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ORIGINAL RESEARCH

Disease and Economic Burden Associated with Recurrent Pericarditis in a Privately Insured United States Population

David Lin · François Laliberté · Christine Majeski · Matt Magestro · Dominique Lejeune · Mei Sheng Duh · Michelle Lim-Watson · John F. Paolini

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ABSTRACT

Introduction: Approximately 30% of patients with a first acute pericarditis episode experience a recurrence ≤ 18 months; ~ 15% experience multiple recurrences. This study assessed the recurrence and economic burden among patients with multiple recurrences.

Methods: Adults with idiopathic pericarditis were identified in the OptumHealth Care Solutions, Inc., database (2007–2017). Recurrent pericarditis (RP) was defined as ≥ 2 episodes of care separated by > 28 days; multiple recurrences were defined as ≥ 2 recurrences.

Results: Among 944 patients with RP, 375 (39.7%) experienced multiple recurrences and were propensity score-matched 1:1 to 375 patients without recurrence. Among patients with multiple recurrences, median disease duration (time from first episode to end of last recurrence, confirmed by a 1.5-year recurrence-free period) was 2.84 years. The multiple recurrences cohort had higher rates of hospitalizations per-patient-per-month (PPPM) than the no recurrence cohort (rate ratio [95% confidence interval (CI)] = 2.22 [1.35–3.65]). Mean total healthcare costs were significantly higher in the multiple recurrences versus no recurrence cohort ($2728 vs. $1568 PPPM, cost ratio [95% CI] = 1.74 [1.29–2.32]), mainly driven by higher hospitalization costs in the multiple recurrences cohort (mean: $1180 vs. $420 PPPM, cost ratio [95% CI] = 2.81 [1.80–4.66]). Mean work loss costs were higher in the multiple recurrences versus no recurrence cohort ($696 vs. $169 PPPM, cost ratio [95% CI] = 4.12 [1.64–9.61]). In patients with multiple recurrences, mean cost of the first episode was $19,189; subsequent recurrences ranged from $2089 to $7366 (second recurrence = $6222).

Conclusion: In conclusion, among patients with multiple pericarditis recurrences, disease symptoms persisted several years, and healthcare and work loss costs were further compounded in this subset of patients.

Keywords: Recurrent pericarditis; Economic burden; Costs; Healthcare resource utilization; Real world

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D. Lin (✉) · C. Majeski
Abbott Northwestern Hospital, Minneapolis, MN, USA
e-mail: David.Lin@allina.com

F. Laliberté · D. Lejeune
Groupe d'analyse, Ltée, Montreal, QC, Canada

M. Magestro · M. Lim-Watson · J. F. Paolini
Kiniksa Pharmaceuticals Corp., Lexington, MA, USA

M. S. Duh
Analysis Group Inc., Boston, MA, USA

Key Summary Points

Approximately 30% of patients with a first acute pericarditis episode experience a recurrence ≤ 18 months; ~ 15% experience multiple recurrences

This study assessed the recurrence/economic burden among patients with multiple recurrences of pericarditis

In this US real-world study, nearly 40% of patients with recurrent pericarditis had multiple recurrences

These patients experienced disease symptoms that persisted several years, and healthcare and work loss costs were further compounded in this subset of patients

FDA-approved, safe and effective corticosteroid-sparing treatment options are warranted to rapidly resolve recurrences and future flares and reduce the economic burden of pericarditis in patients for whom conventional treatments fail to provide adequate disease control

INTRODUCTION

Pericarditis refers to inflammation of the double-walled sac that surrounds the heart and often presents as debilitating chest pain that is sharp and pleuritic [1]. Pericarditis is diagnosed based on the presence of at least two of the following criteria: (1) chest pain, (2) pericardial friction rub, (3) changes observed on electrocardiogram (e.g., diffuse ST segment elevation), and (4) new or worsening pericardial effusion [1]; markers of humoral activation such as C-reactive protein and evidence of inflammation by imaging modalities (e.g., magnetic resonance imaging) can also help support diagnosis [1]. While there are multiple causes of pericarditis (e.g., bacterial infection, cardiac injury, and malignancy), up to 90% of incident cases in developed countries are considered "idiopathic" and commonly presumed to be of viral origin [2]. Rare life-threatening complications, such as cardiac tamponade and effusive-constrictive pericarditis, may emerge and require immediate treatment [3, 4].

Up to 30% of patients with pericarditis experience recurrent disease, defined by the occurrence of a subsequent pericarditis episode following a symptom-free period of at least 4–-6 weeks [3]. Recurrences are often the result of inadequate response to conventional therapies (i.e., patients who are refractory or intolerant to colchicine and/or non-steroidal anti-inflammatory drugs [NSAIDs]) or some form of immunogenic response that perpetuates the underlying disease [3, 5]. While most cases of recurrent pericarditis (RP) are classified as "idiopathic" [6], autoinflammation plays a central role in the onset of recurrences in patients with evidence of inflammation, either alone or in conjunction with other known causes, such as pericardial injury syndromes (e.g., after pericardiotomy) [1, 4, 6–8]. RP is associated with a diminished health-related quality of life (HRQoL) due to the direct and indirect symptoms of the disease, underlying comorbidities, and adverse events associated with conventional treatments [1, 3, 5, 9, 10]. Up to 55% of patients with one recurrence go on to experience multiple recurrences (approximately 15% of the incident pericarditis population) [3, 11], often despite treatment with colchicine [5].

Successful management of pericarditis involves treating pericardial inflammation to rapidly resolve symptoms, prevent recurrences, and improve HRQoL [3, 9]. While there is a lack of treatment guidelines for pericarditis in the USA, current therapies used to manage pericarditis include anti-inflammatory treatments such as NSAIDs or aspirin, colchicine, and corticosteroids, along with exercise restriction [1]. However, until recently there were no Food and Drug Administration (FDA)-approved therapies for recurrent pericarditis, and disease management with conventional treatment has been associated with clinically important limitations. Despite rapid resolution of pericarditis symptoms with their use, corticosteroids are

associated with an increased risk of recurrence [12], and their use (especially at high doses and both short and long-term) is discouraged because of the risk of corticosteroid-dependence and numerous associated long term adverse events [13–16]. RP patients typically receive prolonged periods of treatments prescribed off-label, including NSAIDS, colchicine, chronic corticosteroids, immunosuppressants, or pericardiectomy—an invasive and surgical procedure to remove all of the pericardium [1, 3]. While colchicine in combination with NSAIDs demonstrated efficacy among patients with multiple recurrences [17], a significant proportion of patients treated with this regimen will subsequently experience RP. Consequently, patients with multiple recurrences may suffer from a higher disease burden and use more healthcare services [4, 18]. Thus, there is clearly a high unmet need for new treatments among patients with multiple pericarditis recurrences [5].

