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Interstitial Cystitis

Cost, Treatment and Co-morbidities in an Employed Population

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Abstract

Introduction: Recent literature indicates that interstitial cystitis (IC) may affect 20% of women and a smaller proportion of men, although many individuals with IC may be misdiagnosed or remain undiagnosed. Factors that can contribute to the cost of IC include medical and drug utilisation related to treatment and diagnosis of IC and associated conditions (e.g. depression), as well as employee work loss. This study assesses the direct medical cost and indirect cost of work loss for IC patients in the first year after diagnosis, and evaluates IC treatment patterns and prevalence of co-morbidities.

Methods: Data for patients under the age of 65 years with at least one diagnosis of IC (n = 749) were drawn from a de-identified, administrative database of approximately 2 million beneficiaries that included medical, drug and disability claims for 1999–2002. A 2 **:** 1 matched control sample of patients without an IC diagnosis (non-IC sample) was randomly selected based on patient characteristics. Indirect costs were calculated from a subgroup of 152 IC patients (plus their matched controls) who had disability information available.

Costs incurred in the first year after IC diagnosis and co-morbidities were compared between IC patients and the non-IC sample, with the difference in costs defined as 'excess costs' of IC patients. Treatment patterns were profiled in the 2 months following initial diagnosis of IC. Descriptive statistics are presented. A multivariate two-part model was applied to estimate the IC direct medical cost, indirect cost and total cost to adjust for observed patient demographics and co-morbidities. Statistical significance was evaluated by the bootstrap method.

Results: The average IC patient had 130% higher direct costs ($p < 0.05$) and the average IC employee patient had 84% higher indirect costs than the average non-IC control individual. IC patients also had a higher diagnostic prevalence of prostatitis (relative risk [RR] = 40.0), endometriosis (RR = 7.4), vulvodynia (RR = 6.9), chronic pelvic pain (RR = 5.8) and urinary tract infections (RR = 5.1) [all $p < 0.05$]. IC patients were also more likely to report depression (RR = 2.8) and anxiety (RR = 4.5) than non-IC controls (all $p < 0.05$).

Seventeen percent of IC patients received pentosan polysulfate therapy, the only US FDA-approved oral drug therapy indicated for treating IC, within the first 2 months after diagnosis. Of these patients, 69% received at least one 'other' drug from the non-approved oral medications studied. Approximately one-third of IC

patients received only 'other' drug therapies, and almost half of IC patients received no drug treatment within the first 2 months after the initial diagnosis.
Conclusions: IC is a costly disease associated with co-morbidities. Following diagnosis, patients with IC are commonly untreated or treated with non-approved drug therapies. It is possible that more accurate diagnosis and earlier and more appropriate treatment of IC would lead to better management (or even prevention) of co-morbidities and reduce healthcare costs, and this should be investigated in future studies.

Interstitial cystitis (IC) is a chronic and often severely debilitating painful condition that affects the wall of the urinary bladder. The primary symptoms of IC include persistent chronic pelvic pain, inflammation, urinary urgency, frequent urination and nocturia.[1-3] Approximately 10% of IC patients experience ulcerative IC, which is characterised by lesions on the bladder wall (Hunner's ulcers); the remainder of patients experience non-ulcerative IC.[4]

Recent research indicates that IC is very common and may affect as many as 20% of women.[5] The female to male patient ratio was estimated as about 10 : 1.[6,7] The prevalence of IC is difficult to estimate accurately because the condition is often misdiagnosed as arising from other causes of chronic pelvic pain, such as endometriosis or urinary tract infections.[8] A much smaller group is actually diagnosed with IC, approximately 3 million patients in the US.[8,9] In addition, between 9 million and 15 million women in the US experience various chronic pelvic pain syndromes.[10] Although epidemiological studies provide varying nationwide estimates for IC, there has been consistency in study results indicating that close to 90% of IC patients are women diagnosed for the first time in their early 40s.[2,4,11] There has been some evidence to suggest that the incidence of IC is slowly increasing among young and middle-aged women.[12]

Patients diagnosed with IC experience a reduced quality of life, even when compared with individuals with other painful or debilitating conditions such as rheumatoid arthritis and kidney failure requiring renal dialysis.[1,13] IC patients have reported having difficulty performing normal activities, diminished energy levels, poorer social functioning and mental health, and extreme physical pain.[6,13] Over 50% of patients are unable to work full-time and approximately 70% experience disruptions in family relationships and responsibilities.[6]

Adverse mental health status, often reported by IC patients, may be attributable to the persistent pain of IC. Also, the patient may feel isolated and unable or unwilling to discuss the condition because of social taboos regarding the discussion of urinary disorders.[1] According to Koziol et al.,[6] >55% of patients with IC reported depression and approximately 30% felt undeserving or worthless.

