

## The Seasonal Pattern of Acute Pericarditis and Concurrence of Recurrent Pericarditis with Vitamin D Deficiency

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### Abstract

**Background:** Many environmental, behavioural, and immunological mechanisms have been proposed for the seasonality of many viral pathogens. We aim to identify whether acute idiopathic pericarditis has seasonal variations and examine vitamin D level in the patients with recurrent pericarditis.

**Methods:** We retrospectively examined 216 patients diagnosed with acute pericarditis between February 2012 and November 2017. The patients with non-infectious pericarditis and myocardial involvement (myopericarditis) were exclusion criteria. Demographic, clinical, and biochemical information, and follow-up findings obtained during the acute attack were collected. To identify possible seasonal patterns, the incidence rates of acute pericarditis were categorized according to months. Moreover, vitamin D levels was obtained through blood test (in time first pericarditis attack time and recurrent pericarditis). The vitamin D levels of pericarditis cases were compared.

**Results:** 216 patients with acute idiopathic pericarditis consisted of 173 male (80%) and 44 females (20%). Mean ages was  $32 \pm 6.3$  years (min 17- maximum 56 years). High-sensitivity troponin I was  $0.26 \pm 1.19$  ng/mL. High-sensitivity C-reactive protein was  $0.99 \pm 0.74$  mg/L. Recurrence ratio of acute pericarditis was 26.3% (n=57). There were two peak appearances in the 12-month analysis in acute pericarditis. The incidence of acute pericarditis reached a peak in the periods of April-May and September. The recurrent pericarditis had no co-existence with seasonal pattern. The vitamin D levels in the patients with recurrent pericarditis was found to be lower level than first pericarditis attack levels ( $23.31 \pm 4.16$  ng/ml,  $39.16 \pm 9.67$  ng/ml, respectively,  $p < 0.001$ ).

**Conclusion:** We found that idiopathic pericarditis had a seasonal pattern and no seasonal pattern in recurrent pericarditis cases. Moreover, the vitamin D levels in the patients with recurrent pericarditis was established to be lower level than first pericarditis attack. Therefore, care should be taken for seasonality and disease preventive measures in acute pericarditis and recurrent pericarditis.

**Keywords:** Acute pericarditis; Viral infections; Seasonal pattern; Vitamin D deficiency

### Introduction

Acute pericarditis is a disease caused by the inflammation of the pericardium [1]. Pericarditis is responsible for 0.1% of all hospital admissions and 5% of emergency room admissions for chest pain [2,3]. The causes of the acute pericardial diseases are aetiologically classified into infectious and non-infectious [4]. The most frequent cause of acute pericarditis is idiopathic in developed countries [5,6]. Idiopathic pericarditis is believed to be associated with a viral infection [7,8]. The most frequently seen viral pathogens are enteroviruses (Coxsackie viruses, Echoviruses), Herpes Viruses (Epstein-Barr Virus, Cytomegalovirus, and Human Herpes Virus-6), Adenoviruses, and Parvovirus B19 [4]. It has been known that climatic conditions affect infectious diseases for centuries [9]. Influenza and several other infectious diseases exhibit cyclic seasonal patterns, which may be explained by climate. A sudden drop in outdoor temperature might trigger the annual influenza epidemic [10]. The transition periods from summer to autumn or from winter to spring may be related with this

condition. For example, Coxsackie virus B heart infections arise mainly during autumn and winter and other enterovirus infections peak in September to November [11-13]. Several environmental, behavioral, and immunological mechanisms have been proposed for the distinct seasonality of many viral pathogens [14,15]. If concomitance of viral infections and seasonality exist, the relationship between seasonality and acute viral pericarditis can be expected as well. However, there is little research into such a possible relationship. Moreover, vitamin D has an important role in the modulation of both innate and cellular immune responses [16]. The presence of vitamin D deficiency in the recurrent pericarditis is not known. Therefore, we investigated seasonal variations of acute pericarditis and concurrence of recurrent pericarditis with vitamin D level.

### Methods

We retrospectively examined 216 patients diagnosed with acute pericarditis between February 2012 and November 2017. A written informed consent was obtained from each patient. The study protocol was approved by Medicana International Ankara Hospital Ethics Committee [Numbered: 2017/1]. The study was conducted in

