Original Article

New Perspective on the Clinical and Laboratory Characteristics of Rheumatoid Pleural Effusion: A 29-Case Series

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Number of text pages: 18

Number of figure legends: 2

Number of tables: 4

Number of figures: 2

Abstract

Objective

Rheumatoid pleural effusion (RPE) usually occurs in middle-aged men. Pleural fluid analyses have revealed high lactate dehydrogenase (LDH) levels and low pH and glucose levels in RPE. We aimed to investigate the clinical and laboratory features of patients with RPE since the beginning of the 21st century.

Methods

Medical records of patients with RPE were reviewed between May 2006 and October 2021. The patients were divided into <60-year (younger) and ≥60-year (older) groups.

Results

The younger group comprised 6 patients (median age 53.5 years, female 33%) and older group comprised 23 patients (median age 76 years, female 52.2%). Compared to the younger group, the older group had fewer cases of fever (83.3% vs. 18.2%, p = 0.007) and chest pain (66.7% vs. 8.7%, p = 0.008). In pleural fluid analysis, the older group presented higher pH (p = 0.004) and lower LDH levels (p = 0.044). Seven patients died during the follow-up period.

Conclusion

Most patients with RPE were over 60 years of age, and approximately half of them were female. The pleural fluid analysis showed milder inflammation in older patients than in middle-aged patients. The mortality rate of patients with RPE was distinctly higher than that previously reported.

Keywords: lactate dehydrogenase, pH, pleural effusion, pleurisy, rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) is a relatively common chronic autoimmune disease. In a global meta-analysis conducted between 1980 and 2019, the prevalence rate of RA was 0.46% (1). Patients with RA mainly present with inflammatory polyarthritis; however, approximately 40% of patients with RA also show extra-articular involvement, such as pulmonary, cardiovascular, and gastrointestinal diseases; osteoporosis; and depression (2-4). Moreover, the mortality rate of patients with extra-articular involvement is higher than that of individuals without extra-articular involvement (5). In patients with pleural disease, a common extra-articular condition, rheumatoid pleural effusion (RPE), is observed. The incidence of RPE varies among studies. The annual incidence of RPE was reported to be 0.34% in female individuals and 1.54% in male individuals in an observational study involving 157 female and 77 male individuals (6). Symptomatic pleural effusion is observed in 3%–5% of all patients with RA; however, the number of patients with RPE detected through chest radiography is relatively high (7).

RPE usually occurs in middle-aged men with rheumatoid factor (RF)-positive RA (6, 8, 9). Generally, RPE shows features of pleural fluid acidosis, high lactate dehydrogenase (LDH) levels, and very low glucose levels (7). However, to the best of our knowledge, these findings are based on very few case series and reports, most of which were published in the early 2000s (7, 8). Moreover, most of the patients included in these studies were younger than 60 years, with very few patients over 60 years of age.

Recently, we have encountered several older patients with RA and RPE with atypical symptoms in our hospital. Therefore, we aimed to conduct a case series of RPE in a single institution to redefine the clinical characteristics of patients with rheumatoid pleurisy in the 21st century.

Materials and Methods

Study design

We conducted a retrospective cohort study. This study was conducted at Tenri Hospital, a 715-bed hospital in Tenri, Nara, Japan. Medical records of patients with RPE were retrospectively reviewed between May 2006 and October 2021. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology statement for reporting observational studies (10).

This study was approved by the research ethics committee of Tenri Hospital (No. 1261). All procedures involving human participants were conducted in accordance with the ethical standards of the institutional research committee and the 1964 Helsinki Declaration, including its later amendments or comparable ethical standards.

