

RESEARCH ARTICLE

Clinical characteristics and prognostic factors of pneumonia in patients with and without rheumatoid arthritis

Aya Wakabayashi[☉][‡]^{*}, Takashi Ishiguro[☉], Yotaro Takaku[‡], Yosuke Miyahara[‡][‡], Naho Kagiya[‡], Noboru Takayanagi[☉]

Department of Respiratory Medicine, Saitama Cardiovascular and Respiratory Center, Kumagaya, Saitama, Japan

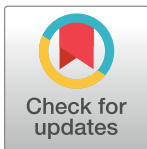
☉ These authors contributed equally to this work.

‡ Current address: Department of Respiratory Medicine, Showa University Fujigaoka Hospital, Yokohama, Kanagawa, Japan

‡ Current address: Miyahara Clinic, Kumagaya, Saitama, Japan

‡ These authors also contributed equally to this work.

* ayamewakame@yahoo.co.jp



Abstract

Background

To elucidate the characteristics of pneumonia in rheumatoid arthritis (RA) patients and to assess whether pneumonia in RA patients differs from that in non-RA patients.

Methods

We retrospectively divided pneumonia patients into two groups, those with RA and those without RA, and compared the two groups. We evaluated the risk factors for mortality with univariate and multivariate logistic regression analysis.

Results

Among 1549 patients, 71 had RA. The RA patients with pneumonia were 71.0±8.9 years old, 54.9% were female, 40.9% had a smoking history, and 71.8% had underlying respiratory disease. Female sex, non-smoker, and respiratory comorbidities were statistically more frequent in the RA patients than non-RA patients. The most frequent causative microbial agents of pneumonia in the RA patients were *Streptococcus pneumoniae*, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, and influenza virus, whereas those of pneumonia in non-RA patients were *S. pneumoniae*, influenza virus, *M. pneumoniae*, *Legionella* spp., *P. aeruginosa*, *H. influenzae*, and *Moraxella catarrhalis*. Polymicrobial infection were identified as etiologies more frequently in the RA patients than non-RA patients. Although the severity of pneumonia did not differ between the two groups, mortality was statistically higher in the RA patients than non-RA patients. Multivariate analysis showed RA to be an independent risk factor for mortality.

OPEN ACCESS

Citation: Wakabayashi A, Ishiguro T, Takaku Y, Miyahara Y, Kagiya N, Takayanagi N (2018) Clinical characteristics and prognostic factors of pneumonia in patients with and without rheumatoid arthritis. PLoS ONE 13(8): e0201799. <https://doi.org/10.1371/journal.pone.0201799>

Editor: Amarjit Mishra, Auburn University College of Veterinary Medicine, UNITED STATES

Received: May 20, 2018

Accepted: July 23, 2018

Published: August 3, 2018

Copyright: © 2018 Wakabayashi et al. This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data Availability Statement: All relevant data are within the paper.

Funding: The authors received no specific funding for this work.

Competing interests: The authors have declared that no competing interests exist.

Conclusions

P. aeruginosa, *H. influenzae*, *M. catarrhalis*, and polymicrobial infection were statistically more frequent etiologies of pneumonia in the RA patients than non-RA patients. RA itself was found to be an independent risk factor for mortality from pneumonia.

Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease that results in worsening of physical function and extra-articular manifestations. Because of these manifestations, patients with RA have been reported to have a shorter life expectancy than controls [1,2] and are at increased risk of developing infections compared with the general population [3,4]. Furthermore, although many studies have reported favorable results of treatment, since the introduction of a new class of anti-cytokine drugs, problems associated with increased rates of serious infection in RA patients have emerged.

Lower respiratory tract infections are the most frequent infectious events occurring in RA patients [5], and bacterial pneumonia is associated with increased mortality in RA patients [4–6]. A nested case-control study that included 17,172 cases of pneumonia diagnosed between 1996 and 2005 determined that RA was an independent risk factor for community-acquired pneumonia (odds ratio, 1.84; 95% confidence interval [CI], 1.62–2.10) [7]. Recently, a favorable effect of vaccination against influenza and pneumococcus to reduce the prevalence of hospitalized cases of pneumonia in RA patients has been reported [8,9].

Pneumonia may be one of the most important infectious complications of RA patients, but there have been no reports investigating the etiology, severity, and mortality of pneumonia in these patients. Therefore, the objectives of the present study were to clarify the characteristics, etiology, severity, outcome, and prognostic factors of pneumonia in RA patients in comparison with non-RA patients.

Materials and methods

Patients and study design

We performed a retrospective study of patients treated with pneumonia at our institution in Saitama, Japan, between January 2002 and December 2011. Characteristics, severity, outcome, and etiology of pneumonia in the RA patients were compared with those in the non-RA patients also treated in our institution during the same period. The following variables were assessed as possible risk factors for mortality from pneumonia: age (≥ 65 years), male sex, smoking habit, presence of comorbid illness, respiratory comorbidity, RA patient, severe pneumonia, and healthcare-associated pneumonia (HCAP), which we previously reported as risk factors for mortality from CAP [10]. RA was diagnosed by rheumatologists certified by the Japan College of Rheumatology according to established classification criteria [11]. The study protocol was approved by the Ethics Committee of Saitama Cardiovascular and Respiratory Center (Approval no. 2012041) and waived patient consent because this was a retrospective study and anonymity was secured. The study was conducted in compliance with the Declaration of Helsinki.

