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The impact of high-risk and chronic opioid use among commercially insured endometriosis patients on health care resource utilization and costs in the United States

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Abstract

Objectives: Evaluate all-cause and endometriosis-related health care resource utilization and costs among newly diagnosed endometriosis patients with high-risk versus low-risk opioid use or patients with chronic versus non-chronic opioid use.

Methods: A retrospective analysis of IBM MarketScan® Commercial Claims data from 2009 to 2018 was performed for females aged 18 to 49 with newly diagnosed endometriosis (International Classification of Diseases, Ninth Edition code: 617.xx; International Classification of Diseases, Tenth Edition code: N80.xx). Two sub-cohorts were identified: high-risk (⩾1 day with ⩾90 morphine milligram equivalents per day or ⩾1-day concomitant benzodiazepine use) or chronic opioid utilization (⩾90-day supply prescribed or ⩾10 opioid prescriptions). High-risk or chronic utilization was evaluated during the 12-month assessment period after the index date. Index date was the first opioid prescription within 12 months following endometriosis diagnosis. All outcomes were assessed over 12-month post-assessment period while adjusting for demographic and clinical characteristics.

Results: Out of 61,019 patients identified, 18,239 had high-risk opioid use and 5001 chronic opioid use. Health care resource utilization drivers were outpatient visits and pharmacy fills, which were higher among high-risk versus low-risk patients (outpatient visits: 17.49 vs 15.51; pharmacy fills: 19.58 vs 16.88, $p < 0.0001$). Chronic opioid users had a higher number of outpatient visits (19.53 vs 15.00, $p < 0.0001$) and pharmacy fills (23.18 vs 16.43, $p < 0.0001$) compared to non-chronic opioid users. High-risk opioid users had significantly higher all-cause health care costs compared to low-risk opioid users (US$16,377 vs US$13,153; $p < 0.0001$). Chronic opioid users also had significantly higher all-cause health care costs compared to non-chronic opioid users (US$20,930 vs US$12,272; $p < 0.0001$). Similar patterns were observed among endometriosis-related HCRU, except pharmacy fills among high-risk and chronic sub-cohorts.

Conclusion: This analysis demonstrates significantly higher all-cause and endometriosis-related health care resource utilization and total costs for high-risk opioid users compared to low-risk opioid users among newly diagnosed endometriosis patients over 1 year. Similar trends were observed for comparing chronic opioid users with non-chronic opioid users, except for endometriosis-related pharmacy fills and associated costs.

Keywords

cost, endometriosis, health care resource utilization, opioid, pain, real-world evidence

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Introduction

Endometriosis, a chronic gynecological disease, is defined by an endometrial-type tissue outside of the uterine cavity that leads to inflammation and pelvic pain.[1] Approximately 6%–10% of the United States, Canadian, and European women of reproductive age are affected.[2–6] Endometriosis symptoms can include severe pelvic pain, even infertility.[7] In a global survey of 1000 women with endometriosis, including women from the United States, 68%–71% presented with pain, 22%–30% presented with infertility, and 7.3%–29% presented with an endometrioma.[8] Additional symptoms include bowel and bladder dysfunction, dysmenorrhea, abnormal uterine bleeding, low back pain, non-menstrual chronic pelvic pain, dyspareunia, and chronic fatigue.[1,4,7,8] Sexual dysfunction in women with endometriosis exacerbates psychological symptoms, such as depression and alexithymia.[9,10]

Endometriosis is a progressive disease where many patients deteriorate over time; therefore, timely diagnosis and treatments are important.[11] First-line treatment consists of nonsteroidal anti-inflammatory drugs (NSAIDs) and hormonal agents including estrogen-progestin contraceptives or progestin-only medications.[4,12,13] Second-line treatment have historically included agents such as gonadotropin-releasing hormone agonists or danazol which have additional side effects.[4,12,13] Emerging therapies, such as oral gonadotropin-releasing antagonists, are presenting additional options for therapy. If medical management fails for deep infiltrating disease, women may proceed with surgical evaluation and treatment with laparoscopy to excise/ablate the lesions; or even to hysterectomy with or without ovarian conservation.[4,12,13] In the United States, more than 100,000 hysterectomies are performed annually for endometriosis.[14]

Women with endometriosis have a greater risk at receiving opioids.[15,16] Compared with matched women without endometriosis, women with endometriosis have a greater risk to fill a prescription for an opioid (adjusted risk ratio (RR): 2.91) and for filling prescriptions for prolonged use, a higher dose, and/or a benzodiazepine.[15] Women with endometriosis also have a greater risk at chronic opioid use (adjusted RR: 2.11).[15,16] A 2019 retrospective analysis of opioid-using women with endometriosis found that the average (standard deviation, SD) number of opioid prescriptions received was 4.6 (6.7), average days supply was 61.1 (128.6) days, and 18.1% received $\geqslant$90 days of opioids.[17] A 2016 survey of fellows conducted by the American College of Obstetricians and Gynecologists (ACOG) fellows found that 24% of patients with endometriosis received opioid medication prescribed by US OB/GYNs.[16] A similar percentage of OB/GYNs were reported (27.6%) in a 2019 retrospective analysis, with other top opioid-prescribing specialties including family (23.4%) and internal medicine (9.2%) physicians.[17]

