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Necrotizing Enterocolitis in Preterm Infants Born to Mother with COVID-19  
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The Differences of Left Lateral and Head Elevation Position toward Heart Rate of Newborns with Asphyxia in the Perinatology Room RSUD Dr. Soediran Mangun Sumarso Wonogiri  
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Determinant Factors of Stunting in Under-Five Children  
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Prevalence of Sleep Disorders in Adolescents and its Relation with Screen Time during the COVID-19 Pandemic Era  
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Pro-and Anti-vaccination among Mothers in Deciding Children's Immunization: A Qualitative Study  
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### Serum Biomarkers of Environmental Enteric Dysfunction and Growth Perspective in Egyptian Children

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## Announcements

**Happy New 2023 Year!**



# Clinical Signs and Laboratory Parameters as Predictors of Mortality among Hospitalized Human Immunodeficiency Virus-Infected Adult Patients at Tertiary Hospital in Surabaya

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## Abstract

**BACKGROUND:** The morbidity and mortality rates due to human immunodeficiency virus (HIV) infection are still high despite various and advanced efforts in the management given for HIV/AIDS patients.

**AIM:** This study proposed that clinical signs and laboratory parameters could be expected to predict the patient's mortality.

**METHODS:** This retrospective study was done by collecting 408 medical records of adult HIV/AIDS inpatients at a tertiary hospital in Surabaya from January 1, 2017, to December 31, 2019. Bivariate analysis using Chi-square test was carried out on nine variables, which were Glasgow Coma Scale (GCS) <15, hypotension, PaO<sub>2</sub>/FiO<sub>2</sub> <400 mmHg, elevated liver enzymes, hemoglobin levels <10 mg/dl, platelet count <150,000/mm<sup>3</sup>, eGFR <60 ml/min/1.73 m<sup>2</sup>, albumin levels <3.5 mg/dl, and body mass index (BMI) <18.5 kg/m<sup>2</sup>. Variables which met the criteria would be included in the multivariate analysis using logistic regression.

**RESULTS:** Based on bivariate analysis, mortality was found to be significantly associated with GCS <15, hypotension, PaO<sub>2</sub>/FiO<sub>2</sub>, elevated liver enzymes, platelet count <100,000 mm<sup>3</sup>, eGFR <60 ml/1.73kg/m<sup>2</sup>, albumin levels <3.5 mg/dl, and BMI <18.5 kg/m<sup>2</sup>. However, based on multivariate analysis, there were five variables which were found to be able to independently predict the patients' mortality, those were GCS <15 (OR 11.625), hypotension (OR 6.062), PaO<sub>2</sub>/FiO<sub>2</sub> < 400 mmHg (OR 7.794), eGFR <60 ml/min/1.73 m<sup>2</sup> (OR 2.646), and albumin levels <3.5 mg/dl (OR 4.091).

**CONCLUSION:** GCS <15, hypotension, PaO<sub>2</sub>/FiO<sub>2</sub> <400 mmHg, eGFR <60 ml/1.73g/m<sup>2</sup>, and albumin levels <3.5 mg/dl were found as the independent risk factors which could predict the hospitalized HIV/AIDS patients' mortality.

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## Introduction

Human immunodeficiency virus (HIV) is a retrovirus that attacks human immune cells, especially CD4 T cells, resulting the decreasing of the number of CD4 T cells which then can cause the weakening of body's immune system [1]. HIV can directly damage body's tissues and organs through an inflammatory process that causes organ dysfunction and leads to mortality. Heretofore, HIV/AIDS has been becoming a global health problem with a high mortality rate and increasing number of sufferers every year [2], [3].

There have been various studies conducted to deepen the understanding of the characteristics and predictor factors of HIV-infected adult people's mortality. Some mortality predictors reported were

platelets, glomerular filtration rate, liver function, serum albumin, CD4 values, and body mass index (BMI) [4], [5], [6]. The previous retrospective and prospective studies showed a variety of data relating to the characteristics of the research subject, socioeconomic conditions, and the length of the study conducted [7], [8], [9], [10].

