Burden of Recurrent Pericarditis on Health-Related Quality of Life

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The extent to which recurrences of pericarditis episodes impact patients' health-related quality of life (HRQOL) remains poorly understood. This study aimed to evaluate HRQOL and work productivity in patients with recurrent pericarditis (RP). Adult patients from a centralized recruitment database for the rilonacept Phase 2/3 clinical trials were invited to participate in a survey. Inclusion criteria were confirmed RP diagnosis and ≥1 recurrence within the previous 12 months. The 11-Point Pain Numeric Rating Scale, Patient Global Impression of Pericarditis Severity, Patient-Reported Outcomes Measurement Information System (PROMIS) Global Health v1.2, PROMIS Short Form Sleep Disturbance 8b, Work Productivity and Activity Impairment v2.0, and customized questions about fear and economic impact were used. In total, 83 patients (55% female, average age = 49.3 years) completed the survey. The median time since pericarditis diagnosis was 3.0 years at the time of survey completion; 49% experienced ≥3 recurrences in the previous 12 months. Forty percent had an emergency room visit, and 25% were hospitalized for their most recent recurrence. Sixty-six percent of participants rated the symptoms of their last recurrence as severe. The mean value for worst pericarditis pain (0 to 10 scale) during the most recent recurrence was 6.1. The average T-scores for PROMIS physical and mental health were 37.6 and 42.8, respectively, compared with 50 in the general population. Participants reported 50% of overall work impairment and 62% of activity impairment due to RP. In conclusion, patients with RP experienced a high number of recurrences with severe symptoms that substantially reduced their HRQOL and work productivity. **(Am J Cardiol 2021;141:113−119)**

Recurrent pericarditis (RP) is a common and troublesome complication of acute pericarditis and occurs in 15% to 30% of patients.[1,2] It is characterized by the recurrence of signs and symptoms of acute pericarditis (i.e., sharp and pleuritic chest pain) after a symptom-free period of at least 4 to 6 weeks. Although many patients with an initial recurrence respond to conventional treatment, some experience multiple recurrences[3] and high disease morbidity[4] due to inadequate treatment response and persistent underlying disease. The ways and extent to which RP affects patient health-related quality of life (HRQOL) remains poorly understood, although disease symptoms mimic those of acute myocardial infarction and cause psychological distress and anxiety.[5] To our knowledge, no published real-world studies have documented the HRQOL of patients with RP treated with conventional therapies. A cross-sectional survey in patients with RP was conducted to evaluate how they perceive their symptoms, HRQOL, sleep quality, fear, and work activity impairment during RP episodes.

Methods

Patients with RP were identified from a centralized recruitment database for the Phase 2 and Phase 3[6] clinical trials for rilonacept. All were invited by e-mail to participate in an online survey approved by an institutional review board conducted between September 6, 2019 and December 11, 2019 (see Supplementary material for survey questions). Although the survey did not ask whether patients participated in the clinical trials, patients who reported receiving rilonacept were excluded from the final analysis. Participants provided informed consent before responding to the survey, and were compensated with a $50 gift card for completing the survey. All enrolled participants had a self-reported diagnosis of RP, were age 18 years or older at the time of the survey, and experienced ≥1 recurrence during the previous 12 months, including participants experiencing a recurrence at the time they completed the survey. Data were de-identified, and all study materials were approved by the New England Independent Review Board.