Definition of pneumonia

Pneumonia was diagnosed on the basis of symptoms suggestive of lower respiratory tract infection and the development of new infiltrations on chest X-ray. HCAP was defined when the criteria of the American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) guidelines [12] were satisfied. Severe pneumonia was defined when at least one major criterion or three minor criteria of the IDSA/ATS guidelines [13] were present. Patients with acquired immunodeficiency syndrome, tuberculosis, non-resected lung cancer, or a confirmed alternative diagnosis until the end of follow-up were excluded from the study.

Microbiological identification

Diagnosis of causative microorganisms was based on the results of semiquantitative cultures of respiratory samples or blood, paired sera, urinary antigen tests for *Streptococcus pneumoniae* and *Legionella pneumophila*, and nasopharyngeal swabs for influenza virus as reported previously [10]. The antibiotic regimen was chosen by the attending physician in accordance with the recommendations of the ATS/IDSA guidelines [12].

Statistical analysis

Results are presented as the frequency and percentage or mean \pm SD, unless otherwise indicated. Risk factors for mortality from pneumonia in RA patients were evaluated with univariate and multivariate logistic regression analysis. Variables showing significance by univariate analysis were included in the multivariate logistic regression analysis with backward elimination method. The 95% CI for all comparisons is also reported. In all instances, a two-tailed *P* value of ≤ 0.05 was considered to indicate statistical significance. All statistical analyses were performed with Statistical Analysis System software (SAS version 9.1.3; SAS Institute, Inc., Cary, NC).

Results

Characteristics of pneumonia patients with and without RA

Overall, 71 patients with RA and 1478 patients without RA were investigated. Characteristics of the RA patients with pneumonia are shown in Table 1. Among these patients with RA, the age at diagnosis was 71.0 ± 8.9 years, 39 (54.9%) patients were female, and 29 (40.9%) patients had a smoking history. Underlying respiratory diseases were identified in 51 (71.8%) patients, and systemic comorbidities were identified in 33 (46.5%) patients. The ratio of females (54.9% vs 30.5%, $p < 0.001$) and the frequency of underlying respiratory disease (71.8% vs 52.2%, $p = 0.001$) were significantly higher in the RA patients, but the presence of a smoking history (40.9% vs 62.1%, $p < 0.001$) was significantly higher in the non-RA patients.

Compared with RA patients without underlying respiratory disease, the mean age of those having respiratory comorbidities was significantly older and the rate of male sex was significantly higher (Table 2). Therapeutic drugs for RA were administered in 57 patients (biologics [$n = 5$], methotrexate [MTX] [$n = 17$], corticosteroid [$n = 31$], and DMARDs [disease-modifying anti-rheumatic drugs] other than MTX [$n = 27$]). Patients with respiratory comorbidities tended to be less frequently treated with MTX or biologics (Table 2). There were no differences in the characteristics of the RA patients between those with severe versus non-severe pneumonia (Table 2). Compared with the RA patients who did not survive, those who did survive tended to be more frequently treated with a steroid or immunosuppressant.

Table 1. Characteristics of the patients with and without RA.

| Characteristic | RA (n = 71) | Non-RA (n = 1478) | p value |
|--------------------------------------|-------------------------|----------------------|---------|
| Age (years) | 71.0 ± 8.9 ^a | 66.9 ± 17.1 | <0.001 |
| ≥65 years | 53 (74.6) | 956 (64.7) | 0.097 |
| Female sex | 39 (54.9) | 451 (30.5) | <0.001 |
| Smokers | 29 (40.8) | 918 (62.1) | <0.001 |
| HCAP | 23 (32.4) | 484 (32.7) | 1.000 |
| Comorbidity | | | |
| None | 10 (14.1) | 339 (22.9) | 0.008 |
| Pulmonary disease | 51 (71.8) | 772 (52.2) | 0.001 |
| COPD | 12 (16.9) | 324 (21.9) | 0.377 |
| Asthma | 1 (1.4) | 149 (10.1) | 0.012 |
| Bronchiectasis | 9 (12.7) | 91 (6.2) | 0.043 |
| Nontuberculous mycobacteriosis | 10 (14.1) | 65 (4.4) | 0.002 |
| Old pulmonary tuberculosis | 3 (4.2) | 105 (7.1) | 0.477 |
| Chronic pulmonary aspergillosis | 1 (1.4) | 25 (1.7) | 1.000 |
| Interstitial pneumonia | 21 (29.6) | 85 (5.8) | <0.001 |
| Post lung cancer operation | 1 (1.4) | 57 (3.9) | 0.517 |
| Other pulmonary disease ^b | 12 (16.9) | 56 (3.8) | <0.001 |
| Systemic disease | 33 (46.5) | 655 (44.3) | 0.716 |
| Steroid or immunosuppressant | 46 (64.8) | 87 (5.9) | <0.001 |
| Severe | 7 (9.9) | 218 (14.7) | 0.303 |
| Mortality | 8 (11.3) | 74 (5.0) | 0.050 |

RA, rheumatoid arthritis; HCAP, healthcare-associated pneumonia; COPD, chronic obstructive pulmonary disease.

^aData are presented as means ± standard deviation or n (%).

