Etiologies and Outcomes of Rheumatology Patients with Acute Respiratory Failure Requiring Intensive Care: A Single-Center Cohort Study of 259 Patients

Yan Shi
Peking Union Medical College Hospital
Jiu-liang Zhao
Peking Union Medical College Hospital
Han-yu Qin
Peking Union Medical College Hospital
Xiao-yun Hu
Peking Union Medical College Hospital
Wei Jiang
Peking Union Medical College Hospital
Chun-yao Wang
Peking Union Medical College Hospital
Li Weng
Peking Union Medical College Hospital
Qian Wang
Peking Union Medical College Hospital
Xiao-feng Zeng
Peking Union Medical College Hospital
Jin-min Peng (pjm731@hotmail.com)
https://orcid.org/0000-0002-4307-0717
Bin Du
Peking Union Medical College Hospital

Research

Keywords: Infection, Systemic rheumatic disease, Acute respiratory failure, Etiology

Posted Date: January 29th, 2020

DOI: https://doi.org/10.21203/rs.2.22151/v1

Abstract

Background: The etiologies of acute respiratory failure (ARF) in critically ill rheumatology patients remain unknown. We aimed to describe the clinical features, etiologies and outcomes of adult patients with systemic rheumatic diseases (SRDs) who were admitted to intensive care unit (ICU).

Methods: We performed a retrospective study of all SRD patients with ARF who were admitted to a medical ICU between 2014 and 2018. We collected data on demographics, clinical characteristics, reasons for ICU admission and outcomes. Etiologies of ARF were classified as infection, SRD exacerbation, and undetermined. Independent predictors of ICU mortality were identified with multivariate logistic regression analysis.

Results: A total of 259 patients admitted to ICU due to ARF were included in final analysis. Systemic lupus erythematosus, dermatomyositis/polymyositis (DM/PM), vasculitis and rheumatoid arthritis were the most common SRDs (78% of patients). Etiologies of ARF included infection (n = 209, 80.7%), SRD exacerbation (n = 71, 27.4%), and undetermined (n = 21, 8.1%). The most common pathogen was Pneumocystis jirovecii (39.8%), followed by Aspergillus spp. (33.2%), and cytomegalovirus (23.2%). One hundred and fifty-five patients (59.8%) died during ICU. Higher acute physiology and chronic health evaluation II score (odds ratio [OR] 1.118, 95% confidence interval [CI] 1.054 to 1.186, $p < 0.001$) and PaO2/FiO2 < 100 mmHg (OR 3.918, 95% CI 2.199 to 6.892, $p < 0.001$), DM/PM (OR 4.898, 95% CI 1.949 to 12.309, $p = 0.001$), vasculitis (OR 3.007, 95% CI 1.237 to 7.309, $p = 0.015$) and Pneumocystis pneumonia (OR 2.345, 95% CI 1.168 to 4.705, $p = 0.016$) were independent predictors of ICU mortality.

Conclusions: Opportunistic infections and SRD exacerbation were the most common etiologies of ARF in patients with SRDs requiring ICU admission, with high ICU mortality. Development of a standard protocol for differential diagnosis in this group of immunocompromised patients might help initiate definitive therapy and improve clinical outcome.

Keywords: Infection, Systemic rheumatic disease, Acute respiratory failure, Etiology

Background

Despite different immunological mechanisms and clinical manifestations, rheumatology patients are often characterized by chronic inflammation, multiorgan involvement, and acute exacerbation (flare-up) [1, 2]. Among all hospitalized rheumatology patients, up to one third need admission to intensive care unit (ICU) [1] while mortality rates are highly variable (from 16–80%), depending on underlying systemic rheumatic diseases (SRDs), reasons of ICU admission, severity of acute illness, and organ involvement/dysfunction [3–12].

Acute respiratory failure (ARF) is the leading cause of morbidity and mortality in rheumatology patients who require admission to ICU [1, 2]. This may be related to the fact that respiratory system is the most commonly affected system by SRDs, including airway, lung parenchyma, alveolar capillaries, lung

vessels, pleura, or ventilatory muscles [1, 2]. As a result, etiologies of ARF may include acute exacerbation of pre-existing manifestations of SRDs (e.g. interstitial lung disease [ILD]), pulmonary and/or extrapulmonary infections, pulmonary complications secondary to other organ dysfunction (e.g. acute pulmonary edema due to myocarditis or pericarditis), and drug-related pulmonary toxicity [2]. The broad spectrum of the etiologies of ARF among rheumatology patients very often, if not always, necessitate comprehensive diagnostic investigation as well as specific therapeutic approach.

Both multicenter [3] and single-center [4–12] studies have been performed among rheumatology patients admitted to the ICU during the past two decades, reporting characteristics and clinical outcome in patients with all forms [3–10] or a specific form of SRDs [11, 12]. However, only one study focused on rheumatology patients admitted to ICU due to ARF [7]. In addition, although some studies have identified important prognostic factors in multivariate regression analysis, most did not include laboratory tests [3, 5, 7, 8, 11], such as $CD4^+$ T-lymphocyte or lymphocyte count, which is an independent risk factor for mortality [12].

Therefore, we performed this retrospective single-center study to describe clinical characteristics, etiologies, laboratory findings, and outcomes of all rheumatology patients with ARF requiring ICU admission in our institution.

Methods

Patients

We conducted a retrospective cohort study in Medical ICU at Peking Union Medical College Hospital (PUMCH) from January 2014 to December 2018. This study was approved by the institutional review board. Given the retrospective design, informed consent was waived.

Eligible patients were aged 18 years or older, with a diagnosis of any kind of SRDs [13], and admitted to ICU due to ARF, defined as PaO_2/FiO_2 ratio < 300 mmHg [14]. Exclusion criteria were ICU length of stay (LOS) < 2 days (i.e. insufficient data for diagnostics), newly diagnosed SRDs during ICU stay, and organ-specific autoimmune diseases.

Data Collection

For all enrolled patients, we extracted demographic and clinical data from medical records, including age, sex, comorbidities, and SRDs (Additional file 1: Table S1). Severity of illness was assessed by Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) score on ICU admission [15, 16]. We also collected data of laboratory tests (including microbiological investigation), definitive treatment for SRDs (pulse steroids, intravenous immunoglobulin, and therapeutic plasma exchange), life-sustaining therapies, complications, and clinical outcomes (Additional file 1: Table S1).