Stress is frequently mentioned as a cause of IC. However, little evidence exists to support this claim.[1] Various potential causes are currently under investigation and include allergies, infection, reflex sympathetic dystrophy and toxic urinary agents. The lack of knowledge about the origin of IC poses several obstacles to diagnosing the condition as well as developing a cure for it. Barger and Woolner[14] estimated that between 91% and 95% of IC cases in the US remain undiagnosed.[14] It is not uncommon for patients to visit up to five physicians and wait up to 5 years for proper diagnosis.[15] In addition to difficulties with diagnosis, once a patient is diagnosed there is no cure for their condition. Treatment, therefore, remains palliative and is administered to lessen the severity of IC-related symptoms.[1]

Pentosan polysulfate (PPS) is the only US FDA-approved oral drug therapy indicated to treat the bladder pain and discomfort associated with IC. Patients may also receive other non-indicated drug therapies such as aspirin (acetylsalicylic acid), ibuprofen, antihistamines or antidepressants to control the symptoms. Hydrodistention, bladder instillation and surgery may also be used to treat patients with IC.

Despite the growing awareness of IC as a distinct debilitating and painful medical condition, little is

known about the disease's economic burden. One objective of this study is to quantify the magnitude of both the direct and indirect costs of IC in the first year after diagnosis from both the private third-party payer's and the employer's perspective. A second objective is to characterise the treatment pattern of IC patients, particularly regarding use of PPS. Additionally, the prevalence of selected co-morbidities in patients with IC was investigated.

Methodology

Data

This study was based on data from a de-identified administrative claims database containing medical and demographic information on employees, retirees and their spouses, and dependants of 16 large self-insured companies in the US. The companies have national operations and coverage of approximately 2 million lives in a broad array of industries and occupations. Administrative claims data for fee-for-service managed care plans were available for the period from January 1999 to December 2002; no health maintenance organisation enrolees were included. The data included all the medical and prescription drug claims for all enrolees (and their spouses and dependents) as well as disability claims for enrolees who were also active employees; all enrolees have a drug benefit. The inclusion of both the medical and disability claims for these individuals allowed for the estimation of both the direct and the indirect costs of IC patients and their matched controls. Monthly eligibility data were also available for all enrolees.

Identification of Interstitial Cystitis (IC) Patients Study Sample

Individual enrolees under the age of 65 years with at least one IC diagnosis (International Classification of Disease [ICD]-9-CM of 595.1x) were identified as IC patients. The date of the first IC diagnosis following a minimum period of 12 weeks with continuous insurance plan eligibility (enrolment) was defined as the index date, and the 12-week period prior to it as the pre-index period. The 52-week period following the index date was defined as the study period, or post-index period. Patients without a minimum of 12 weeks (3 months) continuous eligibility for the pre-index period or a minimum of 52 weeks (12 months) continuous eligibility for the study period were excluded from the study. Patients older than 64 years on their index dates, (i.e. older than 65 years by the end of the study period) were excluded because their claims data would be incomplete.

The analysis of treatment patterns excluded *a priori* PPS patients who used a narcotic analgesic more than once a week during the 90 days following the start of PPS, because PPS has not been formally approved for use in this patient population. However, all IC patients were included in the cost analysis to provide a complete understanding of the 'real world' excess costs of IC patients, irrespective of whether they received an indicated treatment.

Identification of Matched Control Samples

A non-IC patient was defined as a patient without any diagnosis of IC. For every IC patient, we randomly selected two non-IC patients with an age difference of <5 years and the same gender, geographic region of residence and employee status. Because control patients cannot have an IC diagnosis, they do not have a natural index date. The comparable lag time between initial insurance enrolment and the index date of IC patients was used to derive index dates for the control sample.

