ORIGINAL ARTICLE

# PREDICTOR FACTORS FOR LENGTH OF STAY BASED ON SERUM BIOMARKERS IN MODERATE TO SEVERE COMMUNITY-ACQUIRED PNEUMONIA

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## ABSTRACT

**Background:** Community-acquired pneumonia (CAP) is a high-risk disease with a high global incidence of morbidity and mortality. Serum biomarkers can be used to predict the length of hospital stay (LOS) in patients with CAP. This study aims to establish a scoring system using procalcitonin, C-reactive protein (CRP), leukocytes, lactic acid, D-dimer, and albumin for LOS in patients with moderate to severe CAP.
**Method:** A prospective cohort design was conducted on patients with moderate to severe CAP treated in the Emergency Department (ED), Intensive Care Unit (ICU), and High-Care Unit (HCU) at RSUPN dr. Cipto Mangunkusumo from May 2022 to July 2023, using multivariate logistic regression analysis.
**Results:** This study involved 360 subject, with 204 (56.67%) having LOS >14 days and 156 (44.44%) having LOS ≤14 days. Lactic acid and albumin were consistently influencing predictor variables for LOS, with RR 1.305 (95% CI 1.097–1.551, p=0.003) and 2.234 (95% CI 1.164–2.156, p=0.003), respectively. ROC curve analysis showed weak predictive ability (AUC=0.629), but Hosmer-Lemeshow test showerd good validation (0.562). Other biomarkers considered significant were procalcitonin and CRP, with RR 1.481 (95% CI 1.121–1.954, p=0.006) and RR 2.465 (95% CI 1.141–5.326), respectively. Leukocytes were not significant as a biomarker for moderate to severe CAP (p=0.947).
**Conclusion:** There is a relationship between procalcitonin, C-reactive protein, lactic acid, and albumin with the length of hospital stay in patients with moderate to severe CAP. However, no scoring model is available.

**Keywords:** pneumonia, length of stay, serum biomarkers

## ABSTRAK

**Latar belakang :** Pneumonia komunitas (PK) merupakan penyakit dengan insiden morbiditas dan mortalitas global yang tinggi. Serum biomarker dapat digunakan sebagai prediktor untuk lama rawat pada pasien PK. Studi ini bertujuan untuk mendapat sistem skoring menggunakan beberapa serum biomarker seperti prokalsitonin, C-reactive protein (CRP), leukosit, asam laktat, D-dimer dan albumin terhadap lama rawat pasien PK sedang berat.
**Metode :** Studi ini menggunakan desain kohort prospektif pasien PK sedang berat yang dirawat di IGD/ICU/HCU RSUPN dr. Cipto Mangunkusumo periode Mei 2022 s/d Juli 2023. Variabel-variabel prediktor lama rawat pasien PK sedang berat didapatkan dari hasil analisis multivariat dengan regresi logistik.
**Hasil :** Dari total 360 subjek yang memiliki lama rawat >14 hari sebanyak 204 subjek (56,67%) dan ≤14 hari sebanyak 156 subjek (44,44%). Variabel prediktor yang secara konsisten mempengaruhi lama rawat adalah asam laktat dengan RR 1,305 (IK 95% 1,097 – 1,551, p=0,003) dan albumin dengan RR 2,234 (IK 95% 1,164– 2,156, p=0,003). Analisis kurva ROC menunjukkan kemampuan prediksi lemah (AUC=0,629). Performa kalibrasi dengan uji Hosmer-Lemeshow test menunjukkan validasi baik (0,562). Biomarker lain yang dianggap signifikan dalam analisis bivariat yaitu prokalsitonin dengan RR 1,481 (IK 95% 1,121-1,954, p=0,006) dan CRP dengan RR 2,465 (IK 95% 1,141-5,326). Leukosit tidak dinilai signifikan sebagai biomarker PK sedang berat (p = 0,947).
**Kesimpulan :** Terdapat hubungan antara prokalsitonin, CRP, asam laktat dan albumin dengan lama rawat pasien PK sedang berat. Tidak terdapat model skoring lama rawat pasien PK sedang berat.
**Kata Kunci :** pneumonia, lama rawat, serum biomarker

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PREDICTOR FACTORS FOR LENGTH OF STAY BASED ON SERUM BIOMARKERS IN MODERATE TO SEVERE COMMUNITY-ACQUIRED PNEUMONIA