Our review of published literature did not identify published studies that have assessed the economic burden of pericarditis in patients with multiple recurrences. Three prior studies evaluated the cost of pericarditis-related hospitalizations in the US but did not stratify analyses based on the number of recurrences [19–21]. Therefore, it is important to better document clinical and economic outcomes in this subpopulation. The objectives of this study were to (1) describe the clinical characteristics and recurrence burden (i.e., disease duration and recurrence frequency) and (2) assess direct healthcare costs and indirect work loss costs of patients with "idiopathic" pericarditis who had multiple recurrences relative to those of patients with no recurrence in the US.

METHODS

Data Source

Data from Optum Health Care Solutions, Inc., collected from January 1, 2007, through March, 31, 2017, were analyzed for this study. This database contains administrative claims for > 19.1 million privately insured individuals (i.e., employees, spouses, dependents, and retirees) covered by 84 self-insured Fortune 500 companies. Information on plan enrollment, duration of eligibility, individuals' demographics, medical diagnoses (reported with International Classification of Diseases [ICD] codes), procedures, and prescription drugs is available. In addition, work loss data are available for 43 of the 84 companies (i.e., approximately 4.4 million lives), including short- and long-term disability claims. The data are anonymized and comply with the Health Insurance Portability and Accountability Act; therefore, no reviews by an institutional review board were required per Title 45 of CFR, Part 46.101(b)(4) [22].

Study design and population

A retrospective cohort design was used (Fig. 1). Adult patients who had at least one medical claim with a diagnosis of pericarditis were included (see Table S1 for complete list of International Classification of Diseases [ICD] codes); the index date was defined as the date of the first of these claims. Furthermore, only patients with non-health maintenance organization and non-Medicare coverage were included to ensure that relevant drug and medical claims were captured. Patients were additionally required to have at least 12 months of continuous health plan eligibility prior to the index date (i.e., baseline period) and ≥ 18 months of subsequent eligibility post-index date.

Patients with non-idiopathic pericarditis (i.e., pericarditis not of viral origin) were excluded, as they represent a small fraction of incident cases in developed countries, based on the presence of claims specific for non-idiopathic pericarditis (e.g., bacterial infection) or a related condition or procedure recorded in the 90 days (or 30 days for physical trauma, post-pericardiotomy syndrome [PSS], and cardiac procedure [e.g., percutaneous coronary intervention (PCI)]) preceding the index date.

Pericarditis-related health care resources and costs, including follow-up visits for each pericarditis episode, were aggregated into an 'episode of care.' An episode of care was defined as all pericarditis-related claims recorded

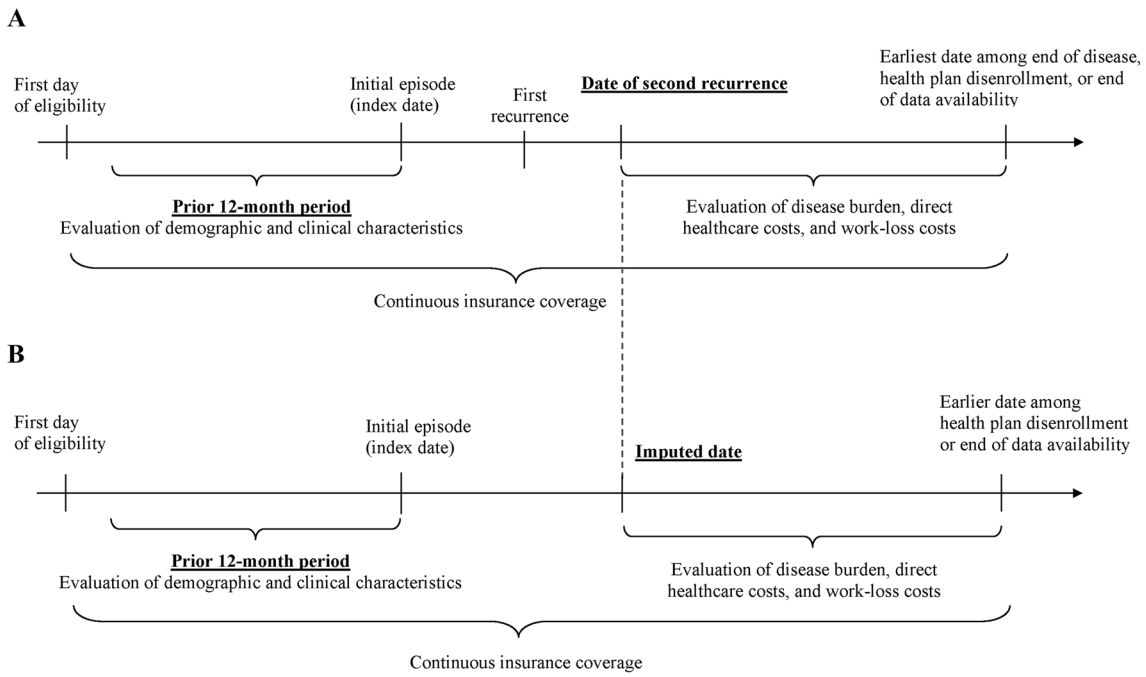

Fig. 1 Study design scheme for **A** patients in the multiple recurrences cohort and **B** patients in the no recurrence cohort

sequentially without a gap > 28 days. Patients were classified in the 'multiple recurrences' cohort if they had at least two recurrent episodes of care.

Study outcomes

Recurrence burden was evaluated among patients with multiple recurrences and included disease duration and frequency of recurrences. Disease duration was defined as the time from the first pericarditis diagnosis to the end of the last episode of care; this period needed to be followed by ≥ 1.5 years without a pericarditis diagnosis for a patient to be deemed disease-free; otherwise, patients were censored at health plan disenrollment or end of data availability and considered to have persistent disease. The frequency of recurrences was evaluated in the subset of patients with multiple recurrences and at least 3-year disease duration to ensure sufficient follow-up.

