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Case Series

Clinical features, management and outcome of rheumatoid arthritis patients with pulmonary involvement in intensive care unit: a retrospective observational case series study

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ABSTRACT

Rheumatoid arthritis (RA) is one of the rheumatic diseases with life-threatening complications that may require admission to the intensive care unit (ICU). In this study, we aimed to evaluate the clinical features, management and factors that may influence the course and prognosis of RA patients with pulmonary involvement in ICU. A retrospective observational study was conducted and the medical records of RA patients with pulmonary involvement who admitted to ICU in a large tertiary hospital from January 2014 to May 2025 were reviewed. A total of twenty patients were enrolled during the study period. The leading causes of ICU admission were interstitial lung disease with respiratory failure, followed by severe pneumonia. Eight patients died within 30 days after admission to ICU. Infections led to a fatal outcome in most cases. Poor prognostic factors in the non-survival group were lower oxygenation index, renal dysfunction, higher SOFA scores, invasive mechanical ventilation and vasoactive medication requirement. The study emphasizes RA patients in ICU have a rather poor prognosis, particularly in the presence of pulmonary involvement. Early and accurate diagnosis of critical conditions, along with timely and appropriate interventions, is essential to reduce mortality.

Keywords: Rheumatoid arthritis, Intensive care unit, Interstitial lung disease, Outcome

INTRODUCTION

Patients with autoimmune diseases (ADs) are at high risk of requiring admission to intensive care unit (ICU), with approximately one-third of all hospitalized ADs patients needing ICU care and support.[1] Infection and deterioration or outbreak of the underlying ADs have been reported to be the main reasons for ICU admission. Over the past few decades, the prevalence of ADs in ICU has changed, with systemic lupus erythematosus becoming the most frequent AD in ICU, followed by rheumatoid arthritis (RA), systemic vasculitis, and dermatomyositis.[2] RA, a chronic joint disease affecting 0.5–1% of global population, is characterized by inflammation of the synovial membrane.[3] It is also a systemic disease associated with severe comorbidities and complications, including infection, malignancy, and organ failure.[4,5] The acute exacerbation of illness itself, worsening comorbidities and complications in RA patients necessitate intensive management and aggressive treatment, thus leading to ICU admission. Over the last 50 years, the improved patient survival has been attributed to advancements in RA management. However, studies have shown a higher mortality risk among RA patients when compared to the general population.[6,7] Most research on multiple ADs has identified various causes of ICU admission and outcomes,

but only a limited number of studies have investigated the clinical features and prognostic factors for RA patients in the critical care setting. A recent study by Fujiwara et al demonstrated that RA patients admitted to ICU have high 30-day (21%), 90-day (27%) and 1-year (37%) mortality rates, with cardiovascular complications and infections being the primary reasons for ICU admission. Non-use of conventional synthetic disease-modifying antirheumatic drugs, elevated acute physiology and chronic health evaluation II (APACHE II) score, and coagulation abnormalities were identified as predictors of poor prognosis in RA patients.

RA patients usually have multiple risk factors for in-hospital mortality and are more likely to require ICU care, which represent a major challenge for the ICU team. In our experience, accompanying pulmonary involvement in RA patients is the major concern for an ICU physician, as the lung is the most common site of extra-articular disease and frequently affected during acute progression. Evaluation of lung manifestations in RA patients necessitates consideration of various potential causes, including interstitial lung disease (ILD), respiratory opportunistic infections following immunosuppressive agents, drug-induced pulmonary toxicity. Both underlying illness and the severity of the complications requiring ICU admission can influence RA patients' outcome. This study focuses on RA patients with pulmonary involvement in the ICU to investigate their clinical characteristics, progression, outcomes, and related risk factors, with the aim of providing valuable insights and appropriate therapeutic strategies.

CASE SERIES

This retrospective study was designed to analyze the management and outcome of RA patients with lung involvement who admitted to the department of Medical Intensive Care Unit in the Third Affiliated Hospital of Sun Yat-Sen University, over a period from January 2014 to May 2025. A total of 20 patients' electronic medical records were reviewed. The following information was retrieved: demographic characteristics including age, gender, duration of RA, causes of ICU admission and length of ICU stay. Data regarding comorbidities, detailed recorded treatments in the 3 months prior to admission to hospital, need for critical management （i.e., mechanical ventilation, vasopressor support were registered. Laboratory parameters were also obtained, including blood routine examination, arterial blood gas analysis, albumin, anti-cyclic citrullinated peptide (anti-CCP) antibodies, rheumatoid factor (RF), C-reactive protein (CRP), procalcitonin (PCT) and pathogen detection of clinical specimen. The severity of the illness was assessed within 24 h after ICU admission by adopting the APACHE II score and sequential organ failure assessment (SOFA) score. We classified patients into distinct clinical clusters based on their reasons for ICU admission and outcomes. The purpose of clustering is to identify achieving a structured understanding of disease severity, guiding management strategies, and evaluating prognosis factors in RA patients with pulmonary involvement in ICU. Data were analyzed using SPSS. Continuous variables were presented as means and standard deviations or medians and interquartile ranges. Category variables were presented as numbers and percentages. Further comparisons were performed for continuous variables using Mann–Whitney U test and for categorical variables using chi-square test or Fisher's exact test. P values <0.05 were considered statistically significant.

