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# Anemia and metabolic acidosis are a predictor for mortality in children with severe acute malnutrition at Sanglah General Hospital, Bali



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## ABSTRACT

**Background:** Severe acute malnutrition (SAM) is one of the leading causes of morbidity and mortality in children in developing countries. Nutritional disorders are frequent in hospitalized patients, of which malnutrition is the most prevalent. Anemia and PH disturbance was commonly found in this condition. This study aims to determine the association between anemia and metabolic acidosis with the mortality among children with severe acute malnutrition.

**Methods:** A retrospective cohort study was conducted among 135 severe acute malnutrition children in the pediatric care unit of Sanglah General Hospital from the 2017-2018 period. The inclusion criteria were children

aged 1 month to 18 years diagnosed with SAM. Exclusion criteria were a patient diagnosed with a hematological disorder or renal disorder. Data were analyzed using SPSS version 20 for Windows.

**Results:** Anemia was diagnosed in 89 (65.9%) subjects in this study. Anemia increases the risk of death significantly by 3.98 times (95% CI 2.167-10.389;  $p < 0.001$ ). Metabolic acidosis was found in 35 (25.9%) subjects; this condition was also shown to significantly increase the risk of death by 1.5 times (95% CI 1.005-2.145;  $p = 0.018$ ).

**Conclusion:** Anemia and metabolic acidosis can be used as predictors for mortality in severe acute malnutrition patient significantly.

**Keywords:** Severe Acute Malnutrition, Anemia, Metabolic Acidosis, Mortality

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## INTRODUCTION

Childhood malnutrition is an important indicator of the health of a population.<sup>1</sup> A worldwide analysis recently identified childhood malnutrition as the leading risk factor for the global burden of disease.<sup>1</sup> Severe acute malnutrition (SAM) is one of the leading causes of morbidity and mortality in children in developing countries.<sup>1,2</sup> Nutritional disorders are frequent in hospitalized patients, of which malnutrition is the most prevalent.<sup>2</sup> In developed countries, the frequency of malnutrition among pediatric patients is around 24%.<sup>3</sup> Surveys conducted over the past two decades report 15% to 65% malnutrition rates in pediatric patients admitted to the intensive care unit (ICU), with malnourished children presenting a higher incidence of both infection and mortality.<sup>4</sup> Recent data have revealed that malnutrition in critically ill hospitalized children ranges from 10% to 24%. However, no independent association with mortality has been found.<sup>5</sup> In 2013 prevalence of severe acute malnutrition in Indonesia was 5.7%.<sup>6</sup>

This condition that kills children and intellectually maims those who survive. The complications caused by malnutrition very diverse. These changes include lowered immune response, atrophy, and increased permeability of the intestinal epithelial barrier, which facilitates infection and bacterial

translocation.<sup>7</sup> Malnourished patients also suffer from more inadequate healing of wounds, higher incidence of pneumonia, sepsis, and other conditions that can lead to increased mortality, length of hospital stay, and health care costs.<sup>7-9</sup> Malnutrition is responsible directly or indirectly for about 50% of deaths among children under five. Factors associated with mortality in children with severe acute malnutrition are blood glucose level, severe anemia, comorbidity, kwashiorkor as a type of SAM and dehydration.<sup>10,11</sup>

Anemia prevalence in children is high, especially in developing countries, and frequently is multifactorial.<sup>12</sup> It is often associated with childhood malnutrition, producing interlinked factors, several of which could be causally related to mortality risk. These factors include lack of hematinic (e.g., iron, folate, vitamins A, B-12 and C, and copper), impairment of red cell production by acute or sub-acute inflammation (with an increase in stored iron) and increased red cell destruction either via specific infections (e.g., malaria) or particular nutrients (e.g., vitamin A). Research in India found a high incidence of severe anemia in SAM with a large proportion (25%) of its requiring blood transfusion.<sup>12</sup> The study in Nigeria also revealed high mortality rates among malnutrition children who with severe anemia.<sup>13</sup>

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Severe acute malnutrition is a metabolic disorder characterized by profound disturbance of water, electrolytes, minerals, protein, fat, carbohydrates, and energy metabolism, along with disturbances in the function and composition of almost all tissues of the body.<sup>14</sup> Nutrition has long been known to influence acid-base balance strongly. Malnutrition is a state of catabolism and severe malnutrition is a state of severe catabolism. In a healthy body, homeostasis is maintained mainly by kidney, lungs, minerals and body fluids, and it is altered in malnutrition.<sup>14</sup>