^b“Other pulmonary disease” includes the following incidences of each disease: bronchiolitis (n = 6), chronic eosinophilic pneumonia (n = 2), and others (n = 5) in the RA patients, and pneumoconiosis (n = 13), sarcoidosis (n = 9), chronic empyema (n = 8), pulmonary thromboembolism (n = 6), asbestos pleuritis (n = 4), pulmonary hypertension, alveolar proteinosis (n = 3 each), and others (n = 10) in the non-RA patients. Some patients had more than one comorbidity.

<https://doi.org/10.1371/journal.pone.0201799.t001>

Microbiological etiology of pneumonia in patients with and without RA

Pathogens were identified in 40 (56.3%) of the RA patients and 824 (55.8%) of the non-RA patients (Table 3). The five most frequently isolated pathogens in the RA patients were *S. pneumoniae* (18.3%), *Pseudomonas aeruginosa* (14.1%), *Haemophilus influenzae* (9.9%), *Mycoplasma pneumoniae*, and influenza virus (8.5% each). In contrast, the four most frequently isolated pathogens in the non-RA patients were *S. pneumoniae* (23.2%), influenza virus (9.4%), *M. pneumoniae* (8.1%), and *Legionella* spp. (4.7%) (Table 3). *P. aeruginosa* (14.1% vs 4.5%, p = 0.002), *H. influenzae* (9.9% vs 4.2%, p = 0.035), *M. catarrhalis* (7.0% vs 0.9%, p = 0.001), and polymicrobial infection (23.9% vs 8.3%, p < 0.001) were identified as etiologies statistically more frequently in the RA patients than in the non-RA patients (Table 3).

The four most frequently isolated pathogens in the RA patients with underlying respiratory diseases were *P. aeruginosa* (19.6%), *S. pneumoniae* (15.7%), *H. influenzae* (13.7%), and *M. catarrhalis* (9.8%) (Table 4). All of the patients with *P. aeruginosa*, *H. influenzae*, and *M. catarrhalis* infection had respiratory comorbidities. Pathogens isolated in the non-survivors with RA were *S. pneumoniae*, *P. aeruginosa* (n = 3 each), *M. pneumoniae*, *H. influenzae*, and *M. catarrhalis* (n = 1 each) (Table 4). There were no significant differences in etiologies between the RA patients with or without underlying respiratory disease, between the RA patients treated or

Table 2. Characteristics of the patients with RA.

| Characteristic | Pulmonary comorbidity | | | Therapeutic agents for RA | | | Severity | | | Non-Survivors | | |
|------------------------------|-------------------------|---------------|---------|--------------------------------------|-----------------|---------|----------------|---------------------|---------|-----------------------|--------------------|---------|
| | Present (n = 51) | None (n = 20) | p value | Biological agent and/or MTX (n = 18) | Others (n = 53) | p value | Severe (n = 7) | Non-severe (n = 64) | p value | Non-survivors (n = 8) | Survivors (n = 63) | p value |
| Age (years) | 73.0 ± 8.1 ^a | 66.1 ± 9.1 | 0.002 | 68.1 ± 10.0 | 72.0 ± 8.3 | 0.100 | 74.4 ± 8.4 | 70.7 ± 8.9 | 0.289 | 73.9 ± 7.4 | 70.7 ± 9.0 | 0.339 |
| Female sex | 24 (47.1) | 15 (75.0) | 0.038 | 10 (55.6) | 29 (54.7) | 1.000 | 2 (28.6) | 37 (57.8) | 0.231 | 4 (50.0) | 35 (55.6) | 1.000 |
| Smokers | 24 (47.1) | 5 (25.0) | 0.112 | 7 (38.9) | 22 (41.5) | 1.000 | 4 (57.1) | 25 (39.1) | 0.433 | 2 (25.0) | 27 (42.9) | 0.458 |
| HCAP | 18 (35.3) | 5 (25.0) | 0.574 | 5 (27.8) | 18 (34.0) | 0.774 | 1 (14.3) | 22 (34.4) | 0.415 | 1 (12.5) | 22 (34.9) | 0.261 |
| Steroid or immunosuppressant | 31 (60.8) | 15 (75.0) | 0.287 | 18 (100.0) | 28 (52.8) | <0.001 | 2 (28.6) | 44 (68.8) | 0.088 | 2 (25.0) | 44 (69.8) | 0.019 |
| Comorbidity | | | | | | | | | | | | |
| None | 0 (0.0) | 10 (50.0) | <0.001 | 5 (27.8) | 5 (9.4) | 0.036 | 2 (28.6) | 8 (12.5) | 0.687 | 0 (0.0) | 10 (15.9) | 0.254 |
| Pulmonary disease | 51 (100.0) | 0 (0.0) | <0.001 | 9 (50.0) | 42 (79.2) | 0.031 | 4 (57.1) | 47 (73.4) | 0.394 | 8 (100.0) | 43 (68.3) | 0.095 |
| Systemic disease | 23 (45.1) | 10 (50.0) | 0.794 | 6 (33.3) | 27 (50.9) | 0.275 | 3 (42.9) | 30 (46.9) | 1.000 | 5 (62.5) | 28 (44.4) | 0.459 |
| Severe | 4 (7.8) | 3 (15.0) | 0.394 | 2 (11.1) | 5 (9.4) | 1.000 | 7 (100.0) | 0 (0.0) | <0.001 | 3 (37.5) | 4 (6.3) | 0.027 |
| Mortality | 8 (15.7) | 0 (0.0) | 0.095 | 0 (0.0) | 8 (15.1) | 0.105 | 3 (42.9) | 5 (7.8) | 0.027 | 8 (100.0) | 0 (0.0) | <0.001 |

RA, rheumatoid arthritis; HCAP, healthcare-associated pneumonia.