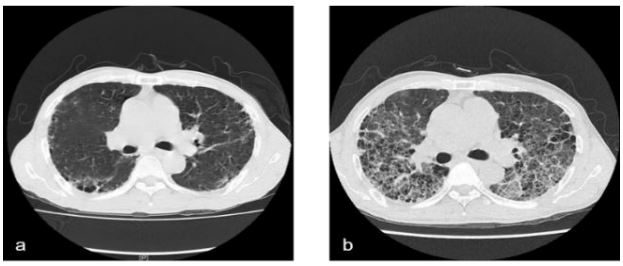

Figure 1: A male patient, aged 59, who presented with acute exacerbation of rheumatoid arthritis–interstitial lung disease for 2 months. (a) The HRCT was taken 2 months prior to ICU admission. (b) The HRCT after 2 months showed predominant reticular abnormalities and honeycombing.

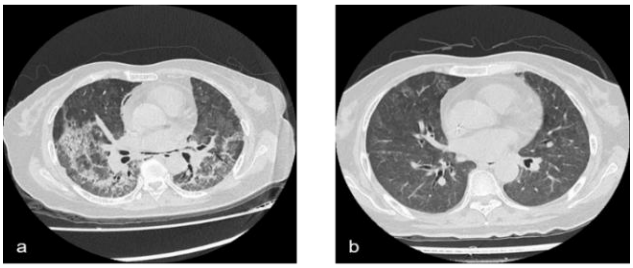

Figure 2: A female patient, aged 55, who presented with newly diagnosed rheumatoid arthritis–interstitial lung disease. (a) HRCT on ICU admission revealed bilateral ground-glass opacification. (b) HRCT showed improvement of bilateral ground-glass opacification after treatment in ICU.

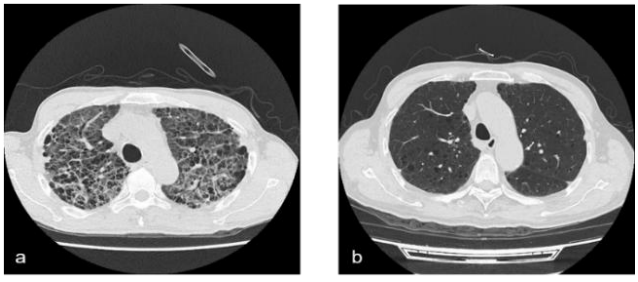

Figure 3: A male patient, aged 66, who presented with methotrexate-induced interstitial lung disease. (a) HRCT on ICU admission revealed diffuse ground glass inflammatory change. (b) HRCT showed improvement of bilateral ground-glass change after treatment in ICU.

Cluster 1: Interstitial lung disease with respiratory failure for ICU admission (n=11)

The major reason for ICU admission in this study was ILD with respiratory failure in 11 patients. Six patients were admitted to ICU with acute exacerbation of RA-ILD (Figure 1), which was defined using proposed criteria for RA-ILD8. One patient was confirmed as MTX-induced pneumonia, since ILD developed within 1 year after initiation of MTX (Figure 2). Four patients were newly diagnosed with RA-ILD after admission, one of whom performed a pulmonary function test (Figure 3), while the other 3 patients failed to conduct a test because of critical illness.

Due to their lung involvement in our patients, patients required invasive mechanical ventilation or non-invasive ventilation, based on their respiratory status and arterial blood gas results. Vasopressor treatment, intravenous immunoglobulin (IVIG) pulse therapy, immunosuppressive agents and anti-fibrotic drugs were prescribed in a subset of patients (Table 1).

Table 1: ICU course and outcome of rheumatoid arthritis patients.