All-cause healthcare resource utilization (HCRU) and all-cause direct healthcare costs were assessed per patient per month (PPPM) among patients with multiple recurrences and those without recurrence. All-cause HCRU included hospitalizations, outpatient visits, and emergency department (ED) visits; all-cause healthcare costs were stratified into medical and pharmacy costs, with medical costs further broken down into hospitalization, outpatient, ED, and other costs (i.e., transportation, dentist, laboratory, home healthcare, and all costs not included in the other categories). For patients in the multiple recurrences cohort, these outcomes were evaluated from the date of the second recurrence to the end of disease duration. For patients in the no recurrence cohort, these outcomes were evaluated from a randomly imputed date after the index date to the earlier event among health plan disenrollment or end of available follow-up data. The imputed date for patients in the no recurrence cohort allowed for both cohorts to be assessed at a similar point in time after the index date.

Work loss costs, including medically related absenteeism and short-/long-term disability costs, were also assessed in the subset of employed patients with work loss coverage in both cohorts. Medically related absenteeism costs were calculated based on the assumption

that a hospitalization required employees to miss a full day of wage equivalent and that ED, outpatient, and other visits required employees to miss half a day of wage equivalent. Disability costs were evaluated for employees based on short- and long-term disability benefits.

The total cost of each pericarditis episode, stratified into all-cause healthcare costs and work loss costs, was evaluated among patients in the multiple recurrences cohort for each pericarditis episode starting from the index episode. Healthcare costs associated with the occurrence of one specific type of healthcare visit (i.e., mean cost per hospitalization, outpatient visit, or ED visit) were additionally evaluated among patients in the multiple recurrences cohort during two periods: (1) over the entire disease duration (as defined earlier) and (2) during episodes of care.

Statistical Analysis

Continuous variables were reported using means (± standard deviations [SDs]) and medians, and categorical variables were reported using frequencies and proportions. Disease duration was evaluated using Kaplan-Meier analysis. Patients with persistent disease (i.e., without a 1.5-year pericarditis-free period) after their last recurrence episode were censored at the earlier event among end of data availability (i.e., March 31, 2017) or end of continuous health plan eligibility.

Patients with multiple recurrences were matched 1:1 to patients with no recurrence using exact matching on employee status (i.e., availability of work loss coverage) and propensity score matching (5% propensity score intervals). Variables used in the propensity score calculation included age, gender, region, insurance type, site of care of the first pericarditis diagnosis (i.e., hospital, ED, or outpatient clinic), year of first pericarditis diagnosis, relationship to healthcare plan holder, Quan-Charlson comorbidity index (Quan-CCI) score, RP-related and Elixhauser comorbidities (with a prevalence over 5%) [23], and baseline HCRU and costs. After matching, standardized differences were used to assess the balance of patient characteristics between cohorts, with standardized differences below 10% considered a negligible imbalance [24].

Rates of HCRU were compared between matched cohorts using rate ratios (RRs). Direct healthcare costs, medically related absenteeism costs, and disability costs were compared between the matched cohorts using cost ratios, with 95% confidence intervals (CIs) and *p*-values generated using non-parametric bootstrapping. Costs were adjusted for inflation using the US consumer price index for medical services from the Bureau of Labor Statistics [25] and were reported in 2019 US dollars.

All analyses were conducted using SAS Enterprise Guide software version 7.1 (SAS Institute, Cary, NC).

RESULTS

Of 11,925 patients with pericarditis, 3001 (25.2%) and 8924 (74.8%) had a non-idiopathic and "idiopathic" disease etiology, respectively (Fig. 2). The most common non-idiopathic etiologies were metastatic neoplasm (6.9%) and systemic autoimmune disease (6.5%). Among those with "idiopathic" disease, 1389 (15.6%) experienced at least one recurrence, and 7535 (84.4%) had no recurrence. After applying remaining inclusion criteria, 944 eligible patients had ≥ 1 recurrence—including 375 (39.7%) with multiple recurrences (i.e., multiple recurrence cohort)—and 4202 had no recurrence (i.e., no recurrence cohort). All 375 patients in the multiple recurrences cohort were matched 1:1 to 375 patients in the no recurrence cohort.

Baseline Demographic and Clinical Characteristics

Propensity score matching adequately balanced the characteristics of the multiple recurrences and no recurrence cohorts (Table 1). After matching, mean (SD) age was 51.38 (13.18) years in the multiple recurrences cohort and 51.01 (12.99) in the no recurrence cohort; the proportion of female patients was 54.7% in the multiple recurrences cohort and 51.5% in the