High-risk or chronic opioid use may act as gateways to opioid addiction, opioid-use disorders, illicit opioid use, and even opioid-related overdose deaths, thereby increasing the health care resource utilization (HCRU) and costs.[18,19] A previous study of adults without cancers had shown a high HCRU and expenditures among patients on chronic opioid therapy (COT) compared to patients without COT.[20] Similarly, in addition to poor quality of life[21] and pain,[22] endometriosis has also been linked to increased direct and indirect costs.[23–27] Compared to women without endometriosis, HCRU are significantly higher among endometriosis patients, including higher all-cause hospitalizations, emergency room (ER) visits, physician visits, outpatient visits, OB/GYN visits, and endometriosis-related surgical procedures.[24–26,28] Similarly, all-cause costs among endometriosis patients are significantly higher compared to controls, ranging from US$11,556–US$42,020 versus US$4315–US$6124 annually, respectively.[24–28] The total annual societal burden of endometriosis-associated symptoms was estimated at US$78.05 billion.[20]

However, to our knowledge, no studies provided insights on the impact of high-risk or chronic opioid use on HCRU and costs among endometriosis patients with opioid use. Therefore, a retrospective cohort study was conducted among newly diagnosed commercially insured endometriosis patients in United States to evaluate both all-cause and endometriosis-related HCRU and costs by service categories (outpatient, ER, inpatient, and pharmacy) among opioid-using endometriosis patients with high-risk or chronic opioid utilization.

Methods

Data source

This study is based on IBM® MarketScan® Commercial administrative claims database from 1 January 2009 to 30 September 2018 (study period). The Commercial Claims and Encounters database is comprised of fully adjudicated medical and pharmaceutical claims for more than 225 million unique patients from 300 contributing employers and 40 contributing health plans across the United States, which is approximately 62.9 million covered lives per year. It includes inpatient and outpatient diagnoses (in both International Classification of Diseases, Ninth Edition (ICD-9) and Tenth Edition (ICD-10) format) and procedures (in Current Procedural Terminology (CPT) and Health care Common Procedure Coding System (HCPCS) formats) and both retail and mail-order prescription records. Available data on prescription records include the National Drug Code (NDC), J-codes, as well as the quantity of the medication dispensed. Additional data elements include demographic variables (age, gender, and geographic region), health plan type (e.g. health maintenance organization (HMO) and preferred provider organization), provider specialty, and eligibility dates related to plan enrollment and participation. These data represent commercially insured lives, and data contributors are generally self-insured employers.

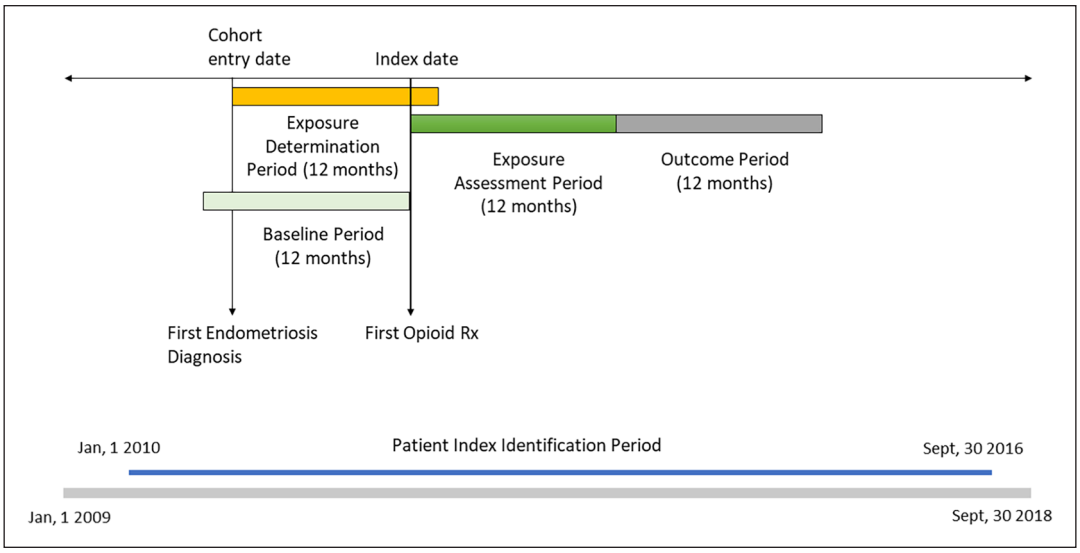

Figure 1. Timeline for evaluation of outcomes associated with high-risk and chronic opioid use.
Exposure determination period: time period from date of new endometriosis diagnosis running out to 12 months after diagnosis, which was used for determination of exposure (opioids vs no opioids). The date of first opioid prescription in the exposure determination period was determined as the index date.
Exposure assessment period: 12 months post-index date used for determination of high-risk and chronic opioid use.
Baseline period: 12 months prior to index date (not including index date) for evaluation of baseline covariates.
Outcome period: 12 months after the end of the exposure assessment period for determination of HCRU and costs.
Patient index identification period: time period for the potential index date of a patient. The period is between 1 January 2010 and 30 September 2016 since a minimum enrollment of 12 month prior to and 24 month post-index date was required for each patient.

