JACC: ASIA VOL. 4, NO. 10, 2024

ORIGINAL RESEARCH

Diversity in Acute Autoimmune Pericarditis

Nationwide Analysis of In-Hospital Outcomes and Recurrence

Hirohiko Aikawa, MD,[a,b] Masashi Fujino, MD, PhD,[a,c] Kazuhiro Nakao, MD, PhD,[a] Michikazu Nakai, PhD,[d,e] Koshiro Kanaoka, MD, PhD,[d] Yoko Sumita,[d] Yoshihiro Miyamoto, MD, PhD,[d] Kensuke Takagi, MD,[a] Fumiyuki Otsuka, MD, PhD,[a] Yu Kataoka, MD, PhD,[a] Yasuhide Asaumi, MD, PhD,[a] Yoshio Tahara, MD,[a] Stephen J. Nicholls, MBBS, PhD,[c] Kenichi Tsujita, MD, PhD,[f] Teruo Noguchi, MD, PhD[a,b]

ABSTRACT

BACKGROUND Acute autoimmune pericarditis (AAP) is an uncommon disease with diverse etiology. Data regarding AAP diagnosis and outcomes are scant.

OBJECTIVES This study sought to describe the diagnosis and the rates of in-hospital mortality, cardiac tamponade, and readmission of AAP.

METHODS This study used a nationwide Japanese claim-based database to identify patients with AAP from April 2016 to March 2020 compared with patients with acute idiopathic pericarditis (AIP).

RESULTS Of 20,469 hospitalized patients with acute pericarditis, 170 had AAP and 5,027 had AIP of new onset. The diagnosis for AAP was systemic lupus erythematosus in 23.5% (40 of 170), rheumatoid arthritis in 19.4% (33 of 170), systemic sclerosis in 8.2% (14 of 170), other in 17.7% (30 of 170), and undifferentiated in 31.2% (53 of 170). During hospitalization, 1.8% (3 of 170) of patients with AAP and 1.5% (73 of 5,027) of patients with AIP died, and cardiac tamponade occurred in 8.8% (15 of 170) of AAP patients and 4.7% (237 of 5,027) of AIP patients. The incidence of cardiac tamponade was highest in patients with systemic lupus erythematosus (15.0%; 6 of 40). AAP was more associated with cardiac tamponade than AIP (adjusted OR: 1.82; 95% CI: 1.02-3.23). There was no difference between the AAP and AIP groups with regard to rehospitalization, although this was more common in patients with undifferentiated forms of autoimmune disease ($P = 0.001$).

CONCLUSIONS This Japanese national registry study of acute pericarditis revealed no differences in rehospitalization for recurrence between patients with AAP and AIP. It also underscored the diversity in AAP diagnosis, with more than 30% of patients lacking a differentiated diagnosis. (JACC Asia. 2024;4:721-731) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

From the [a]Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, Suita, Japan; [b]Department of Advanced Cardiovascular Medicine, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan; [c]Victorian Heart Institute, Monash University, Clayton, Australia; [d]Department of Medical and Health Information Management, National Cerebral and Cardiovascular Center, Suita, Japan; [e]Clinical Research Support Center, University of Miyazaki Hospital, Miyazaki, Japan; and the [f]Department of Cardiovascular Medicine, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received April 1, 2024; revised manuscript received June 17, 2024, accepted June 18, 2024.

ISSN 2772-3747 https://doi.org/10.1016/j.jacasi.2024.06.008

ABBREVIATIONS AND ACRONYMS

AAP = acute autoimmune pericarditis

AIP = acute idiopathic pericarditis

DPC = Diagnosis Procedure Combination

ESC = European Society of Cardiology

ICD-10 = International Classification of Diseases-10th revision

JROAD = Japanese Registry of All Cardiac and Vascular Diseases

SLE = systemic lupus erythematosus

UCTD = undifferentiated connective tissue disease

Acute pericarditis has many different causes.[1] Because the prognosis for one cause, acute autoimmune pericarditis (AAP), used to be considered comparable with that for acute idiopathic pericarditis (AIP), unlike cancerous and tuberculous disease, patients with AIP were candidates for randomized clinical trials of drugs to prevent recurrence.[2,3] A recent letter from a single institution reported that the recurrence rate of AAP was higher than that of idiopathic pericarditis among patients with recurrent pericarditis.[4] The European Society of Cardiology (ESC) guidelines for pericardial disease state that autoimmune causes include systemic autoimmunity, autoinflammatory diseases,[1] and systemic vasculitis. This diversity complicates the diagnosis and treatment of pericarditis. Previous single-center observational studies have investigated the etiology of pericarditis. There were very few patients with AAP: only 3 to 25 (1.7%-3.0%) patients.[5-7] There are few studies on the diagnosis and prognosis of AAP because of its rarity, especially in large datasets, which could be one approach to investigate rare diseases.[8] Previous studies based on nationwide data have not focused on the clinical characteristics or prognosis of AAP.[9-13] Furthermore, approximately 20% of patients referred to a connective tissue disease clinic have a diagnosis of undifferentiated connective tissue disease (UCTD),[14] which might also be a concern in the diagnosis and treatment of acute pericarditis. Therefore, using a nationwide database, we investigated the characteristics and outcomes of patients with AAP vs AIP and the prevalence of AAP without a differentiated autoimmune diagnosis and associated outcomes.

METHODS

DATA SOURCE. The Japanese Registry of All Cardiac and Vascular Diseases (JROAD) dataset was used for this analysis; it has been previously described in detail.[15,16] Briefly, JROAD was launched by the Japanese Circulation Society in 2004 and provides real-world, nationwide, and primary data from an annual survey on hospitalizations for cardiovascular diseases that includes information about resources (hospital beds, number of certified cardiologists or surgeons), number of hospitalized patients, and mortality. The purpose of JROAD is to evaluate the clinical activities of teaching hospitals in Japan and provide appropriate feedback to them. All cardiovascular teaching hospitals participate in JROAD because the database is essential for physicians to become certified cardiologists in Japan and for hospitals to be accredited by the Japanese Circulation Society. The JROAD Diagnosis Procedure Combination (DPC) is a nationwide claim-based database in which the JROAD database is united with the DPC system, which includes data on patient age and sex, admission status (emergency or planned), primary diagnosis, comorbidities, complications after admission, examinations, procedures, treatments, length of stay, costs, and discharge status (death or transportation to another hospital). Each hospital anonymizes patient identification numbers using the code-change equations made by each hospital in the original DPC data, which are sent to the Ministry of Health, Labour and Welfare. The attending physician is obliged to refer to the medical record to register the diagnosis in Japanese to optimize diagnostic accuracy.[17] Since 2016, the diagnosis can be extracted from this database based not only on the International Classification of Diseases-10th revision (ICD-10) codes but also on detailed diagnosis input by each physician. This research study was approved by the Institutional Review Board of the National Cerebral and Cardiovascular Center (R22013). Patients were notified through websites or posters in the National Cerebral and Cardiovascular Center that their information was being used for this study. Written consent from each patient was waived because of the observational nature of this study.