Patients and baseline characteristics

RPE was identified according to the following five conditions, based on a previously reported diagnostic approach (7): (i) confirmation of RA diagnosis by two authors (Japan Collage of Rheumatology-board certified rheumatologists, S.S.M. and R.M.S.); (ii) presence of exudative pleural effusion according to Light's criteria (11); (iii) negative results of pleural fluid culture (bacterial and mycobacterial); (iv) negative results of pleural fluid cytology; and (v) exclusion of parapneumonic effusion or empyema defined as no antibiotic use or ineffectiveness of antibiotics during the clinical course. The patients were divided into two groups according to their age at diagnosis: <60-year-old (the younger group) and ≥60-year-old (the older group) (12-15). Clinical data, including the duration of RA, the number of cases wherein RPE preceded RA, treatment,

mortality, and Charlson comorbidity index (CCI) were retrospectively obtained from the medical records (16, 17). Steinbrocker stage classification, class classification, and the presence of fever, chest pain, dyspnea, and cough were also determined from the medical records, with these data taken from the record closest to the thoracentesis (18). Unknown information was treated as missing values.

Blood test

Blood test results for CRP, total protein, LDH, glucose, RF, and anti-cyclic citrullinated peptide (anti-CCP) antibodies were retrospectively obtained from the medical records. Unmeasured laboratory data were treated as missing values. Values below the lower limit of quantification were approximated as 1/2 of the lower limit of quantification except for CRP, which was approximated as 0. Data of white blood cell, lymphocyte, and platelet counts; anti-nuclear, anti-DNA, anti-ribonucleoprotein (anti-RNP), and anti-Smith (anti-Sm) antibodies; urine protein level; and cellular cast were also collected.

Pleural fluid analysis

Data of pH, LDH level, glucose level, cholesterol level, total protein level, number of cells, CH50 level, C3 level, and C4 level were retrospectively obtained from the medical records. The pleural fluid glucose-to-serum glucose ratio was also checked. Unmeasured data were treated as missing values. Values below the lower limit of quantification were approximated as 1/2 of the lower limit of quantification and the data were analysed.

Statistical analysis

We have described the characteristics of the patients using median and interquartile range (IQR) for continuous variables and number and percentage (%) for categorical variables. Comparisons of clinical parameters were performed using Wilcoxon rank-sum test for continuous variables and Fisher's exact test for categorical variables. The Kaplan–Meier method and generalised Wilcoxon test were used for survival analysis. All statistical analyses were performed using JMP Pro (version 16). All *p*-values were two-sided, and results with $p \leq 0.05$ were considered statistically significant.

Results

Baseline characteristics and blood test results

Twenty-nine patients were enrolled in the study. The median age of the patients was 71 (IQR 66.5–78.5) years. Of these patients, 14 (48.3%) were women. The median duration of RA was 93 (IQR 3–161) months. The median duration of follow-up was 42 (IQR 18–60) months. The baseline characteristics, symptoms, and blood test results of the two groups are summarised in Table 1. The younger group (patients aged <60 years) comprised six patients and the older group (patients aged ≥60 years) comprised 23 patients. In the younger group, the median age of patients was 53.5 (IQR 47.8–56.5) years, and there were two (33.3%) women. In the older group, the median age of patients was 76 (IQR 69.0–80.0) years, and there were 12 (52.2%) women. The median duration of RA was shorter in the younger group than in the older group (median 3 vs. 113, IQR 0–23 vs. 50–187 months, p=0.007). The median CCI of the younger group was 1.5 (IQR 1.0–2.0) and that of the older group was 2.0 (IQR 1.0–3.0); however, there was no

considerable difference between the groups. RPE preceded the onset of RA in one patient (16.7%) in the younger group and none in the older group. In the Steinbrocker stage classification, the younger group included patients in stages Ⅰ-Ⅲ, while the older group included patients in all stages from Ⅰ to Ⅳ. In the class classification, more than half of the patients in both groups were in class II. When comparing the number of patients in stages I and II-IV, as well as those in class I and I-IV between the two groups, no significant difference was found. The older group had fewer patients with a fever and chest pain than the younger group (fever 83.3% vs. 18.2%, p = 0.007; chest pain 66.7% vs. 8.7%, p = 0.008). The older group tended to have lower serum CRP levels than the younger group (median 11.1 vs. 3.4 mg/dL). There was no considerable difference in the median RF levels (median 99.7 vs. 74.0 IU/mL) and the number of patients with anti-CCP antibodies (83.3% vs. 93.3%). Anti-nuclear antibody was positive in one patient (>80×), and anti-DNA, anti-RNP, and anti-Sm antibodies were negative in all patients. The anti-nuclear antibody-positive patient didn't meet the American College of Rheumatology (ACR) 1997 criteria, the classification criteria of SLE (19, 20).

