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Original Article

Blood urea nitrogen-to-serum albumin ratio and A-DROP are useful in assessing the severity of *Pneumocystis* pneumonia in patients without human immunodeficiency virus infection

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ABSTRACT

Introduction: There is an increasing incidence of *Pneumocystis* pneumonia (PcP) among individuals without human immunodeficiency virus (HIV) infection (non-HIV PcP). However, prognostic factors for patients with non-HIV PcP have not been identified. Moreover, A-DROP (for classifying the severity of community-acquired pneumonia) or the blood urea nitrogen-to-serum albumin ratio (BUN/Alb), which is reported to be a predictor of mortality of community-acquired pneumonia, has not been established as an efficient prognostic factor in patients with non-HIV PcP. In this study, we analyzed the prognostic factors for non-HIV PcP and evaluated the prognostic ability of A-DROP and the BUN/Alb ratio.
Methods: This retrospective study involved a chart review of the medical records of 102 patients diagnosed with non-HIV PcP between January 2003 and May 2019 at five medical facilities.
Results: Overall, 102 patients were involved in this study. The 30-day mortality rate for non-HIV PcP was 20.5% in this study population. Compared with survivors, non-survivors had significantly lower serum albumin levels and significantly higher age, corticosteroid dosage at the PcP onset, alveolar–arterial oxygen gradient, A-DROP score, lactate dehydrogenase levels, blood urea nitrogen levels, and BUN/Alb ratio. Multivariate analysis showed that a high BUN/Alb ratio at treatment initiation was significantly associated with 30-day mortality risk. The receiver operating characteristic curves showed that A-DROP score had the highest prognostic ability in estimating 30-day mortality.
Conclusions: In patients with non-HIV PcP, a high BUN/Alb ratio is an independent prognostic predictor of mortality risk, and A-DROP is useful for classifying the severity.

1. Introduction

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 is increasing in patients without HIV infection (non-HIV PcP) but with malignancies, such as patients who have undergone organ transplantation and in those undergoing immunosuppressive therapy [2–4]. The mortality rates were 10%–20% and 19.6%–60% in HIV PcP and non-HIV PcP patients, respectively [5,6]. The prognostic factors of non-HIV PcP have not yet been determined; however, several factors, such as high levels

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Abbreviation

A-aDO_2	alveolar-arterial oxygen gradient
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
FiO_2	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
PaO_2	partial pressure of arterial oxygen
PcP	*Pneumocystis* pneumonia
PSI	pneumonia severity index
ROC	receiver operating characteristic
SpO_2	percutaneous oxygen saturation
TMP/SMX	trimethoprim/sulfamethoxazole
TP	total protein

of alveolar-arterial oxygen gradient (A-aDO_2), 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]. A-DROP (age, dehydration, respiratory failure, orientation, and systolic blood pressure) is a scoring system proposed by the Japanese Respiratory Society (JRS) and made by modifying CURB65, which is a prognostic indicator estimated by five factors (confusion, urea, respiratory rate, blood pressure, and age) for CAP severity determination and developed by the British Thoracic Society [12,13]. Because percutaneous oxygen saturation (SpO_2) measuring instruments are widespread in Japan, SpO_2 is often measured instead of a respiratory rate; therefore, SpO_2 was substituted as a component of A-DROP [14]. A-DROP is a simpler scoring system than PSI and is used widely for classifying the severity of patients with CAP in Japan. High BUN and low serum Alb levels are considered poor prognostic factors in patients with CAP [15–18]. Moreover, a high BUN-to-serum Alb (BUN/Alb) ratio is reportedly a useful marker of mortality due to CAP, hospital-acquired pneumonia (HAP), and aspiration pneumonia [19–21]. A previous report suggested that A-DROP might underestimate the severity of non-HIV PcP [22]. Therefore, A-DROP has not been established as a prognostic factor in patients with non-HIV PcP. The effectiveness of the BUN/Alb ratio has not been evaluated in patients with non-HIV PcP. In this study, we aimed to identify significant prognostic factors in patients with non-HIV PcP. We also evaluated the effectiveness of A-DROP, which is a simpler scoring system than PSI, and the BUN/Alb ratio, which is useful in patients with CAP, as prognostic predictors in patients with non-HIV PcP. Because the mortality rate of non-HIV PcP patients is high [5,6], knowing the prognostic predictors of non-HIV PcP may improve patient management and treatment methods.

