A-DROP and Blood Urea Nitrogen-to-Serum Albumin Ratio are Useful in Assessing the Severity of Pneumocystis Pneumonia in Patients Without Human Immunodeficiency Virus Infection: A Retrospective Study

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Abstract

Background: There is an increasing incidence of *Pneumocystis* pneumonia among individuals without the human immunodeficiency virus (HIV) infection (non-HIV *Pneumocystis* pneumonia). However, the prognostic factors for patients with non-HIV *Pneumocystis* pneumonia have not been identified. Moreover, A-DROP (for classifying the severity of community-acquired pneumonia) or the blood urea nitrogen-to-serum albumin ratio, which is reported to be predictor of mortality of community-acquired pneumonia, has not been established as an efficient prognostic factor in patients with non-HIV *Pneumocystis* pneumonia. In this study, we analyzed the prognostic factors for non-HIV *Pneumocystis* pneumonia and evaluated the effectiveness of A-DROP and the blood urea nitrogen-to-serum albumin ratio as prognostic factors.

Methods: This retrospective study involved a chart review of the medical records of 102 patients diagnosed with non-HIV *Pneumocystis* pneumonia between January 2003 and May 2019 at five medical facilities. Prognostic factors associated with the 30-day mortality were assessed using multiple logistic regression analysis.

Results: Among the 102 patients with non-HIV *Pneumocystis* pneumonia, 46 (45.1%) had autoimmune diseases, 19 (18.6%) had hematological malignancies, 18 (17.7%) had solid malignancies, and 19 (18.6%) had other diseases. The 30-day mortality rate for non-HIV *Pneumocystis* pneumonia was 20.5% in this study population. Compared with survivors, non-survivors had significantly lower serum albumin levels and a significantly higher age, corticosteroid dosage at the onset of *Pneumocystis* pneumonia, alveolar–arterial oxygen gradient, A-DROP score, lactate dehydrogenase levels, blood urea nitrogen levels, and blood urea nitrogen-to-serum albumin ratio. The results of multivariate analysis showed that a high A-DROP score and blood urea nitrogen-to-serum albumin ratio at treatment initiation were significantly associated with the 30-day mortality risk.

Conclusions: A high A-DROP score and blood urea nitrogen-to-serum albumin ratio at treatment initiation are independent prognostic predictors of mortality risk in patients with non-HIV *Pneumocystis* pneumonia.

Background

Pneumocystis pneumonia (PcP) is one of the most serious opportunistic infections associated with human immunodeficiency virus (HIV) infection. The introduction of PcP prophylaxis and highly active antiretroviral therapy has reduced the incidence and mortality rates of PcP in HIV-infected patients (HIV PcP) [1, 2]. In contrast, the incidence of PcP in patients without HIV infection (non-HIV PcP) but with malignancies, those who have undergone organ transplantation, and in those undergoing immunosuppressive therapy is increasing [2–4]. The mortality rate was 10–20% in patients with HIV PcP and 19.6–60% in patients with non-HIV PcP [5, 6]. The prognostic factors of non-HIV PcP have not yet been determined; however, several factors, such as high levels of alveolar-arterial oxygen gradient (A-

aDO₂), high lactate dehydrogenase (LDH) levels, high blood urea nitrogen (BUN) levels, low serum albumin (Alb) levels, and high pneumonia severity index (PSI), were reported to be associated with a poor prognosis of non-HIV PcP [7–10]. PSI is a scoring system proposed by the American Thoracic Society/Infectious Diseases Society of America for classifying patients with community-acquired pneumonia (CAP) [11]. Alternatively, A-DROP (age, dehydration, respiratory failure, orientation, systolic blood pressure) is a scoring system proposed by the Japanese Respiratory Society (JRS) [12] and used widely for classifying the severity of patients with CAP in Japan. High BUN and low serum Alb levels are considered as poor prognostic factors in patients with CAP [13–16]. In addition, a high BUN-to-serum Alb (BUN/Alb) ratio is reportedly a useful marker of mortality from CAP, hospital-acquired pneumonia (HAP), and aspiration pneumonia [17–19]. A previous report suggested that A-DROP may underestimate the severity of non-HIV PcP [20]. Therefore, A-DROP has not been established as a prognostic factor in patients with non-HIV PcP. The effectiveness of the BUN/Alb ratio also has not yet been evaluated in patients with non-HIV PcP. In this study, we aimed to identify the prognostic factors for patients with non-HIV PcP. We also evaluated the effectiveness of A-DROP and the BUN/Alb ratio, which are useful in patients with CAP, as predictors of prognosis in patients with non-HIV PcP.

