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The association between C-reactive protein (CRP)/ Albumin Ratio (CAR) and the outcomes of patients with Ludwig's Angina

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ABSTRACT

Background: A severe form of widespread cellulitis that affects the submandibular and submental regions is known as Ludwig's angina. The C-reactive protein/Albumin Ratio (CAR) was utilized to evaluate the prognosis of several different disorders. This research aims to evaluate the correlation between CAR and mortality as well as the outcome of patients with Ludwig's Angina. Additionally, it seeks to determine the optimal CAR ratio threshold for predicting mortality in Ludwig's Angina patients.

Methods: This study presents a retrospective cohort analysis of patients diagnosed with Ludwig's Angina aged over 20 years and underwent operative treatment at RSUD Dr. Soetomo Surabaya between January 2018 and April 2023. Data were analyzed using SPSS version 23.0 for Windows.

Results: 121 patients diagnosed with Ludwig's Angina were recruited for the study. In this study, most research subjects (65.4%) were male. The percentage of cases classified as mild, moderate, or severe was 5.4%, 58.5%, and 36.2%, respectively. The calculated cutoff value for CAR was determined to be 8.87. The model's sensitivity was 66%, indicating its ability to identify positive cases correctly. Similarly, the model's specificity was determined to be 66.3%, demonstrating its ability to identify negative cases correctly. The p-values for the relationship between CAR and patient outcome, severity, and length of stay (LOS) were found to be 0.001, 0.028, and 0.014 in each case.

Conclusion: The C-reactive protein/Albumin (CAR) ratio, which serves as an inflammatory marker, can be utilized to evaluate the mortality rate associated with Ludwig's Angina. This tool can stratify patients diagnosed with Ludwig's Angina.

Keywords: Ludwig's angina, prognosis, mortality, CRP, CRP-albumin ratio.
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INTRODUCTION

Ludwig's Angina is a highly severe and rapidly spreading diffuse cellulitis that impacts submandibular, sublingual, and submental cavities. Due to its anatomical location, Ludwig's angina can pose a life-threatening emergency. In the era before the availability of antibiotics, the mortality rate of this disease surpassed 50% as a result of upper airway obstruction.[1]

Most cases are attributed to odontogenic diseases, including dental infection, tooth extraction, endodontic procedures, periodontal conditions, and dental trauma. The patients exhibit typical symptoms, including fever, malaise, abrupt soft swelling of the floor of the mouth, difficulty swallowing, difficulty breathing, and excessive salivation. Certain patients may exhibit trismus due to a delay in diagnosis and treatment. The cause of death is commonly attributed to sepsis. Furthermore, it is imperative to address the issue of airway obstruction, as it poses a significant risk and necessitates appropriate airway management interventions, such as implementing a tracheostomy procedure.[1]

A study conducted by Sakarozi R et al. examined 96 patients at Dr. Soetomo Hospital in Surabaya. The study revealed a significant correlation between the Neutrophil-Lymphocyte Ratio (NLR) and the severity, cure rate, and length of stay of patients diagnosed with Ludwig's Angina. This observation suggests that further examination of additional infectious factors may be conducted to forecast the prognosis of patients with Ludwig's Angina.[2]

Laboratory tests for measuring C-reactive protein (CRP) and albumin are readily accessible through standard laboratory procedures. CRP is an acute inflammatory protein that can rise to a thousand times at the site of infection or inflammation. The observed response pattern in most patients diagnosed with Ludwig's Angina is consistent with the activation of both host and humoral immunity mechanisms. These mechanisms include the activation of complement, acute phase proteins, cytokines, monocytes, macrophages, and anti-inflammatory mediators. In clinical practice, albumin has been extensively utilized as a diagnostic indicator for malnutrition. Acute and chronic inflammatory conditions impact serum albumin levels through the modification of liver protein metabolism and the induction of capillary leakage. Low levels

of albumin may function as an indicator of inflammatory conditions.[3]

The CRP/Albumin Ratio (CAR) has gained popularity as a reliable indicator of poor prognosis or mortality in various diseases. Extensive research has been conducted on the correlation between elevated levels of CRP and the prognosis and mortality rates among patients in critical condition. Nevertheless, it is widely acknowledged that reduced serum albumin levels are associated with an unfavorable prognosis and higher mortality rates.[4-6]

