Factors Associated with Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome (HIV/AIDS) Related Mortality at Dr. Sardjito Hospital in Indonesia

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ABSTRACT

***Background**: By 2019, the human immunodeficiency virus (HIV) had infected approximately 3.8 million people in Southeast Asia and caused 120,000 deaths. In Indonesia, despite periodic fluctuations, the incidence of HIV/AIDS continues to rise annually. Although antiretroviral therapy (ART) has substantially extended the lives of people living with HIV/AIDS (PLWHA), various risk factors continue to influence treatment outcomes. This study aimed to identify the risk factors significantly associated with mortality among PLWHA undergoing ART therapy at RSUP Dr. Sardjito Hospital, Yogyakarta, Indonesia. **Methods**: In a retrospective cohort design, we reviewed sociodemographic and clinical data of all adult PLWHA (aged ≥18 years) who initiated ARV therapy at RSUP Dr. Sardjito Hospital between January 2008 and December 2021. Patients with incomplete baseline data or those referred from other facilities were excluded. The final cohort was categorized into surviving and deceased groups. Univariate and multivariate logistic regression analyses were conducted to determine the factors linked to mortality, and survival probabilities were estimated using Kaplan–Meier curves. **Results**: Out of 1,591 patients included in the study, 199 died during the follow-up period. Univariate analysis revealed that age over 45 years, tuberculosis status, low CD4+ count, occupation, and advanced clinical stage of HIV/AIDS were significantly associated with mortality. Multivariate analysis further demonstrated that low CD4+ count, employment status, and, most notably, advanced clinical stage (stages 3 and 4) were independent predictors of death. The survival probabilities at 1 and 5 years were 89% and 87%, respectively. **Conclusion**: Occupation, CD4+ count, and clinical stage critically influence mortality in PLWHA on ART therapy, with advanced clinical stage being the most significant. Early diagnosis and prompt ART initiation are essential to enhance survival.*

***Keywords**: HIV, AIDS, antiretroviral therapy, mortality, risk factors, immunocompromised.*

INTRODUCTION

Human immunodeficiency virus (HIV) primarily targets T-cells (CD4+ cells), which are critical components of the immune system. The progressive depletion of these cells leads to acquired immune deficiency syndrome (AIDS), a condition characterized by diminished immunity and increased susceptibility to opportunistic infections.[1]

Globally, HIV continues to be a major public health challenge. In 2019, the Data and Information Center of the Ministry of Health reported that Africa harbors the largest HIV-infected population, with approximately 25.7 million people affected. In Southeast Asia, around 3.8 million individuals are living with HIV, and the region has experienced about 120,000 HIV-related deaths. In Indonesia, despite fluctuations

in incidence, the overall burden of HIV/AIDS has been steadily increasing. Up to September 2020, Indonesia recorded a cumulative total of 409,857 HIV cases, with 127,873 patients having progressed to AIDS.[2] This rising trend is also evident in Yogyakarta, where, as of November 30, 2021, there were 5,765 reported HIV cases, including 1,869 patients in the AIDS phase.[3]

Since a definitive cure for HIV/AIDS remains unavailable, treatment primarily focuses on palliative care and the use of combination antiretroviral therapy (ART) to prolong the life expectancy of people living with HIV/AIDS (PLWHA). According to the Indonesian Ministry of Health, by 2020, a total of 256,536 registered HIV patients had initiated ART therapy. Despite these efforts, recent data show that 45,333 patients died after starting treatment, while 211,203 patients are currently surviving.[2] Various risk factors significantly influence the outcomes of ART therapy, affecting both immune response and mortality rates. Some patients exhibit a slow improvement in immunity despite effective viral load suppression during treatment. This phenomenon is often attributed to specific clinical characteristics present at the initiation of ART therapy, including older age, prolonged duration of HIV infection, specific patterns of immune activation, low CD4+ cell counts, and whether the patient had already progressed to AIDS before beginning therapy.[4]