Etiologies of ARF

Three senior physicians, including one rheumatologist (Zhao JL) and two intensivists (Shi Y and Peng JM), independently reviewed medical records for each patient. As previously reported, we had developed a standard procedure in our institution for microbiological investigation in rheumatology patients with suspected pneumonia, including stain, culture, antigen detection, serology, and nucleic acid amplification, as appropriate [17]. An update of the standard procedure was provided in the supplemental material (Additional file 1: Table S2). Based on results of microbiological investigation, and other relevant information (e.g. radiographic studies, treatment response), etiologies of ARF were classified as infection, SRD exacerbation, and undetermined. Any disagreement was resolved by in-depth discussion and consensus.

Definitions

SRD-related chronic organ involvement included renal, hematological, and neurological involvement, as well as connective tissue disease-associated interstitial lung disease (CTD-ILD). Renal involvement defined as urinary excretion of more than 500 mg protein/24 hours, cellular casts not attributable to infection, or abnormal histology on renal biopsy [11]. Hematological involvement was defined as hemolytic anemia or leucopenia ($< 4 \times 10^9$/L), lymphopenia ($< 1.5 \times 10^9$/L), or thrombocytopenia ($< 100 \times 10^9$/L) in the absence of offending drugs [11]. Neurological involvement included coma (i.e., Glasgow Coma Score < 9), altered mental status, seizures, or motor paralysis [3]. CTD-ILD was defined according to British Thoracic Society guidelines after exclusion of alternative causes (i.e., infection, medication, pulmonary edema) [18]. Multidrug resistant bacteria were those resistant to one or more therapeutic classes of antimicrobial agents [19].

Statistical Analysis

Continuous variables were presented as means and standard deviation (SD) for normally distributed data, and medians and interquartile range (IQR) for all other data, whereas categorical variables were presented as number (percentage). Continuous variables were compared with the use of the Student's t test or Mann-Whitney test, while categorical variables were compared using chi-square test or Fisher's exact test.

For determination of independent predictors for ICU mortality, i.e. the primary endpoint of this study, odds ratio (OR) was estimated on the basis of multivariate logistic regression analysis using stepwise conditional forward entry. In addition, two separate multivariate regression models were constructed for the prediction of pneumonia or SRD exacerbation as etiology of ARF. In all above multivariate regression analyses, variables such as demographics, comorbidities, severity of illness, and laboratory tests were entered into the model if $p < 0.1$ in univariate analysis. Because of the presence of considerable collinearity between lymphocyte count and $CD4^+$ T-lymphocyte count, only the latter was introduced in the multivariate models. In addition, etiologies of ARF (infection, and SRD exacerbation) were forced into the ICU-mortality prediction model in order to examine the effect on patient outcome. Model discrimination

and calibration were assessed by C-statistic and Hosmer-Lemeshow statistics, respectively. All comparisons were unpaired, and all tests of significance were two-tailed. A p value < 0.05 was considered as statistically significant.

Results

Patient Enrolment and Characteristics

There were 327 rheumatology patients admitted to ICU due to ARF during the study period. After exclusion of patients with ICU LOS < 2 days (n = 9), newly diagnosed SRDs during ICU stay (n = 12), and organ-specific autoimmune diseases (n = 47), 259 patients (age 49 ± 17.5 years, female 67.6%) were included in the final analysis (Fig. 1).

Patient characteristics and types of SRDs on ICU admission was listed in Table 1. Systemic lupus erythematosus (SLE), dermatomyositis/polymyositis (DM/PM), vasculitis, and rheumatoid arthritis (RA) were the most commonly SRDs (78% of patients). Apart from hematological manifestations of SRDs which were present in almost all patients, involvement of vital organs (e.g. kidney, lung, and central nervous system) occurred in 133 patients (51.4%).

Table 1

Characteristics of rheumatology patients admitted to ICU due to acute respiratory failure

	All (n = 259)	Survivors (n = 104)	Nonsurvivors (n = 155)	P value
Age, years, mean (SD)	49.0 (17.5)	46.0 (18.4)	52.0 (16.4)	0.019
Female sex, n (%)	175 (67.6)	70 (67.3)	105 (67.7)	0.936
Comorbidities, n (%)				
No comorbidity	140 (50.1)	66 (63.5)	74 (47.7)	0.017
Chronic kidney disease stage 3/4/5	23 (8.9)	7 (6.7)	16 (10.3)	0.319
Hypertension	54 (20.8)	17 (16.3)	37 (23.9)	0.144
Coronary heart disease	34 (13.1)	11 (10.6)	23 (14.8)	0.319
Diabetes	33 (12.7)	10 (9.6)	23 (14.8)	0.217
Chronic cardiac insufficiency	16 (6.2)	6 (5.8)	10 (6.5)	0.823
Chronic lung disease	9 (3.5)	5 (4.8)	4 (2.6)	0.117
Solid cancer	3 (1.2)	1 (1.0)	2 (1.3)	0.808
Type of SRDs, n (%)				
Systemic lupus erythematosus	86 (33.2)	42 (40.4)	44 (28.4)	0.058
Dermatomyositis/polymyositis	46 (17.8)	10 (9.6)	36 (23.2)	0.001
Vasculitis [a]	44 (17.0)	11 (10.6)	33 (21.2)	0.044
Rheumatoid arthritis	26 (10.0)	11 (10.6)	15 (9.7)	0.680
UCTD	20 (7.7)	9 (8.7)	11 (7.1)	0.988
Adult onset Still's disease	14 (5.4)	8 (7.7)	6 (3.9)	0.182

Abbreviations: APACHE acute physiology and chronic health evaluation, CTD-ILD connective tissue disease-associated interstitial lung disease, ICU intensive care unit, IQR interquartile range, SD standard deviation, SOFA sequential organ failure assessment, SRD systemic rheumatic disease, UCTD undifferentiated connective tissue disease, WBC white blood cell

[a] Including ANCA-related vasculitis (n = 31), Behcet's disease (n = 3), Takayasu arteritis (n = 1), large vessel vasculitis (not specified) (n = 3), polyarteritis nodosa (n = 3) and others (n = 3).