This study is based on claims data. All database records are statistically de-identified and certified to be fully compliant with US patient confidentiality requirements set forth in the Health Insurance Portability and Accountability Act (HIPAA). Because this study used only de-identified patient records and did not involve the collection, use, or transmittal of individually identifiable data, institutional review board approval to conduct this study was not necessary.

Study design

This study was a retrospective analysis among female patients with newly diagnosed endometriosis. All-cause and endometriosis-related direct HCRU and costs were evaluated during a 12-month period for patients with high-risk versus low-risk or chronic versus non-chronic opioid use.

Study population

Females newly diagnosed with endometriosis (ICD-9 code: 617.xx; ICD-10 code: N80.xx) in the United States aged 18–49 between 1 January 2010 and 30 September 2015 were included, with the first endometriosis diagnosis date as the cohort entry date (Figure 1). Patients were required to have at least one record of opioids use within 12-month following their cohort entry date. Index date was defined as the first opioid prescription date. A minimum enrollment of 12-month prior to and 24-month post index date was required for each patient. Patients were excluded if they were diagnosed with malignant neoplasm anytime during the study period, had a diagnosis of endometriosis anytime prior to the cohort entry date during the study period, or had specific insurance plan types, such as HMO and point of service (POS) with capitation, during the 12-month baseline and 24-month follow-up periods.

Two stratification methods were used. First, the overall population was stratified into high-risk and low-risk opioid users. High-risk opioid use was defined as at least one day with ⩾90 morphine milligram equivalents per day or ⩾1-day concomitant opioid and benzodiazepine use during 12-month period post-index date (exposure assessment period). Second, the overall population was stratified into chronic and non-chronic opioid users. Chronic opioid use was defined as ⩾90 days of opioid supply prescribed or ⩾10 opioid prescriptions during the 12-month period post-index date (exposure assessment period).

Outcome measures

All-cause and endometriosis-related direct HCRU and costs were evaluated in total and by service category (outpatient, inpatient, ER, and pharmacy) over the 12-month post-exposure assessment period. Pharmacy fills were estimated using adjudicated prescription claims. Total length of stay (LOS) associated with inpatient visits were also evaluated. All costs were adjusted to 2018 costs using medical component of Consumer Price Index (CPI).

Adjudicated claims with primary or secondary diagnoses of endometriosis were used to calculate endometriosis-related HCRU and costs.[29] Endometriosis-related pharmacy fills and costs were further specified for drugs primarily used in endometriosis management (danazol, goserelin, leuprolide, nafarelin, and estrogen/progestin oral contraceptives).

Study variables

Patient demographics measured on the index date, such as age, region, and insurance type, were reported. Clinical characteristics identified in the 12-month baseline period including the pain conditions (back/neck pain, joint pain/arthritis, headache/migraine, neuropathic pain, fibromyalgia, and other pain conditions including chest/visceral pain/wound/trauma), mental health conditions (anxiety/depression, mood disorders, post-traumatic stress disorder (PTSD), and substance-use disorders (SUD)), prior opioid use, prior endometriosis-surgery and pregnancy status, and the Charlson Comorbidity index (CCI) were also represented. CCI is a continuous measure, which was computed using all medical claims (inpatient and outpatient) for 15 conditions (myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, dementia, hemiplegia or paraplegia, diabetes (with and without complications), moderate to severe renal disease, mild and moderate to severe liver disease, peptic ulcer disease, rheumatologic disease, HIV/AIDS), since patients with malignant neoplasms were excluded from this analysis.

Statistical analysis

Categorical variables were presented as counts and percentages; the significance for observed differences between high-risk and low-risk or chronic and non-chronic opioid users were evaluated using chi-square tests. Continuous variables were reported as mean with SD and *t*-tests were used to compare the mean differences between high-risk and low-risk or chronic and non-chronic opioid users.

Multivariable regression analyses were used to produce adjusted results for all outcomes of interest. Covariates included patient demographics and clinical characteristics, baseline outcomes, and index year. For HCRU, generalized linear models (GLM) with negative binomial (NB) distribution and log link function were used. For all-cause costs, GLM with Gamma distribution and log link function were used. A US$1 cost was added to those with zero costs.[30] The 95% confidence intervals (CIs) for the mean ratio were also reported.

Since the percentage of patients with zero costs was greater than 10% for endometriosis-related costs, two-part models were used. First-part model estimated the probability of having a non-zero cost and the second part model estimated the costs encountered for those who have non-zero costs.[31] The 95% CIs for the mean ratio between high-risk and low-risk or chronic and non-chronic opioid users were generated using bootstrapping method (repeated for 500 times).

All statistical analyses were performed using SAS version 9.4 (SAS, Cary, NC). Statistical significance was determined by p value < 0.05.

Results

A total of 61,019 patients were identified in this analysis with 18,239 high-risk opioid users and 5001 chronic opioid users.