accordance with the principles of Declaration of Helsinki. The database was searched for all patients admitted with a first episode of acute pericarditis between February 1, 2012 and November 1, 2017. The patients with non-infectious pericarditis (post-cardiac injury syndrome, autoimmune causes, neoplastic, metabolic, traumatic and iatrogenic, drug-related) were excluded. Myocardial involvement (myopericarditis) was another exclusion criterion. To identify possible seasonal patterns, the incidence rates of acute pericarditis were categorized according to months. The diagnostic examination included physical examination, blood tests (chemistry including renal and liver function tests and C-reactive protein, high-sensitivity cardiac troponin I, complete blood count, chest x-ray, electrocardiogram, echocardiogram. The cardiac tomography imaging was used when indicated. The diagnosis of acute pericarditis was made by the presence of at least 2 of the following 4 criteria: typical pleuritic chest pain, characteristic electrocardiographic changes, pericardial friction rub, and new or worsening pericardial effusion. To identify possible seasonal patterns, the incidence rates of acute pericarditis were categorized according to months. The recurrent pericarditis (57 patients) was defined as the recurrence of pericarditis after a documented first episode of acute pericarditis and a symptom-free interval of 4–6 weeks or more. The nonsteroidal anti-inflammatory drugs (NSAIDs) were used as first-line treatment unless contraindicated. Colchicine was used as additional therapy. Prednisone was not used. Pericardiocentesis was not performed. Demographic, clinical, radiologic, and biochemical information, and follow-up findings obtained during the acute attack were collected. The recurrence was recorded only if there was evidence of hospital readmission or emergency room examination. Moreover, the vitamin D levels tests were done only in 50 recurrent pericarditis cases and in the 40 patients in time first episode of acute pericarditis cases. The blood samples were collected within 12-months. The vitamin D levels of pericarditis cases were compared.

### Statistical analysis

Statistical analyses were performed using SPSS software (version 17.0; SPSS Inc., Chicago, IL, USA). Continuous variables were presented as mean ± SD. Freedman's test (for any deviation from a uniform incidence) was used to analyze deviations, and Edwards's test was used to identify peaks and trough periods (for a harmonic curve (6 months between peak and trough)). The Ratchet circular test was used to identify short seasonal peaks, and Hewitt's rank sum test was used to evaluate a seasonal peak. A P value of <0.05 was considered statistically significant.

### Results

Out of 216 patients with acute pericarditis, 173 were male (80%) and 44 were female (20%). The patient characteristics are given in Table 1. Mean ages was 32 ± 6.3 years (min 17-maximum 56 years). Leukocyte count (WBC) was mean 6.54 (minimum 3.0- maximum 12.0 109 per L). High-sensitivity troponin I was 0.26 ± 1.19 ng/mL. High-sensitivity C-reactive protein was 0.99 ± 0.74 mg/L. Data on follow-up were available for 216 patients. The duration of follow-up ranged from 12 to 36 months. Recurrence ratio of acute pericarditis was 57 (26.3%). There were two peak appearances in the 12-month analysis (Figure 1). The incidence of acute pericarditis reached a peak in April and May (50 and 53 patients, respectively) and in September (45 patients). Peak date in Edwards's test (for a harmonic curve (6 months between peak and trough)) was May 21st, P=0.000 (7.2E-11).

2-month peak in Ratchet circular scan test (for a short seasonal peak) was April to May, p< 0.005. 3-month peak in Ratchet circular scan test was March to May, p<0.005. Hewitt's rank-sum test (for a seasonal peak); 4-month peak: March to June. Rank sum: 38, P > 0.089. 5-month peak: January to May Rank sum: 43, p>0.094. 6-month peak: January to June, Rank sum: 49, P>0.130. While serum 25-hydroxyvitamin D levels in the recurrent pericarditis was 23.31 ± 4.16 ng/ml, this value in first pericarditis attack was 35.70 ± 6.81 ng/ml, p<0.001. The vitamin D levels in acute pericarditis and recurrent pericarditis according to monthly periods were showed Figure 2.

Characteristics	Results
Male n (%)	173 (79.7%)
Age (year), mean	32 ± 6.3 (min 17-maximum 56)
Leukocyte Count (WBC), 109 per L	6.54 ± 2.2 (minimum 3.0-maximum 12.0)
High-sensitivity troponin I (cTn, ng/mL)	0.26 ± 1.19
High-sensitivity C-reactive protein (hs-CRP, mg/L)	0.99 ± 0.74
Recurrence n (%)	57 patients (26.3%)
Vitamin D levels (ng/ml) in acute pericarditis and in the recurrent pericarditis, respectively (<20 deficient, ≥ 20-30 insufficient, ≥ 30 to optimal)	35.70 ± 6.81 23.31 ± 4.16 p<0.001

Table 1: Characteristics of patients with acute idiopathic pericarditis (n=216)