2. Materials and methods

2.1. Study design and population

This study retrospectively evaluated patients with non-HIV PcP between January 2003 and May 2019 in 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, based on the data available in their medical records. The study was approved by the Ethics Committee of Shinshu University (approval number 4213). The study was conducted according to the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Under common law and ethics, informed patient consent was not required for the methods used in this study. However, 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. According to data from previous studies [23], the following four criteria were used in our study for the diagnosis of non-HIV PcP: (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 (Grocott, Diff-Quik, or Giemsa 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 plasma range (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 had malignancies (hematological or solid), patients who were treated with immunosuppressive therapy, or patients who had undergone an organ transplant and hematopoietic stem cell transplant.

2.2. Data collection

Demographic and clinical data were collected from the medical records of non-HIV PcP patients. The variables include age, sex, body mass index, underlying diseases, treatments for underlying diseases, corticosteroid dosage at the PcP onset for underlying diseases, PcP prophylaxis, and days from symptom appearance (PcP onset) to treatment. Additionally, data on physical findings at treatment initiation (SpO_2, blood pressure, and orientation status), respiratory support (invasive positive-pressure ventilation [IPPV]), initial treatment for PcP, adjunctive corticosteroid therapy, A-DROP score, laboratory findings before treatment, and the outcomes were obtained. Corticosteroid dosage was expressed as the equivalent dose of prednisolone. Respiratory failure was defined as the partial pressure of arterial oxygen (PaO_2) ≤60 Torr or SpO_2 ≤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 orientation; (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]. Orientation status was assessed using the Glasgow Coma Scale (GCS), and disturbance of orientation was defined as GCS ≤14. The endpoint of this study was

all-cause mortality in non-HIV PcP patients within 30 days from treatment initiation.

2.3. Statistical analysis

Data were expressed as proportions for categorical variables and as median (range) for continuous variables. Categorical variables were compared using the chi-square or Fisher's exact test, and continuous variables were compared between the survivors and non-survivors using the Mann–Whitney test. 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).

3. Results

3.1. Baseline clinical characteristics of patients with non-HIV PcP

During the investigation period, 105 patients met the diagnostic criteria for non-HIV PcP. Three patients were excluded from the study because their survival, 30 days after treatment initiation, was unknown. The baseline clinical characteristics of 102 patients (55 men [53.9%] and 47 women [46.1%]) are shown in Table 1. Median patient age was 69.5 years (range 22–88 years). Forty-six (45.1%) patients had autoimmune diseases, while 19 (18.6%), 18 (17.7%), and 19 (18.6%) had hematological malignancies, solid malignancies, and other diseases, respectively. 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 this study, seen in 29 (63.0%) of the 46 patients with autoimmune disease. Among the patients, 34 (33.3%) were treated with corticosteroids alone and 53 (53.0%) with corticosteroids in combination with other drugs, such as immunosuppressants, biological agents, and antitumor drugs, while 15 (14.7%) were treated with non-corticosteroid therapies. Corticosteroids were administered to 87 (85.3%) patients at the PcP onset for 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). The 30-day mortality rate in non-HIV PcP was 20.5% (21/102) in this study. Fourteen (66.6%) patients' deaths were PcP-related. Other causes of death included sepsis, acute interstitial pneumonia, multiple organ failure, and underlying disease progression. The cause of death for one patient was unknown from medical records.

3.2. Comparison of clinical data between survivors and non-survivors

In the 30 days after 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, $p = 0.019$), and the prevalence of underlying diseases did not significantly differ between them. However, the use of corticosteroids for the treatment of these underlying diseases was more frequent in the non-survivors, and the dosage administered at the PcP onset was also 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 them. Respiratory failure was significantly more prevalent in non-survivors than in survivors (95.2% vs. 60.4%, $p = 0.002$) at treatment initiation.