Several studies have presented compelling evidence that supports the prognostic significance of the C-reactive protein/Albumin ratio across diverse patient populations. For instance, Ayrancı MK et al. conducted a study investigating the mortality prognosis of patients in intensive care units.[6] However, no research has explored the relationship between CRP/Albumin ratio values and prognostic prediction, specifically in patients diagnosed with Ludwig's Angina. The user's text is too short to be rewritten professionally. Hence, the objective of this study was to evaluate the correlation between the CRP/Albumin ratio and the prognosis of individuals diagnosed with Ludwig's Angina.

MATERIALS AND METHODS

Study Design and Participants

This study employs a retrospective cohort observational analytic research design to establish a correlation between the CRP/Albumin ratio (CAR) and patient outcomes in individuals diagnosed with Ludwig's Angina. The study included a sample of patients diagnosed with Ludwig's Angina who were over 20 years old and underwent operative treatment at Dr. Soetomo Surabaya Hospital between January 2018 and April 2023. The selection of patients for the study was based on fulfilling the predefined inclusion and exclusion criteria. Based on the results of the sample calculation, it has been determined that a minimum of 29 samples is required for this study. The research samples were obtained through consecutive sampling, adhering to the study's inclusion and exclusion criteria from January 2018 to April 2023. The study utilized specific inclusion and exclusion criteria. Inclusion criteria encompassed the medical record data of patients diagnosed with Ludwig's Angina who underwent operative treatment at the Department of Surgery, RSUD, Dr. Soetomo Surabaya. Patients with incomplete medical record data were excluded from the analysis.

C-Reactive Protein /Albumin Ratio (CAR) Value

The independent variable in this study is the value of the C-reactive protein/Albumin ratio (CAR) in the blood. It is categorized as a high CRP / albumin ratio if the value is greater than 34.3 and a low CRP / albumin ratio if it is less than 34.3.

Severity of odontogenic infection

The dependent variables in this study were the severity assessed by the odontogenic infection severity score and the parameters of mortality and length of hospitalization among patients with Ludwig's Angina. The score is determined by evaluating various parameters, including systemic inflammatory response syndrome (SIRS), trismus, dysphagia, affected fascial cavity, signs of dehydration, and comorbidities. The classification is as follows: 0 represents the normal category, while severity scores ranging from 1 to 8 indicate mild severity. Scores between 9 and 16 indicate moderate severity, and scores exceeding 16 indicate severe severity. The data scale in question is ordinal. The severity assessment holds significant importance in planning therapy and predicting the disease course's prognosis, alongside examining physical and laboratory findings.[1]

Statistical Analysis

The statistic collection procedure was conducted utilizing the SPSS version 23.0 software program for Windows. The data obtained from the independent and dependent variables are considered ordinal data. These data will be analyzed using statistical tests such as the Chi-Square and Spearman rank correlation tests. A P-value below 0.05 indicates statistical significance.

RESULTS

Samples characteristics

This study included 130 patients diagnosed with Ludwig's Angina who were above 20 years of age and underwent operative treatment at RSUD Dr. Soetomo Surabaya between January 2018 and April 2023. The demographic attributes of the participants involved in this study are presented in Table 1 and Table 2.

As shown in Figure 1, the optimal sensitivity result is 0.659, while the optimal 1-specificity result is 0.337. The area under the curve (AUC) value was determined to be 0.631, with a significance level of 0.017 ($p < 0.05$), as shown in Table 3. Based on the findings, it can be inferred that there was a significant correlation between the CRP/albumin ratio score and the mortality rate of patients with Ludwig's angina. The test's sensitivity was determined to be 65.9%, while the specificity was calculated to be 66.3%. A ROC analysis table was created to determine the optimal cut-off value for the CAR. The optimum cut-off value for achieving the optimum sensitivity of 0.659 and optimum 1-specificity of 0.337 is 8.87 (Table 4 and Table 5).