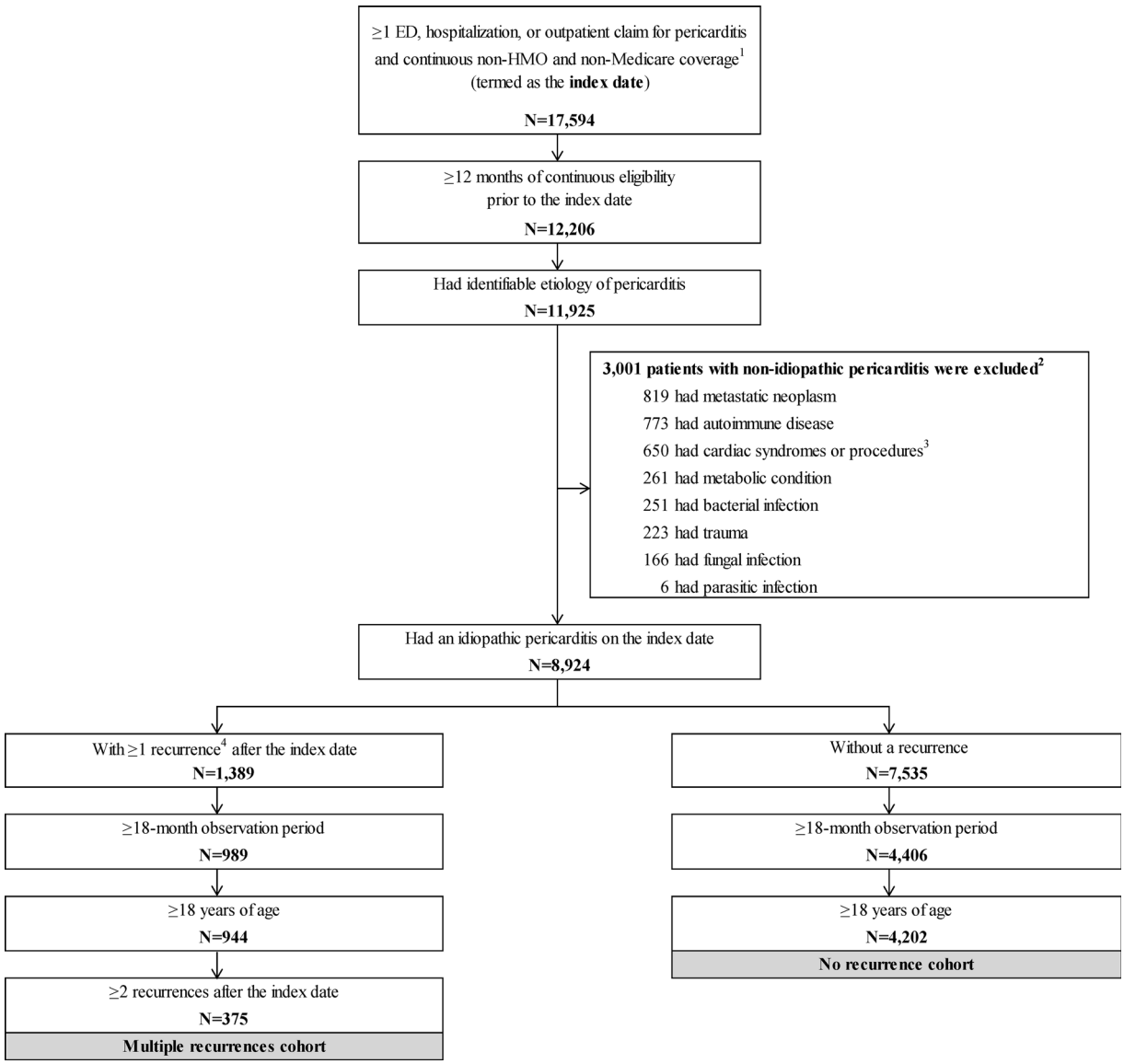

Fig. 2 Patient selection and disposition. *ED* emergency department, *HMO* health maintenance organization, *RP* recurrent pericarditis. 1. Relevant drug and medical claims may not be captured under HMO or Medicare plans coverage. 2. With a first pericarditis claim specifying non-idiopathic pericarditis or a condition or procedure related to non-idiopathic pericarditis (non-mutually exclusive) on or in the 90 days prior to the index date. 3. Cardiac syndromes or procedures were evaluated in the 30 days prior to the index date. 4. All pericarditis claims occurring in sequence without a gap of 4 weeks were considered an episode of care. A recurrence was a subsequent episode of care occurring > 4 weeks after the end of the previous episode of care

no recurrence cohort. Among patients with multiple recurrences, 38.7% were hospitalized for their first pericarditis diagnosis, with a mean (SD) length of stay of 5.38 (5.04) days; similar figures were observed in patients without a recurrence (Table 1). Patients in the multiple recurrences and no recurrence cohorts had a mean (SD) baseline Quan-CCI score of 0.86 (1.37) and 0.91 (1.45), respectively. In both cohorts, the most common comorbidities were hypertension (multiple recurrences: 35.5%, no recurrence: 35.7%), cardiac arrhythmias

Table 1 Demographics and clinical characteristics of matched patients in the multiple recurrences and no recurrence cohorts evaluated during the 12 months prior to the index date

Characteristics	Matched cohorts		Standardized difference (%)
	Multiple recurrences cohort (N = 375)	No recurrence cohort (N = 375)	
Time from initial episode (index date) to second RP[a], months, mean [median] (SD)	15.15 [11] (14.11)	15.69 [12] (12.70)	− 3.9
Site of care of first pericarditis diagnosis[b], *n* (%)			
Hospitalization	145 (38.7)	138 (36.8)	3.9
Length of stay, days, mean [median] (SD)	5.38 [4] (5.04)	5.06 [4] (4.16)	7.0
ED	46 (12.3)	47 (12.5)	− 0.8
Outpatient	184 (49.1)	190 (50.7)	− 3.2
Year of first pericarditis diagnosis[b]			
2008	39 (10.4)	33 (8.8)	5.4
2009	44 (11.7)	49 (13.1)	− 4.0
2010	44 (11.7)	48 (12.8)	− 3.3
2011	50 (13.3)	57 (15.2)	− 5.3
2012	73 (19.5)	80 (21.3)	− 4.6
2013	56 (14.9)	48 (12.8)	6.2
2014	41 (10.9)	37 (9.9)	3.5
2015	28 (7.5)	23 (6.1)	5.3
Age[b], years, mean [median] (SD)	51.38 [53] (13.18)	51.01 [53] (12.99)	2.8
Female[b], *n* (%)	205 (54.7)	193 (51.5)	6.4
Geographical region[b], *n* (%)			
South	99 (26.4)	99 (26.4)	0.0
Northeast	121 (32.3)	119 (31.7)	1.1
Midwest	86 (22.9)	83 (22.1)	1.9
West	40 (10.7)	49 (13.1)	− 7.4
Unknown	29 (7.7)	25 (6.7)	4.1
Relationship to healthcare plan holder, *n* (%)			
Healthcare plan holder (i.e., employee, retiree, leave of absence, LTD)	294 (63.0)	286 (61.2)	3.5
Spouse	151 (32.3)	159 (34.0)	− 3.6
Child	21 (4.5)	22 (4.7)	− 1.0