^aData are presented as means ± standard deviation or n (%).

<https://doi.org/10.1371/journal.pone.0201799.t002>

not-treated with MTX or biologics, between the severe and non-severe RA patients, and between the non-surviving and surviving RA patients.

Severity on admission of pneumonia patients with and without RA

Seven (9.9%) RA patients and 218 (14.7%) non-RA patients met the criteria of severe pneumonia on hospital admission. The frequency of severe pneumonia in the RA patients did not differ from that in the non-RA patients (Table 1).

Outcomes of pneumonia patients with and without RA

Eight (11.3%) RA patients and 74 (5.0%) non-RA patients died (Table 1). The mortality of the RA patients was statistically higher than that of non-RA patients (p = 0.050). All eight non-survivors with RA had respiratory comorbidities (Table 2).

Risk factors for mortality from pneumonia

Multivariate analysis revealed older age, RA, severe pneumonia, and HCAP to be the independent risk factors for mortality from pneumonia (Table 5). The presence of respiratory comorbidities was found to be a significant risk factor for mortality in the univariate analysis, although this factor was not significant in the multivariate analysis.

Discussion

We assessed the characteristics, severity, outcome, and etiology of pneumonia in RA patients. The characteristics of the RA patients with pneumonia differed from those of the non-RA patients with pneumonia in terms of certain patient demographics and in the microbial etiologies of pneumonia. Although the severity of the pneumonia in the RA patients did not differ significantly from that in the non-RA patients, mortality in the RA patients was significantly higher than that in the non-RA patients, and RA itself was an independent risk factor for mortality from pneumonia.

Table 3. Etiology of pneumonia in the RA and non-RA patients.

| Etiology | RA (n = 71) | | Non-RA (n = 1478) | | p value |
|---------------------------------------|-------------|------|-------------------|------|---------|
| | No. | (%) | No. | (%) | |
| <i>Streptococcus pneumoniae</i> | 13 | 18.3 | 343 | 23.2 | 0.388 |
| Influenza virus | 6 | 8.5 | 139 | 9.4 | 1.000 |
| <i>Mycoplasma pneumoniae</i> | 6 | 8.5 | 119 | 8.1 | 0.824 |
| <i>Legionella</i> spp. | 1 | 1.4 | 70 | 4.7 | 0.253 |
| <i>Pseudomonas aeruginosa</i> | 10 | 14.1 | 67 | 4.5 | 0.002 |
| <i>Haemophilus influenzae</i> | 7 | 9.9 | 62 | 4.2 | 0.035 |
| GNEB | 4 | 5.6 | 48 | 3.2 | 0.296 |
| <i>Chlamydomphila pneumoniae</i> | 2 | 2.8 | 30 | 2.0 | 0.656 |
| <i>Chlamydomphila psittaci</i> | 0 | 0.0 | 16 | 1.1 | 1.000 |
| <i>Moraxella catarrhalis</i> | 5 | 7.0 | 14 | 0.9 | 0.001 |
| <i>Streptococcus</i> sp. ^a | 0 | 0.0 | 12 | 0.8 | 1.000 |
| <i>Stenotrophomonas maltophilia</i> | 1 | 1.4 | 1 | 0.1 | 0.090 |
| Others ^b | 5 | 7.0 | 31 | 2.1 | 0.022 |
| Polymicrobial infection ^c | 17 | 23.9 | 123 | 8.3 | <0.001 |
| Unknown | 31 | 43.7 | 654 | 44.2 | 1.000 |

RA, rheumatoid arthritis; GNEB, Gram-negative enteric bacilli.

^a*Streptococcus* sp. means other than *S. pneumoniae*.

^b“Others” includes coagulase-negative *Staphylococci* (n = 3), and methicillin-susceptible *Staphylococcus aureus*, *Haemophilus parainfluenzae* (n = 1 each) in the RA patients, and methicillin-susceptible *S. aureus* (n = 11), methicillin-resistant *S. aureus* (n = 5), *Nocardia* sp. (n = 3), *H. parainfluenzae* (n = 2), and coagulase-negative *Staphylococci*, *S. haemolyticus*, *Acinetobacter baumannii*, *A. calcoaceticus*, Varicella-zoster virus, *H. parahaemolyticus*, *Pseudomonas alcaligenes*, *Citrobacter freundii* (n = 1 each), and anaerobes (n = 7) (*Fusobacterium* sp. [n = 2], and *Clostridium perfringens*, *Prevotella* sp., *Gemella morbillorum*, *Peptostreptococcus prevostii*, and *Veillonella* sp. [n = 1 each]) in the non-RA patients.