Methods

Study design and population

A retrospective study was conducted in patients diagnosed with non-HIV PcP between January 2003 and May 2019 at five medical facilities (Shinshu University Hospital, Nagano Municipal Hospital, Minaminagano Medical Center Shinonoi General Hospital, Japanese Red Cross Society Nagano Hospital, and Japanese Red Cross Society Suwa Hospital) in Nagano Prefecture, Japan, on the basis of the data available in their medical records. According to data from previous studies [21], a diagnosis of non-HIV PcP was made in our study if the patients met the following 4 criteria: (i) immunosuppressive status; (ii) diffuse bilateral ground-glass opacity on chest radiography or computed tomography scans; (iii) detection of *Pneumocystis jirovecii* in respiratory specimens by direct staining or polymerase chain reaction assay; and (iv) elevated plasma (1→3)-β-D-glucan levels. The levels of plasma (1→3)-β-D-glucan were measured using a Wako β-glucan test (Wako Pure Chemical Industries, Osaka, Japan) or a Fungitec G test MK (Seikagaku Corporation, Tokyo, Japan). Infection with PcP was indicated if the plasma (1→3)-β-D-glucan level was over the upper limit of the normal range. The normal range of plasma (1→3)-β-D-glucan level is ≤ 11 pg/mL in the Wako β-glucan test and ≤ 20 pg/mL in the Fungitec G test MK. Immunosuppressive status was defined as reduced immune status and was seen in patients who suffered from malignancies (hematological or solid), in patients who were treated with immunosuppressive therapy, or in patients who had undergone an organ transplant and hematopoietic stem cell transplant.

Data collection

The following demographic and clinical data were collected from the medical records of the patients diagnosed with non-HIV PcP: age, gender, body mass index, underlying diseases, treatments for underlying diseases, corticosteroid dosage at the onset of PcP for underlying diseases, PcP prophylaxis, days from symptom appearance (onset of PcP) to treatment, physical findings at treatment initiation (percutaneous oxygen saturation (SpO₂), blood pressure, and status of consciousness), respiratory support (invasive positive-pressure ventilation [IPPV]), initial treatment for PcP, adjunctive corticosteroid therapy, A-DROP score, laboratory findings before treatment, and final outcome. Corticosteroid dosage was expressed as the equivalent dose of prednisolone. Respiratory failure was defined as partial pressure of arterial oxygen (PaO₂) ≤ 60 Torr or SpO₂ ≤ 90% in room air. A-DROP is a scoring system proposed by the JRS to assess the severity of CAP [12]. A-DROP was evaluated using the following parameters: (i) age (men ≥ 70 years, women ≥ 75 years); (ii) BUN ≥ 21 mg/dL or dehydration; (iii) respiratory failure; (iv) disturbance of consciousness; (v) hypotension (systolic blood pressure ≤ 90 mmHg). Each parameter corresponds to 1 point in the A-DROP score. An A-DROP score of 0 is considered mild; 1–2, moderate; 3, severe; and 4–5, extremely severe [12]. Consciousness status was assessed using the Glasgow Coma Scale (GCS), and disturbance of consciousness was defined as GCS ≤ 14. The endpoint of this study was all-cause mortality in the patients with non-HIV PcP within 30 days from treatment initiation.

Statistical analysis

Data are expressed as proportions for categorical variables and as median (range) for continuous variables. Categorical variables were compared using the chi-squared or Fisher's exact test, and continuous variables were compared using the Mann–Whitney test between the survivors and non-survivors. The independence of each variable was tested using Spearman's rank correlation coefficient. Prognostic factors in relation to 30-day mortality were assessed by multiple logistic regression analysis. The receiver-operating characteristic (ROC) curve was used for evaluating the ability of prognostic factors to estimate 30-day mortality. $P < 0.05$ was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics software, version 26 (IBM, Armonk, NY, USA).