Variable	Cluster		Total
	RA-ILD (n=11)	Pulmonary infection(n=9)	(n=20)
Treatment in ICU			
Immunosuppressant			
Methotrexate	1 (9.1%)	2 (22.2%)	3 (15.0%)
Hydroxychloroquine	2 (18.2%)	1 (11.1%)	3 (15.0%)
Leflunomide	1 (9.1%)	1 (11.1%)	2 (10.0%)
Sulfasalazine	1 (9.1%)	1 (11.1%)	2 (10%)
Methylprednisolone	11 (100%)	7(77.8%)	18 (90.0%)
Cyclophosphamide pulse	3 (27.3%)	2 (22.2%)	5 (25.0%)
Mechanical ventilation	6 (54.5%)	7 (77.8%)	13 (65.0%)
Vasopressor support	5 (45.5%)	4 (44.4%)	9 (45.0%)
IVIG	6 (54.5%)	4 (44.4%)	10 (50.0%)
Anti-fibrotic drugs			
Pirfenidone	4 (36.4%)	1 (11.1%)	5 (25.0%)
Nintedanib	2 (18.2%)	0 (0%)	2 (10.0%)
Cause of death			
Severe pneumonia	1 (9.1%)	4 (44.4%)	5 (25.0%)
Respiratory failure	2 (18.2%)	0 (0%)	2 (10.0%)
Sepsis	0 (0%)	1 (11.1%)	1 (5.0%)
Pathogen findings			
Acinetobacter baumannii	2 (18.2%)	2 (22.2%)	4 (20.0%)
Stenotrophomonas maltophilia	0 (0%)	1 (11.1%)	1 (5.0%)
Escherichia coli	0 (0%)	1 (11.1%)	1 (5.0%)
Aspergillus	0 (0%)	2 (22.2%)	2 (10.0%)
Candida parapsilosis	0 (0%)	1 (11.1%)	1 (5.0%)
Pneumocystis jirovecii	0 (0%)	2 (22.2%)	2 (10.0%)
Herpes simplex virus	0 (0%)	1 (11.1%)	1 (5.0%)
Legionella pneumophila	0 (0%)	1 (11.1%)	1 (5.0%)
Cryptococcus neoformans	0 (0%)	1 (11.1%)	1 (5.0%)
Nocard's bacillus	0 (0%)	1 (11.1%)	1 (5.0%)

Cluster 2: Pulmonary infection for ICU admission (n=9)

This cluster consisted of 9 patients with severe pneumonia involving multiple pathogens. Pathogens were detected in patients' lower respiratory specimens during ICU: *Acinetobacter baumannii*, *Stenotrophomonas maltophilia* and *Escherichia coli*; Aspergillus, *Candida parapsilosis*, *Pneumocystis jirovecii*, herpes simplex virus (HSV), *Legionella pneumophila*, *Cryptococcus neoformans*, *Nocard's bacillus*. Two or more pathogens were detected in 3 patients. And in this cluster, kinds of treatments of patients in ICU were also showed in Table 1.

Furthermore, we analyzed the prognosis and associated factors of the patients in this study. Twelve patients were transferred out of ICU after improvement in their condition. One patient died within 1 year because of respiratory failure during follow-up. The main cause of death in hospital was severe pneumonia. The other causes were ILD with respiratory failure, sepsis. The baseline characteristics and laboratory investigations of the patients are summarized in Table 2 and Table 3, respectively. Although the number of patients included in this study was relatively limited, comparison between survivors and non-survivors revealed that the following factors may be

associated with patients' outcome: lower oxygenation index, renal dysfunction, higher sequential organ failure assessment (SOFA) scores, requirement for invasive mechanical ventilation, and requirement for vasopressor therapy.

Table 2. Clinical characteristics of rheumatoid arthritis patients in ICU.