## BACKGROUND

Community-acquired pneumonia (CAP) is often underdiagnosed and stands as a prominent factor in global mortality. Epidemiological data from the United States indicates that pneumonia is a primary cause of death due to infections, with an annual occurrence of 5-6 million CAP cases, involving 1.1 million individuals receiving treatment and 45 thousand succumbing to the illness.(1) In Indonesia, the statistics for 2021 reveal that 31.4% of the population will experience pneumonia, resulting in a mortality rate of 0.16%.(2)

In contemporary medical practices, the diagnosis of severe community-acquired pneumonia (CAP) is supported through the utilization of various biomarkers. Research indicates that CRP functions independently as a predictor for complications in CAP, while additional biomarkers such as leucocytosis, lactic acid, D-dimer, and albumin offer insights into prognosis.(3,4) Procalcitonin and CRP are recognized as reliable biomarkers for monitoring response to infection and predict the severity of CAP. Nonetheless, the effectiveness of procalcitonin in identifying bacterial infections has limitations, and CRP levels may also be heightened in non-bacterial infections. The assessment of these biomarkers is further complicated by factors such as initial antibiotic usage, corticosteroid administration, and underlying liver or kidney disorders. (5,6) Lactic acid is particularly informative for prognosis, particularly in cases of septic shock, whereas D-dimer is linked to coagulation processes observed in both acute and chronic lung damage in CAP.(7,8) Serum albumin additionally serves as a prognostic indicator in CAP patients, with diminished levels associated with an unfavorable outcome.(9,10)

Looking at it from an economic standpoint, the treatment of patients exhibiting moderate to severe clinical manifestations of CAP is linked to an extended hospitalization duration.(11) Various serum biomarkers can be utilized to assess clinical outcomes, including the length of stay for CAP patients. This evaluation is conducted in addition to routine laboratory tests carried out in the emergency room. The utilization of biomarkers like CRP and procalcitonin proves beneficial in assessing clinical outcomes and influencing decisions related to antibiotic usage. The identification of patients at risk of an extended hospital stay can be accomplished by integrating multiple serum biomarkers into a scoring system, forming a basis for appropriate intervention, which may involve the effective use of antibiotics. A prompt, accurate, and dependable scoring system based on the severity of CAP is also essential to decrease the duration of patient hospitalization.(12)

## METHODS

This study employs an observational approach with a prospective cohort design, intending to examine individuals with moderate to severe community-acquired pneumonia (CAP) in the Department of Internal Medicine, RSCM/FKUI. The research is conducted at the Emergency Room/Intensive Care Unit/High Care Unit (IGD/ICU/HCU) of RSUPN dr. Cipto Mangunkusumo (RSCM), Jakarta, spanning from May 2022 to July 2023. The sample size, consisting of 138 individuals, was determined using the difference in proportion analysis formula. Inclusion criteria encompassed patients aged 18 years and above with moderate to severe CAP, while exclusion criteria involved the use of antibiotics more than 24 hours before treatment and a diagnosis of non-infectious disease ARDS. Data and sample collection adhered to the research flow, and data analysis was conducted using SPSS version 23.0 with various statistical tests. Ethical approval has been obtained for all aspects of this research to safeguard the confidentiality of patient data.

## RESULTS

The study comprised 360 subjects diagnosed with moderate to severe community-acquired pneumonia (CAP) who met the inclusion criteria and had no exclusion criteria. These individuals sought treatment at RSUPN Dr. Cipto Mangunkusumo between May 2022 and July 2023. The diagnosis of

moderate CAP in this research was confirmed through a combination of patient history, physical examination, and supportive tests, such as chest X-rays or chest CT scans indicating pneumonia. The severity of CAP was assessed using the CURB-65 score. In this study, a statistically significant association was found between the severity of CAP and the length of stay ($p < 0.001$).

Patients aged < 65 years constituted the largest proportion of the group in this study, namely 249 subjects (69.17%) cases compared to the group aged ≥ 65 years as many as 111 subjects (30.83%). There were more males than females with 200 subjects (55.56%). The most common comorbidity was hypertension (39.44%), followed by diabetes mellitus (28.06%). Other comorbidities were chronic kidney disease (27.5%), malignancy (26.9%), coronary heart disease (16.67%), cerebrovascular disease (10%), chronic obstructive pulmonary disease (3.06%), HIV (2.8%), autoimmune diseases (2.2%).