^c“Polymicrobial infection” includes *S. pneumoniae* + *M. pneumoniae*, *H. influenzae* + influenza virus, *H. influenzae* + *M. catarrhalis* and *P. aeruginosa* + GNEB (n = 2 each) and *S. pneumoniae* + *H. influenzae*, *S. pneumoniae* + influenza virus, *H. influenzae* + *P. aeruginosa*, *M. pneumoniae* + methicillin-susceptible *S. aureus*, *P. aeruginosa* + *H. parainfluenzae*, influenza virus + coagulase-negative *Staphylococci*, *S. pneumoniae* + *M. catarrhalis* + coagulase-negative *Staphylococci*, *S. pneumoniae* + influenza virus + *C. pneumoniae* and *H. influenzae* + *P. aeruginosa* + *C. pneumoniae* (n = 1 each) in the RA patients, and *S. pneumoniae* + influenza virus (n = 30), *S. pneumoniae* + *H. influenzae* (n = 13), *S. pneumoniae* + *C. pneumoniae* (n = 8), *H. influenzae* + influenza virus (n = 6), *S. pneumoniae* + *Legionella* spp. (n = 5), *S. pneumoniae* + *M. pneumoniae*, *M. pneumoniae* + influenza virus and *H. influenzae* + *P. aeruginosa* (n = 4 each), *S. pneumoniae* + *M. catarrhalis* and influenza virus + *Legionella* spp. (n = 3 each), *S. pneumoniae* + *P. aeruginosa*, *S. pneumoniae* + methicillin-susceptible *S. aureus*, *H. influenzae* + *M. pneumoniae*, *M. pneumoniae* + *P. aeruginosa*, *M. pneumoniae* + *Legionella* spp., influenza virus + GNEB, *P. aeruginosa* + methicillin-resistant *S. aureus*, *P. aeruginosa* + *Legionella* spp. and *S. pneumoniae* + *M. catarrhalis* + influenza virus (n = 2 each) and *S. pneumoniae* + *C. psittaci*, *S. pneumoniae* + GNEB, *H. influenzae* + *M. catarrhalis*, *H. influenzae* + *C. psittaci*, *M. pneumoniae* + *C. pneumoniae*, *M. pneumoniae* + methicillin-susceptible *S. aureus*, influenza virus + *P. aeruginosa*, influenza virus + *M. catarrhalis*, influenza virus + *C. pneumoniae*, influenza virus + methicillin-resistant *S. aureus*, *C. pneumoniae* + *Legionella* spp., *S. maltophilia* + methicillin-resistant *S. aureus*, *Streptococcus* sp. + GNEB, methicillin-susceptible *S. aureus* + *Nocardia* sp., *Prevotella* sp. + *Fusobacterium* sp., *S. pneumoniae* + *H. influenzae* + influenza virus, *S. pneumoniae* + *H. influenzae* + methicillin-susceptible *S. aureus*, *S. pneumoniae* + influenza virus + methicillin-susceptible *S. aureus*, *S. pneumoniae* + influenza virus + *Legionella* spp., *S. pneumoniae* + influenza virus + *C. pneumoniae*, *S. pneumoniae* + *M. catarrhalis* + *C. pneumoniae*, *M. pneumoniae* + *Streptococcus* sp. + *Fusobacterium* sp., influenza virus + *P. aeruginosa* + *A. calcoaceticus*, *P. aeruginosa* + *P. alcaligenes* + *H. parahaemolyticus*, and *G. morbillorum* + *P. prevostii* + *Veillonella* sp. (n = 1 each) in the non-RA patients.

<https://doi.org/10.1371/journal.pone.0201799.t003>

Table 4. Etiology of pneumonia in RA.