Demographic and clinical characteristics

High-risk versus low-risk opioid users. High-risk opioid users had a lower mean (SD) age compared to low-risk opioid users (38.1 (7.2) vs 38.3 (7.4) years, $p = 0.0032$; Table 1). Mean CCI was significantly higher for high-risk opioid users versus low-risk opioid users (0.33 (0.68) vs 0.25 (0.59), $p < 0.0001$). The high-risk opioid group had a significantly greater number of pain conditions compared to the low-risk opioid group (1.36 vs 0.96, $p < 0.0001$). The high-risk group had a higher percentage of prior opioid use pre-index compared to the low-risk group (58.9% vs 39.6%, $p < 0.0001$). Prior endometriosis-related surgery utilization was similar across groups (high-risk opioid users: 51.1%, low-risk opioid users: 51.3%, $p = 0.6242$).

Chronic versus non-chronic opioid users. Similar mean (SD) ages were observed among chronic and non-chronic opioid users (38.1 (7.1) vs 38.3 (7.4) years, $p = 0.0670$; Table 1). The mean CCI was almost two-fold higher among chronic opioid users compared to non-chronic opioid users (0.47 (0.84) vs 0.25 (0.59), $p < 0.0001$). Chronic opioid users had a significantly greater number of pain conditions (2.10) compared to patients without chronic opioid use (0.99, $p < 0.0001$). Prior opioid use pre-index was significantly ($p < 0.0001$) higher among chronic opioid users (93.3%) versus non-chronic opioid users (41.1%). Prior endometriosis-related surgery was reported less frequently among chronic opioid users compared to non-chronic opioid users (43.0% vs 52.0%, $p < 0.0001$).

HCRU outcomes

High-risk versus low-risk opioid users. Results from multivariable regression analyses indicated that HCRU over 1 year was significantly higher for high-risk opioid users compared to low-risk opioid users in all service categories, except for endometriosis-related pharmacy fills (Table 2).

Estimated mean all-cause outpatient visits per patient among high-risk opioid users were higher than that for low-risk opioid users (17.49 vs 15.51, mean ratio: 1.13).

Table 1. Baseline demographic and clinical characteristics for endometriosis patients with opioid use in the United States.

Characteristic	Patients with high-risk opioid use		Patients with low-risk opioid use		p-value	Patients with chronic opioid use		Patients without chronic opioid use		p-value
	N	%	N	%		N	%	N	%	
Number of unique patients	18,239	100%	42,780	100%		5001	100%	56,018	100%	
Age group at index										
18–29	2351	12.9%	5613	13.1%	<0.0001	619	12.4%	7345	13.1%	<0.0001
30–39	7110	39.0%	15,648	36.6%		2010	40.2%	20,748	37.0%	
40–49	8778	48.1%	21,519	50.3%		2372	47.4%	27,925	49.9%	
Age at index										
Mean (SD)	38.1	7.2	38.3	7.4	0.0139	38.1	7.1	38.3	7.4	0.067
Region at index										
Northeast	1969	10.8%	5871	13.7%	0.0034	573	11.5%	7267	13.0%	<0.0001
North Central	4003	21.9%	9683	22.6%		1198	24.0%	12,488	22.3%	
South	9023	49.5%	21,668	50.6%		2355	47.1%	28,336	50.6%	
West	3147	17.3%	5296	12.4%		827	16.5%	7616	13.6%	
Unknown	97	0.5%	262	0.6%		48	1.0%	311	0.6%	
Plan type at index										
Comprehensive	252	1.4%	760	1.8%	0.0011	139	2.8%	873	1.6%	<0.0001
EPO	221	1.2%	585	1.4%		62	1.2%	744	1.3%	
POS	1757	9.6%	4018	9.4%		442	8.8%	5333	9.5%	
PPO	13,256	72.7%	30,175	70.5%		3636	72.7%	39,795	71.0%	
CDHP	1460	8.0%	4356	10.2%		411	8.2%	5405	9.6%	
HDHP	682	3.7%	1741	4.1%		157	3.1%	2266	4.0%	
Unknown	611	3.3%	1145	2.7%		154	3.1%	1602	2.9%	
Charlson comorbidity index (CCI) score*										
Mean (SD)	0.33	0.68	0.25	0.59	<0.0001	0.47	0.84	0.25	0.59	<0.0001
Number of pain conditions (based on the following six pain categories)										
Mean (SD)	1.36	1.27	0.96	1.08	<0.0001	2.10	1.33	0.99	1.09	<0.0001
Number of patients with back/neck pain										
Yes	7108	39.0%	11,760	27.5%	<0.0001	3119	62.4%	15,749	28.1%	<0.0001
No	11,131	61.0%	31,020	72.5%		20,762	37.1%	40,269	71.9%	
Number of patients with joint pain/arthritis										
Yes	8165	44.8%	14,904	34.8%	<0.0001	3082	61.6%	19,987	35.7%	<0.0001
No	10,074	55.2%	27,876	65.2%		1919	38.4%	36,031	64.3%	
Number of patients with headache/migraine										
Yes	2674	14.7%	3712	8.7%	<0.0001	1215	24.3%	5171	9.2%	<0.0001
No	15,565	85.3%	39,068	91.3%		3786	75.7%	50,847	90.8%	
Number of patients with neuropathic pain										
Yes	1048	5.7%	1443	3.4%	<0.0001	524	10.5%	1967	3.5%	<0.0001
No	17,191	94.3%	41,337	96.6%		4477	89.5%	54,051	96.5%	
Number of patients with fibromyalgia										
Yes	1772	9.7%	2141	5.0%	<0.0001	1031	20.6%	2882	5.1%	<0.0001
No	16,467	90.3%	40,639	95.0%		3970	79.4%	53,136	94.9%	
Number of patients with other pain conditions (chest/visceral pain/wound/trauma)										
Yes	4018	22.0%	7162	16.7%	<0.0001	1541	30.8%	9639	17.2%	<0.0001
No	14,221	78.0%	35,618	83.3%		3460	69.2%	46,379	82.8%	
Number of mental health conditions (based on the following four mental health categories)										
Mean (SD)	0.54	0.85	0.29	0.65	<0.0001	0.77	0.97	0.32	0.69	<0.0001
Number of patients with anxiety/depression										
Yes	5523	30.3%	7302	17.1%	<0.0001	2049	41.0%	10,776	19.2%	<0.0001
No	12,716	69.7%	35,478	82.9%		2952	59.0%	45,242	80.8%	
Number of patients with mood disorders										
Yes	3584	19.7%	4464	10.4%	<0.0001	1363	27.3%	6685	11.9%	<0.0001
No	14,655	80.3%	38,316	89.6%		3638	72.7%	49,333	88.1%	