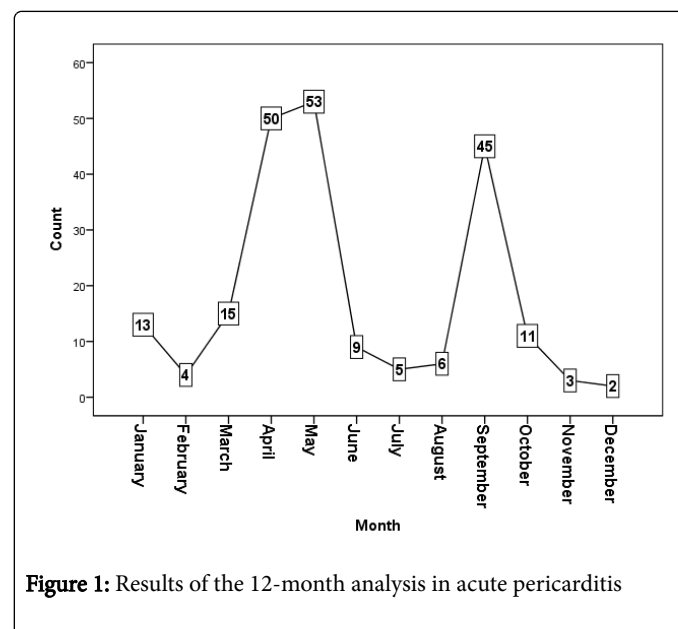
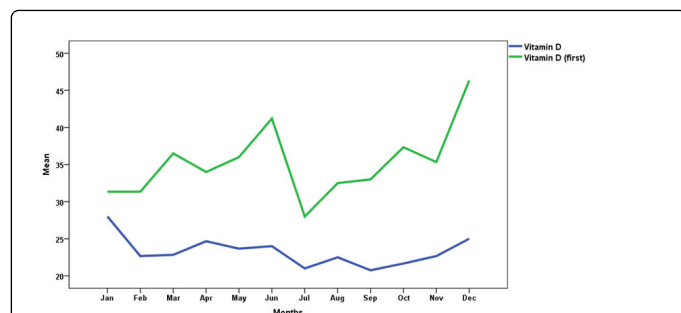


Figure 1: Results of the 12-month analysis in acute pericarditis

### Discussion

Humans have known that climatic conditions affect epidemic diseases for a long time before the role of infectious agents was discovered in the late nineteenth century (9). On the other hand, numerous environmental, behavioral and immunological mechanisms

have been proposed for the distinct seasonality of many viral pathogens [14,15]. For example, a sudden drop in outdoor temperature might activate the annual influenza epidemic in a temperate climate by facilitating aerosol spread in dry air [10].



**Figure 2:** The vitamin D levels in acute pericarditis (first attack) and recurrent pericarditis according to monthly periods (Vitamin D=recurrent pericarditis cases, Vitamin D (first)= acute pericarditis cases).

The most frequent cause of acute idiopathic pericarditis is the unrecognized viral infections. Therefore, it is not productive to try to isolate or identify the potential virus for pericarditis [17]. The most frequent viral pathogens are enteroviruses (coxsackie viruses, echoviruses), herpes viruses (Epstein-Barr virus, Cytomegalovirus, and Human Herpes Virus-6), Adenoviruses, Parvovirus B19 [4]. Rey et al. reported on higher frequency of a recent episode of upper respiratory tract infection or gastroenteritis in patients with acute idiopathic pericarditis [18].

If viral infections and seasonality coexist, the relationship between seasonality and acute pericarditis can be expected as well. For example, as a support to this hypothesis, enteroviruses typically appear in late summer or early autumn periods [19]. Zanettini et al. reported, in 2004, that idiopathic pericarditis had a seasonal pattern in a small (23 patients) group patients and coincided with the period for influenza vaccination [20]. They informed that pericarditis peaked in May and June months. Hammer et al. reported that acute idiopathic pericarditis appears to have a seasonal pattern with a distinct late winter peak, but seasonal pattern was not identified for recurrent episodes [21]. In our study, we found that idiopathic pericarditis had a seasonal pattern. This pattern had two peak appearances in the 12-month analysis. The incidence of acute pericarditis reached its peak in April and May and in September. However, recurrent pericarditis cases were not co-existence with seasonal pattern. Recurrent pericarditis cases included time except for peaked September and April. Our results support the abovementioned studies. In general, the acute pericarditis peaks occurred not only after the winter, which was the expected time for the lowest vitamin D levels, but also in September, when vitamin D levels were expected to be the highest of the year due to the elevations in circulating 25-hydroxyvitamin D levels that follow the summer time. However, vitamin D levels in the patients with recurrent pericarditis was found to be lower level than first pericarditis attack levels and no co-existence with seasonal pattern. We thought whether recurrent pericarditis cases had immunological pattern, and recurrent pericarditis cases should be examined in terms of immunological defect and vitamin D metabolism. Therefore, these cases may be due to low vitamin D levels anytime (figure 2). If acute pericarditis emerges seasonally, can this help in acute pericarditis therapy? Some authors

have suggested that the immunological impact of shortened photoperiods during the winter months could increase population susceptibility to wintertime respiratory illness [15,22]. In addition, the striking mechanism for enhanced wintertime susceptibility would diminish production of active vitamin D metabolites in temperate-zone populations in wintertime [23]. By concentrating on the associations between climate and disease, infection can be decreased by environmental and behavioral factors [24]. As a limitation, it can be stated that serology for common cardiotropic viruses, and immune panels were not examined due to technical insufficiencies.

## Conclusion

We found that idiopathic pericarditis had a seasonal pattern and no seasonal pattern in recurrent pericarditis cases. In addition, relationship between recurrent pericarditis cases and vitamin D deficiency were established. Therefore, care should be taken for seasonality and disease preventive measures in acute pericarditis and recurrent pericarditis.

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