| Etiology | Pulmonary comorbidity | | | Therapeutic agents of RA | | | Severity | | | Mortality | | |
|-------------------------------------|-----------------------|---------------|---------|--------------------------------------|-----------------|---------|----------------|---------------------|---------|-----------------------|--------------------|---------|
| | Present (n = 51) | None (n = 20) | p value | Biological agent and/or MTX (n = 18) | Others (n = 53) | p value | Severe (n = 7) | Non-severe (n = 64) | p value | Non-survivors (n = 8) | Survivors (n = 63) | p value |
| <i>Streptococcus pneumoniae</i> | 8 (15.7) ^a | 5 (25.0) | 0.496 | 1 (5.6) | 12 (22.6) | 0.161 | 4 (57.1) | 9 (14.1) | 0.018 | 3 (37.5) | 10 (15.9) | 0.156 |
| Influenza virus | 3 (5.9) | 3 (15.0) | 0.340 | 3 (16.7) | 3 (5.7) | 0.166 | 1 (14.3) | 5 (7.8) | 0.477 | 0 (0.0) | 6 (9.5) | 1.000 |
| <i>Mycoplasma pneumoniae</i> | 3 (5.9) | 3 (15.0) | 0.340 | 1 (5.6) | 5 (9.4) | 1.000 | 0 (0.0) | 6 (9.4) | 1.000 | 1 (12.5) | 5 (7.9) | 0.526 |
| <i>Legionella</i> spp. | 0 (0.0) | 1 (5.0) | 0.282 | 1 (5.6) | 0 (0.0) | 0.254 | 1 (14.3) | 0 (0.0) | 0.099 | 0 (0.0) | 1 (1.6) | 1.000 |
| <i>Pseudomonas aeruginosa</i> | 10 (19.6) | 0 (0.0) | 0.053 | 2 (11.1) | 8 (15.1) | 1.000 | 1 (14.3) | 9 (14.1) | 1.000 | 3 (37.5) | 7 (11.1) | 0.078 |
| <i>Haemophilus influenzae</i> | 7 (13.7) | 0 (0.0) | 0.179 | 3 (16.7) | 4 (7.5) | 0.359 | 1 (14.3) | 6 (9.4) | 0.533 | 1 (12.5) | 6 (9.5) | 0.584 |
| GNEB | 4 (7.8) | 0 (0.0) | 0.571 | 2 (11.1) | 2 (3.8) | 0.265 | 0 (0.0) | 4 (6.3) | 1.000 | 0 (0.0) | 4 (6.3) | 1.000 |
| <i>Chlamydomphila pneumoniae</i> | 1 (2.0) | 1 (5.0) | 0.487 | 1 (5.6) | 1 (1.9) | 0.445 | 1 (14.3) | 1 (1.6) | 0.189 | 0 (0.0) | 2 (3.2) | 1.000 |
| <i>Moraxella catarrhalis</i> | 5 (9.8) | 0 (0.0) | 0.312 | 1 (5.6) | 4 (7.5) | 1.000 | 2 (28.6) | 3 (4.7) | 0.073 | 1 (12.5) | 4 (6.3) | 0.460 |
| <i>Stenotrophomonas maltophilia</i> | 1 (2.0) | 0 (0.0) | 1.000 | 1 (5.6) | 0 (0.0) | 0.254 | 0 (0.0) | 1 (1.6) | 1.000 | 0 (0.0) | 1 (1.6) | 1.000 |
| Others | 4 (7.8) | 1 (5.0) | 1.000 | 1 (5.6) | 4 (7.5) | 1.000 | 1 (14.3) | 4 (6.3) | 0.414 | 0 (0.0) | 5 (7.9) | 1.000 |
| Polymicrobial infection | 14 (27.5) | 3 (15.0) | 0.471 | 4 (22.2) | 13 (24.5) | 0.505 | 3 (42.9) | 14 (21.9) | 1.000 | 2 (25.0) | 15 (23.8) | 0.677 |
| Unknown | 21 (41.2) | 10 (50.0) | 0.598 | 6 (33.3) | 25 (47.2) | 0.412 | 0 (0.0) | 31 (48.4) | 0.016 | 1 (12.5) | 30 (47.6) | 0.126 |

RA, rheumatoid arthritis; MTX, methotrexate; GNEB, Gram-negative enteric bacilli.

^aData are presented as means ± standard deviation or n (%).

<https://doi.org/10.1371/journal.pone.0201799.t004>

Vaccination against influenza and pneumococcus has been shown to reduce the prevalence of pneumonia in RA patients [8,9]. The present study showed that both *S. pneumoniae* and influenza virus were frequently isolated as pathogens of pneumonia in these patients. This result may be one of explanations for why vaccination against influenza and pneumococcus is associated with a lower prevalence of pneumonia in RA patients. Further prospective studies are needed to clarify the factors contributing to the reduction of the prevalence of pneumonia in RA patients.

A previous report indicated that structural diseases of the lung, smoking history, and cardiovascular diseases were the important risk factors of infections by *P. aeruginosa*, *H. influenzae*, and *M. catarrhalis* [6]. In the present study, infections by these three species were

Table 5. Multivariate analysis of the risk of mortality in the study patients.

| Factor | n | Non-survivors | Univariate analysis | | | Multivariate analysis (final model) | | |
|----------------------|------|---------------|---------------------|-----------------|----------------------|-------------------------------------|-----------------|---------|
| | | | OR | 95% CI | p value ^a | OR | 95% CI | p value |
| Age (≥65 years) | 1009 | 72 | 4.073 | (2.084, 7.958) | <0.001 | 2.233 | (1.101, 4.526) | 0.026 |
| Male sex | 1059 | 61 | 1.365 | (0.821, 2.268) | 0.230 | | | |
| Smoker | 947 | 47 | 0.846 | (0.539, 1.327) | 0.466 | | | |
| Systemic disease | 688 | 43 | 1.405 | (0.900, 2.194) | 0.134 | | | |
| Pulmonary disease | 823 | 58 | 2.218 | (1.363, 3.608) | 0.001 | | | |
| Rheumatoid arthritis | 71 | 8 | 2.409 | (1.113, 5.213) | 0.026 | 3.614 | (1.552, 8.418) | 0.003 |
| Severity, severe | 225 | 50 | 11.536 | (7.203, 18.475) | <0.001 | 10.747 | (6.584, 17.543) | <0.001 |
| HCAP | 507 | 47 | 2.940 | (1.872, 4.617) | <0.001 | 2.372 | (1.454, 3.867) | <0.001 |

OR, odds ratio; CI, confidence interval; HCAP, healthcare-associated pneumonia.

^aValues represent p value for category against the reference.

<https://doi.org/10.1371/journal.pone.0201799.t005>

statistically more frequent in the RA patients than the non-RA patients, and all patients with these infections had respiratory comorbidities. The frequency of respiratory comorbidities in the RA patients was higher than that in the non-RA patients. Our data suggest that a higher frequency of respiratory comorbidities in RA patients may contribute to the difference in microbial etiologies from that in non-RA patients.

