

# Prognostic factors of severe pneumonia in patients treated with rituximab in the intensive care unit

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## Abstract

**Objective:** The aim of this study was to describe the clinical characteristics and prognostic factors of patients treated with rituximab (RTX) who developed severe pneumonia in the intensive care unit (ICU).

**Methods:** We systematically reviewed the medical records of 40 patients who received RTX and developed severe pneumonia in the ICU at our hospital from January 2009 to January 2019 to evaluate the underlying conditions, clinical course, and possible prognostic factors.

**Results:** Most patients had underlying hematologic malignancies ( $n = 21$ , 52.5%), followed by rheumatologic diseases ( $n = 17$ , 42.5%). The most frequent causative pathogens were fungi ( $n = 11$ , 27.5%), followed by bacteria ( $n = 9$ , 22.5%) and *Pneumocystis jirovecii* pneumonia ( $n = 8$ , 20%). Thirty patients (75%) died, and the other 10 patients (25%) survived. Compared with survivors, patients who died were significantly older ( $60.6 \pm 10.6$  vs  $44.4 \pm 18.3$  years) and had chronic lung disease (40% vs 0%).

**Conclusion:** Older age and chronic lung disease were significantly associated with mortality in patients treated with RTX.

## Keywords

Severe pneumonia, rituximab, prognostic factor, underlying condition, mechanical ventilation, intensive care unit

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## Introduction

Rituximab (RTX) is a chimeric mouse/human monoclonal antibody against CD20, an antigen primarily expressed on the surface of B cells of the immune system. It has been widely used for hematologic malignancies, rheumatic diseases, and glomerular diseases.<sup>1,2</sup> RTX causes prolonged hypogammaglobulinemia and failed naive B lymphocyte differentiation into plasma cells.<sup>3</sup> In addition, RTX modulates the T cell compartment.<sup>4,5</sup>

The occurrence of infectious events after RTX therapy has been observed in patients with hematological disorders and autoimmune diseases. These include life-threatening infections and opportunistic diseases, such as *Pneumocystis jirovecii* pneumonia (PCP).<sup>6,7</sup> Lung infection is frequently observed in patients treated with RTX, and acute respiratory failure is a leading cause of intensive care unit (ICU) admission, which is associated with decreased survival.<sup>8,9</sup> However, the prognostic factors for lung infection in patients treated with RTX in the ICU setting have not been well described. To determine the prognostic factors for these patients in the ICU setting, we retrospectively collected data for a consecutive series of patients treated with RTX who required ICU admission from January 2009 to January 2019 in a single center.

## Patients and methods

### Patients

We conducted a retrospective cohort study in three ICUs, including a general ICU, a respiratory ICU, and an emergency ICU, at the First Affiliated Hospital of Wenzhou Medical University from January 2009 to January 2019. Patients with serious pneumonia being treated with RTX were included. All patients were diagnosed according

to the American Thoracic Society criteria for serious pneumonia published in 2007.<sup>10</sup> Patients with any evidence of human immunodeficiency virus (HIV) infection and those who were younger than 18 years of age or pregnant were excluded.

This study was performed after approval from the Wenzhou Medical University Research Ethics Committee (approval number: 2020139) and with the written informed consent of all patients. The reporting of this study conformed to STROBE guidelines.<sup>11</sup>

### Data collection

The following information was collected: demographic and medical data, including age and sex; pulmonary manifestations, including fever, cough, sputum, dyspnea, arterial partial pressure of oxygen, chest computed tomography findings; microbiological findings; underlying diseases, including hematologic, rheumatologic, and glomerular diseases; the number of RTX cycles and dates of administration relevant to the onset of infection; concomitant use of immunosuppressive drugs, particularly glucocorticoids and cytotoxic agents; comorbidities, including chronic pulmonary disease, diabetes, and heart disease; laboratory data, including serum creatinine, serum albumin, serum hemoglobin, white blood cells, leukomonocytes, and globulin and CD4+, CD8+, and CD19+ cell counts; treatments; and patient outcomes. An unfavorable outcome was defined as death associated with the hospitalizations during which pneumonia was diagnosed and treated; survival was recognized as a favorable outcome.

### Statistical analysis

Data were analyzed using IBM SPSS Statistics for Windows, Version 22

(IBM Corp., Armonk, NY, USA) and presented as the mean  $\pm$  SD, median (range), or n (%). The chi-square or Student's t-test was used to compare differences between patients with favorable and unfavorable outcomes, depending on which was appropriate. A two-tailed P value  $<0.05$  was considered statistically significant.