A significant correlation was observed between the CAR and the mortality outcome of patients diagnosed with Ludwig's Angina ($p<0.05$) (Table 6). Patients exhibiting low CAR values demonstrated a survival outcome of 65.2%, whereas patients with high CAR values experienced mortality at a rate of 65.9%. The table additionally presents the positive predictive value (PPV) and negative predictive value (NPV) as 80.6% and 46.6%, correspondingly, in relation to a low CAR score's impact on patient outcome.

There was a strong association between the CAR and the severity of Ludwig's Angina patients ($p<0.05$) (Table 6). Patients with low CAR category 100% had mild severity. While patients with a high CAR category, 52.9% had a high severity level. Moderate CAR category values tended to have moderate severity (56.9%).

A significant correlation was observed between the CAR and the severity of Ludwig's Angina patients ($p<0.05$), as shown in Table 6. Patients classified in the low CAR category exhibited mild severity

in their condition. A significant correlation was observed between patients classified in the high CAR category and an increased severity level, with 52.9% of patients falling into this category. The category values of the moderate CAR tended to be associated with a moderate severity level, accounting for 56.9% of cases.

Table 1. Study subject characteristics

Variable	Frequency (n=130)	Percentage (%)
Gender		
• Male	85	65.40
• Female	45	34.60
Age (years old)		
• <30 years old	5	3.80
• 30-39 years old	33	25.40
• 40-49 years old	37	28.50
• 50-59 years old	30	23.10
• ≥60 years old	25	19.20
Severity of Ludwig's Angina		
• Mild	7	5.40
• Moderate	76	58.50
• Severe	47	36.20
Length of stay (LOS)		
• <7 days	77	59.20
• 7-14 days	36	26.70
• >14 days	17	13.00
Collection in facial space		
• Low severity space	5	3.80
• Moderate severity space	10	7.70
• High severity space	115	88.50
Fever		
• Yes	58	44.60
• No	72	55.40
Dysphagia		
• Yes	113	86.90
• No	17	13.10
Ondontogenic Problem		
• Yes	75	57.70
• No	55	42.30
Comorbidities		
• Yes	115	88.50
• No	15	11.50
Diabetes Mellitus		
• Yes	112	86.20
• No	18	13.80
Outcome		
• Alive	89	68.50
• Dead	41	31.50

Table 2. Characteristics of Variables

Variable	Mean	SD	Min-Max
Age (years old)	47.43	11.854	19-70
Length of stay / LOS (days)	7.05	5.442	1-36
CRP (mg/dl)	21.56	9.47	3-48
Albumin (g/dl)	2.86	0.522	2-4
CRP/Albumin Ratio (CAR)	7.99	4.39	0.85-25.97

SD: Standard Deviation; LOS: Length of Stay; CRP: C-Reactive Protein; Min: Minimum; Max: Maximum

DISCUSSION

Ludwig's Angina is a potentially life-threatening infection of the soft tissues, specifically cellulitis, affecting the floor of the mouth and neck. The process involves the sublingual and submaxillary spaces, two distinct areas located on the floor of the mouth. Several additional factors can potentially accelerate the onset or exacerbate the illness in a patient. These include diabetes, oral cancer, dental caries, alcoholism, malnutrition, and immunocompromised status. The majority of cases, approximately ninety percent, are attributed to the lower molar teeth, specifically the second and third teeth in the dental arch. Dental infections affecting the second or third molars, particularly infections of partially erupted third molars, commonly contribute to the development of Ludwig's angina. Due to the relatively thinner lingual aspect of the tooth socket compared to the buccal aspect, it is more likely for an infection to propagate in the lingual direction rather than the buccal direction. Once the virus has initially disseminated to the sublingual space, it migrates to the submandibular space. Furthermore, the infection can spread to the retropharynx, the area between the tonsils and the pharynx.[7]

The main objective of this study is to examine the correlation between CRP/Albumin ratio values and clinical outcomes in patients diagnosed with Ludwig's Angina. The study included patients diagnosed with Ludwig's Angina, with the youngest individual being 20 years old, the oldest individual being 70 years old, and the average age of the participants being 47.43 years old. The age range of 40-49 accounted for the largest proportion, representing 28.5% of the total sample. The findings align with the research conducted by Botha A et al., indicating that patients diagnosed with Ludwig's angina had a mean age of 43 years. Eleven investigations were conducted, involving 910 patients with a mean age of 47.6 ± 8.2 years and a female population comprising 47.0% of the participants.[8,9] The mean age at presentation was 40.36 years. Patients within this age range typically consist of actively employed individuals who are essential community members. Consequently, it is necessary