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

The laboratory findings before treatment showed that non-survivors presented with significantly higher levels of A-aDO_2 (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 survivors (Table 2). In addition, non-survivors showed significantly lower PaO_2-to-fraction of inspired oxygen (FiO_2) ratio (166.8 vs. 251.9, $p = 0.023$), 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 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).

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 PcP onset 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 the equivalent dose of prednisolone (n = 78). Abbreviations: PcP; *Pneumocystis* pneumonia, HIV; human immunodeficiency virus.

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 PcP onset 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 orientation	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
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
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 the equivalent dose of prednisolone. Abbreviations: PcP; *Pneumocystis* pneumonia, 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.

3.4. 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 non-HIV PcP was significantly more frequent in non-survivors than in survivors (90.4% vs. 70.3%, p = 0.016), and the requirement of IPPV was significantly higher among non-survivors than survivors (61.9% vs. 13.5%, p < 0.001) (Table 2).

3.5. Prognostic factors for non-HIV PcP associated with 30-day mortality

Prognostic factors associated with 30-day mortality were assessed by multiple logistic regression analysis. We compared the data between the two groups and selected A-aDO_2 and LDH levels —poor prognostic factors for non-HIV PcP [7,8]—and A-DROP score and BUN/Alb ratio—useful in measuring CAP [12,21]—as variables for multivariate logistic regression analysis. Multiple logistic regression analysis revealed that the BUN/Alb ratio (OR 1.060; 95% CI 1.006–1.117; p = 0.029) independently associated with 30-day mortality (Table 3).

3.6. Relationship between A-DROP and 30-day mortality

The median A-DROP score was significantly higher in non-survivors than in survivors (3 vs. 1, p < 0.001, Table 2). The 30-day mortality rate was 0%, 3.2%, 29.6%, 36.6%, and 37.5% in patients with an A-DROP score of 0, 1, 2, 3, and 4 or 5, respectively (Table 4). There was a positive correlation between the 30-day

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

Variable	OR	95% CI	P value
A-aDO_2	0.999	0.994–1.004	0.709
LDH	1.003	1.000–1.006	0.068
A-DROP score	1.808	0.983–3.325	0.057
BUN/Alb ratio	1.06	1.006–1.117	0.029

Multivariate analysis was performed using multiple logistic regression analysis. Abbreviations: HIV; human immunodeficiency virus, PcP; *Pneumocystis* pneumonia, A-aDO_2; alveolar-arterial oxygen gradient, LDH; lactate dehydrogenase, BUN; blood urea nitrogen, Alb; albumin, OR; odds ratio, CI; confidence interval.

Table 4
Thirty-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 (%).

mortality rate and A-DROP score, with the mortality rate increasing with an increase in the A-DROP score. Among the various components of A-DROP criteria, the disturbance of orientation (OR 6.214; 95% CI 1.269–30.432; p = 0.024) was most significantly independently associated with 30-day mortality by multiple logistic regression analysis (Table 5).

3.7. Prognostic factors ability to estimate 30-day mortality

ROC curves of the variables included in multivariate logistic regression analysis, BUN, and Alb, were used for evaluating the ability of prognostic factors to estimate 30-day mortality in non-HIV PcP patients (Figs. 1–6). The area under the curve (AUC) was 0.719 for the 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), 0.760 for the A-DROP score (95% CI 0.659–0.860), 0.698 for A-aDO_2 (95% CI 0.565–0.830), and 0.745 for LDH level (95% CI 0.636–0.854). 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 30-day mortality prognosis in non-HIV PcP patients.

4. Discussion

Previous studies have shown that the prognosis of patients with non-HIV PcP was 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 is that the BUN/Alb ratio is a reliable prognostic factor for estimating the 30-day mortality in non-HIV PcP patients.

