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# The relationship between metabolic acidosis as a predictive factor of mortality in Ludwig's Angina patients at Dr. Soetomo General Hospital, Surabaya, Indonesia

Alif Rakhman Prima Adi[1], Marjono Dwi Wibowo[2*], Dwi Hari Susilo[2]

[1]Department of Surgery, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo General Hospital, Surabaya, Indonesia;
[2]Head and Neck Surgery Division, Department of Surgery, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo General Hospital, Surabaya, Indonesia;

*Corresponding author:
Marjono Dwi Wibowo;
Department of Surgery, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo General Hospital, Surabaya, Indonesia;
marjono-d-w@fk.unair.ac.id

## ABSTRACT

**Background:** Mortality in a patient with Ludwig's Angina is usually due to prolonged sepsis. When sepsis is present, acidosis and lactate independently predict mortality in critically ill patients. Patients who develop acidosis after 6 hours are at high risk of death and should be treated more aggressively than septic patients.

**Methods:** A retrospective cohort study to determine the association between metabolic acidosis and mortality in Ludwig's Angina patient at Dr. Soetomo General Hospital Surabaya at Dr. Soetomo between January 2019 - December 2020. We retrospectively reviewed 42 medical records of patients with Ludwig's Angina. We collected patient data such as age, history, physical examination, blood gas analysis, surgical intervention, comorbidities, complications before surgery, and patient outcomes.

**Results:** We analyze a total of 42 patients. 71.40% were male, and 38.60% were in the group of 51-60 years, with a mean age of 45.73 years. 59.50% had metabolic acidosis, and 83.30% died. Based on the comorbidities, there were 28.60% with diabetes mellitus, 21.40% with dental caries and 16.70% with hypertension. A complication of hypoalbuminemia was found in 42.90%, 23.80% with sepsis, and 21.40% with acute kidney injury. Metabolic acidosis and mortality had a significant relationship with a p-value of 0.047, OR 5.00 (95% CI, 0.933-26.785). No comorbidity or complication variables impacted patient outcomes (p > 0.05 for all).

**Conclusion:** There was a significant relationship between metabolic acidosis and mortality of Ludwig's angina patients.

**Keywords:** Ludwig's Angina, metabolic acidosis, mortality, patient outcome.
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## INTRODUCTION

Wilhelm Frederick von Ludwig first described Ludwig's angina as rapidly progressing cellulitis in the submandibular gland region that spreads through anatomical continuity without leading to abscess formation. Dental infection, tooth extraction, endodontic, periodontal, and dental trauma are among the most frequent odontogenic etiologies, accounting for up to 85% of cases.[1,2] Patients with immunocompromised conditions such as AIDS, glomerulonephritis, diabetes mellitus, and aplastic anemia are more likely to get Ludwig's angina. The spreading of odontogenic infection accounts for 57% of deep neck abscesses. With the potential for spreading the infection to the intrapleural space and mediastinal tissues, the mortality rate for mediastinitis ranges from 17-50%. Sepsis usually results in death. In addition, airway obstruction is a serious complication and requires airway management such as tracheostomy.[3,4]

Since the 1940s, Ludwig's angina incidence and mortality have decreased due to antibiotics. In the pre-antibiotic era, the mortality rate for Ludwig's Angina was 50%. Aggressive management with airway protection, intravenous antibiotics and surgical intervention can significantly reduce mortality by less than 10%.[3-5] Several life-threatening conditions in Ludwig's Angina patients include airway obstruction, upper respiratory tract infection, acute respiratory distress syndrome (ARDS), descending mediastinitis, necrotizing fasciitis, pleural empyema, pericarditis, jugular vein thrombosis, carotid artery rupture, septic embolism, sepsis and disseminated intravascular coagulopathy. Death is often due to prolonged sepsis.[6-7] When sepsis is present, acidosis and lactate independently predict mortality in critically ill individuals. In contrast to independents, patients with acidosis (BE -6 and/or pH 7.3) and hyperlactatemia showed a better predictive value. Patients who develop acidosis after 6 hours are at high risk of death and should be treated more aggressively for septic patients.[8]

There is currently very little research exploring metabolic acidosis's role in predicting death in Ludwig's angina patients in Indonesia. The availability of

data on this subject can help clinicians predict results and be considered when deciding what kind of therapy should be administered to patients with Ludwig's angina. Therefore, in this study, the researchers aimed to analyze the role of metabolic acidosis as a predictive factor in mortality in patients with Ludwig's angina in Surabaya, Indonesia.