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The survey collected patient demographic and clinical characteristics, including co-morbidities, cause of pericarditis, time since pericarditis diagnosis, number of RP episodes in the past 12 months, time since the most recent episode, symptoms during the most recent episode, hospitalization and emergency room visits in the past 12 months, and RP treatments received. Patient-reported outcome (PRO) instruments were selected based on the most clinically relevant symptoms of RP and their expected impact on patients, as identified from the literature. Five PRO instruments were used to capture multiple dimensions of RP, including disease symptoms and their impact on HRQOL and work productivity. The 11-Point Numeric Rating Scale (11-point NRS) for the assessment of pain consists of a single item asking participants to rate their worst pain during the most recent pericarditis episode on a scale of 0 to 10, with higher values indicating greater pain.[7] The Patient Global Impression of Pericarditis Severity was used to evaluate the presence and severity of RP symptoms during the most recent pericarditis episode. Work impairment during the most recent RP episode was evaluated using the Work Productivity and Activity Impairment v2.0.[8,9] The Patient-Reported Outcomes Measurement Information System (PROMIS) Global Health v1.2 was used to assess general mental health (MH) and physical health (PH),[10,11] with higher scores indicating better HRQOL. The PROMIS Short Form Sleep Disturbance 8b instrument was used to assess participants' perception of their sleep,[12] with higher scores indicating more sleep disturbance. Lastly, a customized set of questions rated on a 5-point Likert scale was used to evaluate (1) the fear associated with pericarditis episodes and (2) the impact of RP on participants' families and their financial well-being. Participants who reported experiencing at least "a little" fear were asked additional questions about the impact of fear on their activities, life, and work/school.

The original recall period of each instrument (e.g., in the past 7 days, in the past 24 hours) was used to assess participants' ongoing RP episode if they self-reported that they were experiencing a recurrence at the time of the survey. Participants who were not experiencing an RP episode at the time of the survey were asked to complete the PRO instruments based on their recollection of their most recent recurrence episode. Distinctions between patients with an ongoing recurrence and those recalling a past recurrence are only made where data are presented separately for these groups.

For all instruments, means, medians, and standard deviations (SD) were used to summarize continuous variables; frequencies and percentages were used to summarize categorical variables. The summed MH and PH domain raw scores from PROMIS Global Health and the summed total scores from PROMIS Sleep Disturbance were converted into T-scores based on the conversion table in the scoring manual of each instrument. The T-score distributions are standardized so that the average score for the US general population is 50.0 with an SD of 10.0. Thus, a person with a PROMIS PH T-score of 40 would have a PH status one SD worse than that of the US general population (based on a large sample of individuals representing the demography of the 2000 US General Census), whereas the sleep quality of a patient with a 40 T-score for the PROMIS Sleep Disturbance instrument would be one SD better than that of the US general population. For the Work Productivity and Activity Impairment instrument, domain scores for absenteeism, presenteeism, work productivity loss, and activity impairment were calculated according to the scoring manual.[9]

Exploratory analyses were performed to assess the association between the number of RP episodes (1, 2, or ≥3) and the mean pain score from the 11-point NRS using the Kruskal-Wallis test. To evaluate potential recall bias, the association between the length of time since the last RP episode and the mean T-score for the PH and MH domains of PROMIS Global Health was also assessed using the Kruskal-Wallis test.

A sensitivity analysis was conducted to compare study outcomes between the subgroups of participants experiencing a pericarditis episode at the time of the survey versus those not experiencing an episode at the time of the survey. These comparisons were performed using the Wilcoxon rank sum test for continuous variables and the Chi square test (or Fisher's exact test, as appropriate) for categorical variables.

Results

Of 746 potentially eligible patients who were contacted, 83 completed the survey and were included in the analysis, including 21 (25%) who self-reported experiencing a recurrence at the time of the survey. Baseline characteristics and responses to most PROs did not significantly differ between participants who were experiencing a recurrence at the time of the survey and those who had previously experienced a recurrence. Results are presented for the overall study population, unless otherwise specified.

Overall, 55% of participants were female, and the mean age was 49.3 years (SD = 13.7; Table 1). Participants from all regions of the US participated in the study. All participants had at least a high school degree, and 40 (48%) had at least a college degree. Fifty-two (63%) participants had commercial health insurance. Fifty-one (61%) participants were employed during their current or most recent RP episode. Hypertension (n = 32, 39%), anxiety (n = 31, 37%), and depression (n = 28, 34%) were the 3 most commonly reported co-morbid medical conditions.

