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*Original Article*

# Analysis of the influencing factors of the clinical effect of respiratory humidifier in treating AIDS complicated with severe Pneumocystis jiroveci pneumonia

Qi Cao[1*], Wei Zeng[2*], Jingmin Nie[1], Yongjun Ye[3], Yanchao Chen[4]

*[1]First Department of Infectious Diseases, Departments of [2]Emergency, [3]General Surgery, [4]General Internal Medicine, Chongqing Public Health Medical Center, Chongqing 400033, China. [*]Equal contributors and co-first authors.*

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**Abstract:** Objective: To analyze the factors influencing the clinical effect of using respiratory humidifier in patients with AIDS complicated with severe Pneumocystis jiroveci pneumonia (PCP). Methods: According to the treatment results, AIDS patients with severe PCP were divided into two groups, successful group (n=68) and failure group (n=94), to compare the early ventilation changes between the two groups. Results: The ICU ratio of the successful group was lower than that of the failure group ($P$<0.05). The respiratory frequency, heart rate, $PaO_2$, C-reactive protein and SOFA score of the successful group were lower than those in the failure group ($P$<0.05), while $SpO_2$, $FiO_2$, $PaO_2/FiO_2$, $SpO_2/FiO_2$, Rox index and IL-10 levels were increased in the successful group ($P$<0.05). The successful group had higher IL-6 and IL-1β level than that of the failure group. The levels of IL-8 were decreased ($P$<0.05). The success of respiratory humidifier was negatively correlated with the score of SOFA ($P$<0.05). Conclusion: The clinical effect of respiratory humidifier in the treatment of AIDS patients with severe PCP was related to $PaO_2/FiO_2$, $PaO_2$, ROX index, SOFA score, and IL-6 and IL-8 levels.

**Keywords:** AIDS, Pneumocystis jiroveci pneumonia, respiratory humidifier, clinical

## Introduction

AIDS is a highly dangerous infectious disease caused by HIV infection which attacks the human immune system. CD4 T lymphocytes in the human immune system are the main attacking target. Therefore, the human body is easy to be infected with various diseases and attacked by malignant tumors, with high mortality. Pneumocystis jiroveci pneumonia (PCP) is one of the most common AIDS complications [1]. The incidence of PCP in AIDS patients is gradually increasing. The mortality rate of PCP varies from 10% to 30%, and it may be even higher with delayed diagnosis [2, 3]. Invasive mechanical ventilation is the main predictor of death in AIDS patients with severe PCP. Non-invasive ventilation can provide auxiliary ventilation under the condition of non-invasive artificial airway [4]. The initial method of respiratory support for AIDS complicated with severe PCP is based on the standard lung protection strategy of invasive mechanical ventilation. Because of lung injury, it may be harmful to some patients [5]. The breathing humidifier is an active humidifier. It provides fully heated and humidified medical gas at a flow rate of up to 60 L/min, reducing breathing work and providing a constant proportion of oxygen inhalation with sufficient humidification [6]. The purpose of this paper was to evaluate the influencing factors of clinical effect of respiratory hygrometer in AIDS patients with severe PCP.

## Materials and methods

### *General information*

We reviewed the clinical data of AIDS patients with severe PCP who were admitted into ICU in our hospital from January 2017 to December 2020. According to the treatment results, the patients were divided into the successful treatment group (n=68) and the failure group (n=94).

*Diagnostic criteria:* Progressive dyspnea, fever and unproductive cough occurred within sever-

al days to several weeks; Infiltration of diffuse "ground glass" space from hilum in chest X-ray film; $O_2$ gradient of alveoli-artery (A-a) $DO_2$ ≥35 μmmHg, or oxygen in indoor air $PO_2$ <70 μmmHg; The diagnosis of PCP was confirmed by identifying pneumocystis cysts/trophozoites or by detecting pneumocystis DNA with polymerase chain reaction.

*Inclusion criteria:* Patients ≥18 years old; Patients diagnosed with AIDS infection; Patients diagnosed with severe PCP without receiving any antiretroviral treatment.

*Exclusion criteria:* Patients with allergy or intolerance to any prescription drugs; Patients with Hb <60 g/L; Patients suffering from severe heart disease or encephalopathy; Patients suffering from severe mental illness.

*Medical ethics:* The approval number of Ethics Committee is 2020-1001.