Variable	Clinical outcome		Total	P value
	Survivor (n=12)	Non-survivor (n=8)	(n=20)	
Gender				0.357
Male	6 (50.0%)	6 (75.0%)	12 (60.0%)	—
Female	6 (50.0%)	2 (25.0%)	8 (40.0%)	—
Age (years)	60.1±9.8	63.6±15.3	61.6±12.1	0.590
Disease duration (month)	76.1±62.8	135.9±87.3	102.2±78.0	0.132
Length of ICU stay (day)	13.9±9.1	11.7±6.8	12.9±8.0	0.607
Complicated condition				
Renal dysfunction	0 (0%)	6 (75.0%)	6 (30.0%)	<0.001
Pancytopenia	0 (0%)	2 (25.0%)	2 (10.0%)	0.175
Thrombocytopenia	0 (0%)	2 (25.0%)	2 (10.0%)	0.175
Heart failure	1 (8.3%)	1 (12.5%)	2 (10.0%)	1.000
APACHEII score	14.9±3.8	19.0±4.7	16.7±4.6	0.074
SOFA score	3.6±1.5	6.3±3.2	4.8±2.7	0.039
RF positivity	9 (75.0%)	6 (75.0%)	15 (75.0%)	1.000
Anti-CCP positivity	9 (75.0%)	7 (87.5%)	16 (80.0%)	1.000
Prior immunosuppressant within 3 months				
Prednisone	3 (25.0%)	6 (75.0%)	9 (45.0%)	0.126
Methotrexate	3 (25.0%)	4 (50.0%)	7 (35.0%)	0.614
Hydroxychloroquine	1 (8.3%)	0 (0%)	1 (5.0%)	1.000
Leflunomide	2 (16.7%)	6 (75.0%)	8 (50%)	0.132
Baricitinib	1 (8.3%)	0 (0%)	1 (5.0%)	1.000
Reasons for ICU admission				
ILD with respiratory failure	7 (58.3%)	4 (50.0%)	11 (55.0%)	0.614
Severe pneumonia	5(41.7%)	4 (50.0%)	9 (45.0%)	1.000
Treatment in ICU				
Methylprednisolone	10 (83.3%)	8 (100%)	18 (90.0%)	1.000
Mechanical ventilation	5 (41.7%)	8 (100%)	13 (65.0%)	0.041
Vasopressor support	0 (0%)	8 (100%)	8 (40.0%)	<0.001
IVIG	4 (33.3%)	6 (75.0%)	10 (50.0%)	0.585
Cyclophosphamide pulse	1 (8.3%)	4 (50.0%)	5 (25.0%)	0.261

APACHE II: Acute Physiology and Chronic Health Evaluation II; SOFA: Sequential Organ Failure Assessment; RF: rheumatoid factor; anti-CCP: anti-cyclic citrullinated peptide; ILD: interstitial lung disease; IVIG: intravenous immunoglobulin.

Table 3. Laboratory investigations of rheumatoid arthritis patients in ICU.

Variable	Clinical outcome		Total	P value
	Alive (mean±SD)	Death (mean±SD)	(mean±SD)	
White blood cells (x10^9/l)	13.7±9.6	8.25±3.4	11.3±7.8	0.175
Lymphocyte (x10^9/l)	1.0±0.6	0.6±0.4	0.8±0.5	0.141
Hemoglobin (g/l)	111.8±25.4	99.0±19.2	106.2±23.1	0.287
Blood platelet (x10^9/l)	232.6±72.7	159.4±131.7	200.1±105.7	0.178
Albumin (g/l)	29.4±4.3	26.7±5.4	28.2±4.8	0.292
Sodium (mmol/l)	137.3±8.0	138.6±4.0	137.9±6.4	0.714
Potassium (mmol/l)	4.1±0.5	4.2±0.5	4.2±0.5	0.734
C-reactive protein (mg/l)	88.5±54.8	134.4±108.2	108.6±82.7	0.287
Lactate (mmol/l)	1.4±0.4	2.6±1.9	2.0±1.4	0.096
Creatine (umol/l)	60.4±24.7	137.5±66.6	94.2±60.5	0.006
Blood urea nitrogen (mmol/l)	8.2±5.4	14.4±8.5	10.9±7.4	0.095
PO2	100.7±49.1	64.9±11.2	85.0±41.0	0.081

Continued.

Variable	Clinical outcome		Total	P value
	Alive (mean±SD)	Death (mean±SD)	(mean±SD)	
Oxygenation index	180.2±93.6	94.3±26.9	142.6±83.1	0.035
D-dimer (ug/ml)	4.4±3.8	8.3±6.4	6.1±5.3	0.156

DISCUSSION

This study revealed an unfavourable outcome in RA patients admitted to the medical ICU with a 30-day mortality rate of 40.0%, which is higher than the rate reported in previous studies of 13–34.7%.[4,9-11] Notably, a study from 7 tertiary hospitals in Israel involving 124 RA patients admitted to ICU for sepsis reported a high 30-day mortality rate (>50%).[12] Expect for the tertiary nature of our hospital, which deals with more severe illness that is less responsive to therapy, the disparity in mortality is more likely due to genetic or environmental factors, such as race, reasons for admission to ICU, and prior treatment.