Pleural fluid analysis

Pleural fluid characteristics are summarised in Table 2. The older group presented significantly higher pH (median 7.2 vs. 7.5, p = 0.004) and lower LDH levels (median 1810 vs. 136 U/L, p = 0.044) than the younger group (Fig 1A–B). Glucose levels and pleural fluid glucose-to-serum glucose ratio tended to be higher in the older group than in the younger group; however, there were no considerable differences between the groups (glucose, median 58.5 vs. 109 mg/dL, p = 0.449; pleural fluid glucose-to-serum glucose ratio, median 0.41 vs. 1.06, p = 0.153) (Fig 1C). 50% of patients in the younger

group and 9.5% of patients in the older group presented a pleural fluid glucose-to-serum glucose ratio of <0.5. There were no considerable differences in the total protein levels (median 5.1 vs. 4.5 g/dL), number of cells (median 5235 vs. 2760 cells/μL), cholesterol level (median 101 vs. 69 mg/dL), CH50 level (median 9.0 vs. 8.1 U/mL), C3 level (median 36.0 vs. 31.5 mg/dL), and C4 level (median 6.1 vs. 3.9 mg/dL) (Fig 1D).

Sex differences of patients aged 60 years or older

We compared the baseline characteristics, symptoms, blood test results, and pleural fluid characteristics between male and female patients in the older group (Table 3). The median age of male individuals was 78 (IQR 69.0–80.0) years and that of female individuals was 74.5 (IQR 69.3–78.5) years. The number of male patients with chronic heart failure was two, and that of female patients was one. There were no considerable differences in serum CRP (median 4.9 vs. 1.7 mg/dL) and RF levels (median 61.5 vs. 93.2 IU/mL) and the number of patients with anti-CCP antibody (100% vs. 88.9%). Female patients had significantly lower LDH levels (median 309 vs. 131 U/L, p = 0.036) and higher pleural fluid glucose-to-serum glucose ratio (median 0.85 vs. 1.12, p = 0.012) than male patients. There were no considerable differences in pH (median 7.5 vs. 7.5, p = 0.092) between male and female patients.

Treatment

We evaluated the medication that was added and/or changed within 3 months after diagnosis (Table 4). Systemic corticosteroids were started or their dose was increased in 5 (83.3%) and 11 (47.8%) patients, and biological disease-modifying antirheumatic drugs (bDMARDs) were started in 1 (16.7%, adalimumab) and 2 (8.7%,

both of them were abatacept) patients in the younger and older groups, respectively. Two patients in the older group used only conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), but none of the patients in the younger group used them. One patient in the younger group (16.7%) and seven patients in the older group (30.4%, n = 23) did not receive additional medication after RPE diagnosis.

Mortality

Of the 29 patients, 7 (24.1%) died within 5 years; the median follow-up duration was 46 months. One patient (16.7%) died in the younger group and six patients (26.1%) died in the older group. In the younger group, patients who did not receive any medication for RPE died of interstitial pneumonia. In contrast, in the older group, 2 patients died of aspiration pneumonia and 1 died of complications of aspiration pneumonia and urinary tract infection; details of the cause of death of the other three were unknown. Among the six patients in the older group, two did not receive additional medication for RPE. There was no considerable difference in the survival rates between the groups (Fig 2).