Studies discussing about predictors of mortality among HIV/AIDS patients in Indonesia are still limited, whereas knowing the characteristics and factors that influence mortality is very important to improve medical interventions for HIV/AIDS patients. Therefore, this study was aimed to determine the characteristics and factors that could predict the HIV/AIDS patients' mortality using simple parameters through clinical signs and laboratory examinations that have been routinely carried out since the beginning of the patient hospitalization.

## Methods

### Study design and population

This research was conducted at a tertiary referral hospital in Surabaya, the capital of the province of East Java which has the highest number of HIV/AIDS sufferers in Indonesia. This study was a retrospective study done by collecting the medical record data which was obtained using systematic sampling from January 1, 2017, to December 31, 2019. The inclusion criteria included medical record of men and women inpatients aged  $\geq 18$  years who have been diagnosed with HIV/AIDS. The HIV/AIDS diagnosis was obtained from the ICD coding listed on the medical resume. Some data which were excluded in this study were including medical records of HIV/AIDS patients who discharged at their own request, patients who had traumatic brain injury, patients who had organ dysfunction before being diagnosed with HIV/AIDS, patients who had hematological disorders before being diagnosed with HIV/AIDS, patients diagnosed with cancer that was not related to HIV/AIDS, the pregnant patients, the missing data, the incomplete data, as well as the corrupt data.

### Data collection

The data were collected using a data recording form which contained the characteristics and variables of the research. Characteristics of the research's subjects were in the form of demographic and clinical data. The demographic data included the patient's age, gender, place of residence, marital status, education level, HIV risk factors, and length of the hospital stay. Moreover, the clinical data included HIV clinical stage according to the WHO, ART therapy status, Glasgow Coma Scale (GCS),  $\text{PaO}_2/\text{FiO}_2$  ratio, blood pressure, SGOT level, SGPT level, creatinine level, glomerular filtration rate, hemoglobin level, platelet count, serum albumin level, and BMI.

The independent variables in this study were GCS  $< 15$ , hypotension,  $\text{PaO}_2/\text{FiO}_2 < 400$  mmHg, elevated liver enzymes, hemoglobin levels  $< 10$  mg/dl, platelet counts  $< 150.000/\text{mm}^3$ , eGFR  $< 60$  ml/min/1.73  $\text{m}^2$ , albumin levels  $< 3.5$  mg/dl, and BMI  $< 18.5$   $\text{kg}/\text{m}^2$ . Hypotension was defined as systolic blood pressure  $< 100$  mmHg or diastolic blood pressure  $< 60$  mmHg. Elevated liver enzymes were defined as SGOT levels with values above 50  $\mu\text{L}$  or SGPT levels with values above 70  $\mu\text{L}$  [11]. This study used the CKD-EPI formula for the glomerular filtration rate. Many studies suggested that the CKD-EPI formula was more preferable than MDRD and CG for calculating the glomerular filtration rate in the HIV patient population. The CKD-EPI formula did not require any information regarding body weight, unlike CG which used to bias the results of glomerular filtration rate [10], [12], [13].

## Results

In this study, most of the HIV/AIDS patients hospitalized were male with a total of 274 people (67.2%). Furthermore, the female patients were 134 people or 32.8% of total data gained. In terms of age, it was found that the age ranged from 19 years old for the youngest to 70 years old for the eldest. Moreover, data of the patients' marital status were recorded as followed: 204 patients (50%) were married, 158 patients (38.7%) were single, and 46 patients (11.3%) were widowers or widows. In addition, most of the patients, which were 87.5% of total data or 357 patients to be exact, had high school education background.

The average length of HIV/AIDS patient's the hospital stay in this study was 4 days, with 1 day for the shortest treatment duration and 54 days for the longest one. In terms of transmission risk factors, there were 81 patients (19.8%) heterosexual risk, which was the highest risk factor in this study according to the data which has been collected. Most of the patients, specifically 390 patients (95.6%) were domiciled in Surabaya, while only 18 patients (4.4%) were domiciled outside Surabaya. Based on further data from 408 patients who underwent the treatment, it was known that the mortality rate was 31.1% (127/408).