The severe malnutrition may lead to a persistent increase in acid load in the internal milieu of the body, disturbing the internal homeostasis. The normal function of all body cells depends on the regulation of acid-base balance. Arterial Blood Gas (ABG) studies are concerned with respiration, the exchange of gases between the lungs and blood, and between blood and tissues.<sup>15</sup> By analyzing the ABG of malnourished children, it can be ascertained whether any change in the acid-base balance is one of the factors besides many others for the increased morbidity and mortality in the children suffering from acute malnutrition. Study of 85 hospitalized severely malnourished patients have reported metabolic acidosis were in 35.29%, and 12 of them has a distal renal tubular acidosis which confirms the findings by other researchers Research also found, that acidosis can increase the mortality risk in malnourish children.<sup>16</sup>

Based on those mentioned above, this study aims to determine the hemoglobin and blood gas analysis as a predictor of mortality patients with severe acute malnutrition.

## METHODS

This study used a retrospective cohort design study during the 2017 - 2018 period on severe acute malnutrition children in the pediatric care unit of Sanglah Denpasar General Hospital. Severe acute malnutrition is defined by very low weight for height (below  $-3z$  scores of the median WHO growth standards), or mid-upper-arm circumference (MUAC)  $< 115$  mm or the presence of bilateral pitting edema, or both.

The subject of this study was all patients diagnosed with severe acute malnourished who were admitted to the pediatric care unit of Sanglah Hospital among the study period. Inclusion criteria were children aged 1 month to 18 years diagnosed with SAM, and patients had complete data at the start of admission. Exclusion criteria were a patient diagnosed with the hematological disorder and or a renal disorder. The respondents are determined by taking the subject in sequence until the number of subjects is met.

The estimated required sample using the sample formula for a cohort retrospective study was found 50 people for each group. The total needed minimal sample was 100 people. Patients who met the previously mentioned inclusion and exclusion criteria were included in the study. Each subject is then given an identity number and recorded as initials following applicable codes of ethics.

Data of each patient who had been included in the study, prospectively taken in the form of identity, age, diagnosis, gender, hemoglobin level, acid-base status using blood gas analysis, albumin level, and blood sugar level at admission. The analysis was done to determine whether hemoglobin level and acidosis metabolic as predictors of mortality in subjects with severe acute malnutrition. Anemia can be defined as a reduction in red blood cell mass or blood hemoglobin concentration. Anemia measured using WHO's criterion for anemia in children. Children under 5 years old with hemoglobin (Hb) levels  $< 11$  g/dL and Hb level  $< 12$  for older children. Acidosis metabolic was as an arterial pH below the normal range due to a fall in serum bicarbonate concentration. Diagnosed using blood gas analysis when the PH  $< 7.35$  and  $\text{HCO}_3^- < 22$  mmol/L. The outcome is determined by death or survive

Data obtained from the sample then collected and processed into SPSS version 20 for Windows, descriptive analysis used to describe the characteristics of research subjects based on the outcome so that it can be assessed comparability between the two groups. The analysis to evaluate the association between variables as predictors to mortality in SAM and mortality was done by making a  $2 \times 2$  cross-tabulation (dummy table). The statistical test used is the chi-square test with the significance limit of 0.05. A p-value of less than 0.25 was included in multivariate analysis. The analysis used is logistic regression, statistically significant with 95% confidence interval (CI) and P values  $< 0.05$ .

## RESULTS

The study collected as many as 135 subjects with severely malnourished included in this study since 2017 - 2018. We manage 61 subjects as a death group and 74 subjects as control. The majority of subjects were male (57.8%) and younger than 5 years old (59.3%). The subject with anemia was 89 (65.9%) children. From blood gas analysis, we found 35 (25.9%) subjects suffering from metabolic acidosis. The characteristics and laboratory findings were summarized in [Table 1](#).

The predictors for mortality in SAM were summarized in [Table 2](#). There was a statistically significant difference between death and survival

**Table 1** Baseline Characteristics of Respondents

Characteristic	N=135
<b>Sex, n (%)</b>	
Male	78 (57.8)
Female	57 (42.2)
<b>Age, n (%)</b>	
<5 years	80 (59.3)
>5 years	55 (40.7)
Hb (g/dL) (mean±SD)	10.07±2.8
<b>Anemia, n (%)</b>	
Yes	89 (65.9)
No	46 (34.1)
pH (mean±SD)	7.36±0.35
HCO <sub>3</sub> (mmol/L) (mean±SD)	22.99±8.6
<b>Metabolic acidosis, n (%)</b>	
Yes	35 (25.9)
No	100 (74.1)
<b>Type of SAM, n (%)</b>	
Kwashiorkor	2 (1.5)
Marasmus	133 (98.5)
<b>Condition, n (%)</b>	
1	10 (7.4)
2	1 (0.7)
3	26 (19.3)
4	3 (2.2)
5	95 (70.4)