Treatment Pattern Analysis

The pharmacological and non-pharmacological therapies of IC patients were studied using prescription drug claims and medical procedure claims in the 2 months after the index date diagnosis. This 2-month observation period was chosen to minimise potential bias caused by delayed drug prescribing or filling and delay of procedures.

As the only oral therapy indicated for IC is PPS, the prevalence rate of prescription of PPS, either as monotherapy or as polytherapy in combination with other selected drugs (i.e. antidepressants, antihistamines, antispasmodics and anti-inflammatory drugs) was assessed. Additionally, the prevalence rate of prescriptions for these same selected drugs but without the indicated oral drug therapy (PPS) was assessed. The drugs included in the analysis

were selected on the basis of their relevance to the treatment of IC, according to the Interstitial Cystitis Association.[16] In addition, we estimated prevalence rates for use of non-pharmacological treatments, such as bladder distention and bladder instillation.

Compliance with PPS was estimated using medication possession ratios based on the 123 patients who were treated with PPS. Medication possession ratios were examined in three time windows: (i) 90 days, (ii) 180 days, and (iii) 52 weeks following the start of PPS therapy for each patient. In each time period, the percentage of days in which a patient had a supply of PPS was defined as the medication possession ratio for the drug.

Co-morbidities Associated with IC

This study also examined the co-morbidity profile of IC patients. The incidence rates of selected psychiatric and somatic conditions, for the 12-week period before the index date through 52 weeks after the index date, were estimated for IC patients using the diagnosis codes in patients' medical claims. The prevalence rates observed among IC patients were compared with those in the non-IC sample using a measure of relative risk (RR). Chi-square tests were conducted to estimate statistical significance of the RR.

Cost Comparison

Average excess costs of IC patients for the first year after diagnosis were calculated from a private third-party payer's perspective (i.e. direct medical costs) and an employer's perspective (i.e. direct medical and indirect medically related work loss costs). Patients' medical costs (direct costs) were estimated using the amount paid by the insurer for medical and pharmacy claims; patient out-of-pocket costs were not included. Medical costs were also disaggregated into drug, inpatient, outpatient (which included all physician services, as well as hospital outpatient and emergency department care) and other (e.g. home care, independent laboratory) costs. In contrast to the treatment pattern analysis of use of selected drugs relevant to the treatment of IC, the cost analysis included costs for all drugs regardless of indication. The distribution of direct medical costs was examined to understand the extent to which outliers may influence the study's results.

Medically related work loss costs (indirect costs) were calculated using employee patients' disability claims, their imputed absenteeism when associated with a medical visit (i.e. computed as workdays missed while hospitalised and one-half day work loss for medical visits, as well as any work days missed that met disability requirements), and actual employer payments information. Industry-specific average daily salaries were applied to calculate work loss in dollar terms.

In this study, we considered the average costs incurred by IC patients during the first year after diagnosis, rather than the costs incurred during an IC episode. Using the full 52-week cost data immediately following the index date might lead to an overestimate of IC patients' average first-year costs, since part of 52-week costs would be associated with interventions related to the index date event by definition. Therefore, we only used the last 48 weeks of the 52-week post-index period to calculate costs and extrapolated them to annual (52-week) costs. We also conducted a sensitivity analysis using the full 52 weeks following index date to calculate the first year costs. We expected higher direct medical cost estimates for this analysis compared with the extrapolated 48-week analysis as a result of the index date-related medical resource utilisation.

The study sample included patients with bladder cancer. Because it is possible that costs would be driven up by the high costs associated with treatment of bladder cancer, a sensitivity analysis was conducted for IC patients excluding those with bladder cancer (and their matched controls) for both the total patient group and the employee sample.

About 2% of the medical claims were missing information on the amount paid. Stratified hot-deck imputations were applied to randomly selected observed paid amounts from claims with the same procedure code, specialty, place of service and type of service. Patients whose cost values could not be imputed using this method were dropped from the cost analyses. Thus, both IC patients and non-IC controls included in the analyses had complete (or imputed) direct and indirect cost data. When comparing patient costs from a private third-party payer's perspective, we included only medical costs

(e.g. inpatient, outpatient and drug costs) in the analyses. However, to analyse costs from an employer's perspective, only employees with disability information were included in the analyses (i.e. patients for whom the disability claims would have been available had they been submitted).