Studies have shown that high BUN and low serum Alb levels were factors associated with poor prognosis in CAP patients

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

Variable	OR	95% CI	P value
Age	1.56	0.491–4.956	0.451
Dehydration	2.36	0.700–7.955	0.166
Respiratory failure	7.641	0.915–63.771	0.06
Disturbance of orientation	6.214	1.269–30.342	0.024
Hypotension	0.71	0.091	5.125

Multivariate analysis was performed using multiple logistic regression analysis. Components of A-DROP include age, BUN ≥21 mg/dL or dehydration, respiratory failure, disturbance of orientation, and hypotension. Abbreviations: OR; odds ratio; CI, confidence interval, BUN; blood urea nitrogen.

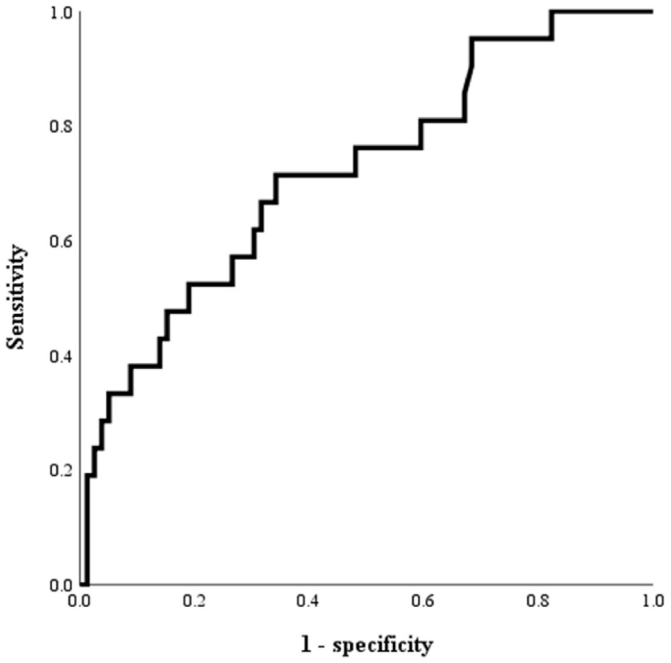

Fig. 1. ROC curve of the BUN/Alb ratio for predicting the 30-day mortality for non-HIV PcP. The AUC was 0.719 (95% CI 0.594–0.844). Abbreviations: ROC; receiver operating characteristic, BUN; blood urea nitrogen, Alb; albumin, HIV; human immunodeficiency virus, PcP, *Pneumocystis* pneumonia; AUC; area under the curve, CI; confidence interval.

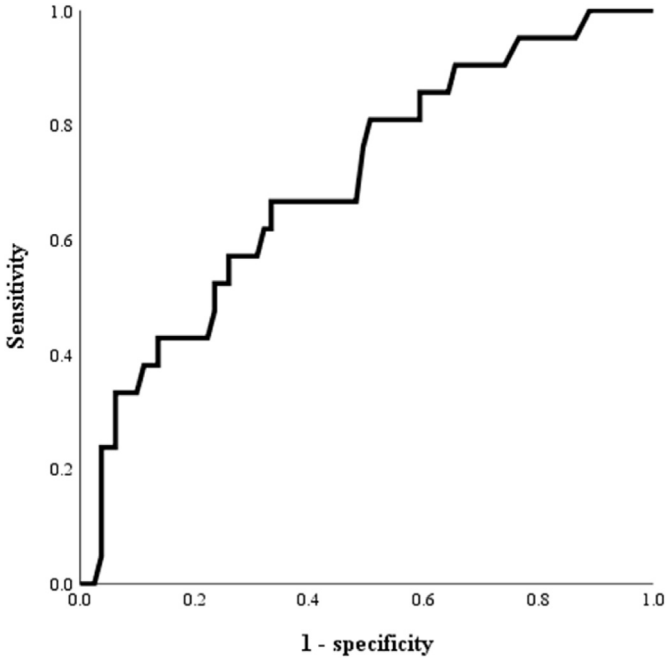

Fig. 2. ROC curve of BUN for predicting the 30-day mortality for non-HIV PcP. The AUC was 0.702 (95% CI 0.577–0.826). Abbreviations: ROC; receiver operating characteristic, BUN; blood urea nitrogen, HIV; human immunodeficiency virus, PcP; *Pneumocystis* pneumonia, AUC; area under the curve, CI; confidence interval.