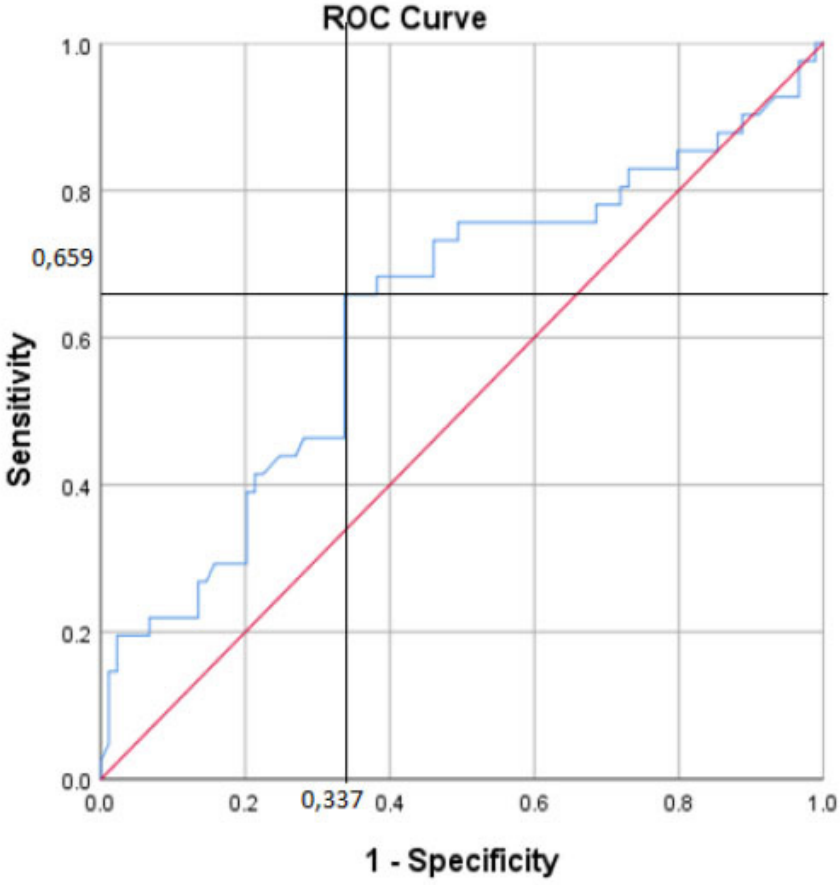

Figure 1. ROC curve of CRP/Albumin Ratio with mortality.

Table 3. AUC value

Area	Sd Error	Sig.	CI (95%)
0.631	0.055	0.017	0.523-0.739

Table 4. ROC coordinate regression

Cut off CRP/Albumin Ratio (CAR)	Sensitivity	1 - Specificity
8.73	0.659	0.360
8.80	0.659	0.348
8.87*	0.659	0.337
8.91	0.634	0.337
8.96	0.585	0.337

*The highest sensitivity and specificity

Table 5. CRP/Albumin Ratio (CAR) Category

CAR Value	Frequency (N=130)	Percentage
High (≥8.87)	58	44.60%
Low (<8.87)	72	55.40%

to consider and respect their time constraints. Individuals in this particular age group also exhibit a greater incidence of newly diagnosed or advanced comorbid conditions. Additionally, this could be attributed to insufficient medical examination records due to a lack of time.[9]