Patient medical costs were adjusted to 2002 $US using the medical Consumer Price Indexes (CPI). Medically related work loss costs were adjusted to 2002 $US using the general CPI.

Excess costs of IC patients were first estimated descriptively as the difference in average first year costs between the IC sample and the control sample. First, t-tests were used to identify statistical significances in the mean cost differences between the IC and control groups. To further control for potential differences (such as co-morbidities) between the IC patients and non-IC control individuals, not accounted for in matching the samples, a multivariate two-part regression model was used to reduce the bias in the estimates of the average first year excess costs of IC.[17] A two-part model was used because 17.4% of the analytic sample had zero direct medical costs. The estimated excess cost of IC was defined as the difference between the observed costs of IC patients and their predicted costs had they been non-IC patients. The model adjusted for observed differences in patient characteristics and co-morbidities between the IC and non-IC samples, while explicitly estimating the probability of the cost being positive, and the actual dollar values conditional on the cost being positive. Age, gender, region, employee status, company and co-morbidities, including cardiovascular conditions (stroke, heart attack, heart failure, hypertensive diseases and other), respiratory conditions (asthma and chronic obstructive pulmonary conditions) and cancer, were included in this model; the co-morbidities were selected on the basis of representing some of the most common and costly conditions that could be expected, and for practical reasons could not be an exhaustive list.

Log transformed costs were used in the model estimation. A White test was used to test for heteroscedasticity using the first and second moments of the independent variables in the regression.[18] Results were retransformed back to dollar values using the smearing estimation method. Statistical significance was evaluated using the 'bootstrap' method.[19]

Results

A total of 749 IC patients were identified in the claims database as our study sample. Of these, 86.2% (n = 646) were women and the average age at the index date was 44.9 years (see table I). Note that the IC sample size is reduced from the overall number of IC patients in the database (n = 1947) by various exclusion criteria and is not reported as a measure of incidence of this condition.

The matched sample comprised 1498 control individuals without IC.

Treatment Patterns for IC

A total of 731 IC patients who were not frequent users of narcotic analgesics were included in the treatment pattern analysis. The treatment patterns for pharmacological therapies of IC are summarised in table II. Of the 731 IC patients, 17% (n = 123) of patients received PPS therapy within the first 2 months after the index date; of these, 69% took one or more 'other' relevant medications (i.e. antidepressants, antihistamines, anti-spasmodics or anti-inflammatory drugs) during the same period. Approximately 37% (n = 268) of patients received

Table I. Demographic characteristics of interstitial cystitis (IC) and non-IC samples

Demographic	IC [n = 749 (%)]	Non-IC [n = 1498 (%)]
Sex [female (%)]	646 (86.2)	1292 (86.2)
Average age (y)[a]	44.9	44.9
Age groups (y)		
0–14	7 (0.9)	14 (0.9)
15–19	27 (3.6)	54 (3.6)
20–24	34 (4.5)	68 (4.5)
25–29	39 (5.2)	78 (5.2)
30–34	38 (5.1)	76 (5.1)
35–39	87 (11.6)	174 (11.6)
40–44	92 (12.3)	184 (12.3)
45–49	112 (15.0)	224 (15.0)
50–54	105 (14.0)	210 (14.0)
55–59	125 (16.7)	250 (16.7)
60–64	83 (11.1)	166 (11.1)

a Patients' age is determined as the age on the index date. Patients older than 64 years on their index dates (i.e. >65 years by the end of the study period) were excluded because of incomplete claims data.

Table II. Treatment patterns – pentosan polysulfate (PPS) and other drug therapies[a] and non-pharmacological treatments for patients with interstitial cystitis (n = 731)[b]

Treatment	n	% of total
Pharmacological treatments		
Any PPS	123	17
PPS monotherapy	38	5
PPS and other selected drugs[c] combined	85	12
No PPS	608	83
Other selected drugs[c]	268	37
No drug treatment	340	47
Total[b]	731	100
Non-pharmocological treatments		
Bladder distention	128	18
Bladder instillation	14	2
TENS	26	4
No medical procedure	595	81
Total[d]	731	100

a Treatment alternatives were based on prescriptions filled during the first 2 months after index date.

b In this analysis, we excluded PPS patients who used narcotic analgesics more often than once every week during the first 90 days of PPS use.

c Other selected drugs included antidepressants, antihistamines, antispasmodics and anti-inflammatories.

d Some patients had more than one nonpharmacological treatment, so numbers add to more than 100%.