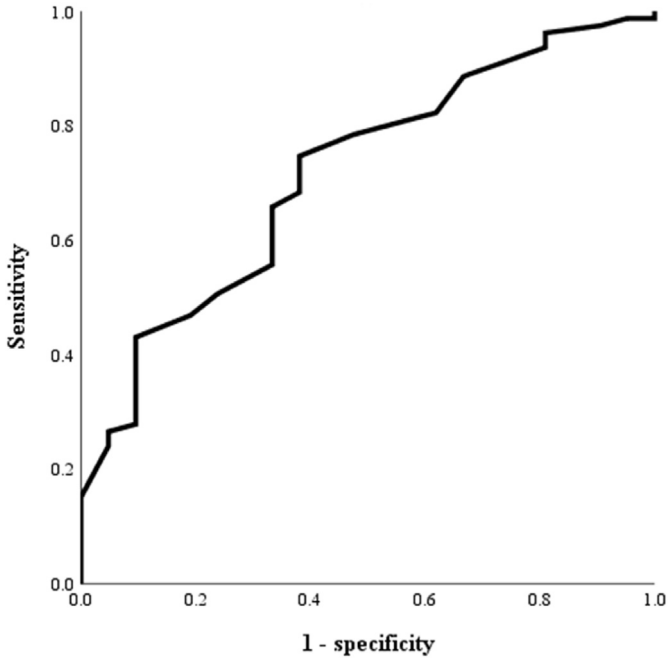

Fig. 3. ROC curve of Alb for predicting the 30-day mortality for non-HIV PcP. The AUC was 0.715 (95% CI 0.598–0.833). Abbreviations: ROC; receiver operating characteristic, Alb; albumin, HIV; human immunodeficiency virus, PcP; *Pneumocystis* pneumonia, AUC; area under the curve, CI; confidence interval.

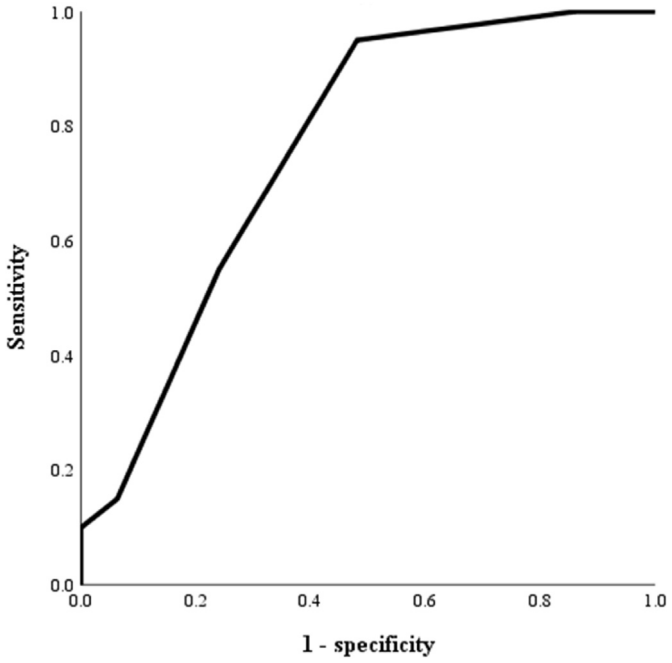

Fig. 4. ROC curve of A-DROP for predicting the 30-day mortality for non-HIV PcP. The AUC was 0.76 (95% CI 0.659–0.860). Abbreviations: ROC; receiver operating characteristic, HIV; human immunodeficiency virus, PcP; *Pneumocystis* pneumonia, AUC; area under the curve, CI; confidence interval.