Table 1 continued

Characteristics	Matched cohorts		Standardized difference (%)
	Multiple recurrences cohort (N = 375)	No recurrence cohort (N = 375)	
Handicapped	1 (0.2)	0 (0.0)	6.6
Insurance plan type[b], *n* (%)			
Preferred provider organization	253 (67.5)	262 (69.9)	− 5.2
Point of service plan	56 (14.9)	50 (13.3)	4.6
Indemnity plan (i.e., fee for service)	60 (16.0)	58 (15.5)	1.5
Other healthcare plan[c]	6 (1.6)	5 (1.3)	2.2
Employee[b], *n* (%)	152 (40.5)	152 (40.5)	0.0
Quan-CCI[d], mean [median] (SD)	0.86 [0] (1.37)	0.91 [0] (1.45)	− 3.2
Comorbidities of interest[d], *n* (%)			
Coronary artery disease	49 (13.1)	50 (13.3)	− 0.8
Hypercholesterolemia	37 (9.9)	35 (9.3)	1.8
Myocardial infarction	9 (2.4)	11 (2.9)	− 3.3
Elixhauser's comorbidities (prevalence > 10%)[d], *n* (%)			
Hypertension	133 (35.5)	134 (35.7)	− 0.6
Cardiac arrhythmias	81 (21.6)	78 (20.8)	2.0
Chronic pulmonary disease	61 (16.3)	61 (16.3)	0.0
Diabetes without chronic complications	54 (14.4)	59 (15.7)	− 3.7
Valvular disease	50 (13.3)	40 (10.7)	8.2
Hypothyroidism	41 (10.9)	35 (9.3)	5.3
Congestive heart failure	38 (10.1)	32 (8.5)	5.5
Depression	38 (10.1)	36 (9.6)	1.8
Prior HRU[d], mean [median] (SD)			
Hospitalization	0.48 [0] (1.10)	0.50 [0] (1.28)	− 1.8
Patients with ≥ 1 hospitalization, *n* (%)	104 (27.7)	101 (26.9)	1.8
ED visits	0.78 [0] (1.24)	0.71 [0] (1.29)	5.1
Outpatient visits	18.06 [13] (18.15)	17.70 [11] (19.80)	1.9
Prior healthcare cost, 2019 USD[d], mean (SD)			
Total healthcare cost	$31,676 (97,285)	$30,890 (82,571)	0.9

Table 1 continued

Characteristics	Matched cohorts		Standardized difference (%)
	Multiple recurrences cohort (*N* = 375)	No recurrence cohort (*N* = 375)	
Medical costs	$28,561 (94,957)	$27,201 (79,451)	1.6
Hospitalization costs	$17,579 (77,351)	$15,964 (61,541)	2.3
ED costs	$1233 (2848)	$1363 (3633)	− 4.0
Outpatient costs	$9286 (21,654)	$9355 (25,745)	− 0.3
Other costs[e]	$464 (1979)	$519 (2848)	− 2.2
Pharmacy costs	$3115 (8425)	$3689 (18,513)	− 4.0

ED emergency department, *LTD* long-term disability, *HRU* healthcare resource utilization, *Quan-CCI* Quan-Charlson comorbidity index, *RP* recurrent pericarditis, *SD* standard deviation, *USD* US dollars

[a] The second RP date was a randomly assigned date for the no recurrence cohort

[b] Evaluated at the index date

[c] Other healthcare plans include locked-in and independent practice association health insurance plan types

[d] Evaluated during the 12 months prior to the index date

[e] Includes transportation, dentist, laboratory, home healthcare, and everything not previously identified

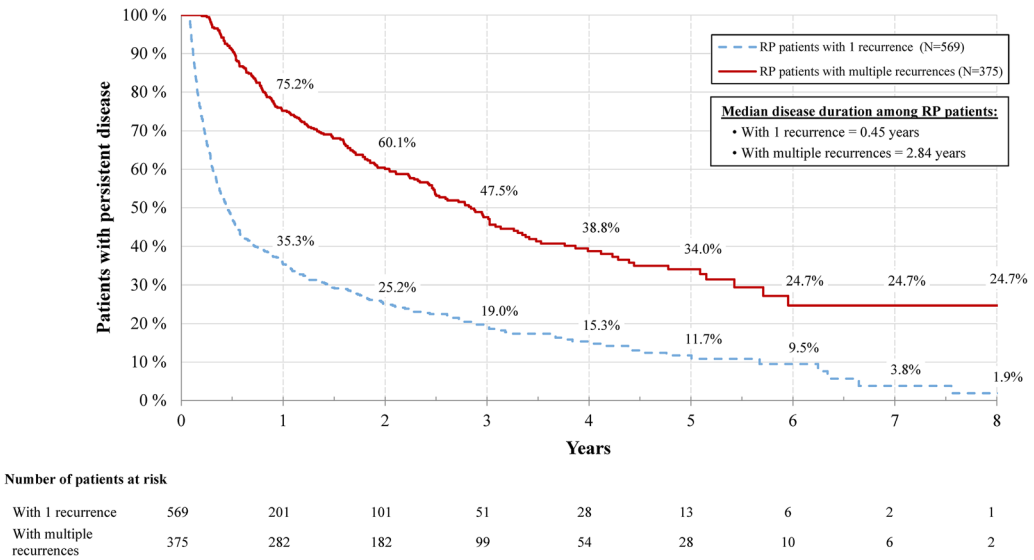

Fig. 3 Kaplan-Meier rates of persistent disease stratified by number of recurrences

(multiple recurrences: 21.6%, no recurrence: 20.8%), and chronic pulmonary disease (multiple recurrences: 16.3%, no recurrence: 16.3%). Mean (SD) baseline all-cause healthcare costs were $31,676 ($97,285) in the multiple recurrences cohort and $30,890 ($82,571) in the no