*Methods*

*Data collection:* Vital signs and arterial blood gas levels were determined at baseline (before the application of respiratory hygrometer) and 6 hours later to compare the early ventilation changes between the success and failure groups of respiratory hygrometer. Record of respiratory hygrometer at least every 3 hours or 6 hours after the start of the hygrometer [7]. For patients intubated before 6 h, the variables that determine the failure of respiratory hygrometer were recorded. Arterial blood gas analysis was performed during the treatment of respiratory hygrometer (until the first 24 hours of using the instrument).

*Treatment:* The respiratory hygrometer (Model: TY-9700 digital temperature and humidity meter; Manufacturer: Yancheng Fangyuan Environmental Protection Technology Co., Ltd) was applied with the use of Hamilton C1 ventilator (Hamilton Medical AG, BunADuz, Switzerland) at a speed of 50-60 L/min, and $FiO_2$ was 0.8-1.0. All subjects received routine treatment of PCP. The combination of TMP-SMZ (trimethoprim-sulfamethoxazole, trimethoxydim) and prednisone was the first choice. If the preferred regimen was intolerable, an alternative regimen would be used. Secondary prevention was started immediately after successful treatment. According to local guidelines, TDF (300 μg/d) +3 TC (300 μmg/d) 3+ EFV (600 μmg/d) is the first choice for antiretroviral therapy, and other therapeutic schemes are optional. After the treatment, the peripheral blood of the two groups was collected, and the expression levels of IL-8, IL-1β, and IL-6 were detected by ELISA.

*Data collection and quality assurance:* In order to ensure the high quality of the test, the members of the Quality Management Committee carefully trained all the researchers involved in the test according to the standard operating procedures before the start of the test. The medical personnel properly consulted each patient before treatment.

*Statistical processing:* All the data in this study were processed by SPSS20.0 statistical analysis software (IBM). The measurement data were expressed by mean ± standard deviation ($\bar{x}$±sd). Independent sample t-test was used for inter-group comparison. The counting data were expressed as percentage (%), and the comparison between groups was conducted using $\chi^2$ test. The diagnostic value of rox-6 in the treatment with respiratory humidifier was analyzed by ROC curve. $P$<0.05 indicated statistically significant difference.

## Results

*General data of AIDS patients with severe pneumocystis yersinia pneumonia in two groups*

A total of 162 AIDS patients with severe pneumocystis Yersinia pneumonia were enrolled in this study. According to the treatment results, they were divided into the successful treatment group and the failure group. There was no statistical difference in age, gender, BMI, underlying disease, $PaO_2$, $PaO_2/FiO_2$, mean arterial pressure and SOFA score between the two groups (P>0.05; **Table 1**).

*Comparison of treatment time and ICU proportion between the two groups*

The average treatment time, which refers to the date from the patient's treatment after admission to the end of the intervention, in the successful treatment group was 6.88±2.43 days, and 33 cases (48.53%) were in ICU. In the failure group, the average treatment time was 2.54±1.16 days, and the proportion of ICU admission was 94 cases (100.00%). The proportion of ICU in the success group was lower than that in the failure group, and the average

**Table 1.** General data statistics of patients in the two groups

| Project | Successful treatment group with respiratory hygrometer | Treatment failure group with respiratory hygrometer | $t/\chi^2$ | P |
|---|---|---|---|---|
| n | 68 | 94 | 12.635 | 0.526 |
| Age (years) | 59.8±8.3 | 59.2±7.8 | 11.328 | 0.231 |
| Gender (male:female) | 33:35 | 45:49 | 14.234 | 0.451 |
| BMI ($kg/m^2$) | 22.18±2.45 | 22.26±1.58 | 10.237 | 0.629 |
| Underlying diseases | 42 (61.76%) | 62 (65.96%) | 8.264 | 0.227 |
| $PaO_2$ (mmHg) | 64.22±3.41 | 63.45±4.87 | 16.597 | 0.631 |
| $PaO_2/FiO_2$ | 263.85±22.17 | 237.43±29.56 | 9.658 | 0.134 |
| Mean arterial pressure (mmHg) | 82.35±7.64 | 79.54±6.26 | 8.527 | 0.268 |
| SOFA score | 3.55±0.65 | 4.13±0.59 | 9.512 | 0.196 |

Note: SOFA: sequential organ failure assessment.