Participants had a median of 3.0 years between their diagnosis with pericarditis and the time of the survey (Table 2). Forty-one (49%) participants reported experiencing ≥3 pericarditis episodes in the 12 months preceding the survey. Fifty (60%) reported experiencing a pericarditis episode within the 3 months before the survey. A significantly higher proportion of participants with an ongoing recurrence during the survey reported having ≥3 pericarditis episodes in the previous 12 months relative to those not experiencing a recurrence at the time of the survey (76% vs 40%, p = 0.011). Twenty-eight (34%) participants had a history of pericardial effusion, 24 (29%) had constrictive pericarditis, and 12 (15%) had cardiac tamponade before completing the survey. In total, 33 (40%) and 21 (25%) participants had emergency room and hospital admission for their current or most recent recurrence, respectively (Table 2). Compared with participants not experiencing a recurrence during the survey, a significantly higher proportion of those experiencing a recurrence during the survey had ≥2 RP-related hospitalizations in the previous

Table 1
Baseline characteristics

Variable	All participants (n = 83)
Women	46 (55)
Age (years, at time of survey), mean [median] (SD)	49.3 [52.0] (13.7)
White	63 (76%)
Black	15 (18%)
American Indian or Alaska Native	1 (1%)
Other	4 (5%)
Hispanic	8 (10%)
Region of residence	
South	29 (35%)
West	24 (29%)
Northeast	16 (19%)
Midwest	14 (17%)
Highest level of education completed	
High school diploma or equivalent (e.g., GED)	8 (10%)
Some college or Associate's degree	35 (42%)
College graduate/bachelor's degree	25 (30%)
Advanced degree	15 (18%)
Health insurance	
Private/commercial insurance	52 (63%)
Public insurance	24 (29%)
No insurance	11 (13%)
Medical conditions	
Hypertension	32 (39%)
Anxiety	31 (37%)
Depression	28 (34%)
Asthma	18 (22%)
Anemia	13 (16%)
Autoimmune disease	13 (16%)
Obesity	13 (16%)
Diabetes mellitus	12 (15%)
Inflammatory bowel disease	7 (8%)
Cancer	3 (4%)
Chronic obstructive pulmonary disease	3 (4%)
Chronic kidney disease	2 (2%)
Stroke	2 (2%)
Liver diseases	1 (1%)
Other*	7 (8%)
None of the above	11 (13%)

Abbreviations: GED, General Education Development, SD, standard deviation

Notes:

* Other medical conditions include atrial fibrillation, hyperthyroidism, coronary artery disease, heart disease, migraine, serositis, and Wolff-Parkinson-White.

Table 2
History of recurrent pericarditis

Variable	All participants (n = 83)
Time (years) since pericarditis diagnosis, median (IQR)*,†	3.0 (2.0-7.0)
Cause of pericarditis	
Unknown reason or idiopathic disease	44 (53%)
Viral, bacterial, fungal, or parasitic infection including HIV/AIDS or tuberculosis	17 (21%)
Heart attack or heart surgery	9 (11%)
Myocarditis	7 (8%)
Autoimmune disease	7 (8%)
Medication side effect	3 (4%)
Other‡	1 (1%)
"Don't remember"	2 (2%)
Related conditions	
Pericardial effusion	28 (34%)
Constrictive pericarditis	24 (29%)
Tamponade	12 (15%)
None of the above	30 (36%)
Don't know/Unsure	10 (12%)
Number of pericarditis episodes in the prior 12 months	
1	19 (23%)
2	23 (28%)
3 or more	41 (49%)
Time since most recent pericarditis episode (months)	
Currently experiencing	21 (25%)
Within 1	13 (16%)
1 - 3	16 (19%)
3 - 6	15 (18%)
6 - 12	18 (22%)
Number of pericarditis hospitalizations in prior 12 months	
0	44 (53%)
1	18 (22%)
2+	21 (25%)
Admitted to hospital for most recent pericarditis episode	21 (25%)
Visited ER for most recent pericarditis episode	33 (40%)

Abbreviations: AIDS, acquired immunodeficiency syndrome, ER, emergency room, HIV, human immunodeficiency virus, IQR, interquartile range, SD, standard deviation.

Notes:

* If participant did not remember month of diagnosis, July was imputed.

† 79 (95.2%) of the 83 participants had available data on time since pericarditis diagnosis.

‡ Other causes of pericarditis include dental procedures.