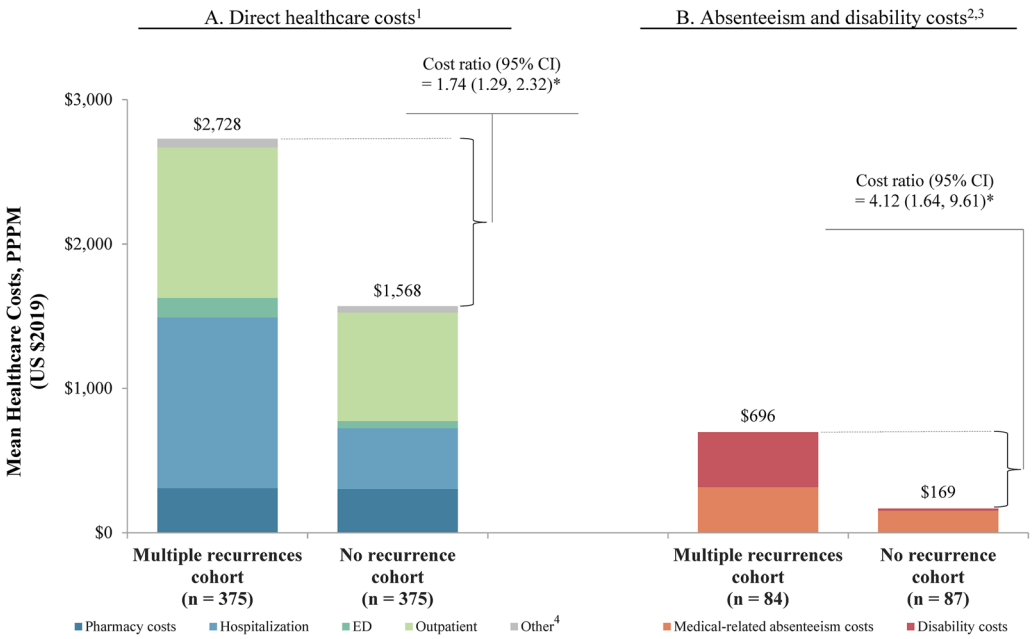

Fig. 4 All-cause direct healthcare and work loss costs in the multiple recurrences versus no recurrence cohort during follow-up. *CI* confidence interval, *ED* emergency department, *PPPM* per patient per month, *RP* recurrent pericarditis, *USD* US dollars. 1. Evaluated over a mean disease duration post-second recurrence of 12.7 months in the multiple recurrences cohort and over 27.9 months of observation in the no recurrence cohort. 2. Sample size (N) for indirect costs corresponded to the number of employees with work loss coverage. 3. Evaluated over a mean disease duration post-second recurrence of 10.3 months in the multiple recurrences cohort and over 21.1 months of observation in the no recurrence cohort. 4. Includes transportation, dentist, laboratory, home healthcare, and everything not previously identified

recurrence cohort. Hospitalization costs accounted for the greatest proportion of total all-cause healthcare costs in both cohorts (multiple recurrences: 55.5%, no recurrence: 51.7%). Patient baseline characteristics of both study cohorts prior to matching are presented in Table S2.

Recurrence Burden

Patients with multiple recurrences had a median disease duration of 2.84 years, which represents 2.39 additional years with persistent disease compared with patients who experienced only one recurrence (Fig. 3).

In the subset of 99 patients with multiple recurrences and at least 3-year disease duration, the mean (SD) time between the first and second episodes of care was 1.06 (1.30) years, 0.97 (1.00) years between the second and third episodes, and 0.61 (0.58) years between subsequent episodes. In this subset, the proportions of patients with three, four, and at least five episodes of care were 28.3%, 25.3%, and 46.4%, respectively (data not shown in tables).

Healthcare Resource Utilization and Healthcare Costs

The mean disease duration post-second recurrence was 12.67 months for the multiple recurrences cohort. Over this period, patients in the multiple recurrences cohort had higher rates of hospitalizations (mean: 0.05 vs. 0.02 PPPM, RR [95% CI] = 2.22 [1.35–3.65], $p < 0.001$), outpatient visits (mean: 1.91 vs. 1.30 PPPM, RR [95% CI] = 1.46 [1.25–1.75], $p < 0.001$), and ED visits (mean: 0.07 vs. 0.04 PPPM, RR [95% CI] = 1.79 [1.23–2.61], $p < 0.001$) than those in the no recurrence cohort.

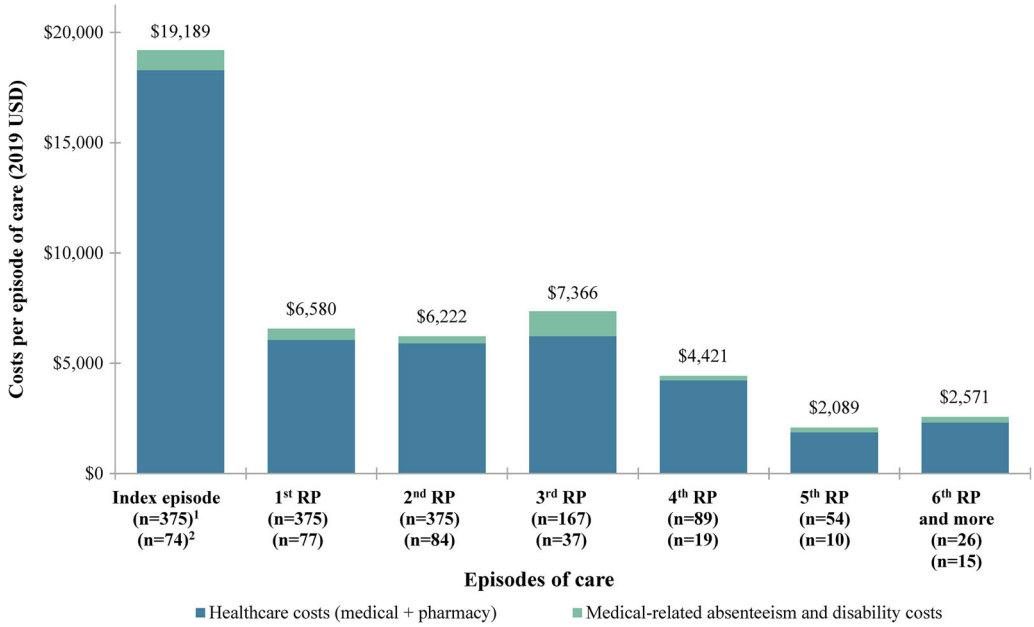

Fig. 5 Healthcare and work loss costs per episode of care among patients in the multiple recurrences cohort ($N = 375$). *RP* recurrent pericarditis, *SD* standard deviation, *USD* US dollars. 1. Total sample size for direct healthcare costs. 2. Total sample size for work loss costs (i.e., number of patients with work loss coverage)

Total all-cause healthcare costs were significantly higher in the multiple recurrences cohort compared with the no recurrence cohort (mean: \$2728 vs. \$1568 PPPM, cost ratio [95% CI] = 1.74 [1.29–2.32], $p < 0.001$; Fig. 4). This difference was driven by significantly higher medical costs in the multiple recurrences cohort relative to the no recurrence cohort (mean: \$2417 vs. \$1265 PPPM, cost ratio [95% CI] = 1.91 [1.39–2.62], $p < 0.001$), while pharmacy costs were similar between both cohorts (mean: \$311 vs. \$304 PPPM, cost ratio [95% CI] = 1.02 [0.58–1.72], $p = 0.846$). The difference in hospitalization costs (mean: \$1180 vs. \$420 PPPM, cost ratio [95% CI] = 2.81 [1.80–4.66], $p < 0.001$) was particularly pronounced.