## MATERIALS AND METHODS

### Study design and participants

This retrospective cohort study was conducted at Dr. Soetomo General Hospital (Surabaya, Indonesia). In this study, we included all patients with Ludwig's Angina who were treated at Dr. Soetomo from when the patient was in the emergency room to going home after treatment from January 2019-December 2020. We excluded patients who were dead on arrival, patients with no complete data in the medical record and patients with an unknown outcome. We used a total sampling method and included all patients who fulfilled the inclusion criteria. In total, we retrospectively reviewed 42 medical records of patient with Ludwig's Angina who was treated at Dr. Soetomo between January 2019 - December 2020. This study was reviewed and approved by the Medical Ethical Committee of Dr. Soetomo General Hospital Surabaya (approval number 0887/LOE/301.4.2/IV/2022), following the guidelines of the Declaration of Helsinki.

### Data collection

We reviewed medical records, and laboratory findings, for all patients with Ludwig's Angina. All the data were obtained from paper-based medical records and electronic medical records. Information collected includes the patient's name, medical record number, age, date of birth, history, physical examination, blood gas analysis, surgical intervention, comorbidities, complications before surgery, and patient outcomes. Ludwig's angina is commonly known as aggressive, widespread cellulitis of the floor of the mouth. In this study, Ludwig's angina was diagnosed when cellulitis of the submandibular, submental, and sublingual space was found in the patient, which may result in the clinical symptom of trismus.

The interpretation of the blood gas analysis result performed the determination of metabolic acidosis status. The authors of this study performed the interpretation of the blood gas analysis result. This study's criteria for diagnosing metabolic acidosis were a decrease in serum bicarbonate ($HCO_3$-), a reduction in $pCO_2$, a decrease in pH below 7.35, and an excess base level below -2.

### Statistical analysis

Statistical analysis was performed using the SPSS statistical software package version 23.0. We categorized the data findings of each patient's metabolic acidosis and outcome into alive and dead patients. The variables were analyzed and presented as frequency distribution and cross-tabulation. We examined the associations between metabolic acidosis and patient outcome using Chi-squared ($\chi^2$) test. A logistic regression test was used to measure the odds ratio (OR) of metabolic acidosis, comorbid and complications of the disease on mortality in patients with Ludwig's angina. The relationship between various variables and patient outcomes will be calculated using multivariate analysis. A p-value of less than 0.05 was considered statistically significant.

## RESULTS

### Sample characteristics

Ludwig's Angina patients at RSUD Dr. Seotomo Surabaya between 2019-2020 were used in this study. This study is an analytical retrospective study with a cross-sectional design. The population and sample of this study were taken from the patient's medical records. The population in this study were Ludwig's Angina patients who were treated at RSUD Dr. Soetomo Surabaya from January 2019 to December 2020. In total, we utilize 42 patients for

**Table 1. Demographic characteristics of Ludwig's angina patients.**

| Demographic characteristics | | n (%) |
|---|---|---|
| Gender | Female | 12 (28.60) |
| | Male | 30 (71.40) |
| Age (Mean) | 45.73 years | |
| | < 30 years | 7 (16.70) |
| | 31-40 years | 7 (16.70) |
| | 41-50 years | 10 (23.80) |
| | 51-60 years | 12 (38.60) |
| | > 60 years | 6 (14.20) |

**Table 2. Characteristics of metabolic acidosis.**

| Characteristics | n (%) |
|---|---|
| Not metabolic acidosis | 17 (40.50) |
| Metabolic acidosis | 25 (59.50) |

further analysis. Our samples consist of 30 males (71.40%) and 12 females (28.60%). Based on age group, most patients were in the age group of 51-60 years with 12 patients (38.60%), followed by the age group of 41-50 years with 10 patients (23.80%), the age group of 31-40 years with 7 patients (16.70%), and the age group of under 30 years with 7 patients (16.70%). The mean age of this research subject was 45.73 years. The demographic data of the research subjects are presented in Table 1.