STUDY POPULATION. This study used JROAD-DPC data from April 2016 to March 2021. We identified patients on the basis of ICD-10 codes. We also used the detailed diagnosis to improve the reliability of diagnosis.[15] Previous trials of the treatment for acute pericarditis included patients with autoimmune and idiopathic (viral) pericarditis as having equivalent prognoses.[2,3] Therefore, we considered patients with these 2 etiologies to have acute pericarditis. Patients aged 20 years and older with acute pericarditis were extracted using the following ICD-10 codes: I30, I310, I318, I319, I321, I328, and I241. From these patients, we excluded patients with diagnoses other than pericarditis, such as postpericardial injury syndrome, acute myocardial infarction, aortic dissection, myocarditis, infectious endocarditis, hematologic disease, inflammatory bowel disease, hemodialysis, sepsis, and tuberculosis according to their respective

ICD-10 codes. In addition, all diagnoses were reviewed. According to the previous trial,[3] patients with chronic, recurrent, or incessant pericarditis were excluded, as were patients with bacterial, uremic, or malignant pericarditis; radiation-induced pericardial disease; or rheumatic fever pericarditis. Autoimmune disease included systemic autoimmune diseases, autoinflammatory diseases, and systemic vasculitides, according to the ESC guidelines.[1] Ultimately, we collected data on patients with AAP and AIP. Undifferentiated AAP was defined as patients with a diagnosis of autoimmune pericarditis or collagen disease pericarditis, without a diagnosis of specific autoimmune diseases. The details of ICD-10 codes and diagnoses used in this study are shown in Supplemental Table 1. We included only the first hospitalization for each patient with acute pericarditis. In the postdischarge analysis, the dates of outpatient visits were identified on the basis of outpatient receipt data. We excluded patients who experienced in-hospital death and patients without outpatient visits or hospitalization after discharge in the postdischarge analysis. In both the in-hospital analysis and postdischarge analysis, we compared the following: 1) patients with idiopathic pericarditis and autoimmune pericarditis among all study patients; and 2) patients with differentiated diagnosis and undifferentiated diagnosis of autoimmune pericarditis.

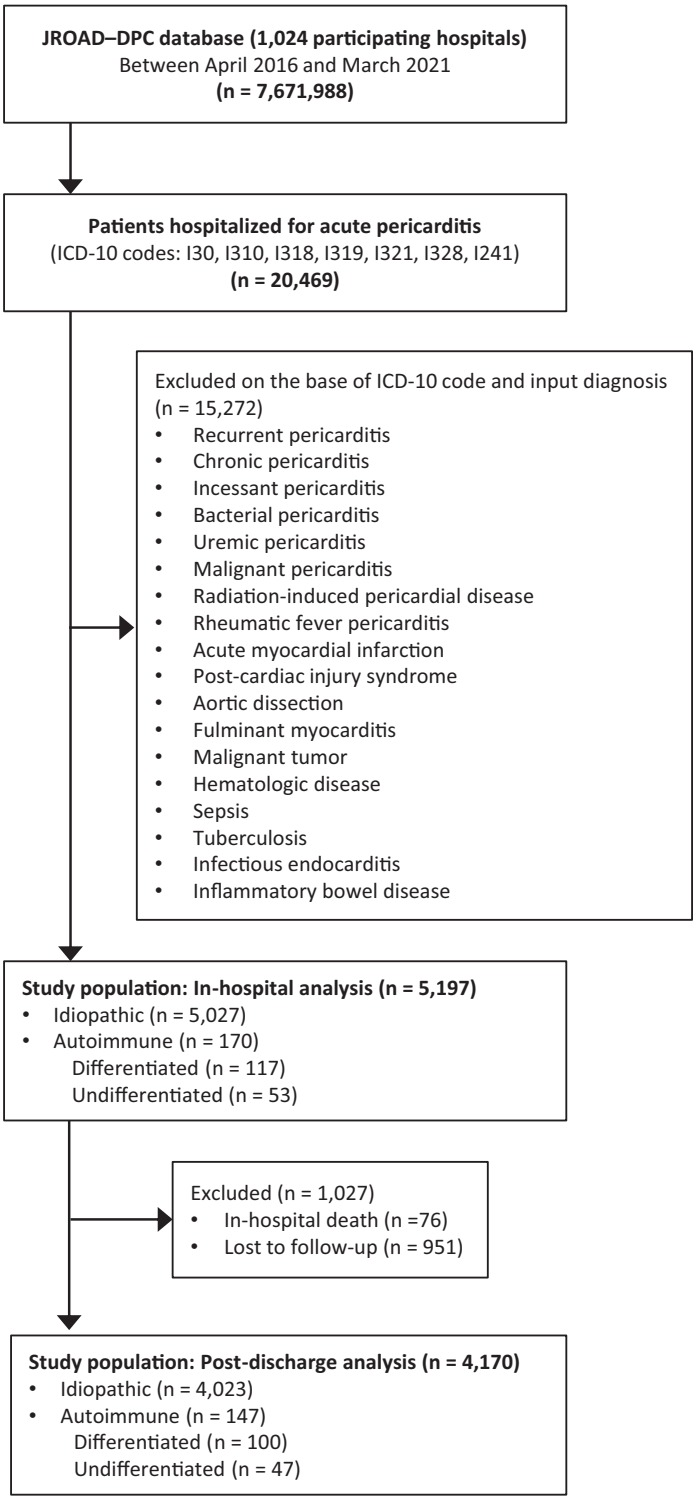
CLINICAL OUTCOMES. The outcomes of the in-hospital analysis were all-cause mortality and cardiac tamponade during the index hospitalization.[18,19] The outcome of the postdischarge analysis was hospitalization caused by recurrent pericarditis. In this study, hospitalization for recurrent pericarditis was defined as hospitalization at 4 or more weeks after discharge.[1] According to a previous study assessing rehospitalization using JROAD-DPC data,[20] we created a dataset to evaluate readmission to the same hospital within 1 year by matching the hospitalization records of the same patient.

STATISTICAL ANALYSIS. Baseline clinical characteristics, medications, and procedures are described with number and percentage for categorical variables or median and interquartile range for continuous variables. The Wilcoxon rank sum and Pearson chi-square tests were used to compare continuous and categorical variables, respectively. The incidence of acute pericarditis was examined on the basis of age categories and stratified by etiology. Uni- and multivariate multilevel mixed-effects logistic regression analyses with institution as a random intercept were performed to identify independent variables associated with in-hospital events. Multivariate models were adjusted for age, sex, body mass index, and etiology of acute pericarditis. In the in-hospital analysis for death and the postdischarge analysis for recurrent hospitalizations, a multivariate, multilevel, mixed-effects Cox regression model was performed, adjusted for age, sex, body mass index, and etiology of acute pericarditis. The database covers the detailed in-hospital information; however, the date of onset of cardiac tamponade was not included in this dataset. Also, we generated event-free curves for recurrent hospitalization because of pericarditis using the Kaplan-Meier method starting on the day of discharge; they were compared using the log-rank test. The Kaplan-Meier curves, along with their 95% CIs, were plotted with different colors to clearly distinguish the curves and their corresponding CIs. All P values of <0.05 were considered statistically significant. Analyses were performed using Stata 16 (Stata Corp).