12 months (16% vs 52%, p <0.001). NSAIDs and colchicine were the most common medications used to treat pericarditis episodes over the 12 months before survey completion (Table 3). Twenty-four (29%) participants reported receiving corticosteroids (CS), and alternative therapies (e.g., anakinra, azathioprine, methotrexate, intravenous immunoglobulin, or mycophenolate) were used in 13 (16%) participants. Eighteen (22%) participants reported using opioids to relieve their pain related to a pericarditis episode.

Commonly reported symptoms and their perceived severity/burden are presented in Table 4. Twenty-four (29%) participants reported that pericarditis-associated pain was the most bothersome aspect of RP, followed by the uncertainty of not knowing the cause of RP episodes (n = 13, 16%), the unpredictability of RP episodes (n = 10, 12%), and not being able to exercise and be active (n = 8, 10%). Fifty-five (66%) participants rated the symptoms of their current/most recent recurrence as moderately severe, severe, or very severe. Participants experiencing a recurrence during the survey reported more symptoms during their ongoing episode than those who did not have an ongoing recurrence and reported the symptoms from their most recent recurrence (4.7 vs 3.8, p = 0.027). Compared with participants not experiencing a recurrence, a significantly lower proportion of those experiencing a recurrence rated the symptoms of their last recurrence as severe (74% vs 43%, p = 0.009). On average, participants rated their worst pericarditis pain during the current or most recent recurrence at 6.1 (SD = 2.3) out of 10; 40 (48%) reported severe

Table 3
Medications used for pericarditis episodes and pain during the prior 12 months

Variable	All participants (n = 83)
NSAIDs	**68 (82%)**
Ibuprofen	51 (61%)
Aspirin	22 (27%)
Naproxen	18 (22%)
Indomethacin	11 (13%)
Colchicine	**52 (63%)**
Corticosteroids	**24 (29%)**
Other Immune Therapy	**13 (16%)**
Anakinra	6 (7%)
Azathioprine	4 (5%)
Methotrexate	3 (4%)
Intravenous immune globulin	2 (2%)
Mycophenolate	1 (1%)
Other drug categories	**22 (27%)**
Painkillers (opioids) such as morphine, methadone, buprenorphine, hydrocodone, oxycodone	18 (22%)
Other*	3 (4%)
None	3 (4%)

Abbreviations: NSAID, non-steroidal anti-inflammatory drug.
Notes:
* Other medications include digoxin, nitroglyclicerin, warfarin, heparin, and plaquenil.

pain (≥7 on the scale). Participants experiencing a recurrence during the survey reported a lower pain score than participants not actively experiencing a recurrence (mean: 4.9 vs 6.5, p = 0.014). The level of pain during the most recent episode was not associated with the number of RP episodes in the previous 12 months (p = 0.655).

The average T-score was 37.6 (SD = 8.6) for PROMIS PH, and 42.8 (SD = 9.9) for PROMIS MH (Figure 1). The average raw scores for overall health and ability to carry out social activities and roles (which are not included in the PH and MH domain scores) were 2.7 and 2.5, respectively, on a scale of 1 (poor) to 5 (excellent). Ability to carry out social activities and roles and fatigue were the most prominently and negatively impacted items among those in PROMIS Global Health. T-scores for the PH and MH domains were not significantly associated with the length of time since the last recurrence episode (p [PH T-score] = 0.845; p [MH T-score] = 0.370). The mean T-score for the PROMIS Sleep Disturbance instrument was 60.6 (SD = 8.3). The extent to which sleep was refreshing or satisfying was the most prominently impacted item in the sleep item set. Fifty-nine of 62 (95%) participants reported some level of fear of pericarditis episodes, with 30 (48%) reporting that level to be "quite a bit" or "very much." Figure 2 shows the degree of fear expressed by survey participants and the areas of their lives that were impacted by this fear.

The impact of RP on work productivity was substantial, with an average 50% overall work impairment (Table 5). Compared with participants not experiencing a recurrence during the survey, those experiencing a recurrence reported less work time missed (28% vs 4%, p = 0.010), less impairment while working (53% vs 32%, p = 0.020), and less overall work impairment (57% vs 35%, p = 0.027).