TENS = transcutaneous electrical nerve stimulation.

only 'other' drug therapies. Approximately 47% of IC patients (n = 340) received no prescription drug treatment for IC within 2 months after the index date.

Table II presents the non-pharmacological interventions that IC patients received within the first 2 months after the index date. Bladder distention was the most common procedure, and was performed on 18% of diagnosed IC patients (n = 128). Approximately 81% (n = 595) of IC patients were not treated with any medical procedure.

As a measure of compliance, the medication possession ratio of PPS for the 123 IC patients who received PPS treatment during the first 2 months after the index date indicated that, on average, patients had a supply for 75% of the 90-day period following the start date; for 63% of the 180-day period following the PPS start date; and for 54% of the up to 52-week period following the start date.

Co-morbidities

Table III compares the prevalence of selected co-morbidities between IC patients and the matched non-IC individuals, for the 12-week period before the IC diagnosis through 52 weeks after the IC diagnosis. As indicated by the higher RRs in patients with IC, there appeared to be an association ($p < 0.05$) between IC and some somatic conditions such as prostatitis (RR = 40.0), endometriosis (RR = 7.4), vulvodynia (RR = 6.9), chronic pelvic pain (RR = 5.8), urinary tract infections (RR = 5.1), irritable bowel syndrome (RR = 4.9) and fibromyalgia (RR = 2.6). IC patients were also approximately 3- to 4-fold more likely ($p < 0.05$) to experience psychiatric conditions such as major depressive disorders (RR = 2.8) and anxiety disorder (RR = 4.4).

Table III. Prevalence of selected co-morbidities[a] in patients with interstitial cystitis (IC)

Co-morbidity	IC (n = 749)		Non-IC (n = 1498)		Relative risk[b]
	count (A)	% (B)	count (C)	% (D)	(B/D)
Prostatitis (acute and chronic) or prostatodynia	21	2.80	1	0.07	40.0
Prostatitis (acute and chronic)	20	2.67	1	0.07	38.1
Endometriosis	26	3.47	7	0.47	7.4
Vulvodynia	137	18.29	40	2.67	6.9
Chronic pelvic pain (male or female)	163	21.76	56	3.74	5.8
Urinary tract infection	283	37.78	110	7.34	5.1
Irritable bowel syndrome	54	7.21	22	1.47	4.9
Anxiety disorder	40	5.34	18	1.20	4.5
Major depression disorder	52	6.94	37	2.47	2.8
Fibromyalgia	65	8.68	50	3.34	2.6

a Co-morbidities are sorted by the relative risk, from high to low.

b All comparisons versus the non-IC population were statistically significant ($p \leq 0.05$).

Table IV. Average cost (2002 $US) comparison for interstitial cystitis (IC) and non-IC patient samples. Direct costs in the 12-month period post-index date: all patients[a]

Direct cost	IC (A) [n = 730]	Non-IC (B) [n = 1460]	Difference	Ratio of IC estimate to control group estimate (A/B)
Drugs				
pentosan polysulfate	234.5	0.0	234.5**	-
antidepressants	131.1	67.6	63.5**	1.9
antihistamines	71.8	42.7	29.1**	1.7
antispasmodics	4.4	1.9	2.5	2.3
anti-inflammatories	43.2	19.6	23.6**	2.2
narcotic analgesics	85.8	13.6	72.2**	6.3
other pain medications	56.8	30.0	26.9**	1.9
all other drugs	944.8	451.9	493.0	2.1
total drug cost	1572.4	627.2	945.2**	2.5
Medical services by type of treatment				
hospital inpatient	1303.9	577.4	726.6*	2.3
outpatient/MD/ED	3463.0	1532.9	1930.1**	2.3
other (e.g. laboratory or patient's home)	274.4	120.6	153.8*	2.3
Total medical cost	5041.3	2230.9	2810.4**	2.3
Total direct cost	6613.7	2858.1	3755.6**	2.3

a Includes all patients aged <65 years.