The clinical characteristics used in this study included ART therapy status, the WHO clinical stage, GCS,  $\text{PaO}_2/\text{FiO}_2$  ratio, systolic and diastolic blood pressure, eGFR, SGOT, SGPT, hemoglobin, platelets, albumin, and BMI. These clinical characteristics are shown in Table 1.

From the medical record data collected, it was known that 207 patients (50.7%) were on ART therapy, 173 patients (42.4%) had never received ART treatment, and 28 patients (6.9%) stopped taking ART treatment. Most of the subjects in this study, as many as 299 patients (73.3%), were at Stage 4 based on the WHO clinical stage. A total of 322 patients (78.9%) had a GCS of 15. The data of  $\text{PaO}_2/\text{FiO}_2$  ratio showed the ratio value of  $\geq 400$  in 286 patients (70.1%) and  $< 400$  in 122 patients (29.9%). As many as 322 patients (78.9%) had systolic blood pressure of  $\geq 100$  mmHg. Moreover, most of the patients had diastolic blood pressure of  $\geq 60$  mmHg, while 46 patients (11.3%) had diastolic blood pressure below 60 mmHg.

Based on the obtained data, there were 312 patients (76.5%) who had eGFR  $\geq 60$  ml/min/1.73  $\text{m}^2$ . The AST data showed that 199 patients (48.8%) had AST  $\leq 50$   $\mu\text{L}$ , which was almost the same as those with AST  $> 50$   $\mu\text{L}$ , specifically 209 patients (51.2%). The SGPT data reported that most patients had SGPT values  $\leq 70$   $\mu\text{L}$ , specifically 332 patients (81.4%). As for the hemoglobin data, there was no significant difference between the ones who had Hb  $\geq 10$  mg/dl and the ones



Table 1: Clinical characteristics

Characteristics	n	%	Result
ART therapy status			
Naive	173	42.4	
Receiving ART	207	50.7	
Loss to follow-up	28	6.9	
WHO clinical stage			
Stage 1	0	0	
Stage 2	0	0	
Stage 3	109	26.7	
Stage 4	299	73.3	
GCS			
GCS =15	322	78.9	
GCS <15	86	21.1	
PaO <sub>2</sub> /FiO <sub>2</sub>			
PaO <sub>2</sub> /FiO <sub>2</sub> ≥400	286	70.1	
PaO <sub>2</sub> /FiO <sub>2</sub> <400	122	29.9	
Systolic blood pressure			
≥100 mmHg	322	78.9	
<100 mmHg	86	21.1	
Diastolic blood pressure			
≥60 mmHg	362	88.7	
<60 mmHg	46	11.3	
eGFR			
eGFR ≥60 ml/min/1.73 m <sup>2</sup>	312	76.5	
eGFR <60 ml/min/1.73 m <sup>2</sup>	96	23.5	
SGOT			
SGOT ≤50 μ/L	199	48.8	
SGOT >50 μ/L	209	51.2	
SGPT			
SGPT ≤70 μ/L	332	81.4	
SGPT >70 μ/L	76	18.6	
Hemoglobin			
Hb ≥10 mg/dl	206	50.5	
Hb <10 mg/dl	202	49.5	
Platelet count			
≥150,000/mm <sup>3</sup>	323	79.2	
<150,000/mm <sup>3</sup>	85	20.6	
Albumin levels			
≥3.5 mg/dl	154	37.7	
<3.5 mg/dl	254	62.3	
BMI			
BMI ≥18.5 kg/m <sup>2</sup>	205	50.2	
BMI <18.5 kg/m <sup>2</sup>	203	49.8	

GCS: Glasgow Coma Scale, BMI: Body mass index.

who had Hb <10 mg/dl. There were at least 206 patients (50.5%) who had Hb ≥10 mg/dl and 202 patients (49.5%) who had Hb <10 mg/dl. In addition, most of the patients, specifically 323 patients (79.2%) had ≥150,000 platelet count. Moreover, there were 254 patients (62.3%) who had an albumin value <3.5 mg/dl and 205 patients (50.2%) had a BMI ≤18.5 kg/m<sup>2</sup>.

