDAI values ranged between 150 to 450 and values of 150 and below are associated with a quiescent disease, values above that indicate active disease, and values above 450 are seen in extremely severe disease.

The final diagnosis was extracted from the records including disease flare-up, cytomegalovirus (CMV) infection, amoebic infection. CMV infection was defined as positive serology for PP65 antigen and/or CMV PCR and/or pathology.

The extent of disease in the case of UC and site(s) of GI involvement in patients with CD were determined according to the endoscopic and/or imaging studies with the most extensive involvement in each patient.

Determination and predictors of hospitalization costs

Data on hospitalization costs were extracted according to the hospital record number of patients with IBD through Hospital Information Systems (HIS) of each hospital. These data include medications, examinations, ward beds, surgery, visit, and consultation.

The cost of biological agents was included in the medications. The cost of laboratory tests, included in examination costs. Consultation cost included in visit cost. Ward bed included the intensive care unit cost and ward cost. The cost of endoscopy was included in the examination costs. Surgery costs included in surgical consumables, medications, anesthetic fees, and operation fees.

The cost was averaged by the number of hospitalizations, patients, and length of stay (LOS).

"Annual hospitalization cost per patient" was defined as the annual hospitalization costs averaged by annual number of individual patients, reflecting the real burden for every patient with IBD.

"Cost per hospitalization" was defined as hospitalization costs averaged by the number of hospital admissions during a certain period. "Daily cost during hospitalization" was defined as hospitalization costs averaged by LOS during a certain period (6). "Annual hospitalization cost per patient", "Cost per hospitalization" and "daily cost during hospitalization" were used for purpose of clearer understanding of hospital costs and uniformity of future studies.

Because of positive skewed distribution of response variables including hospital and patients costs, quantile regression was applied to modelling quartiles of response variables (29).

Age, sex, group, living status, year of study (as of year code), surgical intervention (do surgery or not), LOS, readmission and disease severity scores (CDAI and Mayo score) entered into the quantile regression model. The living status was categorized as "deceased" or "improved" while checking out. The categorical variables of "group" as disease subtypes were UC, CD.

All costs were converted from Rials to International US Dollar (IUSD) each year based on World Bank's data (world economic outlook database, 2014).

Ethics

The present study was approved and supervised by the Ethics Committee of Shiraz University of Medical Sciences, Shiraz, Iran.

Statistical Analysis

Data were analyzed using descriptive and analytical methods on the Stata SE.11 software. Quintile regression was applied separately for CD and UC to explain factors effect on different quartiles of total hospital cost (IUSD) . Spearman correlation was applied to explore the correlation between quantitative variables. The significance level was set at 0.05

RESULTS

Patient characteristics and disease features:

Characteristics of 158 patients with Mean ± SD age 37.48 ± 19.90 are presented in table 1.

99 (63%) patients had UC, of whom 35 (29%) were categorized as having pancolitis. There were 26 pediatric IBD patients (< 18 years old, 16 UC and 10 CD).

Most patients were female (63.3%). The mean ± SD

Table 1: Participants' characteristics and disease features

Age (Year)			37.5 ± 19.9 (35)	
Readmission[a]			15(9.5%)	
LOS[b]			7.5 ± 10 (3)	
Disease activity	Mayo Score[c]		5.8 ± 2.8	
	CDAI[d]		310 ± 50.7	
Sex	Male		58(36.7)	
	Female		100(63.3)	
Number of Death			9(5.9)	
Involvement site of disease subtypes	UC[e]	Proctitis	34 (28.1)	121 (76.6)
		Left-sided colitis	28 (23.1)	
		Extensive and pancolitis	35 (29)	
		Not specified	24 (19.8)	
	CD[f]	Large bowel	8 (21.6)	37 (23.4)
		Small bowel	4 (10.8)	
		Both large and small bowels	25 (67.6)	

Data are presented as n (٪) or Mean ± SD (median if applicable)
[a] Hospital readmission during one month
[b] Length of hospital stay (Day)
[c] Mayo score for disease activity of patients with UC
[d] Crohn's Disease Activity Index
[e] Ulcerative colitis
[f] Crohn's disease

Table 2: Final diagnosis of patients with IBD for Crohn's disease and ulcerative colitis separately

Diagnosis	UC[a]	CD[b]
Disease flare up	110 (90.9)	33 (89.2)
Bacterial infection	5 (4.1)	3 (8.1)
Cytomegalovirus infection	3 (2.5)	1 (2.7)
Amoebic infection	3 (2.5)	
Total	121 (100)	37 (100)

[a] Ulcerative colitis
[b] Crohn's disease

Table 3: Hospital cost indexes for patients with inflammatory bowel disease

Year	2013	2014	2015
Annual hospitalization cost per patient[a]	3056	7590	7400
Cost per hospitalization[b]		5339	
Daily cost during hospitalization[c]		712	

[a] The annual hospitalization costs averaged by annual number of individual patients
[b] Hospitalization costs averaged by the number of hospitalizations during the study period
[c] Hospitalization costs averaged by LOS during the study period
Are data are presented as IUSD (International US Dollar)

of LOS was 7.5 ± 10 days. There were 15 hospital readmissions during the same month of the index hospitalization. 11 (7%) patients had surgery during the study period; all of them with UC.