RESULTS

The dataset included 7,671,988 admission records from 1,024 hospitals. It included 20,469 patients who met the eligibility criteria for acute pericarditis. Ultimately, we analyzed 5,197 patients in the in-hospital analysis after applying exclusion criteria (**Figure 1**). Clinical characteristics of the population in the in-hospital analysis are shown in **Table 1**. The median age was 64.0 years (Q1-Q3: 46.0-76.0 years), and 71.4% (3,711 of 5,197) were male. There were 170 (3.3%) patients with AAP and 5,027 (96.7%) patients with AIP. Among patients with AAP, the most common diagnosis was systemic lupus erythematosus (SLE) (40 of 170; 23.5%), followed by rheumatoid arthritis (33 of 170; 19.4%), systemic sclerosis (14 of 170; 8.2%), and mixed connective tissue disease (8 of 170; 4.7%). There were 53 (31.2%) patients with an undifferentiated diagnosis (**Figure 2**, Supplemental Table 2). Although there were no significant differences in age between the 2 groups, the proportion of female patients was higher in the AAP group than in the AIP group. Antinuclear antibody testing was more commonly performed among patients with AAP than patients with AIP (108 of 170 [63.5%] vs 2,065 of 5,027 [41.1%]; $P < 0.001$). Steroids were prescribed more frequently to patients with AAP than patients with AIP. By contrast, aspirin was more frequently prescribed to patients with AIP. Nonsteroidal anti-inflammatory drugs and colchicine were

FIGURE 1 Study Flowchart



The Japanese Registry of All Cardiac and Vascular Diseases–Diagnosis Procedure Combination (JROAD-DPC) database included 7,671,988 patients between April 2016 and March 2021. Of these patients, 5,197 patients were included in the in-hospital analysis based on the International Classification of Diseases-10th Revision (ICD-10) codes and diagnoses. The postdischarge analysis included 4,170 patients; it excluded patients with in-hospital death or loss to follow-up.

administered equally in both groups (Table 1). The invasive procedures of pericardial drainage and pericardiotomy were more often performed in patients with AAP (Table 1).

The rate of in-hospital death was not significantly different between the AIP and AAP groups (73 of 5,027 [1.5%] vs 3 of 170 [1.8%]; $P = 0.75$), whereas cardiac tamponade was significantly more common in patients with AAP than in those with AIP (237 of 5,027 [4.7%] vs 15 of 170 [8.8%]; $P = 0.023$). Among patients with AAP, SLE was the most common diagnosis associated with cardiac tamponade complications, followed by rheumatoid arthritis and systemic sclerosis (Supplemental Table 3). An age-specific analysis of in-hospital outcomes is shown in Figure 3. The rate of in-hospital death and cardiac tamponade tended to increase with age in patients with AIP. In patients with AAP, in-hospital death occurred in 2 patients in their 50s and in 1 patient in her 70s, and cardiac tamponade occurred in all age groups, especially those in their 30s and 50s. Multivariate logistic regression analysis showed that the adjusted OR for in-hospital death was 1.25 for AAP (95% CI: 0.37-4.23) with AIP as the reference, but the adjusted OR for cardiac tamponade was about twice as high for AAP as that for AIP (1.82; 95% CI: 1.02-3.23). The incidence of in-hospital death in AAP vs AIP had an adjusted HR of 0.70 (95% CI: 0.21-2.33; $P = 0.56$).

After excluding 76 patients who experienced in-hospital deaths and 832 lost to follow-up, the post-discharge analysis included 4,170 patients, consisting of 4,023 (96.5%) patients with AIP and the remaining 147 (3.5%) with AAP (Figure 1). The median age was 64 years (Q1-Q3: 46-75), and 71.8% (2,993 of 4,170) were male. Differences in characteristics between patients with AAP and those with AIP in the postdischarge analysis were similar to those in the in-hospital analysis (Supplemental Table 4). During a median follow-up of 78 days (Q1-Q3: 23-196), 2.3% (97 of 4,170) of patients were rehospitalized because of recurrence. At discharge, patients with AAP were significantly less likely to have been prescribed nonsteroidal anti-inflammatory drugs and significantly more likely to have been prescribed steroids than patients with AIP. The Kaplan-Meier method showed no significant differences in rehospitalization for recurrence between patients with AAP and AIP (Figure 4A, Supplemental Table 5). The multivariable Cox regression analysis showed that the occurrence of rehospitalization for recurrent pericarditis with AAP compared to AIP had an HR of 0.68 (95% CI: 0.24-1.89; $P = 0.46$). Characteristics, medications, and invasive procedures of patients with and without

TABLE 1 Baseline Characteristics, Medications, and Invasive Procedures of Patients Included in the In-Hospital Analysis

	All Patients (N = 5,197)	Acute Autoimmune Pericarditis (n = 170)	Acute Idiopathic Pericarditis (n = 5,027)	*P* Value
Age, y	64.0 (46.0-76.0)	66.0 (48.0-76.0)	64.0 (45.0-76.0)	0.60
Female	1,486 (28.6)	111 (65.3)	1,375 (27.4)	<0.001
Body weight, kg	60 (51.0-69.5)	53.0 (45.7-64.0)	60.4 (51.1-69.8)	<0.001
Height, cm	163 (154-170)	158 (152-165)	163 (154-170)	<0.001
Body mass index, kg/m^2	22.8 (20.5-25.2)	21.5 (19.3-24.2)	22.9 (20.6-25.2)	<0.001
Brinkman index	23.0 (0.0-650.0)	0.0 (0.0-90.0)	44.0 (0.0-672.0)	<0.001
Comorbidities				
Hypertension	1,618 (31.1)	44 (25.9)	1,574 (31.3)	0.13
Dyslipidemia	899 (17.3)	22 (12.9)	877 (17.4)	0.13
Diabetes mellitus	800 (15.4)	31 (18.2)	769 (15.3)	0.30
Chronic coronary syndrome	831 (16.0)	13 (7.6)	818 (15.3)	0.003
Atrial fibrillation	735 (14.5)	17 (10.0)	736 (14.6)	0.09
Medications during hospitalization				
NSAID	3,574 (68.8)	107 (62.9)	3,467 (69.0)	0.10
Aspirin	1,339 (25.8)	23 (13.5)	1,316 (26.2)	<0.001
Colchicine	1,422 (27.4)	40 (23.5)	1,382 (27.5)	0.25
Steroid	731 (14.1)	122 (71.8)	609 (12.1)	<0.001
Invasive procedures				
Pericardial drainage	754 (14.5)	39 (22.9)	715 (14.2)	0.002
Pericardiotomy	65 (1.3)	5 (2.9)	60 (1.2)	0.044
Mechanical circulatory support	16 (0.3)	0 (0.0)	16 (0.3)	0.46

Values are median (Q1-Q3) or n (%).
NSAID = nonsteroidal anti-inflammatory drug.