Results

Baseline clinical characteristics of patients with non-HIV PcP

During the investigation period, 102 patients (55 men [53.9%] and 47 women [46.1%]) met the diagnostic criteria for non-HIV PcP, and the baseline clinical characteristics of the patients are shown in Table 1. The median age of the patients was 69.5 years (range 22–88 years). Forty-six patients (45.1%) had autoimmune diseases, 19 (18.6%) had hematological malignancies, 18 (17.7%) had solid malignancies, and 19 (18.6%) had other diseases. The autoimmune diseases seen in this patient population included rheumatoid arthritis, systemic lupus erythematosus, polymyositis/dermatomyositis, anti-neutrophil cytoplasmic antibody–associated vasculitis, spondyloarthritis, and Goodpasture's syndrome.

Rheumatoid arthritis was the most common autoimmune disease in the present study, seen in 29 of the 46 patients (63.0%) with autoimmune disease. In the entire cohort, regarding treatment modalities for the underlying diseases, 34 patients (33.3%) were treated with corticosteroids alone and 53 patients (53.0%) were treated with corticosteroids in combination with other drugs, such as immunosuppressants, biological agents, and antitumor drugs. Fifteen patients (14.7%) were treated with therapies other than corticosteroids. Corticosteroids were administered in 87 patients (85.3%) at the onset of PcP for the already existing diseases, and the median corticosteroid dosage (prednisolone equivalent) was 15 mg/day (range 2–400 mg/day). Two patients received PcP prophylaxis with trimethoprim/sulfamethoxazole (TMP/SMX).

Patient prognosis was evaluated with 30-day mortality, defined as the mortality at day 30 after initiation of the treatment. The 30-day mortality rate in non-HIV PcP was found to be 20.5% (21/102) in the present study.

Table 1
Clinical characteristics of patients with non-HIV PcP

Variables	n = 102
Age, years	69.5 (22–88)
Gender, male	55 (53.9)
Body mass index, kg/m ²	21.7 (12.6–37.7)
Underlying diseases	
Autoimmune diseases	46 (45.1)
Hematological malignancies	19 (18.6)
Solid malignancies	18 (17.7)
Others	19 (18.6)
Treatment for underlying diseases	
Corticosteroids alone	34 (33.3)
Corticosteroids + other treatments	53 (52.0)
Others (without corticosteroids)	15 (14.7)
Corticosteroid dosage for underlying diseases, mg/day (Prednisolone equivalent, range)	15 (2–400)
PcP prophylaxis	2 (1.9)
Days from onset of PcP to treatment initiation (range)	4.5 (1–36)
Outcome	
30-day mortality	21 (20.5)
Continuous variables are expressed as median (range) and categorical variables are expressed as number (n) with percentage (%). Corticosteroid dosage was expressed as equivalent dose of prednisolone (n = 78). Abbreviations: PcP; <i>Pneumocystis pneumonia</i>	

Comparison of clinical data between survivors and non-survivors

In the 30 days following treatment initiation, 81 patients survived and 21 died. The comparison of clinical data between the survivors and non-survivors is shown in Table 2. Non-survivors were significantly older than survivors (75 years vs. 67 years, $p = 0.019$). The prevalence of underlying diseases did not

significantly differ between the survivors and non-survivors. However, the use of corticosteroids was more frequent in the non-survivors than in the survivors for treatment of their underlying diseases. The corticosteroid dosage administered for therapy of underlying diseases at the onset of PcP was significantly higher in the non-survivors than in the survivors (25 mg/day vs. 15 mg/day, $p = 0.001$). There were no significant differences in PcP prophylaxis between the survivors and non-survivors, and the most frequently used drug for prophylaxis was TMP-SMX, in both survivors and non-survivors. There was no significant difference in the interval of days from the onset of PcP to the treatment initiation between the non-survivors and survivors ($p = 0.162$). Respiratory failure was significantly more prevalent in the non-survivors than in the survivors (95.2% vs. 60.4%, $p = 0.002$) at treatment initiation.