**Table 2.** Comparison of treatment time and ICU proportion between the two groups

| group | n | Treatment time (days) | Proportion of ICU |
|---|---|---|---|
| Successful treatment group with respiratory hygrometer | 68 | 6.88±2.43 | 33 (48.53%) |
| Treatment failure group of respiratory hygrometer | 94 | 2.54±1.16 | 94 (100.00%) |
| $\chi^2$ | - | 8.325 | 15.326 |
| P | - | 0.016 | 0.003 |

**Table 3.** Statistics of 6 h indexes in the two groups

| Group | Successful treatment group with respiratory hygrometer | Treatment failure group with respiratory hygrometer | t | P |
|---|---|---|---|---|
| Respiratory rate (breathing/min) | 35.26±1.34 | 42.75±1.11 | 13.264 | 0.015 |
| Heart rate (beats/min) | 93.89±3.55 | 115.95±5.64 | 11.258 | 0.022 |
| $PaO_2$ (mmHg) | 222.16±13.28 | 337.89±12.56 | 9.654 | 0.024 |
| $SpO_2$ (%) | 93.56±1.23 | 87.89±1.12 | 6.327 | 0.013 |
| $FiO_2$ (%) | 92.87±0.54 | 86.65±0.52 | 8.524 | 0.006 |
| $PaO_2/FiO_2$ | 214.33±11.13 | 189.88±11.16 | 11.540 | 0.011 |
| $SpO_2/FiO_2$ | 105.53±6.56 | 95.35±1.87 | 10.597 | 0.017 |
| Rox index | 3.34±0.53 | 2.28±0.26 | 8.109 | 0.024 |
| CRP (mg/L) | 168.87±12.38 | 249.83±1.53 | 7.032 | 0.013 |
| SOFA score | 2.35±0.33 | 8.62±0.45 | 1.267 | 0.008 |

Note: SOFA: sequential organ failure assessment; $SpO_2$: oxygen saturation; CRP: C-reactive protein.

treatment time was increased (P<0.05; **Table 2**).

*The respiratory rate, heart rate, $PaO_2$, $SpO_2$, $FiO_2$, $PaO_2/FiO_2$, $SpO_2/FiO_2$, Rox index and C-reactive protein SOFA score at 6 h were compared between the two groups.*

After the intervention, the respiratory rate, heart rate, $PaO_2$, C-reactive protein (CRP) and SOFA scores in the successful treatment group were lower than those in the failure group (P<0.05). $SpO_2$, $FIO_2$, $PaO_2/FIO_2$, $SpO_2/FIO_2$ and ROX index were increased (P<0.05; **Table 3**).

*Comparison of inflammatory cytokines between the two groups*

The levels of IL-8, IL-1β and IL-6 in the successful treatment group were lower than those in the failure group (P<0.05), while the level of IL-10 was higher (P<0.05; **Table 4**).

*The successful treatment of respiratory humidifier was negatively correlated with SOFA score*

There was a negative correlation between the success of respiratory humidifier and SOFA score, and the failure of respiratory humidifier

**Table 4.** Comparison of inflammatory cytokines between the two groups

| Project | Successful treatment group with respiratory hygrometer | Treatment failure group with respiratory hygrometer | t | P |
|---|---|---|---|---|
| IL-6 (pg/mL) | 1.45±0.22 | 5.52±0.16 | 13.265 | 0.012 |
| IL-1β (pg/mL) | 1.32±0.13 | 5.37±0.56 | 11.152 | 0.011 |
| IL-8 (pg/mL) | 2.58±0.46 | 8.93±0.47 | 10.328 | 0.006 |
| IL-10 (pg/mL) | 8.55±0.16 | 2.15±0.13 | 6.524 | 0.024 |

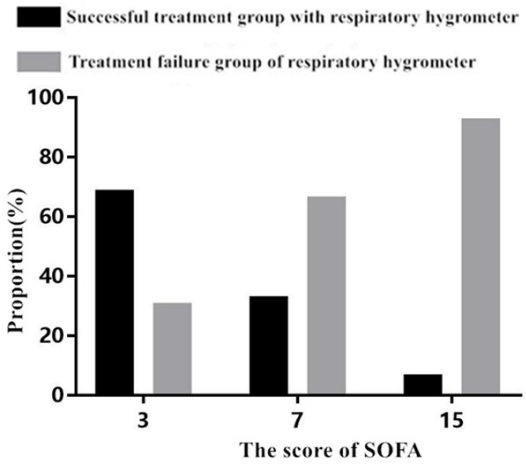


**Figure 1.** Negative correlation between successful treatment of respiratory humidifier and SOFA score. The horizontal axis is the mean value. SOFA: sequential organ failure assessment.

was positively correlated with SOFA score ($P<0.05$; **Figure 1** and **Table 5**).