## Results

Over the study period, a total of 40 patients treated with RTX who developed severe pneumonia in the ICU were analyzed. As shown in Table 1, the mean age at presentation was  $56.5 \pm 13.2$  years, and the ratio of women to men was 18:22. Most patients had underlying hematologic malignancies (52.5%), followed by rheumatologic diseases (42.5%) and glomerular disease (n=2, 5%). The most frequent causative pathogens were fungi (27.5%), followed by bacteria (22.5%) and PCP (20%). The most common clinical manifestation was dyspnea (87.5%), followed by fever (85%) and cough (67.5%). All patients required mechanical ventilation. Overall, 30 patients (75%) died, and the other 10 patients survived.

RTX was generally provided at a dosage of  $375 \text{ mg/m}^2$  at 1- to 2-week intervals, either alone or in combination with other agents. The median number of RTX cycles prior to the development of severe pneumonia was four, and the median cumulative dose was 2600 mg. The mean interval from the first administration of RTX to the development of severe pneumonia was  $3.0 \pm 1.3$  months. In most cases, RTX was used in conjunction with other chemotherapeutic or immunosuppressive drugs, and 36 patients (90%) had received glucocorticoids. Ten patients received trimethoprim-sulfamethoxazole prophylaxis (0.5 tablet/day, at the same time or 1 to 2 months after prednisone usage).

**Table 1.** Characteristics of all patients treated with rituximab in the ICU (n = 40).

Variables	Patients
Men (n, %)	22 (55)
Age (years)	$56.5 \pm 13.2$
Underlying diseases (n, %)	
Hematologic malignancy	21 (52.5)
Rheumatologic diseases	17 (42.5)
Glomerular diseases	2 (5)
Microbiological findings (n, %)	
Bacteria	9 (22.5)
Fungi	11 (27.5)
Virus	5 (12.5)
PCP	8 (20)
Symptom (n, %)	
Dyspnea	35 (87.5)
Fever	34 (85)
Cough	27 (67.5)
Sputum	17 (42.5)
PaO <sub>2</sub> on ICU admission	$47.5 \pm 10.7$
PaCO <sub>2</sub> on ICU admission	$34.8 \pm 13.1$
Comorbidities (n, %)	
Chronic lung disease	12 (30)
Diabetes	9 (22.5)
Heart disease	6 (15)
WBC count (cell/mm <sup>3</sup> )	$8275 \pm 5500$
Hemoglobin (g/L)	$92.2 \pm 21.3$
Albumin (g/L)	$33.2 \pm 16.8$
CRP (mg/L)	$81.3 \pm 34.1$
Globulin (g/L)	$20.9 \pm 4.9$
CD4+ cell count (cells/mm <sup>3</sup> )	$155.6 \pm 115.4$
CD19+ cell count (cells/mm <sup>3</sup> )	11.1 (0–128)
Serum creatinine ( $\mu\text{mol/L}$ )	$94.3 \pm 47.2$
Cumulative rituximab (g)	$2.6 \pm 0.6$
Interval between onset and first rituximab (months)	$3.0 \pm 1.3$
Prednisone usage (n, %)	36 (90)
Chemotherapy drugs <sup>a</sup>	22 (55)
Other immunosuppressive therapy <sup>b</sup>	14 (35)
Mechanical ventilation (n, %)	40 (100)
Died (n, %)	10 (25)

Data are shown as the mean  $\pm$  SD, median (range), or n (%).

<sup>a</sup>Including hydroxydaunorubicin, oncovin, adriamycin, bleomycin, and vincristine.

<sup>b</sup>Including mycophenolate mofetil, cyclosporin A, tacrolimus, azathioprine, and methotrexate.

ICU, intensive care unit; PCP, pneumocystis pneumonia; PaO<sub>2</sub>, arterial partial pressure of oxygen; PaCO<sub>2</sub>, arterial partial pressure of carbon dioxide; WBC, white blood cells; CRP, C-reactive protein.

As shown in Table 2, compared with survivors, patients who died were significantly older ( $60.6 \pm 10.6$  vs  $44.4 \pm 18.3$  years,  $P < 0.001$ ) and had chronic lung disease (40% vs 0%,  $P = 0.019$ ). However, there were no significant differences in underlying diseases, microbiological findings, cumulative RTX doses, prednisone usage, chemotherapy drugs, albumin, globulin, and serum creatinine levels.