Table 4
Severity of symptoms and pain in the current or most recent recurrent pericarditis episode

Variable	All participants (n = 83)
Number of symptoms during most recent pericarditis episode, mean [median] (SD)	4.1 [4.0] (1.7)
Symptoms during most recent pericarditis episode	
Chest pain	77 (93%)
Shortness of breath when reclining or lying down	55 (66%)
Weakness or fatigue	53 (64%)
Arm or shoulder pain	48 (58%)
Heart palpitations	43 (52%)
Cough	25 (30%)
Swelling in the abdomen or legs	16 (19%)
Fever	13 (16%)
Other*	7 (8%)
Most bothersome aspect of pericarditis episodes	
Pain	24 (29%)
Not knowing the cause of pericarditis episodes	13 (16%)
Unpredictability of a pericarditis episode	10 (12%)
Not able to exercise and be active	8 (10%)
Fatigue and weakness	6 (7%)
No cure	6 (7%)
Shortness of breath	4 (5%)
Unable to care for family	4 (5%)
Impact on sleep	2 (2%)
Impact on family plans and social activities	1 (1%)
Impact on work or school	1 (1%)
Weight gain from treatment and not being active	1 (1%)
Other†	3 (4%)
Severity of symptoms during most recent pericarditis episode‡	
Absent, minimal, or mild	7 (8%)
Absent	1 (1%)
Minimal	3 (4%)
Mild	3 (4%)
Moderate	21 (25%)
Moderately severe, severe, or very severe	55 (66%)
Moderately severe	26 (31%)
Severe	21 (25%)
Very severe	8 (10%)
Worst pericarditis pain during most recent episode, mean [median] (SD)§	6.1 [6.0] (2.3)

Abbreviations: SD, standard deviation.
Notes:
* Other symptoms include difficulty swallowing, nausea, chest spasms, pneumonia, dizziness, headaches, pain when breathing, and upper back pain.
† Other bothersome aspects of pericarditis episodes include all of the above, weight gain, and diminished quality of life.
‡ Based on Patient Global Impression of Pericarditis Severity scale (PGIPS).
§ Based on 11-point pain numerical rating scale.

Discussion

In this real-world study, pericarditis episodes were associated with severe pain and morbidity, and patients with RP reported multiple recurrences, reduced PH and MH, reduced sleep quality, and impaired work productivity. Even in patients not experiencing an acute RP episode, the residual impact was significant, with nearly all participants

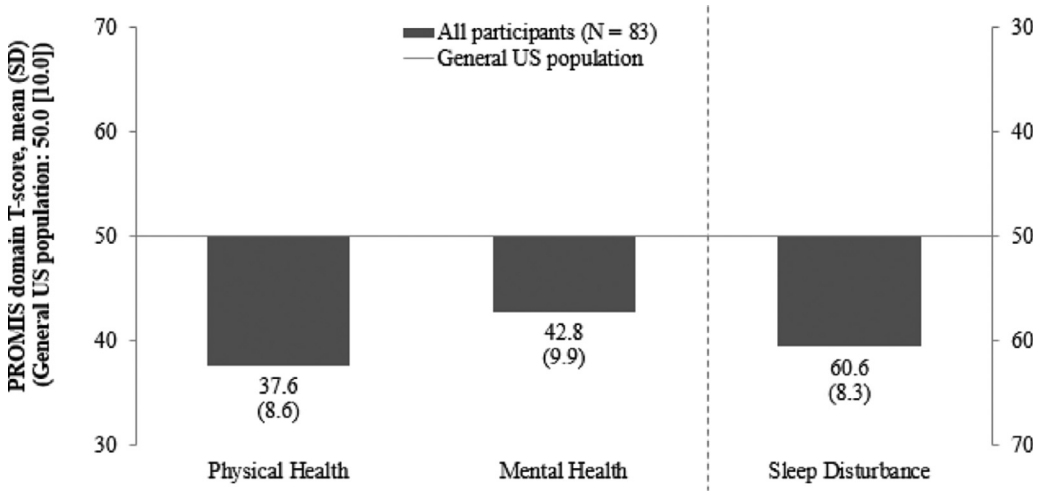

Figure 1. PROMIS physical health, mental health, and sleep disturbance. Abbreviations: PROMIS, Patient-Reported Outcomes Measurement Information System, SD, standard deviation; US, United States.