The number of moderate to severe CAP subjects who had a length of stay of more than 14 days was 204 subjects (56.67%). Based on the CURB-65 scoring, score 2 was found to be 33.9%, score 3 was 45.8%, score 16.1% and score 5 was 3.6%. Based on the severity of CAP, namely moderate CAP (scores 2 and 3) was 80.39% and severe CAP (scores 4 and 5) was 19.61%. The mortality rate was found to be 136 subjects (37.78%).

In the biomarker variables, procalcitonin values ≥ 0.25 were found in 280 subjects (77.78%) and values < 0.25 in 80 subjects (22.22%). C-reactive protein ≥ 5 was found in 339 subjects (94.17%) and < 5 was found in 21 subjects (5.83%). Leukocyte values were 4,000 – 10,000 in 86 subjects (23.89%) and values < 4,000 or > 10,000 were found in 274 subjects (76.11%). Lactic acid values ≥ 2.5 were found in 84 subjects (23.53%) and < 2.5 were found in 273 subjects (76.47%). D-dimer levels ≥ 500 were found in 346 subjects (96.65%) while levels < 500 were found in 12 subjects (3.35%). Albumin levels ≥ 3.5 were found in 67 subjects (18.61%) while levels < 3.5 were found in 293 subjects (81.39%). Further information regarding demographic and laboratory characteristics can be found in Table 1.

**Table 1. Demographic characteristics of subjects**

| Variable | N=360 |
|---|---|
| Age (years), median (IQR) | 58 (48 – 67) |
| Age, n (%) | |
| ≥ 65 years | 111 (30,83) |
| < 65 years | 249 (69,17) |
| Sex, n (%) | |
| Female | 160 (44,44) |
| Males | 200 (55,56) |
| Procalcitonin, Median (IQR) | 1,755 (0,33 – 12,15) |
| Procalcitonin, n (%) | |
| ≥ 0,25 | 280 (77,78) |
| < 0,25 | 80 (22,22) |
| CRP, Median (IQR) | 104,5 (30,7 – 172,9) |
| CRP, n (%) | |
| ≥ 5 | 339 (94,17) |
| < 5 | 21 (5,83) |
| Leukocytes, Median (IQR) | 14.030 (9.940 -20.835) |
| Leukocytes, n (%) | |
| < 4.000 atau >10.000 | 274 (76,11) |
| 4.000 – 10.000 | 86 (23,89) |
| Lactic Acid, Median (IQR) | 1,5 (1,1 – 2,4) |
| Lactic Acid, n (%) | |
| ≥ 2,5 | 84 (23,53) |
| < 2,5 | 273 (76,47) |
| D-dimer, Median (IQR) | 3.105 (1.460 – 6.590) |
| D-dimer, n (%) | |
| ≥ 500 | 346 (96,65) |
| < 500 | 12 (3,35) |
| Albumin | 2,8 (2,4 – 3,35) |
| Albumin, n (%) | |
| ≥ 3,5 | 67 (18,61) |
| < 3,5 | 293 (81,39) |
| Length of Stay, Median (IQR) | 9 (6 – 15) |
| Length of Stay, n (%) | |
| > 14 days | 204 (56,67) |
| ≤ 14 days | 156 (43,33) |
| Mortality, n (%) | |
| Yes | 136 (37,78) |
| No | 224 (62,22) |
| CCI Score, Median (IQR) | 4 (2 – 6) |
| Co-morbidity (CCI 5), n (%) | |
| High | 133 (38,11) |
| Normal | 216 (61,89) |
| Co-morbidity (CCI 4), n (%) | |
| High | 189 (54,15) |

| | |
|---|---|
| Normal | 160 (48,85) |
| CURB65, Median (IQR) | 3 (2 – 3) |
| Community-Acquired Pneumonia, n (%) | |
| Moderate | 287 (80,39) |
| Severe | 70 (19,61) |

The bivariate analysis of the studied factors revealed that all variables statistically exhibited a p-value <0.25, signifying their predictive potential for the length of stay in moderate to severe CAP patients. These variables encompass procalcitonin, CRP, lactic acid, and albumin. Subsequently, a multivariate analysis was conducted to identify variables that could serve as predictors for the length of stay in moderate to severe CAP cases. The outcomes of the multivariate analysis consistently demonstrated that lactic acid and albumin were independently associated with predicting the duration of stay in moderate to severe CAP patients.