RA is a progressive and inflammatory joint disease that often exhibits extra-articular manifestations in up to 50% of patients.[13] Pulmonary involvement is the most prevalent extra-articular manifestation, and RA-ILD is particularly significant due to its high morbidity and mortality.[14,15] The median survival after diagnosis of RA-ILD is 3–7 years, making it a substantial contributor to mortality.[14-16] Unlike earlier studies in which coronary heart disease and infection were the main reasons for ICU hospitalization, our study focused on lung involvement in RA patients.[4,9] In addition, a study by Yael et al. also indicated that infection and respiratory failure were the major causes of admission to ICU, though they did not provide a detailed classification of the causes of respiratory failure.[10]

The association between respiratory disease and increased mortality rate in RA patients has been elucidated in some studies.[17,18] The risk of serious infection is markedly increased in patients with RA.[19] In line with previous studies, infection, predominantly of the respiratory tract, was the leading cause of death in our study, as RA patients are particularly vulnerable to severe infections on account of their underlying disease, comorbidities, and immunosuppressive therapy.[20-22] A significant number of our patients had RA-ILD, making them prone to severe and intractable respiratory failure, even with only mild pulmonary infection. It was therefore not surprising that our patients had a poor outcome.

In the course of our patients' treatment, identifying the etiology of acute respiratory failure, complicated by a wide range of pulmonary shadows radiographically is not always easy, since the clinical entities may present similar HRCT images. If the possibility of acute heart failure can be excluded, three major differential diagnoses are considered in RA patients: RA-ILD, lung infection, and drug-induced pneumonitis. Combined with previous chest HRCT images and medication history of patients, we confirmed the causes of ICU admission: 4 with new onset of RA-ILD, 6 with acute exacerbation of RA-ILD, 1 patient with MTX-associated ILD, and 9 patients with severe pneumonia. Among them, we also encountered two cases of *P. jirovecii* pneumonia, which is a well-known pulmonary infection during treatment with RA, particularly MTX or biologics.[23] Another patient with severe pneumonia refractory to antibiotic therapy was diagnosed with HSV pneumonia that was responsive to acyclovir treatment. These patients were discharged in good condition.

Most of our patients were administrated with glucocorticoid due to acute respiratory distress status, ILD or their disease activity, following consultations with pulmonologists and rheumatologists. The optimal therapeutic regimen for patients with RA-ILD has not been well studied, since no randomized controlled trials have compared treatments of RA-ILD. Glucocorticoids are still the mainstay of therapy in RA-ILD, demonstrating improvements in disease stabilization, radiographic findings, forced vital capacity, and clinical outcomes.[24-26] However, for RA-ILD patients with concurrent infections, the initiation of glucocorticoid therapy poses a challenge to intensivists, especially when it is difficult to judge which condition is in a dominant condition. Although transbronchial lung biopsy is useful for differential diagnosis, it may be challenging to perform owing to rapid deterioration of lung function. The combination of HRCT findings and metagenomic next-generation sequencing (mNGS) detection of bronchoalveolar lavage fluid (BALF) may be valuable in this dilemma.

In fact, antibiotics have been started after admission to ICU in most of our patients. In cases of high severity, high-dose glucocorticoids combined with broad-spectrum antibiotics should be promptly administrated.[21] If clinicians determine that ILD is dominant, augmenting the basic RA therapy and antifibrotic treatment are proposed. Although the efficacy of the treatment is uncertain in the case of acute exacerbation of RA-ILD, drug-induced pneumonitis may improve with high-dose glucocorticoids, as confirmed in our patient diagnosed with MTX-induced pneumonitis.[27] If the response to glucocorticoid therapy is poor, other immunosuppressive drugs such as cyclophosphamide can be started, which has demonstrated the potential improvement of prognosis in patients with acute exacerbation or progressive RA-ILD.[28-30] However, in our 5 patients administrated with cyclophosphamide, only one was discharged from hospital, which indicates that RA-ILD in ICU is a fatal condition with high mortality.

APACHE II and SOFA scores are widely used as tools to predict the patients' outcome in ICU. Previous researches have evaluated the correlation between an increased APACHE II score and poor prognosis in patients with RA.[4,10] Furthermore, the requirement for organ replacement therapy, such as the use of vasopressors, mechanical ventilation, or renal replacement therapy, has been demonstrated as a predictive factor of poor outcome in this populations. Although the small sample size of the study was insufficient to draw definite conclusions, risk factors associated with mortality in RA patients with lung involvement admitted to ICU were found in our present study include lower oxygenation index, higher SOFA scores, renal dysfunction, application of invasive mechanical ventilation and vasopressor support.

CONCLUSION

Life-threatening conditions can occur because of worsening of or development of a new manifestation of RA, which can be the causes of requiring admission to ICU. Despite the recent advances in management of RA, patients in the ICU have a rather poor prognosis, particularly in the presence of pulmonary involvement. Infectious complication is the most common reason of death in our study. The study also reminds that clinicians should individualize the therapeutic strategy, distinguishing radiological patterns, the severity and progression of pulmonary involvement, in order to better target appropriate treatment from a multidisciplinary approach.

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