The findings of this study indicate a higher prevalence of Ludwig Angina in males than females. These results align with the findings of a study conducted by Botha, wherein 69.9% of the participants were identified as male and 28% as female.[9] This discovery was also observed in research carried out by Allareddy et al. in a more extensive sample size.[10] One potential hypothesis that may contribute to understanding this phenomenon within our context is the traditional gender role, wherein men typically assume the role of primary earners in their families. This responsibility may result in limited availability of free time for seeking medical or dental care. A potential explanation for this phenomenon is that males tend to delay seeking medical attention compared to females, resulting in longer wait times on average. Consequently, it is common for men to present with more advanced stages of disease, necessitating more intensive treatment. Furthermore, deeply ingrained cultural beliefs imply that men displaying vulnerability by seeking medical help for illnesses or infections are exhibiting signs of weakness.[9]

Diabetes mellitus is widely recognized as a significant factor that can compromise immune function, impede the healing process of wounds, and elevate the susceptibility to infections. Additionally, individuals with diabetes are more prone to experiencing prolonged hospital stays due to the escalated severity of infections. Based on the research conducted by Chen MK et al., individuals diagnosed with diabetes exhibit an elevated susceptibility to developing bacteremias, pneumonia, and necrotizing fasciitis. This statement applies to our research findings as well. Additionally, it highlights the importance of closely monitoring these patients, maintaining strict control over their blood glucose levels, and promptly implementing aggressive management strategies for both the initial infection and subsequent complications, as evidenced in the study conducted by Chen et al. in 2000.[11]

In the early stages, a severe infection can be characterized by several clinical manifestations, including elevated or abnormally low body temperature, rapid heart rate, increased breathing rate, and low blood pressure. Certain laboratory findings, such as a high leukocyte count and elevated C-reactive protein levels, may also be observed. Based on the findings of Sproston NR and Ashworth JJ, C-reactive protein plays a crucial role in both inflammatory processes and the host's immune response to infection.[12] These

Table 6. Relationship between CRP/Albumin Ratio and Outcome, Severity, and Length of Stay (LOS)

Outcome	CAR Value Category				p
	Low (<8.87)		High (>8.87)		
	% in CAR group	% in outcome	% in CAR group	% in outcome	
Mortality (%)					
Alive	80.60	65.20	53.40	34.80	0.001*
Dead	19.40	34.10	46.60	65.90	
Severity, n (%)					
Mild	7 (100.00)		0 (0.00)		
Moderate	41 (56.00)		31 (43.10)		0.028*
Severe	24 (47.10)		27 (52.90)		
LOS, n (%)					
<7 days	48 (62.30)		29 (37.70)		
7-14 days	20 (55.60)		16 (44.40)		0.014*
>14 days	4 (23.50)		13 (76.50)		

*Statistically significant if p-value less than 0.05

processes encompass various mechanisms, such as complement pathways, apoptosis, phagocytosis, nitric oxide (NO) release, and the production of cytokines, including interleukin-6 and tumor necrosis factor-α. In their case report on Ludwig's angina, Kobayashi M and Watanabe K observed an increase in serum C-reactive protein levels, specifically measuring 2333.38 nmol/L (compared to the normal range of 28.57 nmol/L). It was determined that the patient presented with a diagnosis of angina pectoris. In the context of this specific research project, the average C-reactive protein values of the patients were determined to be 21.56 mg/dl.[13]

The statistical parameter albumin had a mean value of 2.86 g/dl, with a minimum value of 2 g/dl and a maximum value of 4 g/dl. The acceptable range for albumin levels is 2–4 grams per deciliter (g/dL). Hypoalbuminemia has been observed in diverse clinical contexts and linked to critical illness and patient mortality.[14] According to the research conducted by Eckart A et al., it has been noted that both acute and chronic inflammatory conditions have a significant influence on the levels of serum albumin. These conditions, which include pancreatitis, infection, trauma, burns, and organ dysfunction, bring about changes in liver protein metabolism, induce capillary leakage, reduce the half-life of serum albumin, decrease the overall mass of serum albumin, increase the distribution volume, and elevate the expression of vascular endothelial growth factor. Consequently, decreased levels of albumin may serve as an indicator of inflammatory conditions.[15] This statement is further substantiated by several research studies that have established a correlation between decreased levels of albumin and the presence of COVID-19. There were a total of eleven trials conducted, involving a combined sample size of 910 patients. The mean age of the participants was 47.6 ± 8.2 years, and 47.0% of the patients were female. During the admission process, it was observed that the severe COVID-19 group had a weighted mean serum albumin level of 3.50 g/dL (confidence interval: 3.26-3.74 g/dL). In contrast, the non-severe COVID-19 group had a measured mean serum albumin level of 4.05 g/dL (confidence interval: 3.82-4.27 g/dL). The observed results had a significant effect on the statistical measures. Additionally, the index of dispersion was calculated to be 91.2%.[8]