In most people living with HIV/AIDS (PLWHA), mortality is primarily attributed to a progressive decline in immune function, which increases vulnerability to multiple opportunistic infections and leads to organ failure. Opportunistic infections may arise from new exposures to microorganisms—such as bacteria, fungi, or viruses—or from the reactivation of latent infections that, under normal circumstances, would be effectively controlled by a healthy immune system. The development of these infections is a direct consequence of immunodeficiency, as the significant reduction in CD4+ cell counts impairs cell-mediated immunity and compromises the body's ability to mount an effective defense.[5]

Previous studies from various countries have highlighted specific patient characteristics at the initiation of antiretroviral (ART) therapy that are associated with an increased risk of mortality. These factors can be broadly categorized into sociodemographic and clinical domains. Sociodemographic factors include age, sex, education level[6], and occupation[7], while clinical factors encompass the World Health Organization (WHO) clinical stage of HIV[8], tuberculosis (TB) co-infection status[9], CD4+ cell count[10], hemoglobin (Hb) level[11], and history of co-trimoxazole administration.[12]

RSUP Dr. Sardjito Hospital, a major referral center for HIV/AIDS in the Special Region of Yogyakarta (DIY) and Central Java, Indonesia, currently manages over 1,000 HIV cases. This study aimed to investigate the factors associated with mortality among people with HIV/AIDS (PLWHA) undergoing ART therapy at RSUP Dr. Sardjito Hospital, providing valuable insights to enhance patient management and improve treatment outcomes.

METHODS

Study Design and Sample

This observational study employed a retrospective cohort design with a quantitative approach, conducted from December 2021 to February 2022 at RSUP Dr. Sardjito Hospital, Yogyakarta, Indonesia. The study included all adult HIV/AIDS treatment-naïve patients (aged ≥18 years) who received antiretroviral (ART) therapy for the first time between January 2008 and December 2021. The inclusion criteria comprised adult patients with a confirmed HIV/AIDS diagnosis who initiated ART therapy at RSUP Dr. Sardjito Hospital during the study period and had complete baseline sociodemographic and clinical data available in their medical records. Patients were excluded if they were pregnant, referred from other healthcare facilities without complete baseline data, or transferred to other facilities before their treatment outcomes could be documented.

Data Collection

The patient cohort was established by systematically reviewing secondary data from multiple sources, including the ART register at the Edelweiss Clinic, the hospital's pharmacy

department, and both electronic and paper-based medical records. Sociodemographic data (age, sex, education level, and occupation) and clinical data (HIV clinical stage according to the World Health Organization classification, TB infection status, CD4+ count, Hb level, history of cotrimoxazole administration, treatment outcomes, and date of outcomes) were meticulously collected using a structured data collection form to ensure accuracy and consistency. Eligible patients were then categorized into two groups based on treatment outcomes: surviving and deceased. This approach provided a comprehensive dataset to analyze the factors associated with mortality among PLWHA receiving ART therapy at RSUP Dr. Sardjito Hospital.

Data Analysis

The normality of the data distribution was evaluated using the Kolmogorov–Smirnov test. Descriptive statistics were calculated for both categorical and continuous variables to provide an overview of the study population's characteristics. Univariate analyses were performed to examine the relationships between dependent and independent variables, with the strength of associations expressed as odds ratios (ORs). Variables with a p-value of <0.05 in the univariate analysis were included in a multivariate analysis using multiple logistic regression to identify independent predictors of mortality. Kaplan–Meier survival curves were generated to estimate survival probabilities at 1 and 5 years. Statistical significance was set at a p-value of <0.05. All analyses were conducted using R software (version 4.2.2).

Ethical Considerations

Ethical approval for this study was obtained from the Ethics Committee of the Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada under approval number KE/FK/0728/EC/2022. Given the retrospective design of the study, which utilized routinely collected, de-identified data without direct patient contact, a waiver of informed consent was granted. All study procedures adhered to the ethical standards outlined by the institutional and national research committees and complied with the principles of the Declaration of Helsinki and its subsequent amendments.

RESULTS

A total of 1,591 HIV patients were included in this study. At the time of data collection, 1,392 patients (87.5%) were still alive, while 199 (12.5%) had succumbed to the infection. Figure 1 illustrates the trends in HIV/AIDS cases and mortality among PLWHA from 2008 to 2021, highlighting a notable peak in HIV/AIDS-related deaths between 2014 and 2016.