### The metabolic acidosis profiles

In this study, we found that most of the patients had metabolic acidosis. A total of 25 patients (59.5%) had metabolic acidosis, while 17 patients (40.5%) did not, as seen in Table 2. Most patients who died had metabolic acidosis, 10 patients (83.3%), while patients who died without metabolic acidosis were only 2 patients (16.7%). From the group of surviving patients, we found a similar number of patients between patients who had metabolic acidosis and those who did not (Table 3). The most common comorbidities in patients were diabetes mellitus, hypertension or high blood pressure, and dental caries. It was found that there were 12 patients (28.6%) who had diabetes mellitus, 9 patients (21.4%) had dental caries, and 7 patients (16.7%) had hypertension (Table 4). The most common complications in patients with Ludwig's Angina were hypoalbuminemia with 18 patients (42.9%), sepsis with 10 patients (23.8%), and acute kidney injury with 9 patients (21.4%) (Table 5).

**Table 3.** Patient output and metabolic acidosis.

| Characteristics | Not metabolic acidosis (N=17) | Metabolic acidosis (N=25) | Total (N=42) |
|---|---|---|---|
| Alive, n (%) | 15 (50.00) | 15 (50.00) | 30 (100.00) |
| Died, n (%) | 2 (16.70) | 10 (83.30) | 12 (100.00) |

**Table 4.** Comorbidities in Ludwig's angina patients.

| Comorbidities | n (%) |
|---|---|
| Diabetes mellitus | 12 (28.60) |
| Dental caries | 9 (21.40) |
| Hypertension | 7 (16.70) |

**Table 5.** Complications in Ludwig's angina patients.

| Complications | n (%) |
|---|---|
| Hypoalbuminemia | 18 (42.90) |
| Sepsis | 10 (23.80) |
| Acute kidney injury | 9 (21.40) |

**Table 6.** Chi-square test between metabolic acidosis and patient outcome.

| Statistical analysis | p-value | Odds Ratio (95%CI) |
|---|---|---|
| Pearson Chi-Square | 0.047* | 5.00 (0.933-26.785) |

*Statistically significant if p-value less than 0.05

**Table 7.** Logistic regression test on comorbidities and complications variables.

| Variables | p-value | Exp (B) |
|---|---|---|
| Diabetes mellitus | 0. 997 | 6.581 |
| Hypertension | 0.965 | 0.942 |
| Dental caries | 0.998 | 1768 |
| Hypoalbuminemia | 0.517 | 0.375 |
| Acute Kidney Injury | 0.811 | 1.547 |
| Sepsis | 0.997 | 3.817 |

*Statistically significant if p-value less than 0.05

### The association between metabolic acidosis and clinical outcome

The Pearson Chi-Square test showed a significant relationship between metabolic acidosis and patient outcomes, whether alive or dead, with a significance value of 0.047 (P = 0.05). In this analysis, the odds ratio is 5.00 (95% CI: 0.933-26.785). This demonstrates that people with metabolic acidosis have a 5 times higher risk of passing away than those without, as seen in Table 6. Then logistic regression tests were performed on comorbidities such as diabetes mellitus, hypertension, and dental caries, and complication variables such as hypoalbuminemia, acute kidney injury, and sepsis. It was found that no comorbidity or complication variables impacted patient outcomes because none of the variables had significant values (P > 0.05 for all), as presented in Table 7.

### DISCUSSION

According to the study's demographic findings, males dominated the patient population with 30 patients (71.40%), while females comprised only 12 (28.60%). Based on age group, most patients were in the age group of 51-60 years with 12 patients (38.60%), followed by the age group of 41-50 years with 10 patients (23.80%), the age group of 31-40 years with 7 patients (16.70%), and the age group of under 30 years with 7 patients (16.70%). The mean age of this research subject was 45.73 years.

The study by Kumar S et al. in India also showed male dominance in their study of Ludwig's Angina. It was found that 60% of the patients in the study were male, while 40% were female. Meanwhile, from the age variable, it was found that most patients were in the age group of 51-60 years, with 15 patients (37.5%).[8] These findings are consistent with the findings in our study. Another study by Tripathy S et al. in India supported our findings, showing that 71% of patients with Ludwig's Angina were males and only 29% were females. Then in the same study, the age distribution was dominated by the age group of 41-50 years with 14 patients and the age group of 50-60 years with 8 patients.[9] Study by Lin QL

et al. in China found that the mean age of patients in their study was 53.41 years. The dominant age group was the age group over 60 years, with 11 patients, followed by the age group 51-60 years, with 7 patients. The gender of the patients in their study was dominated by males, with 21 patients (72%), while only 8 (28%) were female.[10]