Comparison of laboratory findings before treatment between survivors and non-survivors

The comparison of the laboratory findings before treatment showed that the non-survivors presented with significantly higher levels of A-aDO₂ (194.6 Torr vs. 64.3 Torr, $p = 0.001$), LDH (525 IU/L vs. 374 IU/L, $p = 0.001$), and BUN (31.5 mg/dL vs. 20.0 mg/dL, $p = 0.004$), as well as a higher BUN/Alb ratio (16.0 vs. 7.1, $p = 0.002$) than the survivors (Table 2). In addition, the non-survivors showed significantly lower PaO₂ to fraction of inspired oxygen (FiO₂) ratio (166.8 vs. 251.9, $p = 0.023$) and levels of total protein (TP) (5 g/dL vs. 5.6 g/dL, $p = 0.033$) and serum Alb (2.2 g/dL vs. 2.8 g/dL, $p = 0.002$) than the survivors (Table 2). There were no significant differences in C-reactive protein, KL-6, and plasma (1→3)-β-D-glucan levels between the survivors and non-survivors (Table 2).

Treatments

TMP-SMX was the most frequently used anti-PcP drug in the initial treatment regimen for both survivors and non-survivors. The administration of adjuvant corticosteroid therapy for the treatment of non-HIV PcP was significantly more frequent in the non-survivors than in the survivors (90.4% vs. 70.3%, $p = 0.016$) (Table 2). The requirement of IPPV was significantly higher among the non-survivors than the survivors (61.9% vs. 13.5%, $p < 0.001$, Table 2).

Table 2
Comparison of clinical data between survivors and non-survivors

Variables	Survivors (n = 81)	non-survivors (n = 21)	P Value
Age, years (range)	67 (22–88)	75 (56–86)	0.019
Gender, male	42 (51.8%)	13 (65%)	0.41
Body mass index, kg/m ² (range)	21.4 (12.6–35.0, n = 80)	22.3 (16.0–37.7)	0.621
Underlying diseases			
Autoimmune diseases	38 (46.9%)	8 (38%)	0.469
Hematological malignancies	14 (17.2%)	5 (23.8%)	0.344
Solid malignancies	15 (18.5%)	3 (14.2%)	0.464
Others	14 (17.2%)	5 (23.8%)	0.344
Treatment for underlying diseases			
Corticosteroids alone	24 (29.6%)	10 (47.6%)	0.119
Corticosteroids + other treatments	42 (51.8%)	11 (52.3%)	0.966
Others (without corticosteroids)	15 (18.6%)	0 (0.0%)	0.023
Corticosteroid dosage for underlying diseases, mg/day (Prednisolone equivalent, range)	15 (2–60, n = 59)	25 (8–400, n = 19)	0.001
PcP prophylaxis	1 (1.2%)	1 (5%)	0.371
Days from onset of PcP to treatment initiation (range)	6 (1–36)	4 (1–19)	0.162
Respiratory failure	49 (60.4%)	20 (95.2%)	0.002
Hypotension	8 (9.9%)	2 (9.5%)	0.631
Disturbance of consciousness	3 (3.7%)	6 (28.5%)	0.002
Initial Treatment for PcP			
TMP/SMX	78 (96.2%)	20 (95.2%)	0.608
Pentamidine	2 (2.4%)	1 (4.7%)	0.503
Atovaquone	1 (1.2%)		0.794
Adjunctive corticosteroid therapy	57 (70.3%)	19 (90.4%)	0.016