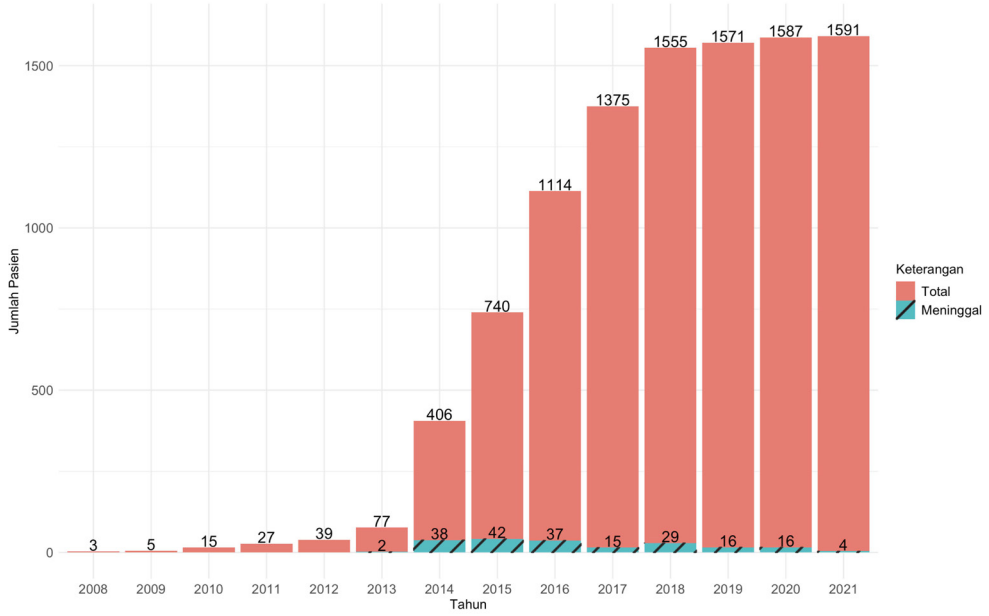
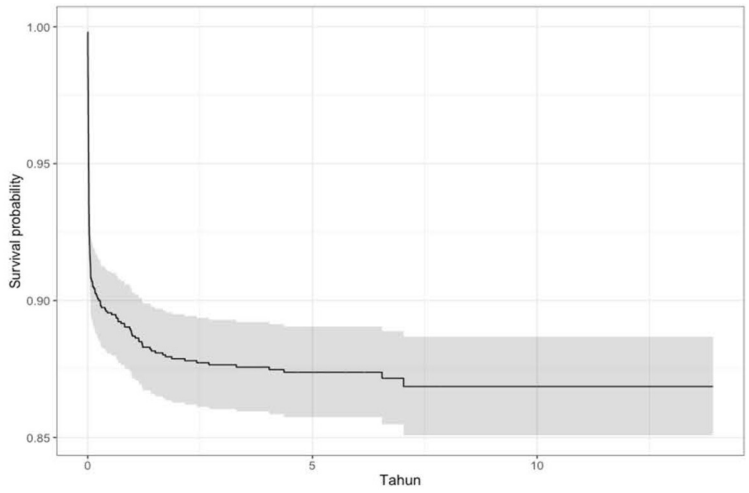


Figure 1. Cumulative number of PLWHA cases and deaths.



Characteristic	1-year survival (95% CI)	5-year survival (95% CI)
Overall	89% (87%, 90%)	87% (86%, 89%)

Figure 2. Mortality Kaplan-Meier Curves: Mortality in HIV Patients.

The Kaplan–Meier survival analysis (Figure 2) showed a survival probability of 89% at 1 year and 87% at 5 years.

The majority of study participants were male (n = 1,063, 76.4%), with females accounting for 329 patients (23.6%). Among the 199 deceased patients, 158 (79.4%) were male and 41 (20.6%) were female. The mean age of the patients was 33 ± 11 years. The study population was categorized into two age groups: 18 to 45 years (n = 1,024, 86.5%) and over 45 years (n = 188, 13.5%). Of the patients who died during the study period, 155 (77.9%) were aged 18 to 45 years, while 44 (22.1%) were older than 45 years.