Discussion

We conducted a retrospective study of 29 patients with RPE. To the best of our knowledge, this is the only large case series published after 2000, barring two small case series reported in 2002 (8, 21-23). In our study, most of the patients with RPE were over 60 years old and nearly half of them were female individuals. These two points were different from those of previous studies, which indicated that RPE usually occurs in middle-aged men. The main reasons for the large number of older patients in our study may be related to the recent increase in the number of older patients with RA. From the

243 late 1900s to early 2000s, the prevalence and annual incidence rate of RA increased
244 globally and in Japan, with the peak shifting to older age (1, 24). In a global study
245 conducted from 1990 to 2017, the number of prevalent cases of RA peaked in the 60s-age
246 group, whereas the prevalence rate peaked in the 70s-age group (24). Similarly, in a study
247 conducted in Japan in 2016, the number of prevalent cases peaked in the 60s-age group,
248 whereas the prevalence rate peaked in the 80s-age group (25). Our single-centre cohort
249 study involved 991 patients, and their median age was 70 (IQR 60–76) years (26). The
250 reason for the higher proportion of female patients with RPE in the older group in this
251 study remains unclear. This observation could not be explained just by the number of
252 patients, as male patient morbidity is higher in late-onset RA than in early-onset RA (11,
253 27-29). We considered the complications of SLE and heart failure as reasons for the high
254 prevalence of RPE; however, neither was revealed to be relevant in our study. SLE is
255 more common in female individuals than in male individuals, and pleural effusions are
256 more common in female patients with heart failure (30, 31). However, in our study, no
257 cases met the classification criteria of SLE. Moreover, 2 male and 1 female patients were
258 diagnosed and treated for heart failure, with no considerable differences between the
259 groups. Additionally, malignant pleural effusions are more common in women than in
260 men (32, 33). Conversely, other diseases, such as tuberculous pleurisy and parapneumonic
261 effusions, reportedly occur more frequently in men than in women (34-36). Further
262 research is needed to determine whether RPE is more common in older female patients,
263 and if so, the reason for it.

264 In our study, we found that most of the patients who were 60 years and older
265 showed milder inflammation in RPE than those in the younger group. In an RPE review
266 published in 2006, it has been described that the typical characteristics of RPE are LDH

> 700 IU/L, pH < 7.3, glucose < 40 mg/dL, and cholesterol > 65 mg/dL (7). In our study, patients in the younger group showed pleural effusion features similar to those reported in this review. However, in the older group, most patients presented lower LDH and higher pH levels. A pleural fluid glucose-to-serum glucose ratio of <0.5 has been demonstrated in 80% of patients with RPE (7). However, there were considerably fewer patients with pleural fluid glucose-to-serum glucose ratio of <0.5 than those previously reported. Furthermore, among the clinical symptoms evaluated, fever, chest pain, and dyspnea are often observed in pleurisy (7). Cough generally indicates underlying lung disease rather than pleurisy (7). In the older group, compared to the younger group, the frequency of fever and chest pain was lower, which also suggests milder inflammation. To the best of our knowledge, this is the first study to present a difference in the characteristics of pleural effusion findings between the older and younger groups in RPE. This result can be attributed to two factors. The first is age. For other diseases, several studies have indicated that older patients tend to have milder inflammation in pleuritis than younger patients. A study involving 26 patients with parapneumonic pleural effusions found that the total protein level in pleural fluid remarkably decreased with increasing age (37). In another study involving 112 patients with tuberculous pleurisy pleural effusions, the older group showed considerably lower total protein levels in the pleural fluid than the younger group (38). In a study involving 160 patients in which pleural fluid adenosine deaminase (ADA) level was examined, the ADA level was considerably higher in younger patients with tuberculous and non-tuberculous pleural effusions, and it remarkably correlated with LDH and total protein levels (39). The second is the high proportion of female patients. As shown in Table 3, female patients had considerably lower LDH levels and a higher pleural fluid glucose-to-serum glucose ratio

than male patients. The proportion of female patients in the older group was considerably higher than that previously reported, accounting for the milder inflammation in pleural effusion in the older group. The milder inflammation in pleural effusion in female patients than in male patients is also a novel finding, as it has not been reported previously. Nevertheless, the reason for this finding remains unclear. The presence of heart failure with transudative pleural effusion could be a reason for the milder pleural effusion inflammation, as pleural effusions due to heart failure are more common in female individuals (30, 31). However, as described above, there were no considerable differences in the prevalence of heart failure between male and female patients in this study. Moreover, it was unclear whether older age or the proportion of female patients had a strong influence on the mildness of pleural effusion inflammation, or whether either was an intermediate variable in the older group.