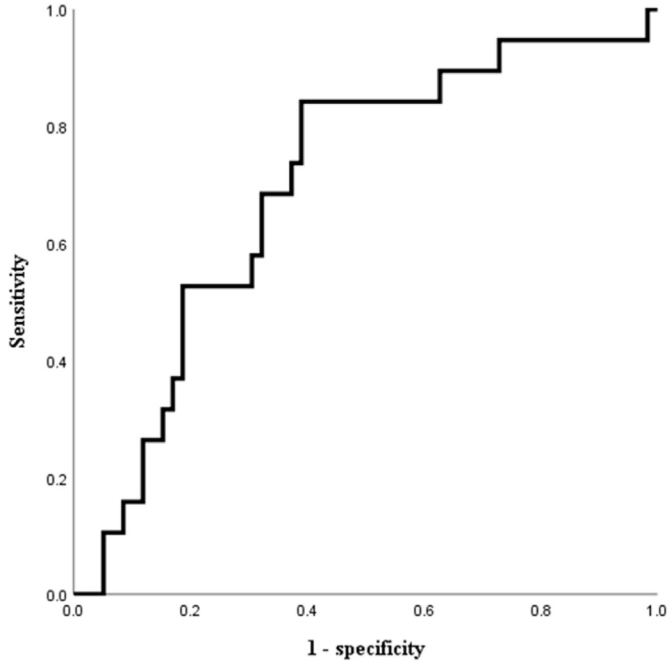

Fig. 5. ROC curve of A-aDO_2 for predicting the 30-day mortality for non-HIV PcP. The AUC was 0.698 (95% CI 0.565–0.830). Abbreviations: ROC; receiver operating characteristic, A-aDO_2; alveolar-arterial oxygen gradient, HIV; human immunodeficiency virus, PcP; *Pneumocystis* pneumonia, AUC; area under the curve, CI; confidence interval.

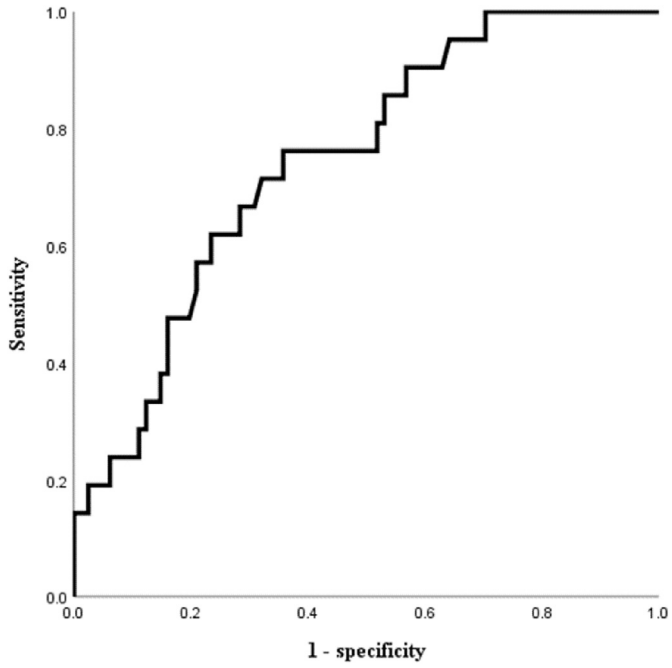

Fig. 6. ROC curve of LDH for predicting the 30-day mortality for non-HIV PcP. The AUC was 0.745 (95% CI 0.636–0.854). Abbreviations: ROC; receiver operating characteristic, LDH; lactate dehydrogenase, HIV; human immunodeficiency virus, PcP; *Pneumocystis* pneumonia, AUC; area under the curve, CI; confidence interval.

[15–18] and non-HIV PcP patients [8,10]. Pneumonia patients 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 [24]. Moreover, non-HIV PcP patients may have increased BUN due to corticosteroids use for underlying diseases. Alb is synthesized only in the liver, and its rate of synthesis varies with nutritional status [25]. The rate of Alb synthesis changes markedly in severe illness, and a sustained inflammatory response may lead to long-term inhibition of Alb synthesis [25]. Serum Alb

levels are reduced during acute and chronic inflammatory processes because of inhibition of Alb synthesis in the liver [26]. Hypoalbuminemia is thought to reflect systemic inflammatory reactions and malnutrition. Hypoalbuminemia in non-HIV PcP patients might be associated with acute inflammation caused by PcP and chronic inflammation resulting from underlying diseases.