The bivariate analysis in this study used Chi-square analysis in which if  $p < 0.05$ , the variable would be feasible to be included in the multivariate analysis. From the results of the bivariate analysis, there were eight variables that had a significant correlation with the HIV/AIDS patients' mortality, namely, GCS <15 ( $p = 0.000$ ), the ratio of PaO<sub>2</sub>/FiO<sub>2</sub> ( $p = 0.000$ ), hypotension ( $p = 0.000$ ), eGFR < 60 ml/min/1.73 m<sup>2</sup> ( $p = 0.000$ ), platelet count <150,000 mm<sup>3</sup> ( $p = 0.012$ ), albumin level <3.5 mg/dl ( $p = 0.000$ ), and BMI ≤18.5 kg/m<sup>2</sup> ( $p = 0.000$ ). These eight variables would be included in the multivariate analysis to see which variable was dominant in influencing the hospitalized HIV/AIDS patients' mortality.

Multivariate analysis in this study used logistic regression analysis. The multivariate analysis which showed significant independent variables on the HIV/AIDS patients' mortality in this study was including GCS <15 (OR 11.625), PaO<sub>2</sub>/FiO<sub>2</sub> <400 mmHg (OR 7.794), hypotension (OR 6.062), eGFR <60 ml/min/1.73 m<sup>2</sup> (OR 2.646), and albumin levels <3.5 mg/dl (OR 4.091). These bivariate analysis and multivariate analysis are shown in Table 2.

Table 2: Analysis univariate and multivariate

Variable	Univariate		Multivariate	
	OR (95% CI)	p-value	OR (95% CI)	p-value
GCS <15	11.960 (6.851–20.878)	0.000	11.625 (5.410–24.981)	0.000
PaO <sub>2</sub> /FiO <sub>2</sub> <400 mmHg	11.705 (7.114–19.259)	0.000	7.794 (4.063–14.950)	0.000
Hypotension	12.738 (7.259–22.240)	0.000	6.062 (2.980–12.329)	0.000
eGFR <60 ml/min/1.73 m <sup>2</sup>	3.317 (2.061–5.340)	0.000	2.646 (1.314–5.328)	0.008
Elevated transaminase enzyme	3.216 (2.051–5.043)	0.000	1.824 (0.946–3.516)	0.104
Hemoglobin <10 mg/dl	1.452 (0.952–2.213)	0.082		
Platelet count <150,000/mm <sup>3</sup>	1.873 (1.143–3.069)	0.012		
Albumin levels <3.5 mg/dl	5.680 (3.274–9.852)	0.000	4.091 (1.846–9.070)	0.001
BMI <18.5 kg/m <sup>2</sup>	2.940 (1.891–4.571)	0.000	1.738 (0.919–3.264)	0.078

GCS: Glasgow Coma Scale, BMI: Body mass index.

## Discussion

Neurological disorders associated with HIV/AIDS include central nervous system infections, neoplasms, vascular complications, peripheral neuropathy, and myopathy. Various studies which have been conducted in developing countries showed that most neurological disorders occurred due to the opportunistic infections [14]. The most frequently used parameter for measuring the impaired central nervous system function is the GCS, which is a neurological scale that aims to assess a person's consciousness. Parameters of organ function disorders, such as APACHE II and SOFA score, classify the central nervous system dysfunction if the GCS is <15 [15].

In this study, GCS <15 was a very significant variable on the hospitalized HIV/AIDS patients' mortality (OR 1.625; CI 95% 5.410–24.981;  $p = 0.000$ ). The results of this study supported previous study's result in which the patients with GCS <15 had death risk of 7.84 times higher (95% CI 2.03–30.27) [16], [17]. The rate resulted from the previous study was lower than the research we conducted. This could be caused by the differences of the study subjects' characteristics.