Work Loss Costs

Among employees with work loss coverage, total work loss costs were significantly higher in the multiple recurrences cohort compared to the no recurrence cohort (mean: \$696 vs. \$169 PPPM; cost ratio [95% CI] = 4.12 [1.64–9.61], $p < 0.001$; Fig. 4). Specifically, both medically related absenteeism costs (mean: \$317 vs. \$154 PPPM; cost ratio [95% CI] = 2.05 [1.05–4.21], $p = 0.036$) and disability costs (mean: \$379 vs. \$15 PPPM; cost ratio [95% CI] = 26.06 [1.40–553.92], $p = 0.036$) were significantly higher among patients in the multiple recurrences cohort relative to those in the no recurrence cohort.

Cost of Episodes of Care and Healthcare Costs by Type of Visit

Among patients in the multiple recurrences cohort, the initial episode of care was associated with a mean cost of \$19,189 (combined direct, medically-related absenteeism, and disability costs); the cost of each subsequent recurrence ranged from \$2089 to \$7366, with a mean cost of \$6222 for the second recurrence (Fig. 5).

The average cost of a hospitalization that occurred any time throughout the duration of the disease was \$23,191, with a mean length of stay of 5.58 days (Table 2). Hospitalizations that occurred during any pericarditis episode (i.e., starting from the initial episode) had a mean

cost of $30,063, with a mean length of stay of 6.44 days. Those that occurred during subsequent episodes of care starting from the second recurrence had a mean cost of $31,286, with a mean length of stay of 7.81 days.

The average cost of each outpatient visit that occurred any time throughout the duration of the disease was $615 (Table 2). Those that occurred during any episode of care had a cost of $604, and those that occurred during subsequent episodes of care starting from the second recurrence had a cost of $555.

The average cost of each ED visit that occurred any time throughout the duration of the disease was $2258 (Table 2). ED visits that occurred during an episode of care each incurred a mean cost of $3834, and those that occurred during subsequent episodes starting from the second recurrence incurred a mean cost of $2586.

DISCUSSION

In this retrospective claims-based analysis, a substantial proportion of patients with RP experienced multiple recurrences of pericarditis over a median disease duration of almost 3 years. Among patients with multiple recurrences, all-cause healthcare costs incurred after the second recurrence were nearly twice as high as those of patients without a recurrence, and a four-fold difference was observed for indirect work loss costs. Additionally, while the initial pericarditis episode was associated with the highest total healthcare and work loss cost in patients with multiple recurrences (mean: $19,189), subsequent recurrences still incurred significant healthcare costs ranging between $2089 and $7366. The average cost associated with a single hospitalization was $23,191 throughout the duration of the disease, and this figure was even more pronounced for hospitalizations that occurred during an episode of care ($30,063).

The results of the present study emphasize the substantial burden associated with multiple recurrences of pericarditis. Approximately 40% of patients with RP included in this study experienced multiple recurrences, which is consistent with prior estimates (range: 24–55%) [3, 11]. In some of these patients, recurrences may cause life-threatening complications such as constrictive pericarditis and cardiac tamponade [4]; a recent systematic literature review of real-world studies showed that cardiac tamponade and constrictive pericarditis occur in 12.7% and 1.84% of patients with RP (i.e., with or without multiple recurrences), respectively [18]. Furthermore, disease duration exceeded 3 years for nearly half of patients with multiple recurrences. Recurrent pericarditis symptoms can be disabling and may require evaluation and treatment. If symptoms do not resolve with pharmacological therapy, pericardiectomy may be considered but is associated with substantial morbidity and mortality [3, 26]. The development of predictive algorithms to identify patients at risk of multiple recurrences, such as with the use of machine learning [27], may help to manage these patients prior to the onset of burdensome recurrences.

In addition to the recurrence burden described above, the current study showed that multiple recurrences of pericarditis are associated with significant HCRU and costs. More than a third of patients with multiple recurrences were hospitalized for their first pericarditis diagnosis, with an average length of stay of 5 days. During follow-up, the observed rates of hospitalizations, outpatient visits, and ED visits were significantly higher among patients with multiple recurrences compared to those with no recurrence. Patients with multiple recurrences may have required more intensive and/or frequent HCRU due to the debilitating symptoms of RP, overall disease and treatment-related morbidity, or clinical complications. Moreover, each pericarditis episode incurred total costs (i.e., healthcare costs and work loss costs combined) ranging between $2089 and $7366 (excluding the cost of the index episode) in patients with multiple recurrences. These costs may in part be driven by the disabling pericarditis symptoms in this subpopulation. Furthermore, all-cause healthcare costs incurred by patients with multiple recurrences after the second recurrence were nearly twice as high as those incurred by patients with no recurrence, highlighting the

Table 2 Healthcare cost per healthcare visit among patients in the multiple recurrences cohort

Healthcare costs by type of visit, 2019 USD, mean (SD)	Multiple recurrences cohort (*N* = 375)
Over disease duration[a] (from initial episode)	
Hospitalization costs (*n* = 713)	$23,191 (43,019)
Length of stay, days, mean [median] (SD)	5.58 [4] (7.96)
Outpatient costs (*n* = 20,008)	$615 (3759)
ED costs (*n* = 735)	$2258 (4893)
During any episode of care[b] (initial episode and after; n = 1513)	
Hospitalization costs (*n* = 363)	$30,063 (53,769)
Length of stay, days, mean [median] (SD)	6.44 [4] (8.40)
Outpatient costs (*n* = 2403)	$604 (1212)
ED costs (*n* = 131)	$3834 (8476)
Episodes of care from the 2nd recurrence (n = 763)	
Hospitalization costs (*n* = 161)	$31,286 (47,810)
Length of stay, days, mean [median] (SD)	7.81 [5] (10.32)
Outpatient costs (*n* = 1606)	$555 (1171)
ED costs (*n* = 54)	$2586 (2291)

ED emergency department, *SD* standard deviation, *USD* US dollars

[a] The time from the first pericarditis claim to the end of the last recurrence and free of a subsequent pericarditis claim for at least 1.5 years

[b] Defined as all pericarditis claims occurring in sequence without a gap of 4 weeks

substantial direct economic burden associated with recurrences.