Reports in the literature even in the pre-steroid era suggest that patients with RA may have an increased susceptibility to infection [14]. RA patients have increased susceptibility to the development of pneumonia [3,5,15]. One possible explanation for this increased rate of pneumonia is the impaired immunologic abnormalities due to RA itself that involve the majority of circulating T cells, which develop from an early stage in the disease course [16]. RA therapy with corticosteroids and other immunomodulatory agents may also contribute to respiratory infection in patients complicated with RA. In fact, Widdifield *et al.* have suggested the associations of both previous and current anti-rheumatic drug use with increased risk of infection for both overall and specific infections [5]. In addition, the respiratory comorbidities that RA patients are often complicated with [15,17] should not be ignored. In the present study, 51 (71.8%) patients with RA had underlying respiratory diseases, which was statistically more frequent than that in the non-RA patients. The presence of these pulmonary and respiratory tract diseases may increase the risk of pneumonia [18].

Although the severity of pneumonia in the RA patients did not differ significantly from that in the non-RA patients, the mortality of the RA patients was significantly higher than that of the non-RA patients. We found that RA itself, older age (≥ 65 years), disease severity, and HCAP were identified as the independent risk factors for mortality.

Tsuchiya *et al.* investigated the outcome and causes of 71 deaths in 144 RA patients who had lung diseases directly associated with RA and reported that the cause of death in 9 (12.7%) of the 71 non-survivors was pneumonia [19], which suggests that pneumonia is an important cause of death in patients with underlying respiratory disease. Furthermore, disease-related factors such as immobility or the presence of extraarticular manifestations of RA were reported to contribute to the mortality of RA patients [20,21]. All 8 non-survivors in the present study had underlying respiratory diseases, and probably, their pulmonary function would also have been impaired. One reason for the difference in mortality between the RA and non-RA patients, and why RA itself was found to be an independent risk factor for mortality may be the impaired pulmonary function due to underlying respiratory diseases in the RA patients. The impaired pulmonary function, including the impaired local defense mechanism in patients with respiratory comorbidities or the impaired host defenses in RA patients, may contribute to its mortality. Physical activities such as performance status are frequently impaired in RA patients, which may have affected the present results [22]. It would be desirable to examine prognostic factors of pneumonia in RA patients in consideration of underlying disease severity in a future study.

The present study has several limitations. First, because it is a retrospective, observational, single-center study, the level of confidence is reduced, and the results may not be applicable in other settings. Second, we did not investigate the disease severity of RA, which may be an important risk factor for mortality. Third, we could not examine the influence of therapeutic drugs for RA on the outcome of pneumonia because few patients were given these drugs, especially MTX or biologics.

Conclusion

Our results showed that there were several differences in patient demographics and etiologies between the RA patients and non-RA patients with pneumonia. The mortality from

pneumonia in the RA patients was significantly higher than that in the non-RA patients, and RA itself was an independent risk factor for mortality from pneumonia. One possible explanation for the difference in clinical characteristics, etiology, and mortality between the RA patients and non-RA patients was the difference in the frequency of underlying respiratory disease. Careful attention should be paid to treating pneumonia in RA patients with respiratory comorbidities.

Acknowledgments

We thank Kosuke Okuma, Mina Gochi, Eriko Kawate, Hideaki Yamakawa, Yoichi Kobayashi, Chie Ota, Keitaro Nakamoto, Kazuyoshi Kurashima, Tsutomu Yanagisawa, and Yutaka Sugita of the Department of Respiratory Medicine, Saitama Cardiovascular and Respiratory Center. We also thank Hideyo Oda of Medical Tokei Co., Ltd. for his valuable advice on statistical analysis.

Author Contributions

Conceptualization: Aya Wakabayashi, Takashi Ishiguro, Noboru Takayanagi.

Data curation: Aya Wakabayashi, Takashi Ishiguro, Yotaro Takaku, Yosuke Miyahara, Naho Kagiya, Noboru Takayanagi.

Formal analysis: Aya Wakabayashi.

Investigation: Aya Wakabayashi, Takashi Ishiguro, Yotaro Takaku, Yosuke Miyahara, Naho Kagiya, Noboru Takayanagi.

Methodology: Aya Wakabayashi, Takashi Ishiguro, Noboru Takayanagi.

Project administration: Aya Wakabayashi, Takashi Ishiguro, Noboru Takayanagi.

Supervision: Aya Wakabayashi, Takashi Ishiguro, Noboru Takayanagi.

Validation: Aya Wakabayashi, Takashi Ishiguro, Noboru Takayanagi.

Visualization: Aya Wakabayashi, Takashi Ishiguro, Noboru Takayanagi.

Writing – original draft: Aya Wakabayashi, Takashi Ishiguro, Noboru Takayanagi.

Writing – review & editing: Aya Wakabayashi, Takashi Ishiguro, Yotaro Takaku, Yosuke Miyahara, Naho Kagiya, Noboru Takayanagi.