Respiratory system disorders are complications which are often found in HIV/AIDS patients and cause morbidity as well as mortality. The mechanism of HIV in causing respiratory system disorders, which in this case is lung damage, is related to systemic and lungs inflammation. Other factors which also play a role in causing lung damage are direct HIV infection to the lungs, smoking, and the effect of ARVs on lung toxicity [18]. PaO<sub>2</sub>/FiO<sub>2</sub> ratio is an indicator of respiratory disorders, which in this study referred to the limit according to the SOFA score. In this study, PaO<sub>2</sub>/FiO<sub>2</sub> ratio had a significant correlation with the mortality of HIV/AIDS patients with an OR 7.794 (95% CI 4.063–14.950). A study using the PaO<sub>2</sub>/FiO<sub>2</sub> ratio was also conducted by Chiliza *et al.* in which the subjects were HIV patients with PCP infection. In this study, the PaO<sub>2</sub>/FiO<sub>2</sub> ratio was considered as a significant predictor of mortality (HR 3.8; 95% CI 1.68.9;  $p = 0.0030$ ) [19]. Likewise, the similar result was also found in a study conducted by Wu *et al.*, in which PaO<sub>2</sub> <70 as one of the mortality predictors had an HR of 7.328 (95% CI 3.621–14.830) on HIV/AIDS patients' mortality [20].

Cardiovascular dysfunction in HIV/AIDS patients can be caused by direct viral mechanisms, opportunistic infections, and the use of ART [21]. The mechanism of the HIV virus in causing myocardial damage remains unclear. However, it is suspected that there are changes in the function of Th lymphocytes which then cause severe inflammation of the myocardium [22]. Opportunistic infections caused by *Toxoplasma gondii*, *Mycobacterium tuberculosis*, and *Cryptococcus neoformans* are common in AIDS myocarditis [23]. Treatment with ARVs, especially for the NRTI group, causes a lot of cardiomyopathy through mitochondrial damage which eventually causes myocardial dilatation and dysfunction. Moreover, hypotension is a condition that occurs due to impaired cardiovascular function. This condition indicates the decreasing of cardiac output which can lead to impaired tissue perfusion [24]. This study found that hypotension correlated significantly with the mortality of HIV/AIDS patients by which an OR of 6.062 (95% CI OR 2.980–12.329). These results supported previous research conducted by Bloomfield *et al.* which resulted IR value of 5.2 (CI 95% 4.8–5.7) [25].

HIV-infected patients have a higher risk of developing kidney disease, terminal renal failure, and death due to kidney disease. A study carried out on 306 HIV/AIDS patients in China found that the prevalence of kidney problems experienced by hospitalized HIV/AIDS patients reached 5.56% [26]. Disruption of kidney function in HIV/AIDS-infected patients can be caused by acute kidney failure, HIV-associated nephropathy, and the presence of comorbid chronic kidney disease [27]. Multivariate analysis done in this study showed that impaired renal function had a significant correlation to HIV/AIDS patients' mortality with an OR 2.646 (95% CI 1.314–5.328). This study supported the research conducted in Jakarta [6] as well as the research conducted by Wyatt *et al.* However, there was a slight difference between the result of this study and a study conducted by Wyatt *et al.* Categorized into acute renal failure and chronic kidney disease, Wyatt *et al.* study stated that acute renal failure (OR=5.84; 95% CI 5.11-6.65) possessed higher mortality risk compared to chronic kidney disease (OR=1.97%; 95% CI 1.59-2.45) [28].

Reduced glomerular filtration rate is associated with the increasing of cardiovascular events causing mortality in general population. In populations with decreased glomerular filtration, there was an increase in apolipoprotein B and a decrease in apolipoprotein A1, which is a risk factor for coronary heart disease. It was also found that there was an increase in fibrinogen and homocysteine, as well as C-reactive protein which is associated with atherosclerosis. The atherosclerosis itself can increase the risk of cardiovascular disease in the decreased glomerular filtration population [29]. The decreasing of erythropoietin hormone can cause anemia which then results in increasing the endothelial activation and left ventricular hypertrophy. This condition can increase the cardiovascular risk which leads to morbidity and mortality [30]. Disorders of electrolytes or

acid base and fluid retention in impaired kidney function can also increase the mortality risk [6].