A subsequent study by Edetanlen BE et al. in Negria in Ludwig's angina patients found that the mean age of the patients was 38.6 years in the surgical group and 41.6 years in the conservative group. The gender of the patients in this study was dominated by males, with 27 patients in the surgical group and 11 in the conventional group. In comparison, only 9 patients in the surgery group and 8 in the conservative group were females.[11] However, compared to these studies, literature studies generally do not have a gender predilection. Another important epidemiological aspect is that Ludwig's Angina cases are usually accompanied by other systemic diseases such as infections and diabetes mellitus.[12] In this investigation, most of the patients had metabolic acidosis. About 25 patients (59.5%) had metabolic acidosis, while 17 (40.5%) did not experience metabolic acidosis. Metabolic acidosis in Ludwig's Angina patients has rarely been studied, and only a few literature sources address this variable. The study by Lin QL et al. found that patients with Ludwig's Angina had an average blood lactate concentration level of 2.06 mmol/L. The minimum value for this study's blood lactate concentration level is 0.6 mmol/L, while the maximum is 6.7 mmol/L.[10]

Increased lactic acid causes acidosis. Acidosis is an increase in blood pH. A similar condition was found in our study. In patients with metabolic acidosis, it was found that patients with acidosis had a higher mortality rate. The normal lactate value is < 2 mmol/L. Hyperlactatemia is a blood lactate level between 2 and 4 mmol/L. Metabolic acidosis was discovered in the Lin QL et al. study. Hyperlactatemia is a type of metabolic acidosis. Many metabolic acidosis conditions are associated with an increased risk of death, organ failure, and shock. Metabolic acidosis can cause decreased cardiac contractility and reduced vascular responsiveness to vasopressors. In addition, metabolic acidosis is also

associated with the worsening of existing comorbidities in patients.[13]

Following evaluation, it was discovered that 10 patients (83.3%) of the total patients who passed away had metabolic acidosis, compared to only 2 patients (16.7%) who passed away without having this condition. From the group of living patients, it was found that the same number of patients experienced metabolic acidosis and did not experience metabolic acidosis. The Pearson Chi-Square test showed a significant relationship between metabolic acidosis and patient outcomes, whether alive or dead, with a significance value of 0.047 (p 0.05). In this analysis, the odds ratio is 5.00 (95% CI, 0.933-26.785). This demonstrates that people with metabolic acidosis have a 5 times higher risk of passing away than those without. A study by Kumar T et al. in India reviewed patients with necrotizing soft tissue infection. In this study, it was found that out of 86 total patients, 25 patients experienced metabolic acidosis. Only three of the 25 patients survived, while 22 patients died. Statistical analysis showed that metabolic acidosis is also a risk factor for death in patients with necrotizing soft tissue infection.[14] Ludwig's angina itself is a soft tissue infection. Hence the findings of this study can be utilized as one of the supporting pieces of evidence showing metabolic acidosis is a risk factor for death in Ludwig's angina, even though this study did not specifically explain the type of necrotizing soft tissue infection the patient experienced.

The most common comorbid in patients were diabetes mellitus, hypertension or high blood pressure, and dental caries. It was found that there were 12 patients (28.6%) who had diabetes mellitus, 9 patients (21.4%) who had dental caries, and 7 patients (16.7%) who had hypertension. Diabetes mellitus is a risk factor for Ludwig's angina. Ludwig's angina generally does not occur in healthy patients but in patients with comorbidities associated with a decreased immune system, one of which is diabetes mellitus.[12] Similar findings were found in the study by Tripathy S et al. It was found in this study that out of 38 patients, around 27 patients (71%) had diabetes mellitus.[9] Then, a study by Lin QL et al. also showed that out

of 29 patients, 10 patients (34.48%) had diabetes mellitus.[10] In addition to small-scale studies, diabetes mellitus in Ludwig's angina patients has been widely reported in various case reviews. A case review by Kovalev VA described a 57 years old patient with severe Ludwig's Angina requiring emergency surgery to open the airway. Comorbidities related to immune system disorders, such as diabetes mellitus and a history of chemotherapy, are associated with the severity of clinical manifestations in patients with Ludwig's Angina.[15]

Ludwig's angina can also be the main clinical manifestation of diabetes mellitus. A case report by Infante-Cossio P et al. found a 28-year-old patient who presented with the initial complaint of a tooth infection. Then the patient experienced complications in the form of diabetic ketoacidosis, which was then exacerbated by the presence of Ludwig's Angina.[16]