[b] including UCTD (n = 20), Adult onset Still's disease (n = 14), Sjogren's disease (n = 11), progressive systemic sclerosis (n = 6), mixed connective tissue disease (n = 3), macrophage activating syndrome (n = 1) and recurrent polychondritis (n = 2).

[c] Anti-CD20 monoclonal antibody or TNFα antagonist

	All (n = 259)	Survivors (n = 104)	Nonsurvivors (n = 155)	P value
Sjogren's disease	11 (4.2)	6 (5.8)	5 (3.2)	0.714
Others [b]	12 (4.6)	7 (5.8)	5 (3.2)	0.698
Organ involvement, n (%)				
Hematological	234 (90.3)	93 (89.4)	141 (91.0)	0.671
Renal	97 (37.5)	37 (35.6)	60 (38.7)	0.679
CTD-ILD	56 (21.6)	12 (11.5)	44 (28.4)	0.005
Neurological	16 (6.2)	6 (5.8)	10 (6.5)	0.918
Steroids therapy				
Number of patients	259 (100)	104 (100)	155 (100)	
Duration of steroids therapy, months, median (IQR)	3 (1, 12)	3.5 (1.6,24)	3.0 (1,12.0)	0.154
Daily prednisolone equivalent dose, mg, median (IQR)	50 (30,70)	50(25,60)	50 (30,70)	0.222
Immunosuppressive therapy within 1 month, n (%)				
Cytotoxic or immunosuppressants	130 (50.2)	54 (51.9)	76 (49.0)	0.648
Pulse steroids therapy	60 (23.2)	29 (27.9)	31 (20.0)	0.681
Biologics [c]	9 (3.5)	4 (3.8)	5 (3.2)	0.892
Laboratory tests on ICU admission				
WBC count, 10^9 cells/L, median (IQR)	8.0 (4.9,11.5)	8.1 (5.6,11.4)	7.8 (4.8,11.8)	0.419
Neutropenia, n(%)	14 (5.4)	3 (2.9)	11 (7.1)	0.142

Abbreviations: APACHE acute physiology and chronic health evaluation, CTD-ILD connective tissue disease-associated interstitial lung disease, ICU intensive care unit, IQR interquartile range, SD standard deviation, SOFA sequential organ failure assessment, SRD systemic rheumatic disease, UCTD undifferentiated connective tissue disease, WBC white blood cell

[a] Including ANCA-related vasculitis (n = 31), Behcet's disease (n = 3), Takayasu arteritis (n = 1), large vessel vasculitis (not specified) (n = 3), polyarteritis nodosa (n = 3) and others (n = 3).

[b] including UCTD (n = 20), Adult onset Still's disease (n = 14), Sjogren's disease (n = 11), progressive systemic sclerosis (n = 6), mixed connective tissue disease (n = 3), macrophage activating syndrome (n = 1) and recurrent polychondritis (n = 2).

[c] Anti-CD20 monoclonal antibody or TNFα antagonist

	All (n = 259)	Survivors (n = 104)	Nonsurvivors (n = 155)	P value
Lymphocyte count, 10^6 cells/L, median (IQR)	435 (241,680)	524 (303,775)	432 (193,617)	0.007
CD4 + T- lymphocyte, 10^6 cells/L, median (IQR)	120 (61,244)	171(94,293)	95 (47,210)	0.008
C-reactive protein, mg/L, median (IQR)	73.9(12.4,116)	63.1(25.7,148)	73.2(14.5,126)	0.814
PaO_2/FiO_2 ratio, mmHg, mean (SD)	168 (69)	215 (77)	132 (62)	< 0.001
Severity of illness at ICU admission				
APACHE II score, mean (SD)	16.9 (5.7)	15.7 (5.3)	17.7 (5.7)	0.006
SOFA score, mean (SD)	6.6 (2.9)	6.0 (2.9)	6.9 (2.9)	0.009
Life-sustaining therapies, n (%)				
Invasive mechanical ventilation	239 (92.3)	87 (83.7)	152 (98.1)	< 0.001
Vasopressor	189 (73.0)	68 (65.4)	121(78.1)	0.037
Renal replacement therapy	35 (13.5)	15 (14.4)	20 (12.9)	0.776
Empiric antibiotics, n (%)	247 (95.4)	100 (96.2)	147 (94.8)	0.622
Specific treatments during ICU, n (%)				
Pulse steroids	17 (6.6)	6 (5.8)	11 (7.1)	0.619
Therapeutic plasma exchange	13 (5)	6 (5.8)	7 (4.5)	0.516
Immunoglobulin	9 (3.5)	3 (2.9)	6 (3.9)	0.633
Complications during ICU stay, n (%)				

Abbreviations: APACHE acute physiology and chronic health evaluation, CTD-ILD connective tissue disease-associated interstitial lung disease, ICU intensive care unit, IQR interquartile range, SD standard deviation, SOFA sequential organ failure assessment, SRD systemic rheumatic disease, UCTD undifferentiated connective tissue disease, WBC white blood cell

[a] Including ANCA-related vasculitis (n = 31), Behcet's disease (n = 3), Takayasu arteritis (n = 1), large vessel vasculitis (not specified) (n = 3), polyarteritis nodosa (n = 3) and others (n = 3).

[b] including UCTD (n = 20), Adult onset Still's disease (n = 14), Sjogren's disease (n = 11), progressive systemic sclerosis (n = 6), mixed connective tissue disease (n = 3), macrophage activating syndrome (n = 1) and recurrent polychondritis (n = 2).