Regarding education levels, 277 (19.9%) surviving patients had completed elementary to middle school, whereas 1,115 (80.1%) had at least a high school or university education. Among the deceased, 46 patients (25.7%) had only elementary to middle-school education, while the majority (n = 134, 74.4%) were high school or college-educated. Employment status also differed between the groups; 355 (25.5%) of surviving patients were unemployed, compared to 19 (10.1%) in the deceased group. Most deceased patients (n = 170, 89.9%) had been employed previously.

Clinical data revealed significant differences in CD4+ counts and hemoglobin (Hb) levels between surviving and deceased patients. CD4+ values were categorized using a threshold of 200 cells/mm³. Among survivors, 243 patients (45.5%) had a CD4+ count of >200, while 291 (54.5%) had <200. In contrast, only 8 deceased patients (9.5%) had a CD4+ count of >200, whereas 76 (90.5%) had a count of <200. Similarly, Hb levels were divided using a threshold of 10 g/dL. In the surviving group, 229 patients (92.7%) had Hb levels ≥10, while 18 (7.3%) had levels <10. Among the deceased, 87 patients (64%) had Hb levels ≥10, while 49 (36%) had Hb levels <10.

Half of the study population (n = 324, 50.7%) had received cotrimoxazole prophylaxis. Among the deceased patients, 86 (55.8%) had received cotrimoxazole, whereas 68 (44.2%) had not. In contrast, the majority of surviving patients (n = 540, 85.2%) did not have tuberculosis (TB), while 30 deceased patients (57.7%) were TB-negative, and 22 (42.3%) had a TB co-infection.

According to the World Health Organization (WHO) HIV clinical staging, 625 (53.7%) of

Tabel 1. Descriptive Table and Bivariate Analysis of Research Subjects

Variable	Level	Survived (N=1392)	Died (N=199)	OR (95% CI)	p-value
Sex	Female	329 (23.6)	41 (20.6)	0.84 (0.58;1.20)	0.344
	Male	1063 (76.4)	158 (79.4)	Ref	
Age	>45	188 (13.5)	44 (22.1)	1.82 (1.25;2.61)	0.001
	18-45	1204 (86.5)	155 (77.9)	Ref	
Education	High school and above	1115 (80.1)	134 (74.4)	0.72 (0.51;1.05)	0.078
	Elementary-Middle school	277 (19.9)	46 (25.6)	Ref	
	Missing	0	19		
Occupation	Employed	1037 (74.5)	170 (89.9)	3.06 (1.93;5.15)	<0.001
	Not employed	355 (25.5)	19 (10.1)	Ref	
	Missing	0	10		
CD4	<200	291 (54.5)	76 (90.5)	7.93 (3.98;18.14)	<0.001 *Missing* 858 and 115
	>=200	243 (45.5)	8 (9.5)	Ref	
	Missing	858	115		
Hb	<10	18 (7.3)	49 (36.0)	7.17 (4.02; 13.3)	<0.001 *missing* 1145 and 63
	>=10	229 (92.7)	87 (64.0)	Ref	
	Missing	1145	63		
Cotrimoxazole	Ya	324 (50.7)	86 (55.8)	1.23 (0.86;1.76)	0.252 *Missing* 753 and 45
	Tidak	315 (49.3)	68 (44.2)	Ref	
	Missing	753	45		
TBC	Yes	94 (14.8)	22 (42.3)	4.21 (2.31;7.59)	<0.001 *Missing* 758 and 53
	No	540 (85.2)	30 (57.7)	Ref	
	Missing	758	147		
Stadium	3 and 4	538 (46.3)	185 (97.9)	53.73 (22.60;175.22)	<0.001 *Missing* 229 and 10
	1 and 2	625 (53.7)	4 (2.1)	Ref	
	Missing	229	10		
ARV	Second line	23 (3.6)	2 (3.3)	0.93 (0.15; 3.24)	0.92 *Missing* 751 and 139
	First line	618 (96.4)	58 (96.7)	Ref	
		751	139		
Loss to Follow-up	Yes	1020 (73.3)	42 (89.4)	3.06 (1.32;8.92)	0.019 *Missing* 0 and 152
	No	372 (26.7)	5 (10.6)	Ref	
	Missing	0	152		

*Missing information was not found in either the HIV polyclinic registry or medical records (paper and electronic)

the surviving patients were in stages 1 and 2, while 538 (46.3%) were in stages 3 or 4. In the deceased group, the vast majority (n = 185, 97.9%) were in advanced stages 3 or 4 of the disease.