As is well known, most of the etiology of Ludwig's angina comes from dental infections.[12] The relationship between diabetes mellitus and dental infection was described by the study of Ko HH et al. in Taiwan. This study shows that patients with diabetes mellitus are prone to dental infections. In this study, it was also found that there was a relationship between diabetes mellitus and the incidence of cellulitis in the facial area. It was found that patients with diabetes mellitus will suffer from cellulitis in the facial area 2 years after suffering from diabetes mellitus.[17] The Tripathy S et al. study reported that 8 out of 38 patients had hypertension.[9] Then, a study by Lin et al. found that out of 29 patients, 6 patients (20.69%) suffered from hypertension.[10] Apart from small-scale studies, there have been many reports in the form of case reviews regarding hypertension as a risk factor for Ludwig's Angina. A case report from Costain N et al. found a 33-year-old man with Ludwig's Angina. At the initial examination, the patient's blood pressure was 220/120 mmHg.[18]

As is well known that tooth infection is the main etiology of Ludwig's angina. Several case reports, such as those written by Costain I et al. and Mohamad E et al., had reported patients with Ludwig's Angina who had dental caries.[18,19] In this study, no association was found

between comorbidities and outcomes in patients with Ludwig's Angina. This may be due to the small sample size used in this study. The next variable is the complication variable. In Ludwig's Angina patients in this study, the most common complications in patients with Ludwig's Angina were hypoalbuminemia with 18 patients (42.9%), sepsis with 10 patients (23.8%), and acute kidney injury with 9 patients (21.4%). A study by Lin QL et al. reported that 2 patients had complications of sepsis (6.89%).[10] Then, a study from Okoje VN et al. found that out of 13 cases of Ludwig's angina, there were 2 patients with sepsis and 1 with acute kidney injury.[20] In this study, no association was found between complications of Ludwig's angina and mortality. This may be due to the small sample size and a small number of complications.

The complications above have not been widely studied in Ludwig's Angina. Studies by Norimatsu Y and Ohno Y in Japan found that hypoalbuminemia is related to cellulitis. Patients with hypoalbuminemia were found to be associated with patients requiring recurrent cellulitis treatment in the hospital. Patients with hypoalbuminemia tend to experience cellulitis recurrences more frequently.[21]

In cellulitis patients, acute kidney injury is a common complication. Epidemiologically, acute kidney injuries in hospitalized patients are acute tubular necrosis and prerenal acute kidney injury. Acute kidney injury can also arise due to the consumption of drugs. In hemodynamically compromised patients, acute kidney injury may also occur. This is relevant in our study because almost all patients undergo surgery which can be a risk factor for acute kidney injury.[22,23] sepsis is one of the most common side effects of Ludwig's angina, just like other infections. Proper antibiotic and surgical management is needed in sepsis to avoid further complications. In this study, we focused on analyzing acidosis metabolic as the predictive factor for outcome. Other laboratory parameters commonly used as a predictive marker for the outcome, such as neutrophil–lymphocyte ratio, platelet to-lymphocyte ratio, and albumin.[24-27]

This study has several limitations. First, this study was carried out in a single health

center. Therefore, the results of this study may not be able to characterize the situation in the Indonesian population. However, we believe that the findings in this study are important to provide preliminary data regarding the use of metabolic acidosis as a parameter to predict the outcome of Ludwig's angina patients in Indonesia. Second, the number of participants in this study is relatively small. Therefore, further research with a larger number of subjects or a multi-center study may be required to provide better results.

## CONCLUSION

There was a significant relationship between metabolic acidosis and mortality of Ludwig's angina patients. Patients with metabolic acidosis have a 5 times higher risk of dying compared to patients who do not suffer from metabolic acidosis.

## CONFLICT OF INTEREST

No competing interests were declared.

## ETHICAL CONSIDERATION

This study has received research permission from the Ethic Commission of the Faculty of Medicine, Universitas Airlangga, Dr. Soetomo General Hospital, Surabaya, Indonesia.

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## AUTHOR CONTRIBUTION

Conceived the study: APA. Designed the study: APA, MDW, and DHS. Analyzed the data: APA, MDW, and DHS. Wrote the manuscript: APA and MDW. Review the manuscript: MDW and DHS.

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