ED = emergency department; **MD** = physician visit; * $p \leq 0.05$, ** $p \leq 0.01$ for comparison between IC and non-IC populations.

Cost of IC

Descriptive Analysis

The cost analysis included 730 IC patients (of the initial 749 patients) with complete observed or imputed cost data, and their corresponding 1460 non-IC controls. Table IV presents the average first year direct costs of IC patients compared with those of the matched samples. From a private third party payer's perspective, the average direct cost of an IC patient for the first year was $US6614, which was 2.3-fold the cost of a non-IC patient ($US2858 annually). The difference ($US3756) was the excess cost of IC patients, which was statistically significant at the 99% significance level.

As we expected, the sensitivity analysis using the full 52 weeks following the index date yielded a higher direct medical cost in the first year after diagnosis ($US7567) compared with using the 48-week period ($US6614). However, the estimates are close enough that it did not affect the overall conclusions of the study.

The sensitivity analysis excluding bladder cancer patients only changed the results marginally. Of the study sample, 11 patients in the 730 IC patient sample with complete cost data (1.5%) and one patient in the 152 IC patient employee sample (0.6%) had bladder cancer. Sensitivity analysis excluding bladder patients led to a 3% reduction of direct healthcare costs for the overall IC patient sample, and a 0.01% reduction for the IC employee sample. An examination of the cost outliers did not change the study's conclusions.

Of the $US6614 first year direct cost of IC patients, $US1572 was spent on drugs (not limited to drugs indicated for IC) and $US5041 was spent on medical services. Outpatient medical services (including physician visits) accounted for the largest portion of medical service costs of IC patients, approximately 69%, or $US3463. Of this amount, approximately 30% ($US1070) was for medical services because of accidents. Table V provides a detailed breakdown of selected medical service costs, including additional statistics on costs associated with emergency services and accidents. While total accident costs of IC patients were 7-fold greater than those of non-IC patients, this difference was not statistically significant.

Table VI summarises the results of the cost analyses from an employer's perspective, which were based on 152 IC employees who had disability information available and their 304 non-IC controls.

Table V. Average cost (2002 $US) comparison for interstitial cystitis (IC) and non-IC patient samples. Selected types of direct costs in the 12-month period post index date: all patients[a]

Cost	IC (A) [n = 730]	Non-IC (B) [n = 1460]	Difference (A − B)	Ratio of IC estimate to control group estimate (A/B)
Emergency services	99.1	39.6	59.5*	2.5
Accidents				
alcohol	253.6	6.7	247.0	38.0
drug	260.4	0.6	259.7	409.8
injury/poisoning	553.3	140.9	412.5	3.9
vehicle accident	2.8	0.9	2.0	3.2
total accident cost	1070.2	149.1	921.1	7.2

a Includes all patients aged <65 years.

* $p \leq 0.01$ for comparison between IC and non-IC populations.

The costs of IC employees followed the same patterns as the costs of the general IC patient population. The average total cost (direct plus indirect cost) of an IC employee in the first year after diagnosis ($US6813) was 2-fold greater than that of a non-IC employee. The difference between the costs of the two groups ($3320) was statistically significant at the 99% significance level. Indirect costs of IC patients exceeded those of non-IC patients by $US726 for 1 year, a difference that was also significant at the 99% significance level. Table VII presents details on the cost breakdown from an employer's perspective for emergency visits and accidents. Employee patients with IC had total accident costs that were 3-fold greater than those of non-IC patients (significant at 95% significance level).

Table VI. Average cost (2002 $US) comparison for interstitial cystitis (IC) and non-IC employee samples.[a] Direct and indirect costs in the 12-month period post index date