(Continued)

Table 1. (Continued)

Characteristic	Patients with high-risk opioid use		Patients with low-risk opioid use		p-value	Patients with chronic opioid use		Patients without chronic opioid use		p-value
	N	%	N	%		N	%	N	%	
Number of patients with post-traumatic stress disorder (PTSD)										
Yes	280	1.5%	230	0.5%	<0.0001	132	2.6%	378	0.7%	<0.0001
No	17,959	98.5%	42,550	99.5%		4869	97.4%	55,640	99.3%	
Number of patients with substance-use disorder (SUD)										
Yes	386	2.1%	243	0.6%	<0.0001	309	6.2%	320	0.6%	<0.0001
No	17,853	97.9%	42,537	99.4%		4692	93.8%	55,698	99.4%	
Number of patients with prior opioid use										
Yes	10,738	58.9%	16,945	39.6%	<0.0001	4666	93.3%	23,017	41.1%	<0.0001
No	7501	41.1%	25,835	60.4%		335	6.7%	33,001	58.9%	
Number of patients with prior endometriosis-related surgery										
Yes	9326	51.1%	21,967	51.3%	0.6242	2149	43.0%	29,144	52.0%	<0.0001
No	8913	48.9%	20,813	48.7%		2852	57.0%	26,874	48.0%	
Number of patients with pregnancy										
Yes	939	5.1%	2477	5.8%	0.0016	240	4.8%	3176	5.7%	0.0103
No	17,300	94.9%	40,303	94.2%		4761	95.2%	52,842	94.3%	

SD = standard deviation.
*CCI score was underestimated for some patients because of the intrinsic study design (i.e. patients with malignant neoplasms in the baseline were excluded from this study).

Table 2. Adjusted mean HCRU for endometriosis patients with opioid use in the United States.

Characteristics	High- vs low-risk opioid users				Chronic vs non-chronic opioid users			
	High-risk opioid users	Low-risk opioid users	Estimated mean ratio with 95% CI	p-value	Chronic opioid users	Non-chronic opioid users	Estimated mean ratio with 95% CI	p-value
All-cause HCRU								
Outpatient visits	17.49	15.51	1.13 (1.11–1.14)	<0.0001	19.53	15.00	1.30 (1.27–1.33)	<0.0001
ER visits	0.71	0.53	1.33 (1.29–1.39)	<0.0001	0.86	0.52	1.67 (1.58–1.77)	<0.0001
Inpatient visits	0.21	0.16	1.30 (1.23–1.38)	<0.0001	0.27	0.14	1.87 (1.72–2.04)	<0.0001
Total LOS	0.83	0.65	1.29 (1.17–1.42)	<0.0001	1.24	0.59	2.10 (1.80–2.46)	<0.0001
Pharmacy fills	19.58	16.88	1.16 (1.14–1.18)	<0.0001	23.18	16.43	1.41 (1.38–1.45)	<0.0001
Endometriosis–related HCRU								
Outpatient visits	0.265	0.223	1.19 (1.11–1.28)	<0.0001	0.336	0.197	1.71 (1.53–1.91)	<0.0001
ER visits	0.008	0.004	1.87 (1.48–2.37)	<0.0001	0.012	0.004	3.19 (2.37–4.28)	<0.0001
Inpatient visits	0.008	0.006	1.42 (1.17–1.71)	0.0003	0.011	0.005	2.33 (1.80–3.01)	<0.0001
Total LOS	0.033	0.022	1.51 (1.10–2.07)	0.0101	0.043	0.019	2.27 (1.37–3.78)	0.0016
Pharmacy fills	0.054	0.056	0.98 (0.86–1.10)	0.6962	0.054	0.055	0.98 (0.79–1.22)	0.8585

CI: confidence interval; ER: emergency room; HCRU: health care resource utilization; LOS: length of stay.