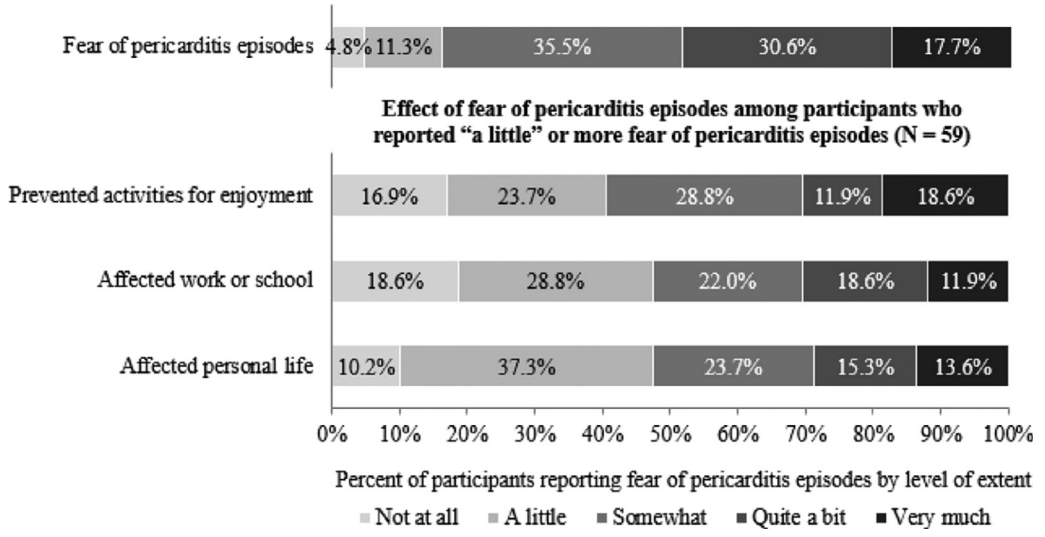

Figure 2. Fear of pericarditis among participants not experiencing a recurrence during the survey (n = 62).

Table 5
Work productivity and activity impairment during the current or most recent recurrent pericarditis episode*

	All participants (n = 83)			
Employed during most recent/current pericarditis episode				
Yes	51	(61%)		
No	32	(39%)		
Domain scores, mean [median] (SD)				
Percent work time missed due to disease	21	[7]	(29)	43
Percent impairment while working due to disease	48	[50]	(29)	48
Percent overall work impairment due to disease	50	[50]	(32)	41
Percent activity impairment due to disease	62	[70]	(27)	82

Abbreviation: SD, standard deviation.

Notes:

* Among participants experiencing a pericarditis episode, questions were assessed during the last 7 days. Among participants not experiencing a pericarditis episode, questions were assessed during the most recent pericarditis episode.

reporting living in fear of a next pericarditis recurrence and over half reporting the fear profoundly impacting their lifestyle. The burden of RP on patients' lives is therefore substantial, highlighting the limitations of the current standard of care and patients' unmet needs for safer, more effective therapies.

This study shows that pericarditis symptoms significantly impact patients' lives. Participants rated their worst pain during their most recent episode at 6.1 out of 10—a figure higher than that reported in cancer (5.3) and rheumatoid arthritis (5),[13] but consistent with that in fibromyalgia[14] or chronic pain syndrome[15] (~6 to 7) using the same instrument. In addition, the recurrence frequency was not associated with a significantly lower pain score, suggesting that patients may not adapt to pain and that recurrences increase the disease burden.