[c] Anti-CD20 monoclonal antibody or TNFα antagonist

	All (n = 259)	Survivors (n = 104)	Nonsurvivors (n = 155)	P value
ICU-acquired infection	89 (34.4)	16 (16.3)	74 (47.8)	0.001
Non-infective complications	46 (17.8)	17 (16.3)	29 (18.7)	0.687
New neutropenia	8(3.1)	1(1.0)	7(4.5)	0.105
New pneumothorax	18 (6.9)	3 (2.9)	15 (9.7)	0.035
Acute coronary syndrome	14 (5.4)	6 (5.8)	8 (5.2)	0.676
Gastrointestinal bleeding	13 (5)	4 (3.8)	9 (5.8)	0.763
Stroke	4 (1.5)	1 (1)	3 (1.9)	0.172
Outcome				
ICU length of stay, days, median (IQR)	9 (5,17)	10 (5,18)	8 (4,16)	0.129
Hospital length of stay, days, median (IQR)	22 (8,37)	34 (24,46)	12 (6,24)	0.001

Abbreviations: APACHE acute physiology and chronic health evaluation, CTD-ILD connective tissue disease-associated interstitial lung disease, ICU intensive care unit, IQR interquartile range, SD standard deviation, SOFA sequential organ failure assessment, SRD systemic rheumatic disease, UCTD undifferentiated connective tissue disease, WBC white blood cell

[a] Including ANCA-related vasculitis (n = 31), Behcet's disease (n = 3), Takayasu arteritis (n = 1), large vessel vasculitis (not specified) (n = 3), polyarteritis nodosa (n = 3) and others (n = 3).

[b] including UCTD (n = 20), Adult onset Still's disease (n = 14), Sjogren's disease (n = 11), progressive systemic sclerosis (n = 6), mixed connective tissue disease (n = 3), macrophage activating syndrome (n = 1) and recurrent polychondritis (n = 2).

[c] Anti-CD20 monoclonal antibody or TNFα antagonist

All 259 patients received long-term steroids on ICU admission, with a median daily prednisone equivalent dose of 50 mg (IQR, 30–70 mg), whereas cytotoxic drugs or immunosuppressive therapy were given in 50.2% of patients. In addition, about one-fourth of patients received pulse steroids therapy within one month prior to ICU admission, due to acute exacerbation of SRDs. Only 9 patients (3.5%) were ever treated with rituximab or tumor necrosis factor-α antagonists.

Etiologies of ARF

The distribution of etiologies of the 259 patients is presented in Fig. 1. The most common reason for ARF leading to ICU admission was microbiologically confirmed infection (n = 209, 80.7%), including pneumonia (n = 205, 79.2%) and bloodstream infection (n = 5, 1.5%) (Table 2). Bacterial, fungal, and viral infection developed in 47 (18.1%), 161 (62.2%), and 68 (26.3%) patients, respectively. Pneumocystis

pneumonia (PCP) was the leading cause (n = 103, 39.8%), followed by invasive pulmonary aspergillosis (IPA) (n = 86, 33.2%), cytomegalovirus (CMV) pneumonia (n = 60, 23.2%), influenza pneumonia (n = 14, 5.4%), and others (Table 3 and Fig. 1).

Table 2
Etiology of acute respiratory failure in rheumatology patients admitted to ICU

	All (n = 259)	Survivors (n = 104)	Nonsurvivors (n = 155)	P value
Infection	209 (80.7)	81 (77.9)	128 (82.6)	0.348
Pneumonia	205 (79.2)	78 (75.0)	127 (81.9)	0.178
Bloodstream infection	5 (1.9)	3 (2.9)	2 (1.3)	0.152
SRD exacerbation	71(27.4)	32 (30.8)	39 (25.2)	0.321
Pulmonary edema	25 (9.7)	10 (9.6)	15 (9.7)	0.987
Cardiogenic	17 (6.6)	8 (7.7)	9 (5.8)	0.548
Noncardiogenic	8 (3.1)	2 (1.9)	6 (3.9)	0.374
Diffuse alveolar hemorrhage	17 (6.6)	9 (8.7)	8 (5.2)	0.266
CTD-ILD exacerbation	17 (6.6)	7 (6.7)	10 (6.5)	0.929
Others	12 (4.6)	6 (5.8)	6 (3.9)	0.476
Acute ventilatory muscle myositis	3 (1.2)	1 (1.0)	2 (1.3)	0.808
Pneumomediastinum	3 (1.2)	1 (1.0)	2 (1.3)	0.808
CAPS/PTE	3 (1.2)	1 (1.0)	2 (1.3)	0.808
Tracheobronchial stenosis	2 (0.8)	2 (1.9)	0 (0)	0.083
Aspiration pneumonitis	1 (0.4)	1 (1.0)	0 (0)	0.221
Infection and SRD exacerbation	42 (16.2)	15 (14.4)	27 (17.4)	0.521
Undetermined	21 (8.1)	6 (5.8)	15 (9.7)	0.259
Data are presented as N (%)				
Abbreviations: CAPS catastrophic antiphospholipid syndrome, CTD-ILD connective tissue disease-associated interstitial lung disease, ICU intensive care unit, PTE pulmonary thromboembolism, SRD systemic rheumatic diseases				

Table 3

Pathogens of infections in rheumatology patients admitted to ICU due to acute respiratory failure

	All (n = 259)	Survivors (n = 104)	Nonsurvivors (n = 155)	P value
Bacteria	47 (18.1)	25 (24.0)	22 (14.2)	0.044
Acinetobacter baummannii	9 (3.5)	5 (4.8)	4 (2.6)	0.337
Mycobacterium spp.[a]	8 (3.1)	2 (1.9)	6 (3.9)	0.374
Pseudomonas aeruginosa	7 (2.7)	4 (3.8)	3 (1.9)	0.353
Legionella pneumophilia	6 (2.3)	5 (4.8)	1 (0.6)	0.029
Klebsiella pneumoniae	5 (1.9)	3 (2.9)	2 (1.3)	0.361
Other bacteria [b]	16 (6.2)	9 (8.7)	7 (4.5)	0.175
Multidrug-resistant	19 (7.3)	11 (10.6)	8 (5.2)	0.101
Fungi	161 (62.2)	54 (51.9)	107 (69.0)	0.005
Pneumocystis jirovecii [c]	103 (39.8)	34 (32.7)	69 (44.5)	0.057
Aspergillus spp.	86 (33.2)	26 (25.0)	60 (38.7)	0.022
Other fungi [d]	4 (1.5)	0 (0)	4 (2.6)	0.099
Virus	68 (26.3)	28 (26.9)	40 (25.8)	0.841
Cytomegalovirus	60 (23.2)	24 (23.1)	36 (23.2)	0.978
Influenza	14 (5.4)	7 (6.7)	7 (4.5)	0.440
Polymicrobial	86 (33.2)	32 (30.8)	54 (34.8)	0.495
Data are presented as N (%)				
Abbreviations: ICU intensive care unit				
a. Including Mycobacterium non-tuberculosis (n = 1)				
b. E. coli (n = 2), Hemophilus influenzae (n = 2), Enterococcus faecalis (n = 2), Nocardia (n = 2), Streptococcus pneumoniae (n = 2), methicillin-sensitive Staphylococcus aureus (n = 2), methicillin-resistant Staphylococcus aureus (n = 1), Staphylococcus hemolyticus (n = 1), Mycoplasma pneumoniae (n = 1), and Chlamydia pneumoniae (n = 1)				
c. Gomori methenamine stain positive for Pneumocystis cyst in 19 patients, Pneumocystis DNA positive in 84 patients				
d. Fusarium (n = 2), mucor (n = 1), and Cryptococcus neoformans (n = 1)				