Hb: hemoglobin; SAM: severe acute malnutrition

**Table 2** Predictors for Mortality in SAM

Variables	Death (N=61)	Survive (N=74)	p
<b>Sex, n (%)</b>			
Male	38 (62.3)	40 (54.1)	0.335
Female	23 (37.3)	34 (45.9)	
<b>Age (years), n (%)</b>			
<5	31 (50.8)	49 (66.2)	0.070
> 5	30 (49.2)	25 (33.8)	
<b>Type of SAM, n (%)</b>			
Marasmus	61 (100.0)	72 (97.3)	0.196
Kwashiorkor	0 (0.0)	2 (2.7)	
<b>Hemoglobin Status, n (%)</b>			
Anemia	54 (88.5)	35 (47.3)	0.0001*
No anemia	7 (11.5)	39 (52.7)	
<b>Blood Gas Analysis, n (%)</b>			
Metabolic acidosis	21 (34.4)	14 (18.9)	0.041*
No metabolic acidosis	40 (65.6)	60 (81.1)	

SAM: severe acute malnutrition; \*P-value was considered statistically significant if less than 0.05

cases with the hemoglobin status ( $p=0.0001$ ) and Blood Gas Analysis ( $p=0.041$ ) (Table 2). In subjects with anemia, the mortality rate was 88.5%. In the subject with metabolic acidosis, the mortality was 34.4% (Table 2).

The risk of age, sex, anemia, and metabolic acidosis for mortality children with severe malnutrition was analyzed in Table 3. The multivariate analysis found significant variables in anemia ( $p=0.001$ ) and metabolic acidosis ( $p=0.018$ ) variables with the risk of mortality (Table 3).

## DISCUSSION

Protein Energy Malnutrition (PEM) is defined as a spectrum of diseases arising as a result of an absolute or relative deficiency of calories and/or protein in the diet. Malnutrition is one of the significant causes of childhood morbidity and mortality. This condition is still a significant challenge in developing nations, were in 2011 about for 3.1 million or 45% of all child deaths causes by this condition.<sup>17</sup>

The majority of subjects were younger than 5 years old. Globally, approximately 19 million children under 5 years are suffering from Severe Acute Malnutrition (SAM) in 2015.<sup>18</sup> The mortality rate in children with SAM is nine times more likely to die as compared to healthy children. Mortality rates as low as 2.2% in India and as high as 42% in Malawi were observed among children treated in the stabilization center.<sup>18</sup>

Anemia can be defined as a reduction in red blood cell mass or blood hemoglobin concentration. In practice, anemia is most commonly defined by reductions in one or more of the following; chronic infection and diseases (including HIV Infection); poor nutrition; autoimmune diseases; adverse drug effects; blood loss, especially chronic blood loss; hemolysis.<sup>19</sup> Anemia is common between severely malnourished children and severe anemia is a medical emergency.<sup>19,20</sup> This study found the prevalence of anemia among children with severe acute malnutrition was 65.9% with mean hemoglobin levels were 10,07 mg/dL. Anemia was significantly associated with malnutrition status.<sup>21</sup> Other studies in India found a similar result, a very high percentage of malnourished children were found to be anemic.<sup>12,22</sup> From the study population, 118 children (90%) children were anemic. Seventy-nine (67%) had severe anemia, 17 (14%) had moderate anemia, and 22 (19%) had mild anemia. One-fourth of the children with anemia required blood transfusion. The most common type of anemia was microcytic, followed by megaloblastic. Mothers also were anemic, with mean Hb 9.1 g/dL.<sup>12</sup> The latest study of 200 cases of severe acute malnutrition found that

**Table 3** Multivariate analysis factors associated with SAM

Variable	Exp (B)	95% CI	p
Age	0.49	0.219-1.107	0.087
Sex	0.11	0.850-4.320	0.117
Anemia	3.98	2.167-10.389	0.001*
Metabolic acidosis	1.51	1.005-2.145	0.018*

Exp (B): exponent B; CI: confidence interval

95% children had anemia, out of which 8 (4%) cases had mild Anemia, 92 (46%) cases had moderate anemia, and 90 (45%) cases had severe anemia.<sup>22</sup> Most of the cases had hypochromic microcytic type anemia.<sup>22</sup> Our study cannot describe the type of anemia due to data limitation in the morphological state for the red blood cell. From this finding, we conclude that poor nutrition was the leading cause of anemia in severe acute malnutrition.