In our study, 7 (24.1%) of the 29 patients died during the median follow-up period of 42 months. To the best of our knowledge, there has been no study on mortality among patients with RPE. In contrast, the mortality of patients with RA-associated interstitial lung disease (RA-ILD) is well known. A systematic review of patients with RA-ILD, encompassing 78 studies, revealed a cumulative mortality rate of 21.4% at 3 years (40). Previously, the prognosis of patients with RPE was considered relatively favourable (7). However, our study showed that the mortality rate among patients with RPE is remarkably high, which was comparable to that of patients with RA-ILD. Conversely, there are no established treatment procedures for patients with RPE. Further investigation is needed to determine if therapeutic interventions are necessary to improve prognosis and, if so, which treatments would be effective.

This study has several limitations. First, this was a single-centre study. Therefore, the lack of statistical significance in some analyses could be due to a lack of power. To further validate these findings, more extensive research involving multiple facilities from different countries is required. Second, this was a retrospective cohort study; therefore, some data were missing. However, LDH in the pleural fluid was measured in all patients, and pH of the pleural fluid was measured in 26 out of the 29 patients. Therefore, we do not consider that missing data would have considerably affected the main results. Third, owing to the absence of information regarding disease activity assessment and functional status assessment measures related to RA in most of the past medical records, we were unable to perform these evaluations.

In conclusion, our study showed that most of the patients with RPE were over 60 years old, and the pleural fluid analysis showed milder inflammation in these patients than in younger patients. Moreover, the mortality rate of patients with RPE was higher than that previously reported. This study highlights the need for multicentre research to evaluate the pathophysiology of patients with RPE, appropriate therapeutic options, and mortality rates.

Data Availability

All data relevant to the study are included in the article. Additional data are available on reasonable request.

Acknowledgments

We thank Mr. Daiki Shimomura for his help in collecting the data.

This research was conducted as a part of the All-Osaka U Research in 'The Nippon Foundation–Osaka University Infectious Disease Response Project'.

Funding

No specific funding was received from any bodies in the public, commercial, or not-for-profit sectors to carry out the work described in this article.

Conflict of Interest

None.

Statement of ethics and consent

This study was approved by the research ethics committee of Tenri Hospital (No. 1261). All procedures involving human participants were conducted in accordance with the ethical standards of the institutional research committee and the 1964 Helsinki Declaration, including its later amendments or comparable ethical standards.

Contributors

SSM and RMS designed the study, acquired the data, and wrote the draft of the manuscript. RMS, HA, YT, and KH revised the manuscript. All authors were involved in development, review, and final approval of the manuscript.

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Table 1. Baseline characteristics, symptoms, and blood test results at the time of diagnosis of patients with rheumatoid pleural effusion

		<60 years (n = 6)	≥60 years (n = 23)	*p*
Baseline characteristics	**Age (years)**	53.5 [47.8–56.5] (n = 6)	76 [69.0–80.0] (n = 23)	
	Female individuals	2 (n = 6, 33.3)	12 (n = 23, 52.2)	0.651
	Duration of RA (months)	**3 [0–23] (n = 6)**	**113 [50–187] (n = 21)**	**0.007**
	CCI	1.5 [1.0–2.0] (n = 6)	2 [1.0–3.0] (n = 23)	0.505
	RPE proceeded RA	1 (n = 6, 16.7)	0 (n = 23, 0)	0.207
	Steinbrocker stage classification	(n = 6)	(n = 20)	0.348
	Ⅰ	4 (66.7)	7 (35.0)	
	Ⅱ-Ⅳ	2 (33.3) (Ⅱ 1, Ⅲ 1, Ⅳ 0)	13 (65.0) (Ⅱ 4, Ⅲ 7, Ⅳ 2)	
	Steinbrocker class classification	(n = 6)	(n = 21)	1.000
	Ⅰ	1 (16.7)	3 (14.3)	
	Ⅱ-Ⅳ	5 (83.3) (Ⅱ 4, Ⅲ 1, Ⅳ 0)	18 (85.7) (Ⅱ 13, Ⅲ 2, Ⅳ 3)	