Cost	IC (A) [n = 152]	Non-IC (B) [n = 304]	Difference (A − B)	Ratio of IC estimate to control group estimate (A/B)
Sample size	152	304		
Drugs				
pentosan polysulfate	333.9	0.0	333.9*	
antidepressants	114.3	81.6	32.7	1.4
antihistamines	54.6	36.2	18.4	1.5
antispasmodics	7.0	2.4	4.5	2.9
anti-inflammatories	35.7	14.5	21.1*	2.5
narcotic analgesics	11.5	3.6	7.8	3.2
other pain medications	45.4	23.1	22.3	2.0
all other drugs	658.0	392.4	265.6*	1.7
Total drug cost	1260.0	553.5	706.5*	2.3
Medical services by type of treatment				
hospital inpatient	906.9	495.1	411.8	1.8
outpatient/MD/ED	2926.4	1343.3	1583.1*	2.2
other (e.g. patient's home or laboratory)	130.0	237.4	−107.3	0.5
Total medical cost	3963.3	2075.7	1887.6*	1.9
Total direct cost	5223.3	2629.2	2594.1*	2.0
Work loss due to medical services	897.0	518.3	378.7*	1.7
Work loss due to disability	692.3	345.3	347.0	2.0
Total indirect cost	1589.3	863.6	725.7*	1.8
Total cost	**6812.6**	**3492.8**	**3319.8***	**2.0**

a Includes all employees aged <65 years with disability information available.

ED = emergency department; **MD** = physician visit; * $p \leq 0.001$ for comparison between IC and non-IC populations.

Table VII. Average cost (2002 $US) comparison for interstitial cystitis (IC) and non-IC employee samples.[a] Direct and indirect costs in the 12-month period post index date

Cost	IC (A) [n = 152]	Non-IC (B) [n = 304]	Difference (A – B)	Ratio of IC estimate to control group estimate (A/B)
Emergency services	100.0	43.4	56.6	2.3
Accidents				
alcohol	0.0	0.0	0.0	
drug	3.8	2.3	1.6	1.7
injury/poisoning	371.6	110.0	261.6*	3.4
vehicle accident	5.2	3.9	1.4	1.4
total accident cost	380.7	116.1	264.5*	3.3

a Includes all employees aged <65 years with disability information available.

* $p \leq 0.05$ for comparison between IC and non-IC populations.

Two-Part Regression Model Analysis

The IC cost estimates from the descriptive analysis may be subject to bias because of observable differences between the IC and non-IC patient samples, for example co-morbid conditions. To adjust for potential bias, we conducted a multivariate regression analysis, adjusting for patient demographics and co-morbidities. A White test using the first and second moments of the independent variables did not reject the null hypothesis of heteroscedasticity ($p = 0.76$). Therefore, the smearing estimate method was applied under the homoscedasticity assumption.

From a private third-party payer's perspective, IC imposes a cost burden of $US2309 in the first year after diagnosis, while from an employer's perspective, we estimated the indirect cost at $US726 per IC patient employee in the first year. All regression results were statistically significant at the 95% level of significance.

While the indirect cost burden (from the employer's perspective) estimated using the regression model closely matches the estimate based on descriptive statistics presented in table VI, the direct cost burden from the private third party payer's perspective is somewhat lower using the regression model adjusting for pre-existing co-morbidities than that based on the descriptive statistics presented in table IV ($US2309 vs $US3756), that is, controlling for co-morbidity and demographic differences between the two samples reduces the excess cost associated with IC based on descriptive statistics.

Discussion

This study finds that IC is a costly disease for both private third-party payers and employers, on the order of that for other painful conditions. For example, the annual excess direct costs of employees treated for arthritis and back and neck disorders were estimated at $US2520 and $US2239, respectively (year of costing 2000), compared with $US2594 for IC employees (table VI.[20] From the private third party payer's perspective, the average IC patient costs $US3756 in excess direct costs and, from the employer's perspective, an IC employee patient incurrs excess costs of $US3320 in both direct and indirect costs in the first year.

The high prevalence of co-morbid physical conditions such as chronic pelvic pain and urinary tract infection among IC patients suggests that these conditions accompany IC more often than may have previously been thought. Furthermore, it might be interesting to conduct clinical studies to investigate the prevalence of IC in patients with these disorders, as IC may occur more commonly than previously expected in such patients. The results presented here suggest that IC patients are also more likely to have mental conditions such as depression and anxiety. Although it is not possible from our data to determine the nature of the relationship between IC and the co-morbidities investigated, our results do seem to highlight the importance of early diagnosis and appropriate treatment of IC to minimise any potential psychological impact of the condition, and possibly better identify and manage (or even prevent) co-morbid conditions.