**Tabel 2. Bivariate analysis of serum biomarkers with length of stay**

| Variable | Length of stay | | RR (CI 95%) | *p* |
|---|---|---|---|---|
| | **> 14 days (n=204)** | **≤ 14 days (n=156)** | | |
| Procalcitonin, n (%) | | | | |
| ≥ 0,25 | 171 (61,07) | 109 (38,93) | 1,481 (1,121-1,954) | **0,006** |
| < 0,25 | 33 (41,25) | 47 (58,75) | | |
| CRP, n (%) | | | | |
| ≥ 5 | 199 (58,70) | 140 (41,30) | 2,465 (1,141-5,326) | **0,022** |
| < 5 | 5 (23,81) | 16 (76,19) | | |
| Leucocyte, n (%) | | | | |
| < 4.000 or >10.000 | 155 (56,57) | 119 (43,43) | 0,993 (0,804 – 1,226) | 0,947 |
| 4.000 – 10.000 | 49 (56,98) | 37 (43,02) | | |
| Lactic acid, n (%) | | | | |
| ≥ 2,5 | 61 (72,62) | 23 (27,38) | 1,406 (1,181 – 1,674) | **<0,0001** |
| < 2,5 | 141 (51,65) | 132 (48,35) | | |
| D-dimer, n (%) | | | | |
| ≥ 500 | 197 (56,94) | 149 (43,06) | 1,139 (0,642 – 2,019) | 0,657 |
| < 500 | 6 (50,0) | 6 (50,0) | | |
| Albumin, n (%) | | | | |
| ≥ 3,5 | 176 (62,19) | 107 (37,81) | 1,710 (1,255 – 2,329) | **0,001** |
| < 3,5 | 28 (36,36) | 49 (63,64) | | |

**Table 3. Multivariate analysis of serum biomarkers with length of stay**

| Variable | *P* | RR (CI 95%) |
|---|---|---|
| Lactic acid | 0,003 | 1,305 (1,097 – 1,551) |
| Albumin | 0,003 | 2,234 (1,164– 2,156) |

The outcomes of the final model in the multivariate analysis using regression revealed that the variables lactic acid and albumin consistently and independently played a role in predicting the duration of stay for moderate to severe CAP patients. The assessment of discrimination performance, conducted through ROC curve analysis, indicated that the prediction model achieved an AUC value of 0.629 with p < 0.001 CI95% (0.579 – 0.679). Consequently, the predictive accuracy of this equation for the length of stay in moderate to severe CAP patients is considered weak, falling within the range of 0.60 – 0.70 (0.629). Regarding the calibration performance evaluation, the obtained equation demonstrated sufficient quality, as evidenced by a p value in the Hosmer-Lemeshow test exceeding 0.05 (0.562).