Symptoms	**Fever ≥ 37.0°C**	**5 (n = 6, 83.3)**	**4 (n = 22, 18.2)**	**0.007**
	Chest pain	**4 (n = 6, 66.7)**	**2 (n = 23, 8.7)**	**0.008**
	Dyspnea	3 (n = 6, 50.0)	11 (n = 22, 50.0)	1.000
	Cough	3 (n = 6, 50.0)	10 (n = 23, 43.5)	1.000
Blood test results	**CRP (mg/dL)**	11.1 [4.5–24.3] (n = 6)	3.4 [0.9–11.7] (n = 23)	0.056
	RF (IU/mL)	99.7 [13–519.5] (n = 6)	74.0 [13.3–253.3] (n = 23)	0.914
	Anti–CCP ab positive	5 (n = 6, 83.3)	14 (n = 15, 93.3)	0.500
	Tp (g/dL)	6.8 [6.4–7.1] (n = 6)	6.4 [6.0–7.3] (n = 23)	0.553
	LDH (U/L)	161 [142–184] (n = 6)	205 [168–220] (n = 23)	0.118
	Glucose (mg/dL)	115 [106–135] (n = 6)	98 [86–129] (n = 22)	0.251

Data are presented as median [interquartile range] (number of patients) or number (number of patients, percent). The total number is sometimes less than the number of patients in each group because of missing data.

Abbreviations: RA, rheumatoid arthritis; RPE, Charlson comorbidities index; CCI, rheumatoid pleural effusion; CRP, C-reactive protein; RF, rheumatoid factor; Anti-CCP ab, anti-cyclic citrullinated peptide antibodies; Tp, total protein; LDH, lactate dehydrogenase; Glu, glucose

Table 2. Pleural fluid characteristics of patients with rheumatoid pleural effusion

		<60 years (n = 6)	≥60 years (n = 23)	*p*
Pleural fluid	**pH**	**7.2 [7.2–7.3] (n = 5)**	**7.5 [7.4–7.5]** (n = 21)	**0.004**
	LDH (IU/L)	**1810 [261–3879] (n = 6)**	**136 [113–309] (n = 23)**	**0.044**
	Glu (mg/dL)	58.5 [5.0–131.3] (n = 6)	109 [93.8–122.3] (n = 22)	0.449
	Tp (g/dL)	5.1 [4.6–5.9] (n = 6)	4.5 [3.6–5.1] (n = 23)	0.112
	Number of cells (/μL)	5235 [2295–10975] (n = 6)	2760 [840–4900] (n = 23)	0.146
	Glu/serum Glu	0.41 [0.04–1.17] (n = 6)	1.06 [0.85–1.18] (n = 21)	0.153
	Glu/serum Glu < 0.5	3 (n = 6, 50)	2 (n = 21, 9.5)	0.056
	Cholesterol (mg/dL)	101 [90–106] (n = 3)	68.5 [59–104] (n = 18)	0.291
	CH50 (U/mL)	9.0 [2.8–24.5] (n = 3)	8.1 [2.5–10.6] (n = 11)	0.532
	C3 (mg/dL)	36.0 [27.0–95.0] (n = 3)	31.5 [21.5–47.5] (n = 12)	0.386
	C4 (mg/dL)	6.1 [3.2–18.5] (n = 3)	3.9 [2.0–7.6] (n = 12)	0.386

Data are presented as median [interquartile range] (number of patients) or number (number of patients, percent). The total number is sometimes less than the number of patients in each group because of missing data.