Most patients with IBD admitted with the final diagnosis of a flare-up (90%). Other final diagnoses of patients with IBD for CD and UC separately are presented in table 2.

Total hospital cost and patient payment:

The sum of total hospital cost was 843,640 IUSD, including 791,520 IUSD for UC, and 52,120 IUSD for patients with CD. Annual hospitalization costs per patient in different years, cost per hospitalization, and daily cost during hospitalization are presented in table 3.

Overall top three high-cost services in IBD belonged to surgery, ward bed, and mediations. Mean and SD of the total cost for different services in different IBD types are described in table 4. The proportion of medication cost to total hospitalization cost was 5%. The medication cost per hospitalization was 26 IUSD.

Mean ± SD (median) of total hospital cost were 3597 ± 5218 (1240) IUSD and 7212 ± 21282 (2475) IUSD for pediatric and adult IBD patients respectively. The difference was not statisticaly significant ($p = 0.43$).

Total hospital bill strongly correlated with LOS ($p < 0.001$, a correlation coefficient of 0.83, and $p < 0.001$, correlation coefficient 0.9, respectively).

Total hospital bills were not significantly different in different involvement sites ($p = 0.1$, $p = 0.05$, respectively).

There was no significant difference in total hospital bills for patients with and without readmission ($p = 0.1$, $p = 0.3$, respectively).

Predictors of total hospital cost

Predictors for all three quartiles of total hospital costs for UC were: LOS, living status on check out, and year of study (all with $p < 0.001$). For almost all these predictors, the stronger effect on total hospital bill was observed at the highest quartiles.

In the highest quartile (75%), patients with UC had 575 IUSD more total hospital costs for one extra day

Table 4: Mean and SD of the total cost for different services in patients with inflammatory bowel disease

Type of service	CD	UC	Total
Visits	13 ± 12	40 ± 87	34 ± 78 (14)
Surgery	0[a]	1565 ± 2647	1565 ± 2647 (352)
Examination	34 ± 23	315 ± 1297	260 ± 1165 (35)
Ward bed	100 ± 241	615 ± 1638	507 ± 1473 (52)
Medication	68 ± 241	445 ± 1153	372 ± 1045 (53)
Total hospital cost	1930 ± 1594	7837 ± 21808	6590 ± 19515 (2046)

TCD: Crohn's disease
UC: Ulcerative colitis
IBDU: inflammatory bowel disease unclassified
Data are presented as mean ± SD (median if indicated), IUSD (International US Dollar)
A: Number of patients with CD who had surgery during the study period

Table 5: Predictors of total hospital bill (International US Dollar: IUSD) using quantile regression, 25, 50, and 75 quartiles for patients with ulcerative colitis

Predictors	Coefficient (B)			SE (B)			*p* value		
	25th	Median	75th	25th	Median	75th	25th	Median	75th
Sex (Female)	-283.27	117.08	369.42	121.65	268.54	410.16	0.028	0.662	0.383
(Hospital stay #Day)	394.16	438.31	574.92	5.04	10.53	15.10	< 0.001	< 0.001	< 0.001
(Living status alive)	-1067.23	-4605.96	-11508.9	205.68	480.10	724.38	< 0.001	< 0.001	< 0.001
Mayo (score)	-11.36	16.36	-60.40	23.83	48.82	88.88	0.616	0.735	0.496
Year	645.16	781.33	954.40	85.57	173.72	258.16	< 0.001	< 0.001	< 0.001
Constant	851.40	3723.66	10499.6	306.82	705.54	1225.0	0.007	< 0.001	< 0.001

Table 6: Predictors of total hospital bill (International US Dollar: IUSD) using quantile regression, 25, 50, and 75 quartiles for Crohn's disease

Predictors	Coefficient (B)			SE (B)			*p* value		
	25th	Median	75th	25th	Median	75th	25th	Median	75th
Sex (Female)	513.83	-49.08	-476.42	207.86	573.54	544.16	0.021	0.805	0.411
(Hospital stay #Day)	264.81	403.70	447.82	19.18	85.41	86.85	< 0.001	< 0.001	< 0.001
CDAI (score)[a]	0.74	4.93	2.21	1.47	4.83	4.80	0.718	0.211	0.610
Constant	-769.87	-1033.75	537.90	566.90	14914.0	1853.6	0.187	0.461	0.774

[a] Crohn's Disease Activity Index

of admission, 11,510 IUSD more if patient deceased in the hospital course and for each year increase in the year of study total hospital cost increased by 954 IUSD.

In patients with CD, LOS predicted higher total hospital costs, especially in higher quartiles. Total hospital cost increased 448 IUSD for one extra day of admission in quartile 75%.

Other independent variables were not significant predictors for total hospital costs. Coefficients of predictors are presented for UC and CD in tables 5, and 6, respectively.