*Diagnostic performance of ROX-6 in the treatment of respiratory humidifier*

The area under ROC curve (AUC) of ROX-6 for predicting the clinical effect of respiratory hygrometer treatment was 0.75. The sensitivity of ROX-6 below 3.7 (critical value A, maximizing sensitivity) was 95.15% (true positive), and the specificity of ROX-6 above 2.2 (critical value B, maximizing specificity) was 93.46% (true negative). The maximum threshold was 2.7. The positive predictive value and negative predictive value of Yoden index were 75.29% and 76.83%, respectively (**Figure 2** and **Table 6**).

*Multivariate analysis of influencing factors of clinical effect of respiratory hygrometer treatment*

Multivariate analysis showed that there was no significant difference between the clinical effect of respiratory humidifier and patient's age, gender and BMI. The clinical effect of respiratory humidifier was significantly correlated with $PaO_2/FiO_2$, $PaO_2$, ROX index, SOFA score, IL-6 and IL-8 (**Table 7**).

## Discussion

The use of respiratory humidifier has increased, and a large number of data support the value of respiratory humidifier in the treatment of hypoxic acute respiratory failure [8]. PCP can affect patients with low immune function, such as those with AIDS infection, solid organ transplantation and malignant tumor [9]. Our research shows that respiratory humidifier can successfully provide respiratory support for AIDS patients with severe PCP. These poor ventilation outcomes can be due to the low socioeconomic status of the patients, multiple complications and high infection rate of AIDS virus, but it also increases the possibility that some patients insist on using the respiratory humidifier, which may delay the need for intubation and in turn affect the clinical results. This further highlights the need to distinguish as early as possible between patients who may benefit from the breath humidifier and those who need mechanical ventilation.

The results of this study showed that higher mortality was observed in patients with failure of the humidifier, and the increased SOFA score was positively correlated with the failure of the humidifier. In addition, the mean $PaO_2/FiO_2$ ratio decreased and $PaO_2$ increased within 3-6 h after the respiratory humidifier was triggered. The higher ROX index measured at 6 h can independently predict the success of respiratory humidifier treatment.

Previous studies have reported that early noninvasive ventilation has a significant survival benefit in patients with cancer or postoperative solid organ transplantation [10]. The respiratory humidifier has been shown to be beneficial to unselected patients with hypoxic acute respira-

**Table 5.** Negative correlation between the success of respiratory humidifier and SOFA score

| SOFA score | Score ≤3 | 3< score <7 | Score ≥7 |
|---|---|---|---|
| n | 71 | 48 | 43 |
| Success rate of respiratory humidifier | 49 (69.01%) | 16 (33.33%) | 3 (6.98%) |
| Failure rate of respiratory humidifier | 22 (30.99%) | 32 (66.67%) | 40 (93.02%) |
| $\chi^2$ | 6.231 | 15.328 | 13.264 |
| P | 0.024 | 0.015 | 0.012 |

Note: SOFA: sequential organ failure assessment.

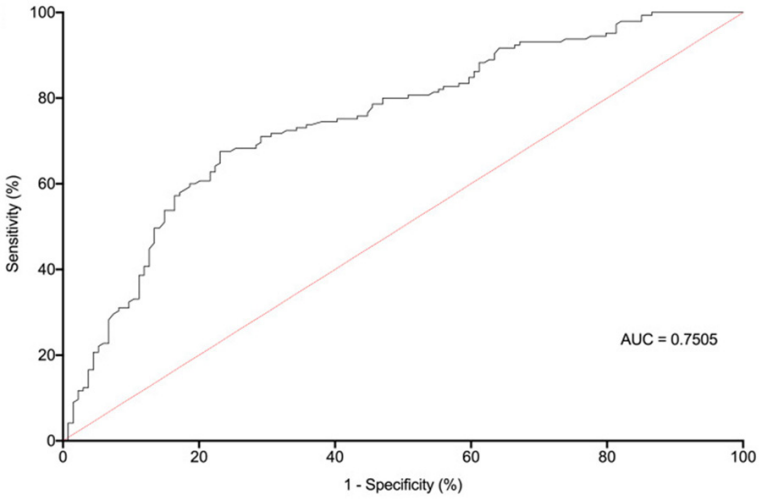


**Figure 2.** ROC curve of ROX-6 predicting the clinical effect of respiratory hygrometer treatment. ROC: receiver operating characteristic.