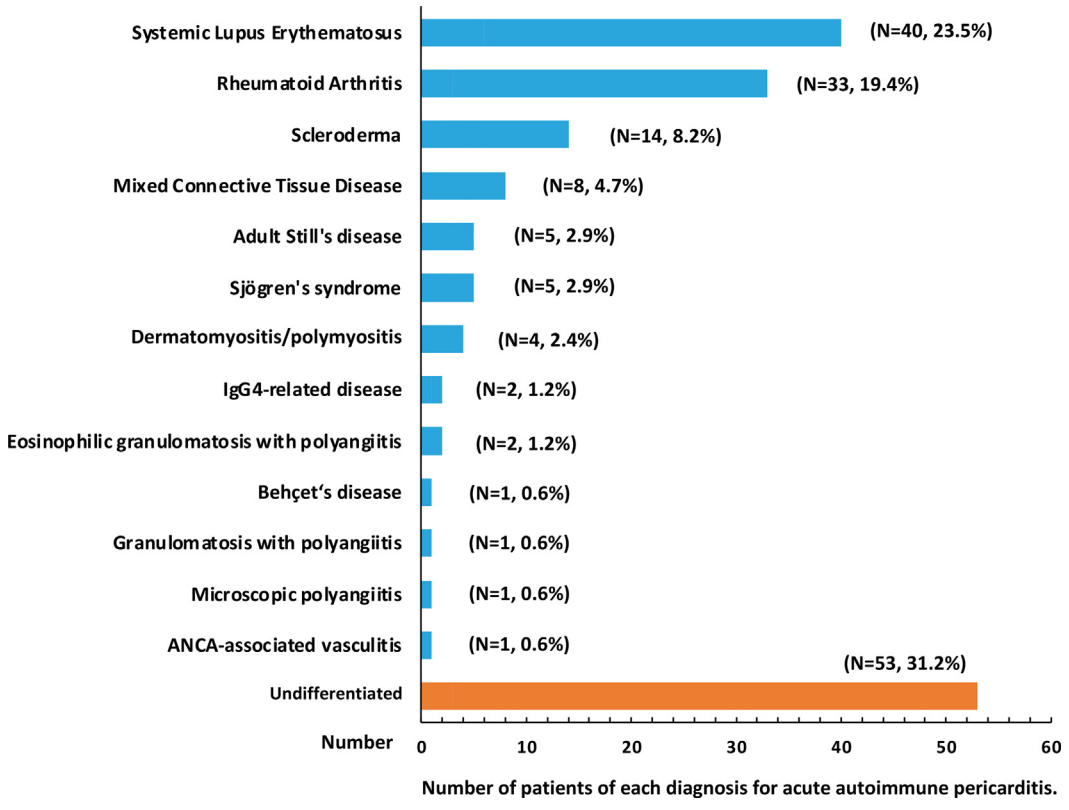
recurrence in AIP or AAP are available in Supplemental Tables 6 and 7.

We compared patients with AAP who had a differentiated diagnosis with those who had a differentiated diagnosis. In the in-hospital analysis, among 170 patients with AAP, 117 of 170 (68.8%) patients had a differentiated diagnosis, and 53 of 170 (31.2%) patients had an undifferentiated diagnosis (**Table 2**). Patients with differentiated AAP were younger and a lower proportion of them were female compared with patients with undifferentiated AAP. Patients with undifferentiated AAP were less likely to have prescriptions of steroids at discharge compared to those with differentiated AAP (79 of 117 [67.5%] vs 14 of 53 [26.4%]; $P < 0.001$). There were no differences in the incidence of in-hospital death (3 of 117 [2.6%] vs 0 of 53 [0.0%]; $P = 0.24$) or cardiac tamponade (12 of 117 [10.3%] vs 3 of 53 [5.7%]; $P = 0.33$) between patients with differentiated and undifferentiated AAP. In the postdischarge analysis, among 147 patients with AAP, 47 patients (32.0%) had an undifferentiated diagnosis (Supplemental Table 8). There were no differences in the rate of antinuclear antibody testing between patients with differentiated and undifferentiated AAP (73 of 117 [62.4%] vs 35 of 53 [66.0%]; $P = 0.65$). No rehospitalization events were observed in patients with differentiated AAP, whereas patients with undifferentiated AAP had a significantly higher recurrence rate than those with differentiated AAP (log-rank test: $P = 0.001$) (**Figure 4B**, Supplemental Table 9). Of note, among 97 patients with rehospitalization, 9 with AIP had a new diagnosis of an autoimmune disease (SLE: n = 1; rheumatoid arthritis: n = 1; mixed connective tissue disease: n = 1; immunoglobulin G4-related disease: n = 1; microscopic polyangiitis: n = 1; undifferentiated autoimmune disease: n = 4). No new diagnoses were identified in patients with undifferentiated AAP.

DISCUSSION

We used a nationwide dataset of more than 20,000 patients with acute pericarditis to describe differences in characteristics and treatment between patients with AAP and patients with AIP in Japan and the contemporary diagnosis of AAP. In addition, we have described that the in-hospital mortality rate of AAP was similar to that of AIP, but there were more complications of cardiac tamponade in patients with AAP. More than 30% of patients with AAP had an undifferentiated diagnosis, and the complication rate varied by diagnosis. The rehospitalization rate for

FIGURE 2 Number of Patients With Acute Autoimmune Pericarditis by Diagnosis



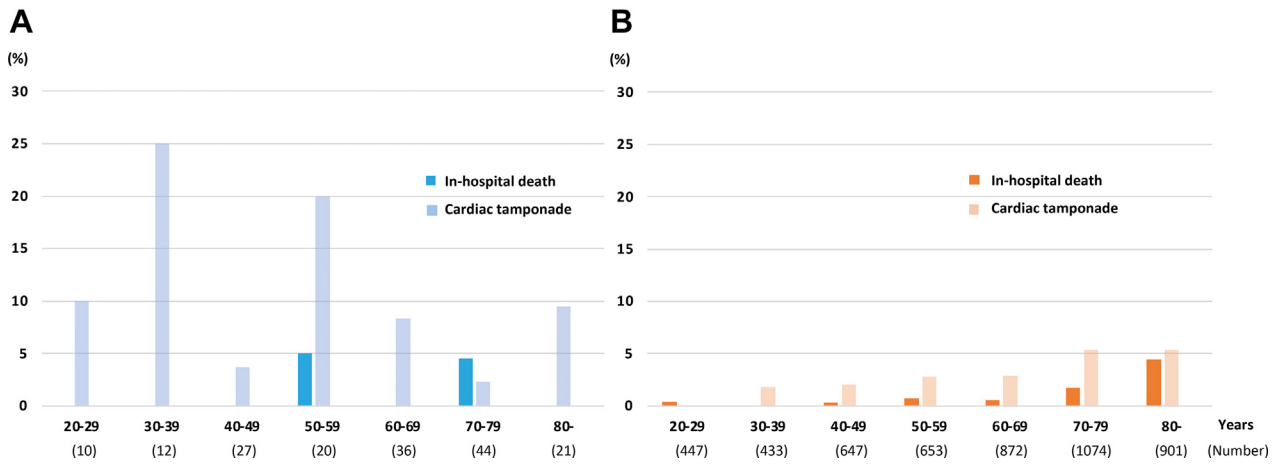
The chart illustrates the distribution of diagnoses associated with acute autoimmune pericarditis, showing the number and proportion of patients by diagnosis. The 5 most common diagnoses were systemic lupus erythematosus (40 of 170; 23.5%), rheumatoid arthritis (33 of 170; 19.4%), systemic sclerosis (14 of 170; 8.2%), mixed connective tissue disease (8 of 170; 4.7%), and adult Still disease (5 of 170; 2.9%); 31.2% (53 of 170) of patients had an undifferentiated diagnosis. ANCA = antineutrophil cytoplasmic antibody; IgG = immunoglobulin G.

recurrent pericarditis was similar between patients with AAP and AIP; however, patients with undifferentiated diagnosis experienced rehospitalization more frequently than those with a differentiated diagnosis (**Central Illustration**).