Eighty-six patients (33.2%) had polymicrobial infections (Additional file 1: Table S3). Among 103 patients with PCP, 59 (57.3%) had concomitant infections, including 38 patients (36.9%) with CMV pneumonia, and 29 patients (28.2%) with IPA. While in 86 patients with IPA, 29 patients (33.7%) had PCP, and 23 patients (26.7%) had concomitant viral pneumonia, including CMV (n = 18, 20.9%) and influenza pneumonia (n = 8, 9.3%). In comparison, 52 out of 60 patients (86.7%) with CMV pneumonia had polymicrobial infections. Older age, immunosuppressants and/or pulsed steroids therapy within one month prior to ICU admission, lower $CD4^+$ T-lymphocyte count, and higher C-reactive protein level are independent risk factors for pneumonia as cause of ARF requiring ICU admission (Table 4 and Additional file 1: Table S4).

Table 4

Multivariate logistic regression analysis of risk factors for pneumonia and SRD exacerbation

	Pneumonia*		**SRD Exacerbation****	
	aOR (95% CI)	P value	aOR (95% CI)	P value
Age	1.035 (1.014–1.056)	0.001		
Female sex			3.202 (1.548–6.624)	0.002
Pulsed steroids	4.198 (2.583–11.129)	0.004	4.100 (2.141–7.852)	< 0.001
Immunosuppressants	2.168 (1.084–4.334)	0.029		
$CD4^+$ T-lymphocyte count	0.998 (0.997–1.000)	0.017	1.001 (1.000–1.003)	0.046
C-reactive protein	1.011 (1.005–1.017)	0.001	0.093 (0.988–0.998)	0.011
Abbreviations: aOR adjusted odds ratio, CI confidence interval, ICU intensive care unit, SRD systemic rheumatic disease				
* C-statistic 0.803 (95% CI 0.751–0.855, p < 0.001), and Hosmer-Lemeshow $\chi 2$ statistic 8.674 (p = 0.371)				
** C-statistic 0.765 (95% CI 0.692–0.819, p < 0.001), and Hosmer-Lemeshow $\chi 2$ statistic 5.013 (p = 0.756)				

SRD exacerbation represented another major reason for ARF (n = 71, 27.4%), mainly manifested as pulmonary edema, diffuse alveolar hemorrhage, and exacerbation of CTD-ILD (Table 2 and Additional file 1: Table S5). Female sex, pulsed steroids therapy within one month prior to ICU admission, higher $CD4^+$ T-lymphocyte count, and lower C-reactive protein level were independent risk factors for SRD exacerbation as etiology of ARF requiring ICU admission (Table 4 and Additional file 1: Table S6).

Forty-two patients (16.2%) had both infection and SRD exacerbation, while in 21 patients (8.1%), the etiology of ARF could not be determined.

Patient Outcome and Prognostic Factors

Of 259 patients included in the study, 155 (59.8%) died in ICU, with another 4 patients died during hospitalization after discharge from ICU, corresponding to hospital mortality of 61.4%. The outcome of patients with different etiologies of ARF was listed in Fig. 1 and no significant difference was observed (Table 2).

Compared with ICU survivors, nonsurvivors were more likely to be older (52.0 ± 16.4 vs. 46.0 ± 18.4 years, $p = 0.019$), and have comoribidities (52.3% vs.36.5%, $p = 0.017$). There were more DM/PM, and vasculitis, as well as CTD-ILD among nonsurvivors (Table 1). On ICU admission, nonsurvivors were more severely ill, as suggested by higher APACHE II and SOFA scores, lower lymphocyte count, lower $CD4^+$ T-lymphocyte count, and lower PaO_2/FiO_2 ratio. During ICU stay, more nonsurvivors received mechanical ventilation and vasopressors, and had more complications such as ICU-acquired infections and newly developed pneumothorax. In multivariate logistic regression analysis, higher APACHE II score, DM/PM, vasculitis, severe hypoxemia (defined as PaO_2/FiO_2 ratio < 100 mmHg), and PCP were independent risk factors of ICU mortality (Table 5). The prediction model of mortality obtained good discrimination (C-statistic, 0.779, 95% CI 0.720–0.838, $p < 0.001$) and was well calibrated with Hosmer-Lemeshow $\chi 2$ statistic of 7.881 ($p = 0.445$).

Table 5

Multivariate logistic regression analysis of risk factors for ICU mortality *

Variables	Odds Ratio	95% Confidence Interval	P value
APACHE II score	1.118	1.054–1.186	< 0.001
Type of SRDs			
Systemic lupus erythematosus	1.00	Ref	
Dermatomyositis/polymyositis	4.898	1.949–12.309	0.001
Vasculitis	3.007	1.237–7.309	0.015
Rheumatoid arthritis	1.230	0.465–3.251	0.676
Other SRDs	0.884	0.411–1.903	0.753
PaO_2/FiO_2 < 100 mmHg	3.918	2.199–6.892	< 0.001
Reasons for ARF			
Infection	0.595	0.262–1.350	0.214
SRD exacerbation	1.058	0.506–2.212	0.881
Pneumocystis jirovecii pneumonia	2.345	1.168–4.705	0.016
See Table 1 legend for expansion of abbreviations			

* Variables in the multivariate logistic regression analysis: age, any comorbidity, type of SRDs (systemic lupus erythematosus, dermatomyositis/polymyositis, vasculitis, rheumatoid diseases, and other SRDs), CTD-ILD, APACHE II score, SOFA score, PaO_2/FiO_2, reason of ARF (infection, SRD exacerbation), pathogens of infections (bacteria, Legionella pneumophilia, Pneumocystis jirovecii pneumonia, Aspergillus spp) and CD4 + T-lymphocyte count on ICU admission.