Estimated mean all-cause ER visits per patient were 0.71 and 0.53 for high- and low-risk opioid users, respectively (mean ratio: 1.33). All-cause inpatient visits per patient for high-risk opioid users were greater than that for low-risk opioid users (estimated mean: 0.21 vs 0.16, mean ratio: 1.30), along with longer total LOS (estimated mean: 0.83 vs 0.65 days, mean ratio: 1.29). On average, all-cause pharmacy fills per patient among high-risk opioid users were 19.58 compared to 16.88 among low-risk opioid users (mean ratio: 1.16). All the comparisons were significant with $p < 0.0001$.

Except for endometriosis-related pharmacy fills, estimated mean of endometriosis-related HCRU was significantly higher for high-risk opioid users compared to that for low-risk opioid users (outpatient: 0.265 vs 0.223, mean ratio: 1.19 and $p < 0.0001$; ER: 0.008 vs 0.004, mean ratio: 1.87 and $p < 0.0001$; inpatient: 0.008 vs 0.006, mean ratio: 1.42 and $p = 0.0003$; total LOS: 0.033 vs 0.022 days, mean

Table 3. Adjusted mean costs for endometriosis patients with opioid use in the United States.

Characteristics	High- vs low-risk opioid users				Chronic vs non-chronic opioid users			
	High-risk opioid users	Low-risk opioid users	Estimated mean ratio with 95% CI	p-value	Chronic opioid users	Non-chronic opioid users	Estimated mean ratio with 95% CI	p-value
All-cause costs								
Total	US$16,377	US$13,153	1.25 (1.22–1.27)	<0.0001	US$20,930	US$12,272	1.71 (1.64–1.77)	<0.0001
Medical	US$14,561	US$11,709	1.24 (1.21–1.27)	<0.0001	US$18,563	US$10,869	1.71 (1.64–1.78)	<0.0001
Pharmacy	US$2255	US$1806	1.25 (1.22–1.28)	<0.0001	US$2809	US$1717	1.64 (1.56–1.71)	<0.0001
Endometriosis-related costs								
Total	US$525	US$420	1.25 (1.12–1.39)		US$656	US$380	1.73 (1.49–2.03)	
Medical	US$520	US$413	1.26 (1.13–1.42)		US$651	US$363	1.79 (1.54–2.07)	
Pharmacy	US$14	US$12	1.10 (0.92–1.34)		US$19	US$15	1.26 (0.90–1.69)	

CI: confidence interval; ER: emergency room; HCRU: health care resource utilization; LOS: length of stay.

ratio: 1.51 and $p=0.0101$). However, high- and low-risk opioid users had similar endometriosis-related pharmacy fills (estimated mean: 0.054 vs 0.056 days, mean ratio: 0.98, $p=0.6962$).

Similar trends were observed for unadjusted all-cause and endometriosis-related HCRU (Supplemental Table 1). On average, high-risk opioid users had higher HCRU per patient compared to low-risk opioid users. All the comparisons were significant with $p<0.0001$ except for endometriosis-related pharmacy fills.

Chronic versus non-chronic opioid users. Results from multivariable regression analyses indicated that HCRU more than 1 year was significantly higher for chronic opioid users compared to non-chronic opioid users in all service categories except for endometriosis-related pharmacy fills (Table 2).

Estimated mean all-cause outpatient visits per patient among chronic opioid users were higher than that for non-chronic opioid users (19.53 vs 15.00, mean ratio: 1.30). Estimated mean all-cause ER visits per patient were 0.86 and 0.52 for chronic and non-chronic opioid users, respectively (mean ratio: 1.67). All-cause inpatient visits per patient for chronic opioid users were greater than that for non-chronic opioid users (estimated mean: 0.27 vs 0.14, mean ratio: 1.87), along with longer total LOS (estimated mean: 1.24 vs 0.59 days, mean ratio: 2.10). On average, all-cause pharmacy fills per patient among chronic opioid users were 23.18 compared to 16.43 among non-chronic opioid users (mean ratio: 1.41). All the differences were significant with $p<0.0001$.

Except for endometriosis-related pharmacy fills, estimated mean endometriosis-related HCRU was significantly higher for chronic opioid users compared to that for non-chronic opioid users (outpatient: 0.334 vs 0.197, mean ratio: 1.71 and $p<0.0001$; ER: 0.012 vs 0.004, mean ratio: 3.19 and $p<0.0001$; inpatient: 0.011 vs 0.005, mean ratio: 2.33 and $p<0.0001$; total LOS: 0.043 vs 0.019 days, mean ratio: 2.27 and $p=0.0016$). However, chronic and non-chronic opioid users had similar endometriosis-related pharmacy fills (estimated mean: 0.054 vs 0.055 days, mean ratio: 0.98, $p=0.8585$).

Similar trends were observed for unadjusted all-cause and endometriosis-related HCRU (Supplemental Table 1). On average, chronic opioid users had higher HCRU per patient compared to non-chronic opioid users. All the comparisons were significant with $p<0.0001$, except for endometriosis-related pharmacy fills.