In this nationwide dataset, there were 170 patients with AAP and 5,027 patients with AIP. This is consistent with previous reports that 2% to 4% of acute pericarditis is caused by autoimmune disease.[5,6,9] There are few studies focusing on the detailed diagnosis of AAP. Previous studies using a nationwide dataset have examined the clinical profile[9-11] and trends in outcomes[12] as well as an economic assessment[13] of acute pericarditis. A single-center observational study reported that 25 of 1,162 patients with pericarditis had AAP. Of these 25 patients, the most common autoimmune disease was SLE (n = 6).[7] Another single-center study with 74 patients who had pericarditis and pericardial effusion reported 8 patients with SLE and 5 with UCTD among 23 patients with AAP.[21] We showed that SLE is the most common cause of AAP, consistent with these previous studies, followed by rheumatoid arthritis and scleroderma. We showed that undifferentiated AAP was comparable to number of patients with SLE among pericarditis patients.

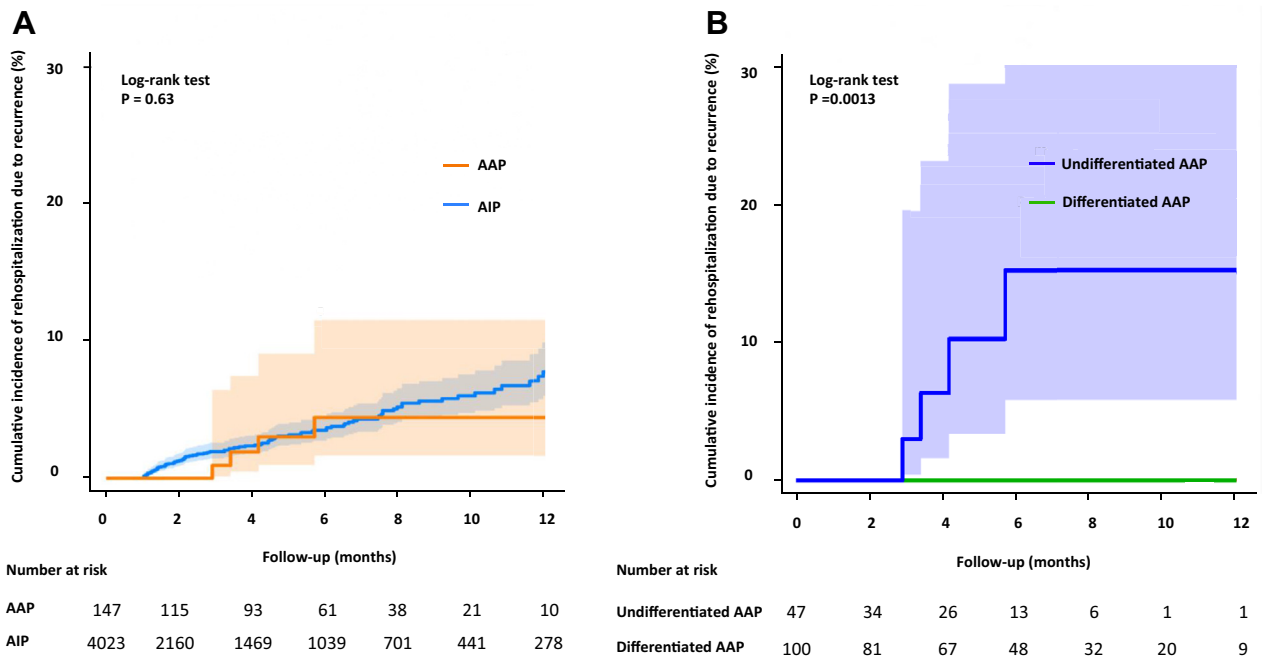
In this study, patients with AIP and AAP had similar in-hospital mortality rates, but cardiac tamponade was more common in patients with AAP than in patients with AIP, even in middle age. AAP had about twice the OR for cardiac tamponade compared to AIP. In particular, in our study, cardiac tamponade was a complication in 15.0% (6 of 40) of patients with SLE and in 9.1% (3 of 33) of patients with rheumatoid arthritis. The rate of cardiac tamponade as a complication of SLE has been reported to be 13% to 25%. SLE pericarditis is more frequently associated with cardiac tamponade than AIP.[22,23] In autoimmune

FIGURE 3 **In-Hospital Outcomes Stratified by Age and Cause of Pericarditis**



The bar graph illustrates the frequency of in-hospital mortality and cardiac tamponade by age among patients with (A) acute autoimmune pericarditis (AAP) and (B) acute idiopathic pericarditis (AIP). In patients with AAP, the rate of in-hospital death and cardiac tamponade have increasing trends with age. In patients with AAP, there were only 3 of 170 (1.8%) patients with in-hospital death in their 50s or 70s, and cardiac tamponade occurred especially in patients in their 30s and 50s.

FIGURE 4 **Recurrence by Etiology and Presence of a Differentiated Diagnosis**



Number at risk

AAP	147	115	93	61	38	21	10
AIP	4023	2160	1469	1039	701	441	278

Number at risk

Undifferentiated AAP	47	34	26	13	6	1	1
Differentiated AAP	100	81	67	48	32	20	9

The Kaplan-Meier method was used to estimate survival curves with 95% CI (in color) for rehospitalization caused by recurrence. The log-rank test was used to assess differences between (A) patients with acute autoimmune pericarditis (AAP) and acute idiopathic pericarditis (AIP) and (B) between patients with differentiated and undifferentiated AAP. There were no significant differences in rehospitalization for recurrence between patients with AAP and those with AIP, but rehospitalization occurred significantly more frequently in patients with undifferentiated AAP than in patients with differentiated AAP.