Variables	Survivors (n = 81)	non-survivors (n = 21)	P Value
Respiratory support with IPPV	11 (13.5%)	13 (61.9%)	< 0.001
A-DROP score (median)	1 (n = 79)	3 (n = 20)	< 0.001
A-DROP score			
0	11 (13.6%)	0 (0.0%)	
1	30 (37.0%)	1 (4.8%)	
2	19 (23.5%)	8 (38.1%)	
3	14 (17.3%)	8 (38.1%)	
4	5 (6.2%)	1 (4.8%)	
5	0 (0.0%)	2 (9.4%)	
unknown	2 (2.4%)	1 (4.8%)	
Laboratory findings before treatment for PcP			
PaO ₂ /FiO ₂ ratio	251.9 (60.1-447.1)	166.8 (64.5-405.2)	0.023
A-aDO ₂ , Torr	64.3 (17.7-548.5)	194.6 (19.1-530.6)	0.001
White blood cell, /μL	8000 (980-19600)	7540 (1850–22600)	0.918
Neutrophils, /μL	6869 (666-18780, n = 80)	6484.5 (1099–22000, n = 20)	0.803
Lymphocytes, /μL	655 (77-3010, n = 80)	634.5 (40-2530, n = 20)	0.823
Total protein, g/dL	5.6 (3.8–7.6, n = 75)	5 (3.6–7.7, n = 19)	0.033
Alb, g/dL	2.8 (1.4–4.1, n = 79)	2.2 (1.6–3.4)	0.002
LDH, IU/L	374 (137–902)	525 (269–1395)	0.001
Total bilirubin, mg/dL	0.56 (0.18–21.06, n = 80)	0.75 (0.1–4.5, n = 20)	0.148
BUN, mg/dL	20 (6-148.7)	31.5 (12–88)	0.004
Creatinine, mg/dL	0.88 (0.36–11.91)	0.83 (0.4-7)	0.685
CRP, mg/dL	7.4 (0.1–31.6)	7.74 (0.5–26.1)	0.901

Variables	Survivors (n = 81)	non-survivors (n = 21)	P Value
KL-6, U/mL	613 (32.1-11109, n = 56)	918.8 (324–3656, n = 15)	0.111
(1→3)-β-D-glucan, pg/mL	67.6 (11.6–912)	99.7 (12.07–9690)	0.983
BUN/Alb ratio	7.1 (1.6–49.5, n = 79)	16 (4.4–45.6)	0.002
Continuous variables are expressed as median (range) and categorical variables are expressed as number (n) with percentage (%). Corticosteroid dosage was expressed as equivalent dose of prednisolone. Abbreviations: PcP; <i>Pneumocystis pneumonia</i> , IPPV; invasive positive pressure ventilation, TMP/SMX; trimethoprim/sulfamethoxazole, PaO ₂ ; partial pressure of arterial oxygen, FiO ₂ ; fraction of inspired oxygen, A-aDO ₂ ; alveolar-arterial oxygen gradient, Alb; albumin, LDH; lactate dehydrogenase, BUN; blood urea nitrogen, CRP; C-reactive protein			

Prognostic factors for non-HIV PcP in relation to 30-day mortality

Prognostic factors in relation to 30-day mortality were assessed by multiple logistic regression analysis. The independence of each variable with a p value < 0.05 obtained upon comparison of the data between the survivors and non-survivors was assessed using Spearman's rank correlation coefficient. Treatment factors were excluded from this analysis to enable examination of the prognostic factors at the beginning of treatment. Age, respiratory failure, PaO₂/FiO₂ ratio and TP, Alb, and BUN levels were not included in the multiple logistic regression analysis because there was a strong correlation between these factors, with a Spearman's rank correlation coefficient of over 0.6. Therefore, the variables of corticosteroid administration and dosage for underlying diseases, disturbance of consciousness, A-DROP score, A-aDO₂, LDH levels, and BUN/Alb ratio were included in the multivariate logistic regression analysis. Multiple logistic regression analysis revealed that the A-DROP score (odds ratio (OR) 0.530; 95% confidence interval (CI) 0.307–0.915; p = 0.023) and BUN/Alb ratio (OR 0.938; 95% CI 0.893–0.986; p = 0.012) were independently associated with 30-day mortality (Table 3).