**Table 6.** Diagnostic performance of ROX-6 on clinical effect of respiratory hygrometer

| Cut-point | Sensibility | Specificity | Positive predictive value | Negative predictive value |
|---|---|---|---|---|
| 3.7 | 95.15% | 39.56% | 58.29% | 82.34% |
| 2.7 | 73.58% | 76.53% | 75.29% | 76.83% |
| 2.2 | 42.15% | 93.46% | 78.96% | 62.17% |

**Table 7.** Multivariate analysis of factors influencing clinical effect of respiratory humidifier

| Project | OR (95% CI) | P |
|---|---|---|
| Age | 1.11 (0.95-1.24) | 0.228 |
| Gender | 1.25 (0.96-1.37) | 0.137 |
| BMI | 1.03 (0.89-1.13) | 0.165 |
| $PaO_2/FiO_2$ | 1.12 (0.95-1.26) | 0.024 |
| $PaO_2$ | 1.33 (1.16-1.48) | 0.013 |
| ROX index | 1.21 (1.06-1.45) | 0.015 |
| SOFA score | 1.08 (0.95-1.24) | 0.014 |
| IL-6 | 1.33 (1.12-1.56) | 0.006 |
| IL-8 | 1.08 (0.96-1.15) | 0.005 |

Note: SOFA: sequential organ failure assessment.

tory failure [11]. Therefore, several studies have evaluated the prognosis of immunocompromised patients with acute respiratory failure treated with respiratory humidifier [12]. These results may be due to the improved survival rate in ICU immunocompromised patients over the past 20 years, even among patients receiving invasive mechanical ventilation [13]. Delayed intubation after failure of noninvasive ventilation or failure of a humidifier was associated with higher mortality [14]. The total mortality rate of AIDS patients with severe PCP receiving respiratory humidifier was 36% [15].

Although there are other causes affecting the outcome of AIDS patients with severe PCP, the evidence of the efficacy of respiratory humidifier in reducing intubation demand is consistent with previous studies. Controlled trials of acute HRF found that respiratory humidifier resulted in lower intubation rate [16, 17]. It is found that the performance of ROX is equivalent to that of mROX, so it is favored because it contains fewer input variables [18]. 191 patients with pneumonia (not associated with AIDS complicated with severe PCP) who received respiratory humidifier therapy were studied. It was found that 68 (35.6%) patients needed intubation [19].

The results of this study and those described in several studies are mutually consistent, suggesting that respiratory humidifier outcomes are early predictors in respiratory failure [19,

20]. Here, we focused on immunocompromised AIDS subjects with severe PCP complicated with acute respiratory failure. The ratio of respiratory rate, heart rate, $PaO_2$, C-reactive protein and SOFA score in the failure group of respiratory humidifier were significantly higher than those in the success group. In addition, the results of multivariate analysis showed that $PaO_2/FiO_2$, $PaO_2$, ROX index, SOFA score, IL-6 and IL-8 were the variables associated with failure of respiratory humidifier treatment.

Because of its retrospective nature, there was no standard to start respiratory humidifier instead of conventional oxygen therapy or noninvasive ventilation. The failure group included subjects who were more suitable to start noninvasive ventilation, while the successful group may produce good results only with conventional oxygen therapy. In addition, it was not feasible to analyze the effect of the humidifier. The immunocompromised AIDS patients with severe PCP will benefit most from the treatment of respiratory humidifier, which provides further evidence and justification for further randomized controlled trial design. Secondly, our study only included immunocompromised AIDS patients with severe PCP. The results of respiratory humidifier may be different when other causes of infection are considered.

In conclusion, the clinical effect of respiratory humidification apparatus in the treatment of AIDS patients with severe PCP was related to $PaO_2/FIO_2$, $PaO_2$, Rox index, SOFA score, IL-6 and IL-8 levels. Further multicenter prospective studies are needed to confirm our findings.

## Disclosure of conflict of interest

None.

**Address correspondence to:** Yanchao Chen, Department of General Internal Medicine, Chongqing Public Health Medical Center, No. 109 Geleshan Baoyu Road, Shapingba District, Chongqing 400033, China. Tel: +86-023-65392991; Fax: +86-023-65392991; E-mail: 715611761@qq.com; Yongjun Ye, Department of General Surgery, Chongqing Public Health Medical Center, No. 109 Geleshan Baoyu Road, Shapingba District, Chongqing 400033, China. Tel: +86-023-65504182; E-mail: 115394311@qq.com

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