TABLE 2 Characteristics, Medications, and Invasive Procedures in Patients With AIP Included in the In-Hospital Analysis

	Differentiated Autoimmune Pericarditis (n = 117)	Undifferentiated Autoimmune Pericarditis (n = 53)	*P* Value
Age, y	63.0 (47.0-73.0)	71.0 (53.0-79.0)	<0.001
Female	74 (63.2)	37 (69.8)	<0.001
Body weight, kg	52.2 (45.4-65.2)	53.6 (47.5-57.7)	<0.001
Height, cm	158 (152-167)	154 (149-163)	<0.001
Body mass index, kg/m^2	21.5 (19.0-24.2)	21.5 (19.8-23.9)	<0.001
Brinkman index	0.0 (0.0-255.0)	0.0 (0.0-70.0)	0.22
Comorbidities			
Hypertension	30 (25.6)	14 (26.4)	0.32
Dyslipidemia	10 (8.5)	12 (22.6)	0.025
Diabetes mellitus	23 (19.7)	8 (15.1)	0.43
Chronic coronary syndrome	3 (2.6)	8 (15.1)	0.001
Atrial fibrillation	10 (8.5)	7 (13.2)	0.17
Medications at discharge			
NSAID	77 (65.8)	30 (56.6)	0.25
Aspirin	16 (13.7)	7 (13.2)	0.93
Colchicine	30 (25.6)	10 (18.9)	0.33
Steroid	97 (82.9)	25 (47.2)	<0.001
Invasive procedures			
Pericardial drainage	24 (20.5)	15 (28.3)	0.26
Pericardiotomy	3 (2.6)	2 (3.8)	0.67
Mechanical circulatory support	0 (0.0)	0 (0.0)	

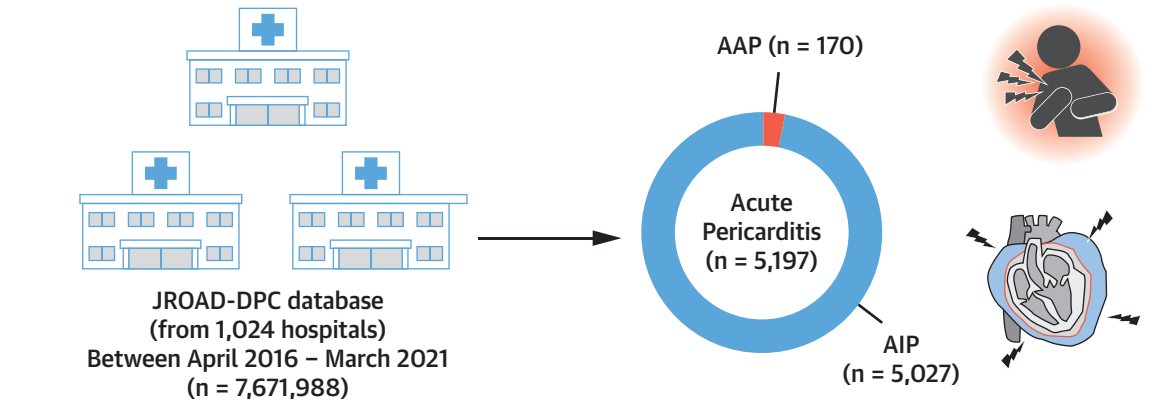
Values are median (Q1-Q3) or n (%).
NSAID = nonsteroidal anti-inflammatory drug.

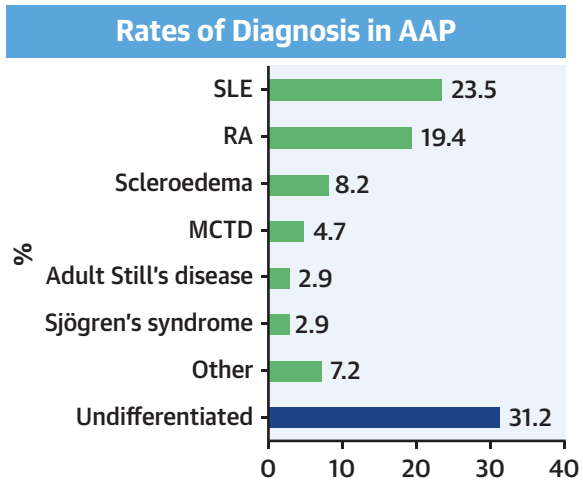
diseases other than SLE and rheumatoid arthritis, the rate of pericarditis as a complication is quite low, at 1% to 3%.[24,25] Cardiac tamponade has only been reported in case reports.[26-30] We found no differences in rates of rehospitalization caused by recurrence between AIP and AAP. A recent single-center observational study of recurrent pericarditis that included 65 patients with autoimmune pericarditis reported that autoimmune pericarditis is associated with significantly more recurrences than idiopathic or cardiac postoperative pericarditis.[4] Our results were not similar to that report. That study examined patients with recurrent pericarditis. Our analysis included 170 patients with a first hospitalization for AAP, making it the largest analysis to date, to our knowledge. Because AAP is very rare, with patient rates in randomized controlled trials ranging from 2.9% to 15.8%,[2,3] the enrollment of AAP patients in clinical trials might not affect the outcome of the study. Nevertheless, our results do not emphasize that the prognosis of AIP and AAP are equivalent. Just as there are many etiologies for acute pericarditis, there are many etiologies for AAP. We would like to indicate to clinicians that complications and prognosis differ depending on diagnosis.

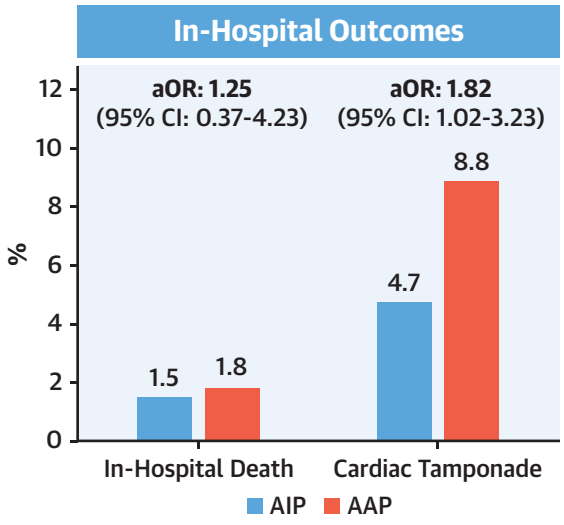
More than 30% of patients with AAP did not have a specific diagnosis. A previous study reported that among 23 patients with pericardial effusion and systemic inflammatory disease, 3 (13.0%) were diagnosed with UCTD.[21] This low proportion of patients with UCTD might be attributable to the small number of patients in a single-center study. In our study, compared with patients with differentiated AAP, patients with undifferentiated AAP had similar rates of in-hospital events but more hospitalizations for recurrence. Although we found no differences in antibody testing rates during the first admission between patients with and without a differentiated diagnosis, steroids were prescribed more often to patients with differentiated AAP than to patients with undifferentiated AAP. These findings suggest an association between diagnosis uncertainty and cautious treatment of autoimmune diseases to avoid side effects. We are not advocating thorough screening tests. However, additional tests based on pretest probability by age, sex, and symptoms should be considered and performed. Although one-third of patients with UCTD were diagnosed with connective tissue disease at follow-up in the previous study,[31] interestingly, in this study, the only patients with a new diagnosis on readmission were those diagnosed with AIP on initial admission. The results suggest the importance of watchful waiting for both AAP and AIP. With recent studies involving big data reporting that pericarditis is a risk factor for the development of cancer,[32,33] it is necessary to develop a consensus on appropriate follow-up protocols for pericarditis.