References

1. Young A, Koduri G, Batley M, Kulinskaya E, Gough A, Norton S, et al. Mortality in rheumatoid arthritis. Increased in the early course of disease, in ischemic heart disease and in pulmonary fibrosis. *Rheumatology (Oxford)*. 2007; 46(2):350–7.
2. Nakajima A, Inoue E, Tanaka E, Singh G, Sato E, Hoshi D, et al. Mortality and cause of death in Japanese patients with rheumatoid arthritis based on a large observational cohort, IORRA. *Scand J Rheumatol*. 2010; 39(5):360–7. <https://doi.org/10.3109/03009741003604542> PMID: 20476859
3. Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Frequency of infection in patients with rheumatoid arthritis compared with controls: A population-based study. *Arthritis Rheum*. 2002; 46(9):2287–93. <https://doi.org/10.1002/art.10524> PMID: 12355475
4. Wolfe F, Mitchell DM, Sibley JT, Fries JF, Bloch DA, Williams CA, et al. The mortality of rheumatoid arthritis. *Arthritis Rheum*. 1994; 37(4):481–94. PMID: 8147925
5. Widdifield J, Bernatsky S, Paterson JM, Gunraj N, Thorne JC, Pope J, et al. Serious infections in a population-based cohort of 86,039 seniors with rheumatoid arthritis. *Arthritis Care Res (Hoboken)*. 2013; 65(3):353–61.

6. Hakoda M, Oiwa H, Kasagi F, Masunari N, Yamada M, Suzuki G, et al. Mortality of rheumatoid arthritis in Japan: a longitudinal cohort study. *Ann Rheum Dis*. 2005; 64(10):1451–5. <https://doi.org/10.1136/ard.2004.033761> PMID: 15878908
7. Vinogradova Y, Hippisley-Cox J, Coupland C. Identification of new risk factors for pneumonia: population-based case-control study. *Br J Gen Pract*. 2009; 59(567):e329–38. <https://doi.org/10.3399/bjgp09X472629> PMID: 19843413
8. Luque Ramos A, Hoffman F, Callhoff J, Zink A, Albrecht K. Influenza and pneumococcal vaccination in patients with rheumatoid arthritis in comparison with age- and sex-matched controls: results of a claims data analysis. *Rheumatol Int*. 2016; 36(9):1255–63. <https://doi.org/10.1007/s00296-016-3516-1> PMID: 27372078
9. Blumentals WA, Arreglado A, Napalkov P, Toovey S. Rheumatoid arthritis and the incidence of influenza and influenza-related complications: a retrospective cohort study. *BMC Musculoskelet Disord*. 2012; 13:158. <https://doi.org/10.1186/1471-2474-13-158> PMID: 22925480
10. Ishiguro T, Takayanagi N, Yamaguchi S, Yamakawa H, Nakamoto K, Takaku Y, et al. Etiology and factors contributing to the severity and mortality of community acquired pneumonia. *Intern Med*. 2013; 52(3):317–24. PMID: 23370738
11. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum*. 1988; 31(3):315–24. PMID: 3358796
12. American Thoracic Society; Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med*. 2005; 171(4):388–416. <https://doi.org/10.1164/rccm.200405-644ST> PMID: 15699079
13. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, et al. Infectious Disease Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis*. 2007; 44 Suppl 2:S27–72.
14. Baum J. Infection in rheumatoid arthritis. *Arthritis Rheum* 1971; 14(1):135–7. PMID: 5542366
15. Brown KK. Rheumatoid lung disease. *Proc Am Thorac Soc*. 2007; 4(5):443–8. <https://doi.org/10.1513/pats.200703-045MS> PMID: 17684286
16. Koetz K, Bryl E, Spickschen K, O'Fallon WM, Goronzy JJ, Weyand CM. T cell homeostasis in patients with rheumatoid arthritis. *Proc Natl Acad Sci USA*. 2000; 97(16):9203–8. PMID: 10922071
17. Yousem SA, Colby TV, Carrington CB. Lung biopsy in rheumatoid arthritis. *Am Rev Respir Dis*. 1985; 131(5):770–7. PMID: 3873887
18. Wolfe F, Caplan L, Michaud K. Treatment for rheumatoid arthritis and the risk of hospitalization for pneumonia: associations with prednisone, disease-modifying antirheumatic drugs, and anti-tumor necrosis factor therapy. *Arthritis Rheum*. 2006; 54(2):628–34. <https://doi.org/10.1002/art.21568> PMID: 16447241
19. Tsuchiya Y, Takayanagi N, Sugiura H, Miyahara Y, Tokunaga D, Kawabata Y, et al. Lung diseases directly associated with rheumatoid arthritis and their relationship to outcome. *Eur Respir J*. 2011; 37(6):1411–7. <https://doi.org/10.1183/09031936.00019210> PMID: 20884744
20. Yelin E, Trupin L, Wong B, Rush S. The impact of function status and change in functional status on mortality over 18 years among persons with rheumatoid arthritis. *J Rheumatol*. 2002; 29(9):1851–7. PMID: 12233878
21. Randovits BJ, Fransen J, Al Shamma S, Eijbsbouts AM, van Riel PL, Laan RF. Excess mortality emerges after 10 years in an inception cohort of early rheumatoid arthritis. *Arthritis Care Res (Hoboken)*. 2010; 62(3):362–70.
22. Ishiguro T, Kagiya N, Uozumi R, Odashima K, Kurashima K, Morita S, et al. Risk factors for the severity and mortality of pneumococcal pneumonia: Importance of premorbid patients' performance status. *J Infect Chemother*. 2016; 22(10):685–91. <https://doi.org/10.1016/j.jiac.2016.07.008> PMID: 27593263