DISCUSSION

The aim of this study was to identify the hospital costs and predictors of higher hospital costs in patients with IBD. We found a very high cost per hospital admission for an individual patient, more than 5,000 IUSD during the study period. Daily cost during hospital admissions in studied patients with IBD was over 700 IUSD. Total hospital costs were the highest for patients with UC. Hospital costs of CD were the least, which is similar to the COIN study in Netherland, in which hospital and surgery costs were higher in patients with UC than CD (25). Similarly, in a 6-month follow up study in the UK, total hospital

cost was more for patients with UC or indeterminate colitis than CD (13). However in most cases mean costs had a relatively smaller median, which indicates that a relatively small group of the patients significantly affects the total cost of treatment of these diseases.

The highest cost services of UC were surgery, ward bed, and medications and for CD were medications, ward bed, and laboratory exams. Higher hospital costs in patients with UC caused overall tendency of total hospital costs (in a way that higher total hospital costs are the same as higher cost services of UC: surgery, ward bed, and medication).

Medication cost in this study seems to be underestimated (6) because patients with IBD received the decision to start biological therapies including anti-tumor necrosis factor alfa (anti-TNF α) in outpatient settings and so the related cost is not included in medication costs. This indicates the lower use of biological treatment in disease flares in Shiraz. The reason could be the fear of reactivation of tuberculosis and the timely test including PPD or gamma interferon assays for latent tuberculosis.

A 24-year cohort study in Olmsted County, Minnesota revealed that surgery was the highest cost service for patients with CD (30). Although to the best of our knowledge there is no published study on cost (and the trend for this cost) of patients with IBD in Iran for comparison, this study showed that the highest hospital cost for patients with CD was incurred by ward bed and most such patients admitted due to the disease flare. It is noteworthy to mention that during the study period, none of the patients with CD had surgery. No registered surgery in such patients might be due to the small sample size, surgery in other hospital settings, the effect of new therapies such as anti-TNF α, and different characteristics of patients with CD in this region.

Lower hospital costs of patients with CD (than patients with UC) might be due to the lack of registered surgery in this group or shift of IBD cost from hospitalization and surgery toward anti-TNF α therapy in outpatient clinics as mentioned above (31). This needs to be evaluated in prospective studies.

This study showed that LOS for UC and CD and prognosis in UC were strong predictors for hospital costs. This finding was in line with a hospital cost study in China, which found these two predictors of cost in addition to other predictors (6). The strongest predictor for high hospital costs was infliximab in the mentioned study (6).

Year of admission was also a stronger predictor for total hospital costs in higher quartile (75%) of hospital costs for patients with UC. Such patients had higher hospital cost by an increase in the year of study from 2013 through 2015. One possibility for prediction of higher total cost by year may be due to overall increase in cost of patients with IBD over time (6); although this study also revealed that annual hospitalization cost per patient doubled in the year 2014 compared with one year before implementation of HSTP. Increased total hospital costs after health system reform have been documented before (32-34).

The effect of year on the prediction of total hospital cost and double increase in annual hospitalization cost after HSTP could be an important red flag for increased total hospital costs after HSTP despite efforts for a decrease in hospital share of patients in the first round of HSTP. Total hospital cost could be increased mainly due to increase in health sector inflation rate (31.7 in 2014 and 23.8 in 2015) and updated relative value units of health services for regularize public and private service providers' payments, which was launched at the third phase of the HSEP (September 29, 2014) (35).

We found a correlation between disease severity and total hospital cost of patients with UC. Disease severity was not correlated with the total hospital cost of patients with CD probably due to the relatively smaller sample size. Disease severity was not a significant predictor for total hospital costs in our studied patients with IBD. There is a paucity of data on this aspect of cost as for instance in the study from China on the cost of IBD the severity was not reported (6) and in the study from the UK although there was correlation between overall cost of illness and disease severity, the researchers did not specifically look at hospital cost (13).

Recognizing potential ways for cost reduction and quality improvement is imperative in the era of the transition of the health care system away from fee-for-service and moving toward more value-based reimbursement strategies. Surveillance of health care costs of patients with IBD, active identification, and having predicting tools for high-cost IBD patients, as

well as monitoring the cost for early warning, may prevent potentially avoidable unplanned care (36).

This study on in-hospital cost of IBD is probably one of the first in Iran. We need larger prospective studies for more accurate results. Population-based studies on direct medical costs rather than hospitalization and direct non-medical and indirect costs of Iranian patients with IBD are suggested in the future for understanding the most important economic factors that influence the cost profiles of such patients (37).

CONCLUSION

Patients with UC had higher hospital costs than patients with CD. Most of the patients with CD admitted due to disease flare up and none for surgery. LOS was a strong predictor of the total hospital cost of IBD. Living status on discharge and year also strongly predicted higher total hospital costs for patients with UC. Further prospective studies with a large sample size on direct as well as indirect costs of IBD and its determinants are strongly recommended.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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Authors' contributions

KBL, and SGh had substantial contributions to the conception or design of the work, SGh, AHB, MH, MP, AM, MZ contributed to the acquisition, analysis, or interpretation of data for the work; ALL AUTHORS contributed to drafting the work and revising it critically for important intellectual content. ALL AUTHORS approved the final version to be published.

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