Additionally, there were no significant differences in respiratory support between the survivors and non-survivors treated with RTX (Table 3).

## Discussion

In this observational study, we retrospectively analyzed the clinical characteristics and possible prognostic factors of patients

**Table 2.** Possible prognostic factors of severe pneumonia in patients treated with rituximab in the ICU (n = 40).

Variables	Non-survivors (n = 30)	Survivors (n = 10)	P-value
Men (n, %)	17 (56.7)	5 (50)	0.731
Age (years)	$60.6 \pm 10.6$	$44.4 \pm 18.3$	$<0.001$
PaO <sub>2</sub> on ICU admission	$46.6 \pm 10.5$	$50.4 \pm 11.6$	0.324
PaCO <sub>2</sub> on ICU admission	$35.7 \pm 13.2$	$32.4 \pm 11.7$	0.254
Underlying diseases (n, %)			
Hematologic malignancy	17 (56.7)	4 (40)	0.473
Rheumatologic diseases	12 (40)	5 (50)	0.717
Glomerular diseases	1 (3.3)	1 (10)	0.442
Microbiological findings (n, %)			
Bacteria	6 (20)	3 (30)	0.665
Fungi	10 (33.3)	1 (10)	0.233
Virus	4 (13.3)	1 (10)	1.000
PCP	6 (20)	2 (20)	1.000
Comorbidities (n, %)			
Chronic lung disease	12 (40)	0 (0)	0.019
Diabetes	6 (20)	3 (30)	0.665
Heart disease	5 (16.7)	1 (10)	1.000
Cumulative rituximab (g)	$2.7 \pm 0.6$	$2.3 \pm 0.9$	0.213
Prednisone usage (n, %)	28 (93.3)	8 (80)	0.256
Chemotherapy drugs <sup>a</sup>	16 (53.3)	6 (60)	1.000
Other immunosuppressive therapy <sup>b</sup>	11 (36.7)	3 (30)	1.000
WBC count (cell/mm <sup>3</sup> )	$8800 \pm 6000$	$6700 \pm 4300$	0.123
Hemoglobin (g/L)	$91.2 \pm 23.4$	$95.3 \pm 19.6$	0.417
Albumin (g/L)	$32.4 \pm 16.5$	$35.7 \pm 18.6$	0.307
CRP (mg/L)	$79.3 \pm 33.5$	$87.6 \pm 38.4$	0.265
Globulin (g/L)	$20.4 \pm 4.8$	$22.6 \pm 5.1$	0.315
CD4+ cell count (cells/mm <sup>3</sup> )	$152.4 \pm 116.7$	$165.5 \pm 110.9$	0.611
CD19+ cell count (cells/mm <sup>3</sup> )	8.2 (0–38)	19.6 (0–128)	0.209
Serum creatinine (μmol/L)	$93.2 \pm 47.4$	$97.7 \pm 45.1$	0.721

Data are shown as the mean  $\pm$  SD, median (range), or n (%).

<sup>a</sup>Including hydroxydaunorubicin, oncovin, adriamycin, bleomycin, and vincristine.

<sup>b</sup>Including mycophenolate mofetil, cyclosporin A, tacrolimus, azathioprine, and methotrexate.

ICU, intensive care unit; PCP, pneumocystis pneumonia; PaO<sub>2</sub>, arterial partial pressure of oxygen; PaCO<sub>2</sub>, arterial partial pressure of carbon dioxide; WBC, white blood cells; CRP, C-reactive protein.

**Table 3.** Comparison of respiratory support between the survivors and non-survivors in all patients treated with rituximab (n = 40).