Hospitalizations were the main driver of the difference in all-cause healthcare costs between the multiple recurrences and no recurrence cohorts. Specifically, a nearly three-fold difference in hospitalization costs was observed between both cohorts. The average cost per hospitalization was $23,191 over the entire disease duration and increased to $30,063 during a pericarditis episode. The high hospitalization cost observed over the entire duration of the disease suggests that patients with multiple recurrences of pericarditis represent a substantial burden for healthcare systems. Nonetheless, these estimates are much higher than that reported by Mody et al. (i.e., $9982 per hospitalization) in a recent study of Medicare-insured patients with pericarditis (idiopathic or not) [20]. This discrepancy may be due to differences in patient populations (e.g., insurance coverage and disease etiology) and the fact that Mody et al. did not stratify their analysis based on the number of recurrences [20]. In a separate analysis of the National Readmission Database by Sreenivasan et al., the cost of a hospital readmission following a hospitalization for acute pericarditis totaled $36 million (~ $13,000 per readmission) [21]. Importantly, any readmission within 30 days of the initial hospitalization is likely associated with the initial acute pericarditis, since the definition of RP requires a symptom-free period of at least 4 to 6 weeks. Thus, the patients included by

Sreenivasan et al. may not have had RP, which would explain the lower hospitalization costs.

In the current study, indirect work loss costs incurred by patients with multiple recurrences after the second recurrence were also significantly higher than those of patients with no recurrence. While the indirect costs of pericarditis have not been assessed in the literature, HRQoL can be severely affected by frequent recurrences and associated chest pain [9, 28], which may lead to pain-related disability and work loss [29].

The observed protracted disease course and high costs associated with multiple recurrences of pericarditis emphasize the need for new, targeted treatments in this population with high unmet needs. Conventional treatments fail to provide adequate symptom control and prevention of future recurrences for many patients with pericarditis. Sustained NSAIDs and systemic steroids are complicated by serious side effects [4, 12, 18, 30, 31]. Until recently, there were no FDA-approved treatments for pericarditis; rilonacept was recently approved for treatment of recurrent pericarditis and reduction in risk of recurrence. The off-label use of therapies and lack of US treatment guidelines lead to inconsistencies in patient treatment and disease management strategies and adversely affect clinical outcomes [5, 18].

Emerging evidence in pericarditis supports that the proinflammatory cytokine interleukin-1 (IL-1) plays a central role in maintaining an autoinflammatory state that results from tissue damage of the pericardium; therefore, IL-1α and β signaling blockade is a reasonable approach for targeted treatment in RP [3, 8, 32]. The once-daily IL-1 receptor antagonist anakinra has been shown to reduce the risk of pericarditis recurrence, hospitalization, and emergency department admission among patients with colchicine-resistant and corticosteroid-dependent "idiopathic" pericarditis who had ≥ 2 previous recurrences [28, 33]. However, anakinra is not approved by the FDA for the treatment of RP. In contrast, the IL-1 trap rilonacept was recently approved by the FDA for the treatment of RP and reduction in the risk of recurrence in adults and children 12 years and older [34]. Rilonacept is a once-weekly, subcutaneously-injected, IL-1 trap that works by binding to IL-1α and IL-1β, thereby effectively blocking the signaling pathway [34, 35]. The approval was supported by the Phase 3 study RHAPSODY, in which rilonacept led to a rapid resolution of pericarditis episodes and substantially reduced the risk of pericarditis recurrence by 96% (HR = 0.04, $p < 0.0001$) among patients with RP and systemic inflammation [8]. The introduction of this effective and approved treatment option to address the pathophysiology of RP with targeted immunomodulation may help to reduce the risk of pericarditis recurrences and associated complications, reduce clinical burden and impact to HRQoL for patients, as well as provide cost savings for payers and employers.

The results of the current study should be interpreted in light of some limitations. First, the limited duration of follow-up and inability to capture episodes of care not resulting in a healthcare encounter likely resulted in an underreported recurrence burden. Second, due to the nature of health insurance claims databases, coding delays, inaccuracies, or omissions in procedures and diagnoses may have occurred. As a result, using the first recorded pericarditis diagnosis as the index date may not have been accurate in some patients. Third, limitations inherent to the identification of the study population may have impacted study outcomes, including (1) the fact that some ICD codes used to identify patients were not specific to pericarditis, (2) the lack of a specific code for RP, (3) the inability to ascertain RP diagnoses with health insurance claims data, and (4) in particular the exclusion of patients with pericarditis due to cardiac injury. Fourth, disease duration was determined using a 1.5-year recurrence-free period, but we cannot exclude that some patients may have experienced recurrence over a more extended period. Fifth, the study sample may not be representative of the general population of patients with pericarditis in the real world. Indeed, the minimum of 18 months of continuous eligibility after the index date was imposed as an inclusion criterion to ensure that patients had sufficient follow-up, but this criterion may have introduced a selection bias. Moreover, this study was

conducted in a privately insured population; therefore, the results may not be generalized to patients with other types of insurance coverage such as Medicare or Medicaid beneficiaries or the uninsured patient. Use of a nationally representative database (e.g., Nationwide Readmission Database [27] or the US public system) in future studies may provide more generalizable insight. Sixth, residual confounding due to unmeasured confounders may have remained despite the use of propensity score matching to account for observable differences in characteristics between the no recurrence and multiple recurrences cohorts.

CONCLUSIONS

In this US, real-world, payer's perspective study of a privately insured population covered by employers, nearly 40% of patients with RP had multiple recurrences. Most patients with multiple recurrences experienced episodes of care during several years (median disease duration: 3 years). Patients without any recurrence exhibited a high burden in terms of HCRU, healthcare costs, and work loss costs, and this burden was further compounded among patients with multiple recurrences. Hospitalization costs and disability costs respectively acted as the major drivers of the differences in healthcare costs and work loss costs between patients with multiple recurrences and those with no recurrences. Among patients with multiple recurrences, the cost associated with each pericarditis episode and each hospitalization (especially those occurring during episodes of care) was substantial, further highlighting the high disease burden in this difficult-to-treat population. While these findings represent real-world clinical practices in privately insured patients diagnosed with "idiopathic" recurrent pericarditis, more research is needed to confirm these findings of disease and economic burden in the entire community and in patients with similar pericarditis inflammatory presentations due to cardiac injury.

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