The disease history reported by participants illustrates the substantial burden of RP. On average, participants had received their first pericarditis diagnosis more than 6 years before the survey, and ~50% had experienced ≥3

recurrences in the previous 12 months. Nearly half reportedly had ≥1 hospitalization for pericarditis in the previous 12 months, suggesting RP imposes a high burden on healthcare systems. In addition, the proportion of participants who reportedly had a previous diagnosis or treatment for anxiety (37%) and depression (34%) was higher than that of the US general population (31% anxiety and 17% depression).[16]

In the current study, the mean T-scores for PROMIS PH (37.6) and PROMIS MH (42.8) were considerably lower than those of the US general population (mean = 50.0, SD = 10, for both domains), indicating that participants' perception of their health status is worse than that of the general population. These figures are similar to those previously reported in patients with stroke (mean T-score: PH = 38.2, MH = 41.5),[17] but lower (i.e., worse) than those reported for patients with breast cancer (PH = 48.4, MH = 52.7), prostate cancer (PH = 50.6, MH = 52.1), and osteoarthritis (PH = 47.6, MH = 49.9).[18,19] Moreover, the mean T-score for the PROMIS Sleep Disturbance instrument was 60.6, suggesting participants' sleep quality is also worse than that of the general population (mean calibrated at 50.0). The reported level of sleep disturbance was similar to that in fibromyalgia (59.9), but higher (i.e., worse) than that in chronic pain (49.8), multiple sclerosis (50.8), and spinal cord injury (49.5).[20]

RP was also associated with substantial work productivity impairment. Participants who were employed during the recurrence reported 21% absenteeism, 48% presenteeism, and 50% overall work impairment due to RP. These figures are higher than those previously reported for rheumatoid arthritis (absenteeism: 9%, presenteeism: 24%, and overall work impairment: 29%),[21] lung cancer (absenteeism: 15%, presenteeism: 31%, and overall work impairment: 37%),[22] and locally recurrent or metastatic breast cancer (absenteeism: 20%, presenteeism: 30%, and overall work impairment: 40%).[23] Additionally, respondents reported a 62% impairment in their daily activities, a figure higher than those previously reported for rheumatoid arthritis (33%),[21] lung cancer (53%),[22] and locally recurrent or metastatic breast cancer (30%)[23].

Consistent with current clinical guidelines,[24] most patients reportedly received nonsteroidal anti-inflammatory drugs (82%) and/or colchicine (63%) in the previous 12 months. However, a substantial proportion reported receiving CS (29%) or other immune therapies (16%), indicating that several patients failed to achieve adequate symptom control with conventional therapies. The high use of CS for RP is concerning given the known morbidity associated with their use.[25,26] Furthermore, there is evidence that chronic CS use may exacerbate the frequency of recurrences. Altogether, these treatment patterns indicate that patients with RP have unmet needs with currently available therapies.

The present study was subject to some limitations. First, the sample size was small and patients may not be representative of the overall RP population since they expressed interest in participating in rilonacept trials. Second, data were self-reported; thus, some variables (e.g., cause of RP and treatments) may have been subject to recall bias. However, the lack of significant correlation between the PROMIS Global Health T-Scores and the length of time since the most recent recurrence suggests that the impact of recall bias was minimum. Third, results are based on HRQOL assessments at a single time point, but disease symptoms and burden may change across different episodes. Fourth, all data from this study are reported by patients, and their accuracy is therefore contingent on patients' ability to understand and accurately report information. Consequently, the accuracy of certain variables, such as related conditions or complications (e.g., pericardial effusion, cardiac tamponade, and constrictive pericarditis), may be more limited than what can be obtained in chart review studies. Further, results on the etiology of RP do not distinguish between viral, bacterial, and fungal causes due to concerns that patients may not be able to accurately report this information.

In conclusion, patients with RP reported severe levels of pain and a high number of recurrences with symptoms that reduced their HRQOL and work productivity. When not experiencing recurrences, patients lived in fear of pericarditis recurrences, which impact their daily activities. The significant use of CS further suggests that currently available conventional therapies are inadequate to achieve symptom control and prevent recurrences. Safe and more effective disease-modifying treatments are needed to rapidly resolve recurrences, prevent future flares, and alleviate the burden of RP.

Authors contribution

Martin LeWinter: Conceptualization; Methodology; Writing - Reviewing and Editing; and Supervision.

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Mei Sheng Duh: Writing - Reviewing and Editing; and Supervision.

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Matt Magestro: Writing - Reviewing and Editing; Supervision; and Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relations that could have appeared to influence the work reported in this study.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.11.018.

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