Variables	Non-survivors (n = 30)	Survivors (n = 10)	P-value
IPPV during ICU stay (n, %)	24 (80)	10 (100)	0.307
VT maximal (mL/kg)	7.3 ± 2.5	7.9 ± 3.1	0.214
PEEP maximal (cmH <sub>2</sub> O)	10.5 ± 4.5	11.4 ± 3.8	0.673
NPPV on ICU admission (n, %)	6 (20)	2 (20)	1.000
IPAP (cmH <sub>2</sub> O)	11.4 ± 3.9	13.5 ± 4.6	0.326
EPAP (cmH <sub>2</sub> O)	7.2 ± 3.1	7.9 ± 2.3	0.112
IPPV on ICU admission (n, %)	15 (50)	6 (60)	0.721
VT (mL/kg)	6.5 ± 2.2	6.9 ± 2.1	0.727
Pplat (cmH <sub>2</sub> O)	25.6 ± 4.7	24.7 ± 7.8	0.828
PEEP (cmH <sub>2</sub> O)	10.1 ± 4.2	11.1 ± 3.7	0.745
FiO <sub>2</sub>	0.67 ± 0.13	0.76 ± 0.15	0.653
Recruitment maneuvers (n, %)	9 (30)	3 (30)	1.000
NRM on ICU admission (n, %)	8 (26.7)	4 (40)	0.451

IPPV, invasive positive pressure ventilation; ICU, intensive care unit; VT, tidal volume of predicted body weight; PEEP, positive end-expiratory pressure; NPPV, noninvasive positive pressure ventilation; IPAP, inspiratory positive airway pressure; EPAP, expiratory positive airway pressure; Pplat, plateau pressure; FiO<sub>2</sub>, fraction of inspired oxygen; NRM, non-rebreathing mask.

treated with RTX who developed severe pneumonia in the ICU. The main findings were that the overall mortality of these episodes was 75% (30/40), and older age and lung disease (mainly interstitial pneumonia) were significantly associated with hospital mortality in patients with severe pneumonia who were admitted to ICU and treated with RTX.

RTX is a monoclonal antibody that targets the CD20 antigen on B lymphocytes, causing prolonged hypogammaglobulinemia and failed naive B lymphocyte differentiation into plasma cells, and the depletion of B lymphocytes may adversely alter the generation of T lymphocytes.<sup>12</sup> In our study, most patients had lower CD19+ cell counts, globulin, and CD4+ cell counts than normal. The mean interval from the first administration of RTX to the development of severe pneumonia was 3 months, similar to the peak of infection after immunosuppressive drugs.<sup>13,14</sup> Moreover, three patients received RTX as the single immunosuppressive agent. Together, these findings indicate that

RTX itself may be a primary cause of severe pneumonia, consistent with the results of previous studies.<sup>15,16</sup> Tudesq et al. analyzed the medical records of 101 patients treated with RTX and found that infectious events after treatment with RTX were extremely severe, especially in patients immunocompromised by several other drugs.<sup>15</sup> Isabel et al. reported that 30 patients developed PCP during treatment with RTX, indicating that PCP occurred in association with RTX.<sup>16</sup> However, there were no statistically significant differences in cumulative RTX between the survivors and non-survivors, which indicated that RTX did not increase hospital mortality in these patients.

The mortality rate of patients with severe pneumonia is extremely high because of its rapid development, long disease course, predisposition to respiratory failure, other organ involvement, and effects on the quality of life and prognosis of patients.<sup>17,18</sup> Pulmonary complications were reported to occur in 35 of 77 non-Hodgkin and Hodgkin lymphoma patients after

autologous bone marrow transplant, with an associated mortality of 26%.<sup>19</sup> Another study showed that the mortality rate for non-HIV PCP patients requiring ICU admission was 75.6%, and prognostic factors included age, white blood cell count, and pneumomediastinum.<sup>20</sup> The most interesting finding of our study was that older age and lung disease were associated with increased hospital mortality. Compared with younger populations, the elderly have impaired mucociliary clearance, more underlying comorbid diseases, and a waning immune system.<sup>21</sup> Pre-existing lung disease, especially interstitial lung disease, is common among patients with connective tissue disease and an important contributor to morbidity and mortality.<sup>22</sup> According to a review article, patients with rheumatoid arthritis-related interstitial lung disease are at high risk of serious infection and increased mortality due to the lung disease itself.<sup>23</sup>

This study had some limitations. First, the sample size of patients was small, and the study lacked a control group and sufficient samples to detect infection risk regarding the RTX dosing regimens. Second, there was heterogeneity among patients, although this may also improve the generalizability of our findings. Third, we lost some patients with severe pneumonia who were not admitted to ICU; most of these patients were refusing further treatment.

In conclusion, we investigated the clinical characteristics and possible prognostic factors of patients treated with RTX who developed severe pneumonia in the ICU. The overall mortality of these episodes was high, and older age and chronic lung disease were significantly associated with mortality in these patients.


#### Declaration of conflicting interest


The authors declare that there is no conflict of interest.

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