Discussion

In this large single-center cohort study of rheumatology patients with ARF admitted to ICU, we found that infection (mainly pneumonia) and SRD exacerbation were the major reasons for ARF in 80.7% and 27.4% of patients, respectively. Pneumocystis jirovecii, Aspergillus spp., and CMV were the most common pathogens. The observed ICU-mortality was 59.8%, with severity-of-illness (as suggested by higher APACHE II score and lower PaO_2/FiO_2 ratio), type of SRD (DM/PM, vasculitis), and specific infection (i.e. PCP) as independent risk factors of ICU mortality.

The mortality rate of our patients was comparable to that in a Korean study, which reported a mortality rate of 62% among 66 patients with CTD requiring ICU admission for respiratory failure [7]. It had been reported that the mortality from lung diseases in patients with SRDs, such as RA was about twice as that of the general population [20–22]. In a multicenter observational study of 363 critically ill patients with

SRDs, ICU mortality rate was 21.0%, whereas respiratory involvement accounted for only 56.8% of ICU admissions [3]. The high mortality rate attributable to ARF merited extensive investigation of etiologies, which might result in early recognition, prompt treatment, and improved clinical outcome.

Similar to other studies, pulmonary infection was the leading cause of ICU admission [1–3, 7]. However, we observed significantly different pathogen profile compared with other studies [3, 7, 8, 11]. For example, in the above-mentioned multicenter study, bacteria were the most predominant pathogens in patients admitted for infection, while only 7 patients developed PCP [3]. Likewise, among 149 patients with SRDs in a French ICU over a 20-year period, there were only 4 cases of PCP [8]. In comparison, PCP was the leading cause (39.8%) of ICU admission in our study, as well as an independent prognostic factor. The high prevalence of PCP in our study might be explained, at least in part, by the use of the standard procedure in our ICU for extensive microbiological investigation in immunocompromised patients with suspected pneumonia. In addition, it might also reflect the influence of different SRDs, among which more than 40-fold difference in the frequency of PCP was reported by Ward and coworkers [23]. As a matter of fact, the incidence rate of PCP had been increased among immunocompromised non-HIV patients, with mortality rate ranging from 48–67% [24–26]. In particular, in a retrospective study of 82 critically ill patients with PCP in whom 80% of patients had SRDs, overall hospital mortality rate was up to 75.6% [10].

Consistent with our clinical experience and other studies, certain types of SRDs, such as DM/PM and vasculitis, were independently associated with ICU mortality [7, 8, 12]. Lee and coworkers reported that patients with systemic vasculitis, DM/PM, and RA had a higher mortality rate (60–93%) [7]. Moreover, DM/PM was an independent predictor of 30-day mortality rate in ICU patients with SRDs (OR 9.2, $p = 0.04$) [8]. In a retrospective study of 102 critically ill patients with idiopathic inflammatory myopathies, we reported that 81 patients (79.4%) died during ICU stay [12]. Etiologies of ARF and relevant treatment response might explain the observed high mortality. For example, in patients with DM/PM, CTD-ILD exacerbation and fungal infections were the most common causes of ARF, which were often refractory to treatments [27–29]. In contrast, bacterial pneumonia and diffuse alveolar hemorrhage were major reasons of ARF in patients with SLE, often associated with good treatment response [3].

The strengths of our study included that 1) this was the largest observational study investigating etiologies of ARF in rheumatology patients requiring intensive care; and 2) employment of multiple microbiological techniques, including stain, culture, antigen detection, serology, and nucleic acid amplification, enabled us to report majority, if not all, of potential pathogens in rheumatology patients with suspected pneumonia [17].

Our study was also subject to several limitations. First, the study results from this single-center retrospective study necessitated validation from future multicenter prospective studies. Second, determination of etiologies of ARF was somewhat arbitrary. However, consensus had been reached among 3 senior physicians experienced in the management of critically ill rheumatology patients. Third,

next-generation sequencing had not been incorporated into our standard protocol during the study period. We believe that this novel technique may help identify nonbacterial and nonculturable pathogens.

Conclusions:

This single-center study of critically ill rheumatology patients demonstrated the complexity of ARF etiologies in this group of immunocompromised hosts. Development of a standard protocol, which included comprehensive microbiological techniques for the identification of likely pathogens, might help the clinicians to confirm the infective etiology and initiate appropriate definitive antimicrobial therapy, in order to improve clinical outcome of these vulnerable high-risk patients.

Abbreviations

ARF:acute respiratory failure; APACHE:Acute Physiology and Chronic Health Evaluation; BALF:bronchoalveolar lavage fluid; CAPS:catastrophic antiphospholipid syndrome; CMV:cytomegalovirus; CTD-ILD:connective tissue disease-associated interstitial lung disease; DM/PM:dermatomyositis/polymyositis; ICU, intensive care unit; ILD, interstitial lung disease; IPA:invasive pulmonary aspergillosis; IQR, interquartile range; LOS:length of stay; MCTD:mixed connective tissue disease; OR, odds ratio; PCP:Pneumocystis pneumonia; PCR:polymerase-chain-reaction; pSS:progressive systemic sclerosis; PTE:pulmonary thromboembolism; RA:rheumatoid arthritis; RP:recurrent polychondritis; SD:standard deviation;SLE:Systemic lupus erythematosus; SOFA:Sequential Organ Failure Assessment; SRDs:systemic rheumatic diseases; UCTD:undifferentiated connective tissue disease; WBC:white blood cell

Additional Files

Additional file 1

Table S1. Data collected from medical records. Table S2. Microbiological tests in the standard procedures. Table S3. Detailed information of pathogens in patients with polymicrobial infection. Table S4. Univariate analysis of risk factors for pneumonia as etiology of acute respiratory failure. Table S5. Detailed information of SRD exacerbation as etiology of acute respiratory failure in 71 rheumatology patients. Table S6. Univariate analysis of risk factors for SRD exacerbation as etiology of acute respiratory failure. (DOCX 44 kb)

Declarations

Ethics approval and consent to participate

This study is approved by the ethics committee of Peking Union Medical College Hospital. Given the retrospective design, informed consent was waived.