Table 3
Prognostic factors for 30-day mortality for non-HIV PcP

Variable	OR	95% CI	P value
A-DROP score	0.53	0.307–0.915	0.023
BUN/Alb ratio	0.938	0.893–0.986	0.012
Multivariate analysis was performed using multiple logistic regression analysis. Abbreviations: HIV; human immunodeficiency virus, PcP; <i>Pneumocystis pneumonia</i> , BUN; blood urea nitrogen, Alb; albumin, OR; odds ratio, CI; confidence interval			

Relationship between A-DROP and 30-day mortality

A-DROP was used for estimating the disease severity of patients at treatment initiation. The median A-DROP score was significantly higher in the non-survivors than in the survivors (3 vs. 1, $p < 0.001$, Table 2). The 30-day mortality rate was 0% in the patients with an A-DROP score of 0, 3.2% in those with a score of 1, 29.6% in those with a score of 2, 36.6% in those with a score of 3, and 37.5% in those with a score of 4 or 5 (Table 4). There was a positive correlation between 30-day mortality rate and A-DROP score, with the mortality rate rising with an increase in the A-DROP score. Among the various components that form the A-DROP criteria, (age, $\text{BUN} \geq 21$ mg/dL or dehydration, respiratory failure, orientation, and hypotension), respiratory failure (OR 6.62; 95% CI 1.61–27.17; $p = 0.009$) and disturbance of consciousness (OR 16.6; 95% CI 2.22–124.87; $p = 0.006$) were significantly independently associated with 30-day mortality by multiple logistic regression analysis (Table 5).

Table 4
The 30-day mortality rate classified by A-DROP score

A-DROP score	Number of patients (%)	30-day mortality (%)
0	11 (11.1%)	0 (0%)
1	31 (31.3%)	1 (3.2%)
2	27 (27.3%)	8 (29.6%)
3	22 (22.2%)	8 (36.3%)
4 or 5	8 (8.1%)	3 (37.5%)
Data are presented as number (%)		

Table 5
Determination of prognostic factors for 30-day mortality with the components of A-DROP

Variable	OR	95% CI	P value
Respiratory failure	6.62	1.61–27.17	0.009
Disturbance of consciousness	16.6	2.22-124.87	0.006
Multivariate analysis was performed using multiple logistic regression analysis. Components of A-DROP include age, $\text{BUN} \geq 21$ mg/dL or dehydration, respiratory failure, disturbance of consciousness, and hypotension. Abbreviations: OR; odds ratio; CI, confidence interval, BUN; blood urea nitrogen			

Ability of prognostic factors to estimate 30-day mortality

ROC curves were created for evaluating the ability of prognostic factors to estimate 30-day mortality in patients with non-HIV PcP (Figs. 1–4). The area under the curve (AUC) was 0.719 for BUN/Alb ratio (95% CI 0.594–0.844), 0.702 for BUN level (95% CI 0.577–0.826), 0.715 for Alb level (95% CI 0.598–0.833), and 0.760 for the A-DROP score (95% CI 0.659–0.860). The cutoff levels were 9.50 (sensitivity, 71.4%; specificity, 65.8%) for BUN/Alb ratio and 1.50 (sensitivity, 95.0%; specificity, 51.9%) for the A-DROP score for the estimation of prognosis of 30-day mortality in the patients with non-HIV PcP.

Discussion

Previous studies have shown that the prognosis of patients with non-HIV PcP is worse than that of patients with HIV PcP [5, 6]. The mortality rate associated with non-HIV PcP ranged between 19.6% and 60% in previous studies [5, 6], while the 30-day mortality rate was 20.5% in the present study. The remarkable finding of this study was that the A-DROP score and BUN/Alb ratio were reliable prognostic factors that can be used for estimating the 30-day mortality in patients with non-HIV PcP.