Abbreviations: LDH, lactate dehydrogenase; Glu, glucose; Tp, total protein; Glu/serum Glu, pleural fluid glucose-to-serum glucose ratio

494 **Table 3.** Sex differences in baseline characteristics, symptoms, blood test results at the

495 time of diagnosis, and pleural fluid characteristics of patients aged ≥60 years

		Male (n = 11)	Female (n = 12)	*p*
Baseline characteristics	Age	78.0 [69.0–80.0] (n = 11)	74.5 [69.3–78.5] (n = 12)	0.622
	Duration of RA (months)	108 [55–154] (n = 10)	161 [38–284] (n = 11)	0.438
	CCI	**2 [2.0–4.0] (n = 11)**	**1 [1.0–1.8] (n = 12)**	**0.027**
	Presence of CHF	2 (n = 11, 18.2)	1 (n = 12, 8.3)	0.600
Symptoms	Fever ≥ 37.0°C	3 (n = 11, 27.3)	1 (n = 10, 10.0)	0.587
	Chest pain	1 (n = 11, 9.1)	1 (n = 12, 8.3)	1.000
	Dyspnea	4 (n = 10, 40.0)	7 (n = 12, 58.3)	0.670
	Cough	3 (n = 11, 27.3)	7 (n = 12, 58.3)	0.214
Blood test results	CRP (mg/dL)	4.9 [2.6–12.1] (n = 11)	1.7 [0.4–11.0] (n = 12)	0.110
	RF (IU/mL)	61.5 [11.7–253.3] (n = 11)	93.2 [25.5–264.4] (n = 12)	0.758
	Anti–CCP ab positive	6 (n = 6, 100)	8 (n = 9, 88.9)	1.000
Pleural fluid	pH	7.5 [7.2–7.5] (n = 10)	7.5 [7.5–7.6] (n = 11)	0.092
	LDH (IU/L)	**309 [134–691] (n = 11)**	**131 [92–159] (n = 12)**	**0.036**
	Glu (mg/dL)	105 [62–123] (n = 11)	97 [99–122] (n = 11)	0.411

	Tp (g/dL)	4.5 [3.9–5.0] (n = 11)	4.1 [3.4–5.2] (n = 12)	0.538
	Number of cells (/μL)	3920 [1790–8800] (n = 11)	1400 [530–3765] (n = 12)	0.079
	Glu/serum Glu	**0.85 [0.70–1.06] (n = 11)**	**1.12 [1.05–1.33] (n = 10)**	**0.012**
	Glu/serum Glu < 0.5	2 (n = 11, 18.2)	0 (n = 10, 0)	0.476
	Cholesterol (mg/dL)	74 [58–103] (n = 9)	63 [59–108] (n = 9)	0.860

Data are presented as median [interquartile range] (number of patients) or number (number of patients, percent). The total number is sometimes less than the number of patients in each group because of missing data.

Abbreviations: RA, rheumatoid arthritis; CCI, Charlson comorbidities index; CHF, chronic heart failure; CRP, C-reactive protein; RF, rheumatoid factor; Anti-CCP ab, anti-cyclic citrullinated peptide antibodies; LDH, lactate dehydrogenase; Glu, glucose; Tp, total protein; Glu/serum Glu, pleural fluid glucose-to-serum glucose ratio

506 **Table 4.** Additional medication used in each group

	<60 years (n = 6)	≥60 years (n = 23)	*p*
Total CSs used	5 (83.3)	11 (47.8)	0.183
CSs only	2 (33.3)	8 (34.8)	1.000
CSs+csDMARDs	2 (33.3)	3 (13.0)	0.269
CSs+csDMARDs+bDMARDs	1 (16.7)	0	0.207
csDMARDs	0	2 (8.7)	1.000
bDMARDs	0	2 (8.7)	1.000
No additional medication	1 (16.7)	7 (30.4)	0.647
Unknown	0	1 (4.4)	1.000

507

508 Data are number (percent). CS, corticosteroid; csDMARD, conventional synthetic
509 disease-modifying antirheumatic drug; bDMARD, biological disease-modifying
510 antirheumatic drug

511

Figure 1. Major pleural fluid data comparison between the groups

Pleural fluid data of pH, lactate dehydrogenase, total protein, and glucose levels. There were significant differences in the pH and LDH levels between the younger group (patients aged <60 years old) and older group (patients aged ≥60 years old).

Abbreviations: LDH, lactate dehydrogenase; TP, total protein; Glu, glucose

Figure 2. Five-year survival of each group analysed using the Kaplan–Meier method

There were no significant differences between the groups (p = 0.120).