Consent for publication

Not applicable.

Availability of data and materials

All data supporting the conclusions of this article are included in this article and its additional file.

Competing interests

The authors declare that they have no competing interests

Funding

This work was supported by the Clinical Research Special Fund of Wu Jieping Medical Foundation of China (Grant number 320.6750.18428) and by CAMS Innovation Fund for Medical Sciences (CIFMS) 2016-I2 M-1-014 from Chinese Academy of Medical Sciences. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Author contributions

1. S., J. P and B. D. are the principal investigators and guarantors of the paper, taking responsibility for the integrity of the work as a whole, from inception to published article. Y. S., J. P. and B. D. contributed to the conception and design of the study; the acquisition, analysis, and interpretation of the data; and the drafting of the manuscript. J. Z. contributed to the conception and design of this study, analysis and interpretation of data, and manuscript review. H. Q., X. H., W. J., C. W., L. W., Q. W., and X. Z. contributed to the conception and design of this study, the acquisition and interpretation of data, and manuscript review.

Acknowledgements

Not applicable

References

1. Janssen NM, Karnad DR, Guntupalli KK. Rheumatologic diseases in the intensive care unit: epidemiology, clinical approach, management, and outcome. Crit Care Clin. 2002;18:729-48.
2. Papiris SA, Manali ED, Kolilekas L, Kagouridis K, Maniati M, Filippatos G, et al. Acute respiratory events in connective tissue disorders. Respiration. 2016;91:181-201.
3. Dumas G, Géri G, Montlahuc C, Chemam S, Dangers L, Pichereau C, et al. Outcomes in critically ill patients with rheumatic disease: a multicenter study. Chest. 2015;148:927-35.
4. Camargo JF, Tobón GJ, Fonseca N, Diaz JL, Uribe M, Molina F, et al. Autoimmune rheumatic diseases in the intensive care unit: experience from a tertiary referral hospital and review of the literature.

Lupus. 2005;14:315-20.

5. Moreels M, Mélot C, Leeman M. Prognosis of patients with systemic rheumatic diseases admitted to the intensive care unit. Intensive Care Med. 2005;31:591-3.
6. Cavallasca JA, Del Rosario Maliandi M, Sarquis S, Nishishinya MB, Schvartz A, Capdevila A, et al. Outcome of patients with systemic rheumatic diseases admitted to a medical intensive care unit. J Clin Rheumatol. 2010;16:400-2.
7. Lee J, Yim J, Yang S, Yoo C, Kim YW, Han SK, et al. Outcomes of patients with connective tissue disease requiring intensive care for respiratory failure. Rheumatol Int. 2012;32:3353-8.
8. Faguer S, Ciroldi M, Mariotte E, Galicier L, Rybojad M, Canet E, et al. Prognostic contributions of the underlying inflammatory disease and acute organ dysfunction in critically ill patients with systemic rheumatic diseases. Eur J Intern Med. 2013;24:e40-
9. Wang M, Su S, Lv J, Zhou G, Wang Q, Guo C. Analysis of clinical features and prognostic factors in Chinese patients with rheumatic diseases in an intensive care unit. Egypt Rheumatol. 2018;40: 63-6.
10. Weng L, Huang X, Chen L, Feng LQ, Jiang W, Hu XY, et al. Prognostic factors for severe Pneumocystis jiroveci pneumonia of non-HIV patients in intensive care unit: a bicentric retrospective study. BMC Infect Dis. 2016;16:528.
11. Hsu CL, Chen KY, Yeh PS, Hsu YL, Chang HT, Shau WY,et al. Outcome and prognostic factors in critically ill patients with systemic lupus erythematosus: a retrospective study. Crit Care. 2005;9:R177-83.
12. Peng J, Du B, Wang Q, Weng L, Hu XY, Wu CY, et al. Dermatomyositis and polymyositis in the intensive care unit: a single-center retrospective cohort study of 102 patients. PLoS ONE. 2016;11:e0154441.
13. Fauci A, Langford CA. Allergy, clinical immunology and rheumatology, In: Fauci A, Braunwald E, Kasper DL, editors. Harrison's Principles of Internal Medicine. 17th ed. New York, NY: McGraw-Hill Medical; 2008. p. 885-915
14. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, et al. Acute respiratory distress syndrome: the Berlin definition. JAMA. 2012;307:2526-33.
15. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: A severity of disease classification system. Crit Care Med. 1985;13:818-29.
16. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. Intensive Care Med. 1996;22:707-10.
17. Shi Y, Rui X, Xie XL, Zhang XJ, Tang B, Liu Y, et al. Effect of diagnostic protocols on etiology and outcome in immunocompromised host with pulmonary infiltrate. Zhong hua Yi Xue Za Zhi. 2013;93:684-9.
18. Bradley B, Branley HM, Egan JJ, Greaves MS, Hansell DM, Harrison NK, et al. Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. Thorax. 2008; 63 Suppl 5: v1-58.