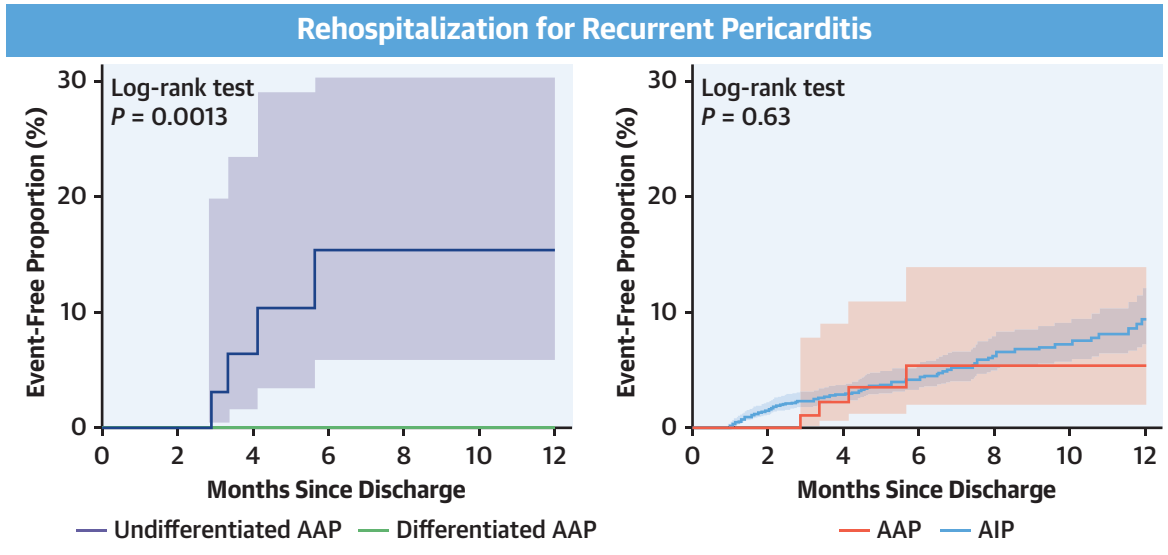
STUDY LIMITATIONS. First, we lacked access to laboratory data, information regarding physiologic and imaging tests, and hemodynamic data. Consequently, we were unable to evaluate factors known from previous reports to be adverse prognostic indicators for pericarditis, such as fever, elevated inflammatory markers, onset patterns, pericardial effusion volume, and response to medical therapy. Second, there are a lack of ICD-10 codes for UCTD. A previous study of rheumatic diseases used ICD-10 codes for other rheumatic diseases, but the diagnosis of UCTD was based on medical record review.[34] In this analysis, we defined undifferentiated AAP as patients with a diagnosis of autoimmune pericarditis or collagen disease pericarditis, each of which has its own ICD-10 code, and without a diagnosis of specific autoimmune diseases. Thus, our study may have included patients diagnosed with UCTD despite having a specific autoimmune disease. Third, because this study evaluated rehospitalization caused by recurrent pericarditis, it

CENTRAL ILLUSTRATION **Diversity of Acute Idiopathic Pericarditis: In-Hospital Outcomes and Rehospitalization for Recurrence**









Aikawa H, et al. JACC Asia. 2024;4(10):721–731.

From the nationwide database, 170 patients had AAP, and 5,027 had AIP of new onset. AAP exhibited diversity in diagnosis. AAP had a significantly higher incidence of cardiac tamponade compared to AIP. There were no significant differences observed in rehospitalization for recurrence between patients with AAP and AIP. However, rehospitalization was significantly more common in patients with undifferentiated AAP. The Kaplan-Meier method was used to estimate survival curves with 95% CIs (in color) for rehospitalization caused by recurrence. AAP = acute autoimmune pericarditis; AIP = acute idiopathic pericarditis; aOR = adjusted OR; Apr. = April; JROAD-DPC = Japanese Registry of All Cardiac and Vascular Diseases–Diagnosis Procedure Combination; Mar. = March; MCTD = mixed connective tissue disease; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus.

is difficult to make direct comparisons with previously reported rates of recurrent pericarditis, which did not require hospitalization. In addition, because the readmissions in this study were investigated in the same hospital, recurrence might have been underestimated in some untraceable patients because of the possibility that some of them were readmitted to different hospitals, even though rehospitalization for heart failure was validated using the JROAD-DPC database.[20] Furthermore, because the JROAD database transitioned from using ICD-9 to ICD-10 codes and altered data collection methods in April 2016, we were unable to analyze information sequentially before that date. Thus, this analysis may have included some patients with previous hospitalizations for acute pericarditis. Fourth, our study followed the ESC guidelines for eligibility of autoimmune pericarditis as systemic autoimmune and auto-inflammatory disease. Although it is controversial whether autoinflammatory disease is included in autoimmune pericarditis, we showed all results for each diagnosis. Finally, although our analysis included admissions to cardiovascular wards throughout Japan, most of the patients were Japanese, and our findings need to be evaluated along with reports from other countries.

CONCLUSIONS

AAP was similar to AIP in terms of in-hospital mortality and prognosis, despite the more frequent complication of cardiac tamponade. In particular, undifferentiated AAP was associated with more hospitalizations for recurrence than differentiated AAP. These findings indicate the importance of understanding the diverse etiologies of AAP and the importance of appropriate diagnosis and management of pericarditis.

ACKNOWLEDGMENTS The authors appreciate the contributions of all the investigators, clinical research coordinators, and data managers involved in the JROAD-DPC study.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This study was supported by a grant from the Naohiko Miyata-Asahi Intecc Foundation for Medical Technology and Research. This study was also funded by the Intramural Research Fund for Cardiovascular Disease of the National Cerebral and Cardiovascular Center (23-B-7). Dr Kataoka has received research support from Kowa, Nipro, and Abbott and honoraria from Nipro, Abbott, Kowa, Amgen, Sanofi, Astellas, Takeda, and Daiichi-Sankyo. Dr Nicholls has received research support from AstraZeneca, Amgen, Anthera, CSL Behring, Cerenis, Eli Lilly, Esperion, Resverlogix, New Amsterdam Pharma, Novartis, InfraReDx, and Sanofi-Regeneron and is a consultant for Amgen, Akcea, AstraZeneca, Boehringer Ingelheim, CSL Behring, Eli Lilly, Esperion, Kowa, Merck, Takeda, Pfizer, Sanofi-Regeneron, Vaxxinity, CSL Sequiris, Cyclarity, and Novo Nordisk. Dr Tsujita has received research support and honoraria from Beyer. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Masashi Fujino, Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, 6-1 Kishibe-Shimmachi, Suita, Osaka 564-8565, Japan. E-mail: fujinom@ncvc.go.jp. X handle: @MasashiFujino.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The diagnosis of AAP and the frequency of complications varied widely, with a considerable number of patients with undifferentiated AAP and a high recurrence rate.

TRANSLATIONAL OUTLOOK: Further worldwide studies are warranted to establish tailored diagnostic and monitoring protocols for AAP.

REFERENCES

1. Adler Y, Charron P, Imazio M, et al. 2015 ESC guidelines for the diagnosis and management of pericardial diseases: the Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC)Endorsed by: the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2015;36:2921–2964.