This study further revealed that non-survivors had significantly higher levels of BUN and lower levels of serum Alb than those in survivors. Studies have shown that the BUN/Alb ratio was useful in predicting the mortality of patients with CAP [21,27]. Moreover, the BUN/Alb ratio was also a useful marker for predicting mortality in patients with HAP and aspiration pneumonia [19,20]. These findings are consistent with those of 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. Patients with CAP are often dehydrated at the time of admission, and we often see cases where the Alb levels at the time of admission decline rapidly after intravenous rehydration [28]. Patients' hydration status should be considered when evaluating pneumonia patients' blood test results because water deficiency develops rapidly and insidiously in patients with pneumonia [21,24]. Because the elevation of blood urea nitrogen levels is frequently observed in the dehydrated condition, the BUN/Alb ratio is associated with critical illness [21]. Moreover, because the BUN/Alb ratio can be evaluated as a comprehensive physical reserve by taking into account the four conditions of malnutrition, dehydration, hepatic reserve, and renal reserve [28], the BUN/Alb ratio is more useful for assessing disease severity than either BUN or serum Alb alone. From the results of the ROC curves of the present study, the BUN/Alb ratio also seems superior to either BUN or serum Alb alone in predicting prognosis 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. However, it was significantly higher in non-survivors than in survivors at treatment initiation [22]. Consistent with this study, the A-DROP score was be significantly higher in non-survivors than in survivors at treatment initiation. Although it was reported that the A-DROP score underestimated the severity of patients with non-HIV PcP, which developed as CAP [22,29], the 30-day mortality rate increased with increased A-DROP score at treatment initiation in the present study. A-DROP score did not reach statistical significance in multivariate analysis. However, A-DROP score had the highest prognostic factors ability to estimate 30-day mortality in patients with non-HIV PcP in the ROC curves of the present study. Therefore, A-DROP might help classify patients' severity and prognosis 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%, 0%–3.1%, 3.1%–4.6%, 9.9%–15.9%, and 19.6%–34.0% for CAP patients with an A-DROP score of 0, 1, 2, 3, and 4 or 5, respectively [14,30,31]. Although comparison of our results with the 30-day mortality rate of CAP patients might not be accurate, 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 an A-DROP score of 4 or 5 was relatively the same.

The components of the A-DROP score, such as dehydration, disturbance of orientation, and hypotension, are also the components of the PSI and CURB65. Dehydration, respiratory failure, disturbance of orientation, and hypotension indicate an overall poor condition in patients. Multivariate analysis regarding the relationship between the A-DROP components and 30-day mortality demonstrated that disturbance of orientation was significantly independently associated with the 30-day mortality of non-HIV PcP patients in the present study. This study indicated that patients with non-HIV PcP and an A-DROP score of $\geq$2, or those with disturbance of consciousness at treatment initiation, demonstrate poor prognosis. Because in Japan, respiratory rate is not often measured; rather, SpO_2 measuring instruments are widespread, and SpO_2 is used as a component of the A-DROP [14]. This study was a retrospective study, and it was difficult to evaluate PSI because there were many unmeasured respiratory rates and other PSI components missing. Therefore, we evaluated only A-DROP as a useful score in CAP in this study.

A high BUN/Alb ratio at treatment initiation was an independent prognostic predictor of mortality risk in patients with non-HIV PcP. BUN and serum Alb are commonly measured biochemical markers in patients with non-HIV PcP; therefore, evaluating the BUN/Alb ratio at treatment initiation is convenient and useful for predicting the prognosis. A-DROP is useful for classifying the severity and might be an effective prognosis predictor for non-HIV PcP.

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

5. Conclusions

In conclusion, a high BUN/Alb ratio is an independent prognostic predictor of mortality risk, and A-DROP is useful for classifying the severity in non-HIV PcP patients. More attention needs to be focused on the treatment strategies for patients with non-HIV PcP presenting a high BUN/Alb ratio and/or A-DROP score because of the high risk for poor prognosis. Further prospective studies are needed to confirm the findings of this study.

Authorship statement

All authors meet the ICMJE authorship criteria. 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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Declaration of competing interest

None.

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