19. Cohen AL, Calfee D, Fridkin SK, Huang SS, Jernigan JA, Lautenbach E,et al. Society for Healthcare Epidemiology of America and the Healthcare Infection Control Practices Advisory Committee. Recommendations for metrics for multidrug-resistant organisms in healthcare settings: SHEA/HICPAC position paper. Infect Control Hosp Epidemiol. 2008;29:901-13.
20. Anaya JM, Diethelm L, Ortiz LA, Gutierrez M, Citera G, Welsh RA, et al. Pulmonary involvement in rheumatoid arthritis. Semin Arthritis Rheum. 1995;24:242-54.
21. Perez T, Remy-Jardin M, Cortet B. Airways involvement in rheumatoid arthritis: clinical, functional, and HRCT findings. Am J Respir Crit Care Med. 1998;157:1658-65.
22. Doyle JJ, Eliasson AH, Argyros GJ, Dennis GJ, Finger DR, Hurwitz KM, et al. Prevalence of pulmonary disorders in patients with newly diagnosed rheumatoid arthritis. Clin Rheumatol. 2000;19:217-21.
23. Ward MM, Donald F. Pneumocystis carinii pneumonia in patients with connective tissue diseases: The role of hospital experience in diagnosis and mortality. Arthritis Rheum. 1999;42:780-9.
24. Bienvenu A-L, Traore K, Plekhanova I, Bouchrik M, Bossard C, Picot S. Pneumocystis pneumonia suspected cases in 604 non-HIV and HIV patients. Int J Infect Dis. 2016;46:11-7.
25. Morris A, Norris KA. Colonization by Pneumocystis jirovecii and its role in disease. Clin Microbiol Rev. 2012;25:297-317.
26. Falagas ME, Manta KG, Betsi GI, Pappas G. Infection-related morbidity and mortality in patients with connective tissue diseases: a systematic review. Clin Rheumatol. 2007;26:663-70.
27. Fujisawa T, Hozumi H, Kono M, Enomoto N, Hashimoto D, Nakamura Y,et al. Prognostic factors for myositis-associated interstitial lung disease. PLoS ONE. 2014;9:e98824.
28. Won Huh J, Soon Kim D, Keun Lee C, Yoo B, Bum Seo J, Kitaichi M,et al. Two distinct clinical types of interstitial lung disease associated with polymyositis-dermatomyositis. Respir Med. 2007;101:1761-9.
29. Chen IJ, Tsai WP, Wu YJ, Luo SF, Ho HH, Liou LB,et al. Infections in polymyositis and dermatomyositis: analysis of 192 cases. Rheumatology (Oxford). 2010;49:2429-37.

Figures

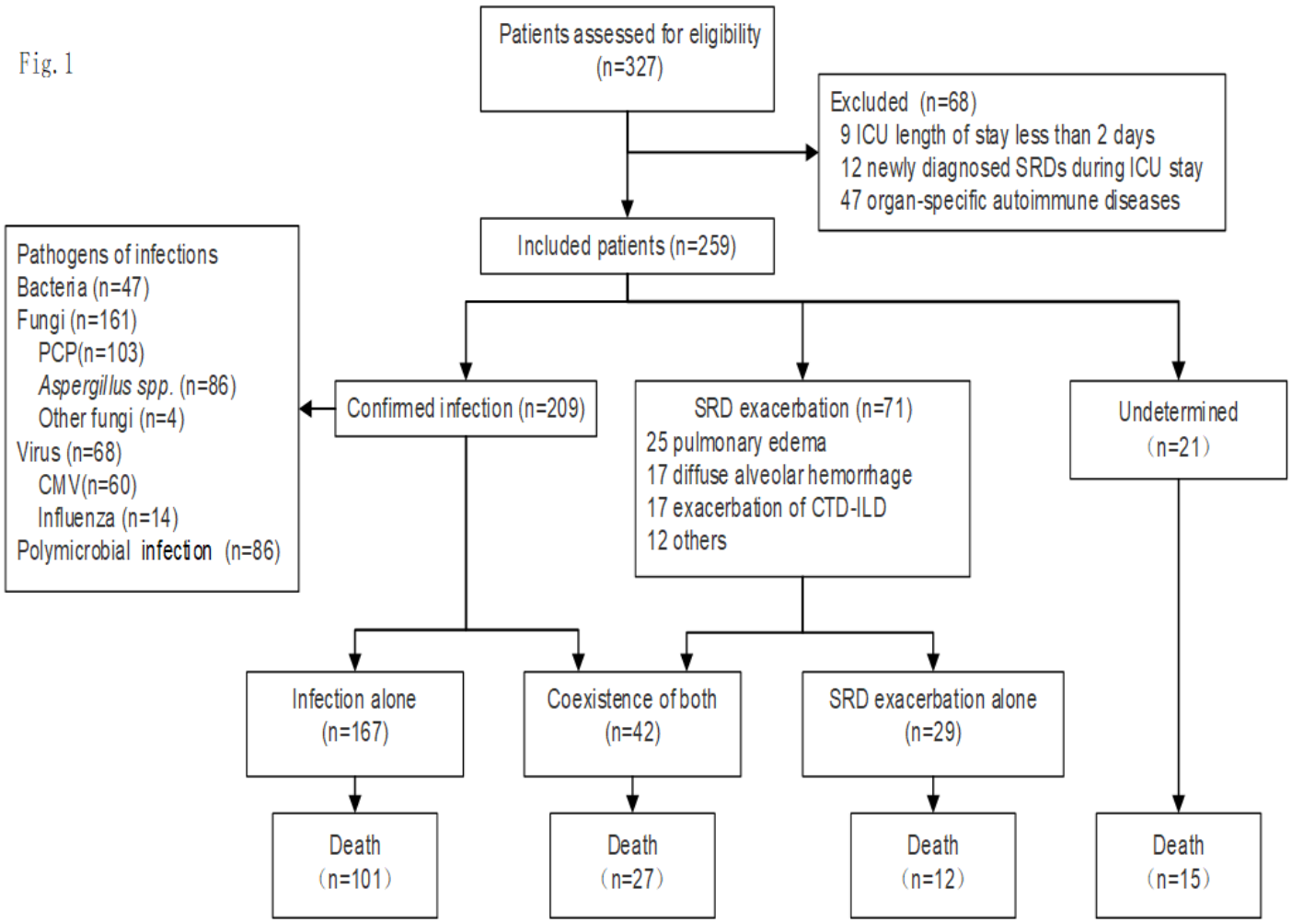

Figure 1

Flowchart of the included patients, etiologies of ARF and outcome in the ICU. ARF, acute respiratory failure; CMV, cytomegalovirus; CTD-ILD, connective tissue disease-associated interstitial lung disease; ICU, intensive care unit; PCP, Pneumocystis pneumonia; SRD, systemic rheumatic diseases.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementalmaterial.docx