A previous study reported that an increase in PSI score was associated with mortality in non-HIV PcP [7]. It has been shown that the A-DROP score was not significantly different between the non-HIV PcP survivors and non-survivors at admission, but it was significantly higher in the non-survivors than in the survivors at treatment initiation [20]. Consistently, in the present study, the A-DROP score was found to be significantly higher in the non-survivors than in the survivors at treatment initiation (3 vs. 1, $p < 0.001$). The 30-day mortality rate was 0% in those with an A-DROP score of 0, 3.2% in those with a score of 1, 29.6% in those with a score 2, 36.6% in those with a score of 3, and 37.5% in those with a score of 4 or 5. Although it was reported that the A-DROP score underestimated the severity of patients with non-HIV PcP, which developed as CAP [20, 22], the 30-day mortality rate increased with increased A-DROP score at treatment initiation in the present study. Therefore, A-DROP might be useful for classifying the severity of patients with non-HIV PcP, especially the A-DROP score at treatment initiation for PcP. Previous studies have shown that the 30-day mortality rate was 0% for patients with CAP with an A-DROP score of 0, 0–3.1% in those with a score of 1, 3.1%–4.6% in those with a score of 2, 9.9–15.9% in those with a score of 3, and 19.6%–34.0% in those with a score of 4 or 5 [23–25]. Although it might not be accurate to compare our results with the 30-day mortality rate of CAP, the 30-day mortality in those patients with an A-DROP score of 2 or 3 was relatively higher in non-HIV PcP than in CAP, and the 30-day mortality rate in patients with an A-DROP score of 4 or 5 was relatively the same in non-HIV PcP and CAP. The components of the A-DROP score, such as dehydration, disturbance of consciousness, and hypotension, are also the components of the PSI and CURB65, which is a prognostic indicator estimated by five factors (confusion, urea, respiratory rate, blood pressure, age) and developed by the British Thoracic Society [26]. Dehydration, respiratory failure, disturbance of consciousness, and hypotension were indicative of an overall poor condition in patients. The multivariate analysis regarding the relationship between the A-DROP components (age, dehydration, respiratory failure, disturbance of consciousness, hypotension) and 30-day mortality demonstrated that respiratory failure and disturbance of consciousness were significantly independently associated with the 30-day mortality of non-HIV PcP patients in the present

study. Patients with non-HIV PcP and an A-DROP score of ≥ 2 , or those with respiratory failure or disturbance of consciousness at treatment initiation, usually demonstrate poor prognosis.

Patients with pneumonia are often dehydrated, resulting in increased reabsorption of urea by the kidneys. Thus, an increase in BUN levels is frequently observed in patients with pneumonia [27]. Patients with CAP and increased BUN levels had higher mortality rates [13, 16]. Increased BUN levels are indicative of renal hypoperfusion and thus help to predict the severity of pneumonia [28]. Increased BUN levels were also found to be a poor prognostic factor in patients with non-HIV PcP [8].

Alb is synthesized only in the liver, and the rate of Alb synthesis varies with nutritional status [29]. The rate of Alb synthesis changes markedly in severe illness, and a sustained inflammatory response may lead to long-term inhibition of Alb synthesis [29]. Serum Alb levels are reduced during acute and chronic inflammatory processes because of inhibition of Alb synthesis in the liver [30]. Hypoalbuminemia is thought to reflect systemic inflammatory reactions and malnutrition. Hypoalbuminemia in patients with non-HIV PcP might be associated with acute inflammation caused by PcP and chronic inflammation caused by underlying diseases. Low serum Alb levels reduce plasma colloid osmotic pressure, thereby increasing pulmonary vascular permeability [31–33]. Hypoalbuminemia was reported to be associated with increased pulmonary vascular permeability and lung injury in critically ill patients [34]. Thus, taking all these points into consideration, hypoalbuminemia can be seen as being associated with poor prognosis in patients with non-HIV PcP, by the same mechanism.

Both high BUN and low serum Alb levels were poor prognostic factors in patients with non-HIV PcP [8, 10]. This study further revealed that the non-survivors had significantly higher levels of BUN and lower levels of serum Alb than those in the survivors. In addition, high BUN and low serum Alb levels were poor prognostic factors for patients with CAP [13–16], and the BUN/Alb ratio was useful in predicting the mortality of patients with CAP [19, 35]. Moreover, the BUN/Alb ratio was also a useful marker for predicting the mortality in patients with HAP and aspiration pneumonia [17, 18]. These findings are consistent with the present study, which revealed that the increased BUN/Alb ratio before treatment was significantly associated with 30-day mortality in patients with non-HIV PcP. Furthermore, the AUC of the ROC curve was 0.719 for BUN/Alb ratio (95% CI 0.594–0.844), with a value of 0.702 for BUN (95% CI 0.577–0.826) and 0.715 for Alb (95% CI 0.598–0.833). The BUN/Alb ratio seems superior to either BUN or serum Alb alone in predicting prognosis in patients with non-HIV PcP. BUN and serum Alb are commonly measured biochemical markers in patients with non-HIV PcP; therefore, the BUN/Alb ratio is a convenient and useful marker for predicting the prognosis of these.