In this study, among 61 children who were dead, 54 children (88,5%) had abnormal hemoglobin levels. From statistical analysis, anemia was strongly associated with mortality, indicates 3.98 times higher risk of death in children with abnormal hemoglobin levels compared with children who had average hemoglobin level. A study from Roy et al in 2011 showed anemia were significantly more likely to die during treatment compared to patients without anemia.<sup>23</sup> The study revealed patients with severe anemia 4,2 times riskier to death based considerably on the previous study.<sup>23</sup> Newest research in Ethiopia showed the same result. Anemia was shown to increase the mortality risk of children with severe acute malnutrition by 2.3 times with AHR (Adjusted Hazard Ratio): 2.3, and 95% CI: 1.2-4.5.<sup>18</sup> Different results found by Savadogo et al in Burkina Faso at 2014 where there is no association between the deaths of children suffering from severe malnutrition and anemia. During hospitalization, the case fatality rate was 13.9%.<sup>24</sup> The mortality rate did not differ significantly from severely malnourished children with anemia at admission and severely malnourished children without anemia at admission.<sup>24</sup> Statistical analysis in his research also showed relative mortality risk was 0.56, 95%CI = [0.28 - 1.14], for severely malnourished children with anemia at admission. Kaplan Meir's survival curves also did not differ significantly between the two groups (p Log Rank = 0.11).<sup>24</sup> The finding of this study that abnormal hemoglobin level risk factors for poor outcomes among severely malnourished children agreed with those previously reported by other authors.

Malnutrition, as mentioned earlier, is a state of catabolism. The severe malnutrition may lead to a persistent increase in acid load that can affect the

normal function of all body cells.<sup>14</sup> The kidneys, lungs, and blood buffers can usually balance acids and bases. Arterial Blood Gas (ABG) studies are concerned with respiration, the exchange of gases between the lungs and blood and between blood and tissues. Analyzing the ABG of malnourished children can be ascertained whether any change in the acid-base balance is one of the factors besides many others for the increased morbidity and mortality in the children suffering from SAM.<sup>14</sup>

Metabolic acidosis is the most common disorder encountered in clinical practice.<sup>25</sup> A study noted that about 56.3% of patients with severe acute malnutrition had metabolic acidosis.<sup>26</sup> Another study conducted to assess the relationship between electrolyte abnormalities and mortality observed electrolyte disturbance in 80% of patients while acid-base disturbance was observed in all patients.<sup>27,28</sup> The prevalence of metabolic acidosis in this study found in 25 subjects (35,9%).

Statistical analysis of the relationship between mortality and metabolic acidosis in malnourished patients in this study found a relationship between the two. Malnutrition sufferers who have metabolic acidosis have a risk of death 1.5 times higher than those who do not suffer from metabolic acidosis. The mortality rate of all the SAM patients from research in India was 4% (4/100). A previous study found that pH < 7.35 found no mortality in the groups of normal pH and pH >7.45, this indicate metabolic acidosis was significantly associated with mortality among SAM patients.<sup>5</sup> Another study showed the same result. The mortality rate of all the SAM patients was 5.4%. It was least (1.1%; n = 1/88) in children with normal pH, followed by 3.8% (n = 3/80) in those with pH > 7.45 and highest (20.6%; n = 7/34) in those with pH < 7.35. This difference was statistically significant (P < 0.0001).<sup>14</sup>

This study used a prospective observational design and conducted at a single center. Other Factors associated with mortality in patients diagnosed with severe acute malnutrition were not analyzed in this study. Further studies still needed to be done to overcome the limitation of this study.

## CONCLUSION

Anemia and metabolic acidosis were a common condition that can be found in malnutrition patients. Anemia and metabolic acidosis are predictor mortality in SAM.

## CONFLICT OF INTEREST

There is no competing interest regarding the manuscript.

## ETHICS CONSIDERATION

The research conducted after the approval of the Ethics Committee of Medical Faculty of Medicine/Sanglah Hospital. Ethical approval no. 2392/UN14.2.2.VII.14/LP/2019.

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## AUTHOR CONTRIBUTION

Both authors are equally contributing to the study from the conceptual framework, data gathering, data analysis, until presenting the results through publication.

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