Several studies have also tried to find a correlation between low albumin levels and mortality in HIV/AIDS patients. Some have found that hypoalbuminemia could be an independent predictor of HIV/AIDS patients' mortality. Low albumin levels (<3.5 g/dl) are associated with the progression of HIV patients to AIDS [8], [28]. In subjects with CD4 <200 who had albumin levels <3.5 g/dl, the mortality rate was 8 times higher than those with albumin levels > 3.5 g/dl [8]. Research on the correlation between serum albumin and mortality in HIV/AIDS patients has also been conducted and showed that patients with albumin levels <3.5 g/dl at the beginning of ART therapy had mortality rate 4.53 times higher than the subjects who had albumin levels >3.5 g/dl (95% CI) [31]. In our study, albumin levels <3.5 mg/dl had a significant correlation with the HIV/AIDS patients' mortality (OR 4.091, 95% CI OR 1.846–9.070). Furthermore, receiver operating characteristic (ROC) curve analysis was also performed for the hypoalbuminemia variable. Based on the analysis of the ROC curve, it was found that the area under the curve was 0.751 with  $p = 0.027$ . The best cutoff point for albumin level to predict mortality outcome was in the value of 3.02 with sensitivity of 71.7% and specificity of 70.5% (Figure 1).

There were also some variable which showed insignificant result in multivariate analysis, those were platelet count, elevated liver enzymes, and BMI. Platelet count <150,000  $\text{mm}^3$  in HIV/AIDS patients causes mortality, generally due to the occurrence

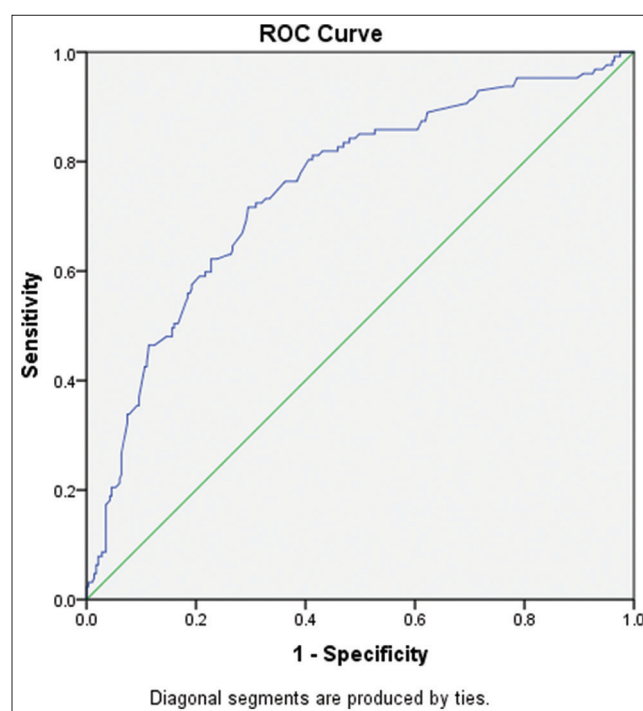


Figure 1: Receiver operating characteristic curve hypoalbuminemia to predict mortality. The best cutoff point value for albumin level for predicting the mortality outcome was 3.02 with sensitivity of 71.7% and specificity of 70.5%

of impaired central nervous system function which caused by intracranial bleeding characterized by the GCS. Elevated liver enzymes can be associated with mortality generally through the occurrence of acute liver failure causing encephalopathy which eventually leads to impaired central nervous system function which is also characterized by GCS. BMI <18.5 kg/m<sup>2</sup> can cause mortality due to susceptibility toward hypoalbuminemia-associated infection, in which hypoalbuminemia itself showed a significant correlation with HIV/AIDS hospitalized patients' mortality in multivariate analysis.

## Conclusion

The mortality percentage of hospitalized HIV/AIDS patients in this study was recorded at the value of 31.1%. Multivariate analysis which showed GCS <15, hypotension, PaO<sub>2</sub>/FiO<sub>2</sub> <400 mmHg, eGFR <60 ml/1.73 kg/m<sup>2</sup>, and albumin levels <3.5 mg/dl was found as an independent risk factors for predicting the hospitalized HIV/AIDS patients' mortality. Early intervention on these significant variables is expected to be able to improve the mortality rate of hospitalized HIV/AIDS patients.

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