This study has several limitations. Some clinical data were missing in this retrospective study. Data regarding the status of disturbance of consciousness and dehydration might be inaccurate because these factors were evaluated on the basis of medical records. In addition, the evaluation of dehydration and disturbance of consciousness were dependent on the subjective observation of the physician, and the reported A-DROP scores might differ among physicians.

Conclusions

In conclusion, a high A-DROP score and BUN/Alb ratio were independent prognostic predictors for 30-day mortality in patients with non-HIV PcP. BUN and serum Alb levels are commonly examined in the clinical sittings in patients with non-HIV PcP. Thus, the BUN/Alb ratio can be a convenient and useful marker for predicting prognosis in these patients. However, more attention needs to be focused on the treatment strategies for patients with non-HIV PcP presenting a high A-DROP score and/or BUN/Alb ratio because of the high risk for poor prognosis. Further prospective studies are needed to confirm the findings of this study.

Abbreviations

A-aDO₂: alveolar-arterial oxygen gradient; A-DROP: age, dehydration, respiratory failure, orientation, systolic blood pressure; Alb: albumin; AUC: area under the curve; BUN: blood urea nitrogen; BUN/Alb: blood urea nitrogen to serum albumin (BUN/Alb); CAP: community-acquired pneumonia; CI: confidence interval; FiO₂: fraction of inspired oxygen; GCS: Glasgow Coma Scale; HAP: hospital-acquired pneumonia; HIV: human immunodeficiency virus; IPPV: invasive positive-pressure ventilation; JRS: Japanese Respiratory Society; LDH: lactate dehydrogenase; OR: odds ratio; PaO₂: partial pressure of arterial oxygen; PcP: *Pneumocystis* pneumonia; PSI: pneumonia severity index; ROC: receiver-operating characteristic; SpO₂: percutaneous oxygen saturation; TMP/SMX: trimethoprim/sulfamethoxazole; TP: total protein

Declarations

Ethics approval and consent to participate

The present study was approved by the Ethics Committees of Shinshu University (approval number 4213). The authors assert that this work has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Under common law and ethics, obtaining informed patient consent was not required for the methods used in this study. This study used an opt-out consent model, and patients could choose to opt out at any time and have their data removed from the registry.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

JA and AU designed the study. JA, AU, MK, AM, TH, FY, and SK collected the data. JA, AU, MK, YI, and MH analyzed and interpreted the data. JA and AU wrote the manuscript. All authors reviewed the manuscript.

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Figures

Figure 1

ROC curve of BUN/Alb ratio for predicting the 30-day mortality for non-HIV PcP. The AUC was 0.719 (95% CI 0.594–0.844). Abbreviations: ROC; Receiver-operating characteristics, BUN; blood urea nitrogen, Alb; albumin, HIV; human immunodeficiency virus, PcP, Pneumocystis pneumonia; AUC; area under the curve, CI; confidence interval

Figure 2

ROC curve of BUN for predicting the 30-day mortality for non-HIV PcP. The AUC was 0.702 (95% CI 0.577–0.826). Abbreviations: ROC; Receiver-operating characteristics, BUN; blood urea nitrogen, HIV; human immunodeficiency virus, PcP; Pneumocystis pneumonia, AUC; area under the curve, CI; confidence interval

Figure 3

ROC curve of Alb for predicting the 30-day mortality for non-HIV PcP. The AUC was 0.715 (95% CI 0.598–0.833). Abbreviations: ROC; Receiver-operating characteristics, Alb; albumin, HIV; human immunodeficiency virus, PcP; Pneumocystis pneumonia, AUC; area under the curve, CI; confidence interval

Figure 4

ROC curve of A-DROP for predicting the 30-day mortality for non-HIV PcP. The AUC was 0.76 (95% CI 0.659–0.860). Abbreviations: ROC; Receiver-operating characteristics, HIV; human immunodeficiency virus, PcP; Pneumocystis pneumonia, AUC; area under the curve, CI; confidence interval