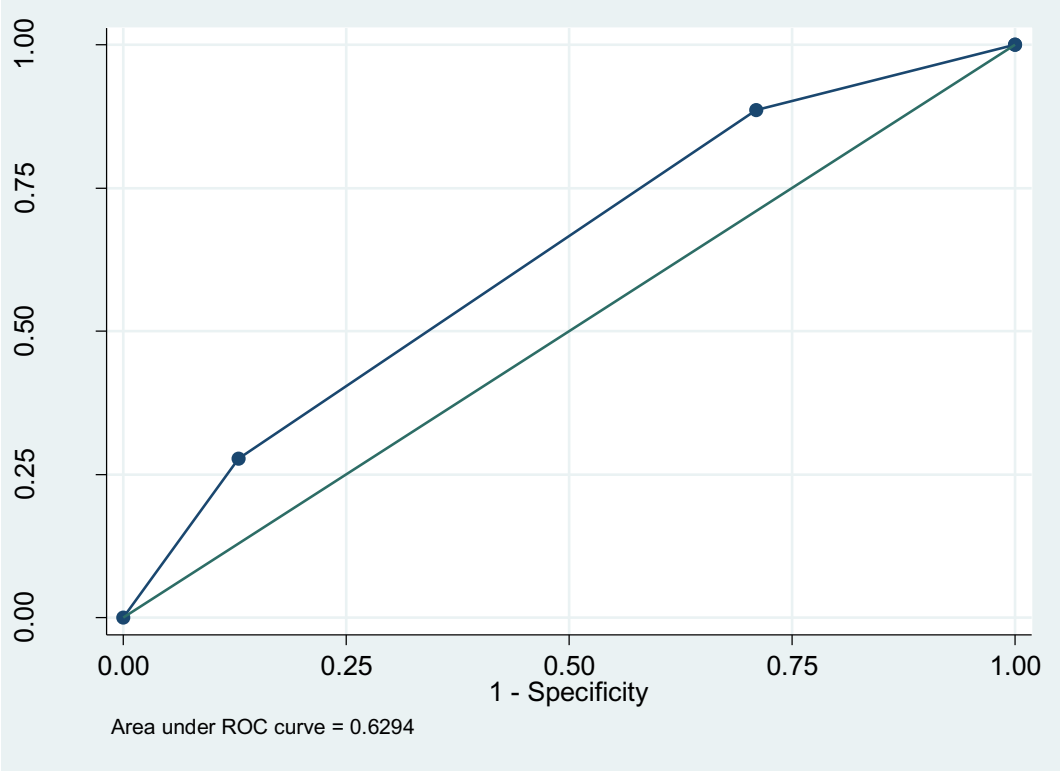


**Figure 1. Evaluation of the discrimination performance of the variables lactic acid and albumin in predicting length of stay in patients with moderate to severe CAP**

## DISCUSSION

The age bracket with the largest participant count is below 65 years, totaling 246 subjects (68.33%). The increased percentage of individuals aged over 65 can be explained by Jakarta's demographic composition, which is predominantly in the productive age range (18 – 59 years). Despite the fewer numbers in the ≥ 65 age group in this study, there is a heightened risk of worsening health, increased mortality rates, and an extended length of stay for CAP.

Immunosenescence and multimorbidity are identified as risk factors contributing to adverse clinical outcomes in the ≥ 65 age group.(13) This study established a noteworthy and statistically significant correlation between comorbid factors and age ($p = 0.001$).

Men constituted the majority of moderate to severe CAP patients, specifically 210 subjects (58.33%). This aligns with findings from previous studies. According to survey data in Japan, Uematsu et al reported that the proportion of male subjects was 57% for community-acquired pneumonia.(14) Several theories can elucidate the higher susceptibility of men to pneumonia. First, men have only one X chromosome, and the X chromosome is associated with the innate immune system, particularly toll-like receptor-7 (TLR-7), which is twice as high in women. Second, the theories are linked to hormone levels, with androgen hormones decreasing toll-like receptor-4 expression (TLR-4) in macrophages, while estrogen increases its expression. Estrogen is also crucial for enhancing nitric oxide synthetase activity (NOS-3), important for macrophages in pathogen elimination. The third theory is related to lifestyles that elevate pneumonia risk, such as smoking, which is more prevalent among men.(15)

This research underscores the importance of factors such as procalcitonin, CRP, leukocytes, D-dimer, lactic acid, and albumin in predicting the length of stay for patients with moderate to severe community-acquired pneumonia (CAP). The study establishes a connection between procalcitonin levels and the duration of stay in individuals with community-acquired pneumonia. The bivariate analysis demonstrated statistical significance ($p = 0.006$) in the relationship between procalcitonin and the length of stay, indicating its crucial role in the context of this disease. However, the results of the multivariate analysis revealed that the significance of CAPan on the procalcitonin variable was diminished ($p = 0.185$) after considering other factors. These findings align with prior research, such as studies conducted by Suter-Widmer et al., which found no association between procalcitonin levels and the length of stay in community-acquired pneumonia patients.(16) Other studies, such as those conducted by Covington EW et al., also noted that procalcitonin levels did not correlate with length of stay in pneumonia patients.(17) However, procalcitonin also has a weak point as a marker of bacterial infection due to its relatively low sensitivity value, as revealed in a meta-analysis by Kamat IS et al. Additionally, typical bacteria like Streptococcus pneumoniae or Haemophilus influenza tend to cause more substantial increases in procalcitonin compared to atypical bacteria.(18)