A relatively small percentage of IC patients in our study sample were treated with PPS (17%), while a substantial proportion of IC patients did not receive any drug therapy following diagnosis of IC (47%). Because PPS is the only FDA-approved oral drug therapy indicated to treat the bladder pain and discomfort associated with IC, these results suggest the potential lack of adequate treatment of the IC patient population, even when IC is diagnosed. Another possibility is that patients may be treated with other drugs that do not have an IC indication.

Future studies should explore the cost impact related to potential misdiagnosis and delayed diagnosis of IC; it is possible that early awareness among clinicians of bladder conditions as a source of pain may reduce healthcare costs that result from incorrect diagnosis and related, unwarranted drug use (such as antibacterial treatment for IC diagnosed as a urinary tract infection). For example, one hypothesis to investigate is that the higher drug costs of patients treated with PPS is offset by lower medical service costs, compared with the costs of IC patients not treated with PPS. Given that IC can be readily mistaken for other conditions that manifest similar symptoms (urinary tract infection, chronic pelvic pain), there may be large medical cost offsets associated with avoiding such cases of misdiagnosis and instituting early and appropriate treatment. However, it needs to be determined whether earlier treatment would introduce higher drug costs and how overall costs would be affected. The present study was aimed at exploring the overall excess cost of IC, and future studies should be conducted to explore the drivers of IC costs.

The results presented here have the common limitation associated with claims data analyses in the absence of detailed clinical information. It is possible that some of the patients included in the study sample were misdiagnosed. Depending on the nature and severity of the true underlying disease, the cost estimate may be biased upwards or downwards. Furthermore, only patients with IC who had a clinically documented IC diagnosis could be included, and previous data have indicated that IC remains undiagnosed in many individuals.[8] Without direct access to the patients, the cost estimates for IC cannot be adjusted directly to account for potential misdiagnosis. Knowledge about the full extent of IC misdiagnosis (and its impact on cost considerations) requires further research using clinical data (linked to cost information). This study was also limited by the restriction to patients under the age of 65 years, which was a necessary restriction because complete medical claims and cost records for Medicare patients were not available.

Medical costs normally have a skewed distribution (i.e. a small proportion of patients use the majority of healthcare resources). Therefore, the distribution of direct medical costs was examined to determine the sensitivity of the results to the presence of outliers. Outliers may only be an issue if one or two patients' costs change the overall estimate significantly, which was not the case. Furthermore, we wished to reflect the costs for patients with IC in the real world, where some individual patients may have unusually high costs.

It should also be noted that costs were based on medical claims, regardless of the medical reason for the claim. Additionally, the drugs included for analysis of treatment patterns were selected for their relevance to the treatment of IC, but we were not able to identify whether these drugs were being prescribed for IC. However, the aim of the analysis was to examine the differences in costs and treatment patterns between individuals with or without with IC, regardless of how these differences were generated.

A further limitation of the analysis is that the indirect costs only included disability claims and absenteeism associated with medical visits, as neither productivity reduction nor absenteeism without any medical claim record can be measured using claims data. Therefore, the indirect costs of IC estimated in this study are likely to be underestimates of the true indirect costs from an employer's perspective.

In the two-part model analysis, the number of potential co-morbidities and co-existing conditions to adjust for could have been very large. The study only adjusted for some of the more common or costly conditions and we understand that the list is not exhaustive. The regression analysis served as a way to reduce, but not necessarily eliminate, the bias caused by uneven distribution of co-existing conditions between the IC and non-IC sample, and also as

a sensitivity analysis to validate the results from the descriptive analysis.

Conclusions

The results of this study indicate that IC is associated with significant costs, with average per-patient costs in the first year after diagnosis being more than $US3000 greater than those in individuals without IC, whether considered from the private third party payer's or employer's perspective.

Our results also suggest that the prevalence of certain co-morbidities such as prostatitis, endometriosis, vulvodynia, chronic pelvic pain and urinary tract infection is higher in patients with IC than previously thought. Although not investigated in the current study, this raises the possibility that more accurate diagnosis and earlier treatment could reduce healthcare costs through better management (or even prevention) of these co-morbidities.

The low rate at which PPS, the only FDA-approved oral drug therapy for IC, is being used was also highlighted in the study. Future studies should investigate whether implementation of earlier and more appropriate treatment decreases the overall costs of IC.

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