Health care costs

High-risk versus low-risk opioid users. Results from multivariable regression analyses indicated that estimated mean total costs over the 1 year was higher for high-risk opioid users compared to low-risk opioid users (Table 3).

Estimated mean all-cause total costs among high-risk opioid users were higher than that for low-risk opioid users (US$16,377 vs US$13,153, mean ratio: 1.25). Estimated mean all-cause medical costs were US$14,561 and US$11,709 for high- and low-risk opioid users, respectively (mean ratio: 1.24). Estimated mean all-cause pharmacy costs for high-risk opioid users were greater than that for low-risk opioid users (estimated mean: US$2255 vs US$1806, mean ratio: 1.25). All the comparisons were significant with $p<0.0001$.

Estimated mean endometriosis-related total costs among high-risk opioid users were higher than that for low-risk opioid users (US$525 vs US$420, mean ratio: 1.25). Estimated mean endometriosis-related medical costs were US$520 and US$413 for high- and low-risk opioid users, respectively (mean ratio: 1.26). Estimated mean endometriosis-related pharmacy costs for high-risk opioid users were greater than that for low-risk opioid users (estimated mean: US$14 vs US$12, mean ratio: 1.10). All the comparisons were significant except for endometriosis-related pharmacy costs.

Similar trends were observed for unadjusted all-cause and endometriosis-related health care costs (Supplemental Table 2). On average, high-risk opioid users had higher all-cause and endometriosis-related health care costs compared to low-risk opioid users. All the comparisons were significant expect for endometriosis-related pharmacy costs. High utilization of outpatient visits was observed in this study for both high- and low-risk opioid users. Outpatient management was the driver of both HCRU magnitude and cost for these populations. Unadjusted all-cause costs for high-risk opioid users were driven by outpatient costs (55%); other contributors were pharmacy costs (20%), inpatient costs (19%), and ER costs (6%). Similar patterns were observed for all-cause costs among low-risk opioid users.

Chronic versus non-chronic opioid users. Results from multivariable regression analyses indicated that estimated mean total costs over 1 year was significantly higher for chronic opioid users compared to non-chronic opioid users (Table 3).

Estimated mean all-cause total costs among chronic opioid users were higher than that for non-chronic opioid users (US$20,930 vs US$12,272, mean ratio: 1.71). Estimated mean all-cause medical costs were US$18,563 and US$10,869 for chronic and non-chronic opioid users, respectively (mean ratio: 1.71). Estimated mean all-cause pharmacy costs for chronic opioid users were greater than that for non-chronic opioid users (estimated mean: US$2809 vs US$1717, mean ratio: 1.64). All the comparisons were significant with $p < 0.0001$.

Estimated mean endometriosis-related health care costs among chronic opioid users were higher than that for non-chronic opioid users (US$656 vs US$380, mean ratio: 1.73). Estimated mean endometriosis-related medical costs were US$651 and US$363 for chronic and non-chronic opioid users, respectively (mean ratio: 1.79). Estimated mean endometriosis-related pharmacy costs for chronic opioid users were greater than that for non-chronic opioid users (estimated mean: US$19 vs US$15, mean ratio: 1.26). All the comparisons were significant except for endometriosis-related pharmacy costs.

Similar trends were observed for unadjusted all-cause and endometriosis-related health care costs (Supplemental Table 2). On average, chronic opioid users had higher all-cause and endometriosis-related health care costs compared to non-chronic opioid users. All the comparisons were significant with $p < 0.0001$, expect for endometriosis-related pharmacy fills. High utilization of outpatient visits was observed in this study for both chronic- and non-chronic opioid users. Outpatient management was the driver of both HCRU magnitude and cost for these populations. Unadjusted all-cause costs for chronic opioid users were driven by outpatient costs (51%), while other contributors were pharmacy costs (22%), inpatient costs (21%), and ER costs (5%). Similar patterns were observed for all-cause costs among non-chronic opioid users.

Discussion

To our knowledge, this is the first study that evaluated all-cause and endometriosis-related HCRU and costs associated with high-risk or chronic opioid use in a commercially insured endometriosis population in the United States. Within this analysis, opioid management is more directly captured in the all-cause outcomes, while endometriosis-related outcomes help characterize the disease-specific management baseline of this population.

Both unadjusted and multivariable analysis results demonstrated that high-risk opioid users had significantly higher outpatient, ER, and inpatient visits, as well as, longer total LOS compared to low-risk opioid users regardless if it was all-cause or endometriosis related. Compared to low-risk opioid users, high-risk opioid users had significantly higher all-cause pharmacy fills, although they had similar endometriosis-related pharmacy fills. This pharmacy fill trend aligns with the author's expectations, as the endometriosis-related pharmacy fills were defined with specific medications (including danazol, goserelin, leuprolide, nafarelin, and estrogen/progestin oral contraceptives), all-cause pharmacy fills would represent opioids and other indications' non-opioid medications. The HCRU analysis stratified by chronic and non-chronic opioid use also showed the same trend. In addition, chronic opioid users were also associated with significantly higher HCRU for all service categories except for endometriosis-related pharmacy fills compared to non-chronic opioid users. The differences in HCRU between chronic and non-chronic opioid users were greater than that between high- and low-risk opioid users. For example, estimated mean all-cause outpatient visits per patient for high-risk opioid users were 13% more than that for low-risk opioid users (mean ratio: 1.13; 95% CI (1.11–1.14)), but chronic opioid users had 30% more all-cause outpatient visits per patient on average compared to non-chronic opioid users (mean ratio: 1.30; 95% CI (1.27–1.33)).