2. Imazio M, Bobbio M, Cecchi E, et al. Colchicine in addition to conventional therapy for acute pericarditis: results of the Colchicine for Acute Pericarditis (COPE) trial. *Circulation*. 2005;112:2012–2016.

3. Imazio M, Brucato A, Adler Y. A randomized trial of colchicine for acute pericarditis. *N Engl J Med*. 2013;369:1522–1528.

4. Yesilyaprak A, Kumar AK, Agrawal A, et al. Prognostic value of etiology in patients with recurrent pericarditis. *J Am Coll Cardiol*. 2023;81:2056–2058.

5. Permanyer-Miralda G, Sagristá-Sauleda J, Soler-Soler J. Primary acute pericardial disease: a prospective series of 231 consecutive patients. *Am J Cardiol*. 1985;56:623–630.

6. Zayas R, Anguita M, Torres F, et al. Incidence of specific etiology and role of methods for specific etiologic diagnosis of primary acute pericarditis. *Am J Cardiol*. 1995;75:378–382.

7. Gouriet F, Levy PY, Casalta JP, et al. Etiology of pericarditis in a prospective cohort of 1162 cases. *Am J Med*. 2015;128:784.e781–784.e788.

8. Bergier H, Duron L, Sordet C, et al. Digital health, big data and smart technologies for the care of patients with systemic autoimmune diseases: where do we stand? *Autoimmun Rev*. 2021;20:102864.

9. Kytö V, Sipilä J, Rautava P. Clinical profile and influences on outcomes in patients hospitalized for acute pericarditis. *Circulation*. 2014;130:1601–1606.

10. Sreenivasan J, Khan MS, Hooda U, et al. Rate, causes, and predictors of 30-day readmission following hospitalization for acute pericarditis. *Am J Med*. 2020;133:1453–1459.e1451.

11. Vecchié A, Chiabrando JG, Dell MS, et al. Clinical presentation and outcomes of acute

pericarditis in a large urban hospital in the United States of America. *Chest*. 2020;158:2556–2567.

12. Kumar N, Pandey A, Jain P, Garg N. Acute pericarditis-associated hospitalization in the USA: a nationwide analysis, 2003-2012. *Cardiology*. 2016;135:27–35.

13. Schwier NC, Tran NT, Skrepnek GH. Clinical and economic outcomes associated with hospitalizations for acute idiopathic pericarditis in the United States. *Heart Lung*. 2021;50:825–831.

14. Mosca M, Tani C, Talarico R, Bombardieri S. Undifferentiated connective tissue diseases (UCTD): simplified systemic autoimmune diseases. *Autoimmun Rev*. 2011;10:256–258.

15. Yamaguchi T, Nakai M, Sumita Y, et al. The impact of institutional case volume on the prognosis of ruptured aortic aneurysms: a Japanese nationwide study. *Interact Cardiovasc Thorac Surg*. 2019;29:109–116.

16. Kondo T, Araki T, Imaizumi T, et al. Prognosis in patients with cardiogenic shock who received temporary mechanical circulatory support. *JACC Asia*. 2023;3:122–134.

17. Isogai T, Yasunaga H, Matsui H, et al. Effect of weekend admission for acute myocardial infarction on in-hospital mortality: a retrospective cohort study. *Int J Cardiol*. 2015;179:315–320.

18. Lazaros G, Vlachakis PK, Theofilis P, et al. D-dimer as a diagnostic and prognostic plasma biomarker in patients with a first episode of acute pericarditis. *Eur J Intern Med*. 2023;116:58–64.

19. Imazio M, Cecchi E, Demichelis B, et al. Indicators of poor prognosis of acute pericarditis. *Circulation*. 2007;115:2739–2744.

20. Nakao K, Yasuda S, Noguchi T, et al. Association of hospital performance measures with readmissions for patients with heart failure: a report from JROAD-DPC study. *Int J Cardiol*. 2021;340:48–54.

21. Assayag M, Abbas R, Chanson N, et al. Diagnosis of systemic inflammatory diseases among patients admitted for acute pericarditis with pericardial effusion. *J Cardiovasc Med (Hagerstown)*. 2017;18:875–880.

22. Kahl LE. The spectrum of pericardial tamponade in systemic lupus erythematosus. Report of ten patients. *Arthritis Rheum*. 1992;35:1343–1349.

23. Goswami RP, Sircar G, Ghosh A, Ghosh P. Cardiac tamponade in systemic lupus erythematosus. *QJM*. 2018;111:83–87.

24. Butt SA, Jeppesen JL, Torp-Pedersen C, et al. Cardiovascular manifestations of systemic sclerosis: a Danish nationwide cohort study. *J Am Heart Assoc*. 2019;8:e013405.

25. Guédon AF, Carrat F, Mouthon L, et al. Heart and systemic sclerosis-findings from a national cohort study. *Rheumatology (Oxford)*. Published online November 7, 2023. https://doi.org/10.1093/rheumatology/kead599

26. Fernández Morales A, Iniesta N, Fernández-Codina A, et al. Cardiac tamponade and severe pericardial effusion in systemic sclerosis: report of nine patients and review of the literature. *Int J Rheum Dis*. 2017;20:1582–1592.

27. Kumar MS, Smith M, Pischel KD. Case report and review of cardiac tamponade in mixed connective tissue disease. *Arthritis Rheum*. 2006;55:826–830.

28. Kurth BJ, Wagler V, Keith M. Cardiac tamponade as a manifestation of severe dermatomyositis. *BMJ Case Rep*. 2016. bcr2016216860.

29. Doumen M, Vankelecom B, Westhovens R, Michiels S. Pericarditis as a manifestation of IgG4-related disease. *Rheumatol Int*. 2022;42:1287–1295.

30. Kaur P, Palya A, Hussain H, Dabral S. Microscopic polyangiitis presenting as early cardiac tamponade. *J Clin Rheumatol*. 2010;16:86–87.

31. Bodolay E, Csiki Z, Szekanecz Z, et al. Five-year follow-up of 665 Hungarian patients with undifferentiated connective tissue disease (UCTD). *Clin Exp Rheumatol*. 2003;21:313–320.

32. Søgaard KK, Farkas DK, Ehrenstein V, Bhaskaran K, Bøtker HE, Sørensen HT. Pericarditis as a marker of occult cancer and a prognostic factor for cancer mortality. *Circulation*. 2017;136:996–1006.

33. Sigvardt FL, Hansen ML, Kristensen SL, et al. Risk factors for morbidity and mortality following hospitalization for pericarditis. *J Am Coll Cardiol*. 2020;76:2623–2631.

34. Sharmeen S, Nomani H, Taub E, Carlson H, Yao Q. Polycystic ovary syndrome: epidemiologic assessment of prevalence of systemic rheumatic and autoimmune diseases. *Clin Rheumatol*. 2021;40:4837–4843.

KEY WORDS autoimmune pericarditis, big data, cardiac tamponade, idiopathic pericarditis, pericarditis, recurrence

APPENDIX For supplemental tables, please see the online version of this paper.