There is an ongoing evaluation of the predictive value of the CRP/albumin ratio in assessing patients with cancer, inflammation, and sepsis.[16,17] There have been prior recommendations regarding the potential integration of albumin and CRP into a unified indicator. Subsequent studies have provided evidence indicating that the CRP/albumin ratio exhibits greater prognostic reliability than CRP or albumin as individual markers. This finding contributed to the recommendation to utilize the integrated CRP and albumin measurement.[18,19] A CRP/albumin ratio is considered high when the value exceeds 34.3, whereas a value below 34.3 indicates a low ratio. Based on the results of a study conducted by Park J et al., it was observed that the CRP level and the CRP/albumin ratio exhibited significantly higher values in non-surviving patients receiving infection treatment, as compared to the surviving patients.[4] Based on the results of another study, it was determined that the ideal CAR cut off value was 37. This value was found to have a significant association with hepatic cancer, as indicated by the Italian program score, as well as vascular disease.[20] On the other hand, the cut-off threshold for CRP/albumin utilized in this investigation was 8.87, indicating a lower value. This may be attributed to patients diagnosed with Ludwig's angina in this study exhibiting a low CRP level.

Despite the limited sample size, our study findings indicate that the CAR remains a reliable prognostic indicator for patients. In predicting mortality beyond 180 days, a CRP/albumin ratio exceeding 5.09 demonstrated the highest levels of sensitivity and specificity. There were notable disparities in the distribution of patients concerning malignancy and age between the non-surviving group and the remaining patients. However, even after accounting for these factors, the CAR remained a significant prognostic indicator. Although the area under the curve (AUC) for the CRP/albumin ratio is only 0.620, suggesting a modest predictive capacity, the effectiveness of this model was confirmed by the observed survival disparity in the Kaplan-Meier curve analysis. Based on the results obtained from our study, it has been determined that a dependable prognostic indicator for patients is the pre-treatment measurement of the CAR. The importance of the

initial values before treatment was also observed in other studies, which showed that the early clinical evaluations often provided the most precise indications of the subsequent physiological disruptions. The CAR at admission can still be used to stratify patients based on their disease severity, even after being discharged from the hospital. This is particularly effective when considered alongside other markers.[21–23]

In addition to the comprehensive physical examination and analysis of laboratory findings, assessing disease severity plays a crucial role in guiding therapeutic interventions and forecasting the prognosis of the disease progression.[24-27] In this study, it was observed that approximately 58.5% of patients diagnosed with Ludwig's Angina demonstrated a moderate level of severity. All patients classified under the low CAR category exhibited a severity level that can be described as modest. A significant proportion of patients, specifically 52.9%, in the category characterized by a high CAR showed a notable degree of severity. On average, there was an association between moderate severity (56.9%) and values of moderate CAR.

This study has several limitations. This examination was conducted in a single university hospital in its entirety. As a consequence of this, the findings of this study may not be adequate to adequately describe the circumstances facing the entirety of the population in Indonesia. On the other hand, the outcomes of this study could be regarded as preliminary data in Indonesia. Second, the number of participants in this research was not particularly large. As a result, additional research with more participants or a study conducted across multiple national centers may be required to obtain more accurate results.

CONCLUSION

CRP/Albumin ratio values are substantially associated with mortality, severity, and length of stay (LOS) in patients with Ludwig's Angina.

CONFLICTS OF INTEREST

No competing interests were declared.

ETHICAL CONSIDERATION

This research was conducted based on the ethical conduct of research from the Ethics Committee of the Dr. Soetomo General Hospital Surabaya with number: 1264/LOE/301.4.2/III/2023.

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AUTHOR CONTRIBUTION

All authors contributed to the study from the conceptual framework, data gathering, and analysis until the study's results were interpreted upon publication.

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