All-cause total, medical, and pharmacy costs for high-risk opioid users were significantly higher than those for low-risk opioid users according to both unadjusted and multivariable analysis. The endometriosis-related costs analysis results showed that significantly higher total and medical costs were observed in high-risk opioid users compared to low-risk opioid users, but not for endometriosis-related pharmacy costs. Similar results were also identified when comparing chronic opioid users to non-chronic opioid users. In addition, the differences in costs between chronic and non-chronic opioid users were greater than that between high- and low-risk opioid users. For example, chronic opioid users had 71% more all-cause total costs per patient compared to non-chronic opioid users (estimated mean: US$20,930 vs US$12,272, mean

ratio: 1.71; 95% CI (1.64–1.77) but high-risk opioid users had 25% more all-cause total costs per patient compared to low-risk opioid users (estimated mean: US$16,377 vs US$13,153, mean ratio: 1.25; 95% CI (1.22–1.27).

Based on this study, total direct health care costs for newly diagnosed endometriosis patients with opioid use were largely driven by medical costs. Specifically, around 70% of medical costs were outpatient costs, followed by 25% inpatient costs and 5% ER costs. Patients with high-risk opioid use incurred all-cause total costs of US$1365 per patient per month (PPPM) compared to patients with low-risk opioid use (US$1096 PPPM), which were aligned with the existing literature (total costs of endometriosis ranged US$963–3502 PPPM).[24–28] For patients with chronic opioid use, all-cause total costs were US$1744 PPPM compared to patients with non-chronic opioid use (US$1023 PPPM), which was also consistent with previous studies.[24–28]

The results for both of these populations align with the existing literature on HCRU.[24] The two drivers were physician office visits and prescription claims among endometriosis patients verse the control population (percentage of patients with office visits: 97% vs 87%; outpatient prescription claim: 96% vs 83%). Other contributors identified were ER (32% vs 18%) and inpatient visits (29% vs 6%).[24] Outpatient management is observed to drives cost, but this is a medical complex population at-risk for further HCRU. As this is a newly diagnosed population, we may expect HCRU utilization to continue to rise in the future.

One of the strengths of this analysis is that the controls in this analysis are endometriosis patients, unlike the existing endometriosis literature which has previously used patients without endometriosis.[20,24–28,32,33] Another strength of this study is the exposure period is separated from the outcomes period. Finally, this study utilizes a geographically diverse commercial database.

Limitations

This study has several limitations inherent to claims data. The findings of this study are limited to IBM MarketScan commercial population and may not be generalizable to the entire United States. Claims data do not allow use of certain variables such as race, pain, and severity. Chronic opioid use was defined as at least 90 days of opioid supply prescribed or at least 10 opioid prescriptions during the 12-month period post-index date. The exact reason for chronic opioid use cannot be determined from the claims data; only observed according to the definition of chronic use. Reasons for chronic opioid use among endometriosis patients may vary and be impacted by the type, location, severity, and persistence of pain and symptoms. Women with endometriosis can experience pain in many areas, including low back pain, non-menstrual chronic pelvic pain, dyspareunia, dysmenorrhea, dyschezia, or pain in the vaginal and abdominopelvic area. In addition, the persistence of symptoms, such as bowel/bladder dysfunction, abnormal uterine bleeding, or infertility, in the setting of failed medical (first-line use of NSAIDs or hormonal agents) or surgical management (laparoscopy or hysterectomy) may lead to chronic opioid use. This analysis does not capture opioid prescriptions paid for by cash or illicitly obtained for or administered during an inpatient study. Upcoding or miscoding may not reflect actual estimations and the analysis can only identify prescriptions filled and not prescriptions taken. The statistical differences do not imply clinical differences. Zero cost was observed for some patients in the cohort, which might be caused by billing error or claims adjustment in the database. The uncertainty of this may underestimate the true health care costs. However, appropriate modeling techniques were adopted in order to minimize the bias. The study's objective was to describe the impact of opioids use patterns on health care burden among newly diagnosed endometriosis patients in the United States, but did not include identifying the underlying reason for using opioids, so patients may be prescribed opioids for a condition other than endometriosis. Finally, causal inference cannot be drawn from this analysis considering the intrinsic observational study design.

Conclusion

This study provides valuable and detailed information on the economic burden for newly diagnosed endometriosis patients with high-risk or chronic opioid use. Results from this analysis demonstrated significantly higher all-cause and endometriosis-related HCRU and total costs associated with high-risk or chronic opioid use in this population, except for endometriosis-related pharmacy fills and associated costs. From a managed care perspective, the burden of early management appears to be driven by outpatient services. Given the likely need for continued pain management in this population, trends in HCRU and costs may be expected to further rise as women will need care throughout their lifetime for this chronic disease management.

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Supplemental material

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