CRP also plays a significant role in identifying moderate to severe CAP. The bivariate analysis revealed statistical significance ($p = 0.022$) between CRP levels and the length of stay. However, the multivariate analysis resulted in a p-value of 0.073, indicating a loss of significance after considering other factors. These findings align with the research conducted by Farah et al., indicating that CRP levels at admission were not associated with the length of stay, but significant correlation emerged with serial measurements on the second and fifth days of treatment.(19) Travlos et al. concluded that CRP can serve as a predictor of length of stay in community-acquired pneumonia, especially when measured on the fourth and seventh days of treatment.(20) Bruns et al.'s study demonstrated that the decline in CRP levels on day 3 and day 7 of treatment can be utilized to assess the effectiveness of antibiotic therapy. A decrease of less than 60% from days 0–3 or less than 90% from days 0–7 raises the risk of inadequate antibiotics. However, elevated CRP levels do not exclusively indicate a bacterial infection but can also result from non-bacterial infections such as malaria. Comorbid factors such as diabetes mellitus, hypertension, and obesity can also influence CRP levels.(21)

Leucocytosis is among the minor criteria used to evaluate the severity of CAP. Nevertheless, in this study, bivariate tests

revealed that leukocyte levels did not exhibit a significant association with the length of stay in community-acquired pneumonia (CAP) patients, as indicated by a p-value of 0.947. Consequently, further multivariate analysis was not pursued. These results align with a comparable study by Giorgia LC et al., which similarly found no significant correlation between leukocyte levels and the length of stay in CAP patients in Switzerland (p = 0.938).(22)

In this study, the outcome of bivariate analysis showed that D dimer levels did not exhibit a significant relationship with length of stay in moderate to severe community-acquired pneumonia (CAP) patients, as reflected in a p-value = 0,657. Consequently, this variable was not included in the multivariate analysis as a predictor of length of stay. These findings align with the research conducted by Snidjers et al., which also concluded that D-dimer had inadequate AUC values in predicting mortality and clinical outcomes at 30 days in CAP patients. However, a different study by Agapakis et al. demonstrated the utility of D-dimer in predicting the length of stay in CAP patients. They observed that patients with D-dimer values ≥ 600 µg/L had a longer treatment duration compared to patients with D-dimer values < 600 µg/L.(23)

Both bivariate and multivariate analyses revealed that lactic acid was a statistically significant variable, exerting a substantial influence on the length of stay for moderate to severe CAP. Consistent support for these findings is evident in a cohort study conducted by Chen YX et al. and research by Frenzen et al. Chen YX et al.'s study, involving individuals with pneumonia in the emergency department, affirmed that elevated lactate levels were associated with an increased risk of mortality, hospitalization, and admission to the intensive care unit (ICU).(24) A parallel observastion was made in the study by Frenzen et al., where lactate, both individually and in combination with scores CURB-65, demonstrated higher predictive power for composite outcomes, including mortality, invasive mechanical ventilation or vasopressor use, and ICU admission.(25)

Albumin levels play a crucial role in predicting length of stay in patients with moderate to severe community-acquired pneumonia (CAP). The outcomes of bivariate analysis, with a p-value of 0.001, confirm a substantial association between albumin levels and the length of stay. Further multivariate analysis substantiates that albumin remains a statistically significant factor influencing the duration of stay for moderate to severe CAP. These study results align with the discoveries of Akirov et al., who demonstrated noteworthy differences in the length of stay among patients with mild hypoalbuminemia, moderate hypoalbuminemia, and normal albumin levels.(26) Additionally, research by Suter-Widmer et al. supported these findings, indicating that low albumin levels (<3.0 grams/dL) were linked to an increase in the length of stay for CAP patients.(16)

## CONCLUSION

Procalcitonin, CRP, lactic acid, and albumin exhibited a notable correlation with the treatment duration in individuals diagnosed with moderate to severe CAP. Conversely, there was no significant connection identified between leukocyte count and D-dimer levels and the duration of hospital stay in this particular group of patients. Despite attempts to construct a predictive model for the length of stay in moderate to severe CAP patients using variables such as procalcitonin, CRP, D-dimer, and leukocyte count, a meaningful predictive model could not be established. However, lactic acid and albumin were found to have a significant association with the length of stay, suggesting their clinical potential as reliable predictors in this context. Consequently, directing attention towards the monitoring and management of lactic acid and albumin could prove valuable in predicting treatment duration and enhancing the overall treatment strategy for individuals with moderate to severe CAP.

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