In terms of antiretroviral (ART) therapy, 618 (96.4%) of surviving patients received first-line ART treatment, with only 23 (3.6%) receiving second-line therapy. A similar trend was observed among the deceased patients, where 58 (96.7%) had been treated with first-line ART and only 2 (3.3%) had received second-line therapy. Follow-up data showed that a significant proportion of patients in both groups were lost to follow-up, with 1,020 (73.3%) of surviving patients and 42 (89.4%) of deceased patients not completing the full study period.

Variables demonstrating statistically significant differences between the surviving and deceased groups (p-value < 0.05) were subsequently included in the multivariate analysis using a logistic regression model (**Table 2**).

Table 2. Multivariate Logistic Regression Analysis

	Model 1			Model 2		
Variable	**Odds Ratios**	**CI**	**p-value**	**Odds Ratio**	**CI**	**p-value**
Age [>45]	1.27	0.46 – 3.17	0.619			
Occupation [employed]	3.60	1.01 – 22.97	0.091	3.62	1.02 – 23.12	0.084
CD4 [<200]	4.15	1.16 – 26.55	0.061	4.28	1.21 – 27.32	0.023
TBC [Yes]	1.42	0.64 – 3.10	0.384	1.36	0.62 – 2.93	0.575
Clinical Stadium [3 and 4]	30.65	6.05 – 560.24	0.001	31.23	6.18 – 570.37	0.001

Information:
- The hemoglobin variable was not included in the multivariable analysis because there was too much missing data
  Model 1: Variables based on bivariate analysis results
  Model 2: Selection of variables from Model 1 using the backward method

The logistic regression analysis (**Table 2**, Model 2) revealed that employment status, CD4+ count, and tuberculosis (TB) infection were not significantly associated with HIV-related mortality. The only factor that independently increased the risk of death was the presence of advanced HIV disease, specifically clinical stages 3 and 4, with an odds ratio (OR) of 30.65 (95% confidence interval [CI]: 6.05–560.24). The variable "loss to follow-up" was excluded from the logistic regression model due to the very small sample size in the 'without loss to follow-up' group, which prevented reliable statistical analysis. The logistic regression model (Model 1) used to predict the probability of death in HIV patients can be represented using the following formula:

log (mortality = -7,7334 + (0,24 x age) + (1,28 x occupation) + (1,24 x CD4) + (0,34 x TB + (3,42 x Clinical stadium)

Table 3 provides example data for two scenarios in which the probability of death was calculated using the logistic regression formula described above.

DISCUSSION

Consistent with previous studies, our findings indicate that age, tuberculosis (TB) status, CD4+ count, occupation, and clinical stage are associated with mortality in HIV patients receiving antiretroviral (ART) therapy. Older age is a well-established risk factor for accelerated HIV progression and increased AIDS-related mortality.[13] In this study, patients aged over 45 years were 1.82 times more likely to die compared to those aged 18–45 years.

Our results align with Kusumaadhi et al. (2021), who reported that TB coinfection significantly increases the risk of death among HIV patients.[13] Specifically, our study found that HIV patients with TB were 4.21 times more likely to die than those without TB. This finding is supported by the 2020 World Health Organization (WHO) report, which noted a 63% decrease in TB-related deaths among HIV patients from 2010 to 2019, yet the global mortality figure still exceeded 200,000 annually.

Low CD4+ count was another critical predictor of mortality, as patients with CD4+ counts below 200 cells/mm^3 were 7.93 times more likely to die than those with higher counts. A low CD4+ count is strongly linked to

Table 3. Simulation of the predicted probability of death in HIV patients

Patient	Age	Occupation	CD4	TBC	Clinical stadium	Mortality Probability
1	18-45	Bekerja	<200	Ya	1.2	0.9%
2	>45	Bekerja	<200	Ya	3.4	36.09%

increased morbidity and mortality in people with HIV/AIDS (PLWHA), as it elevates the risk of opportunistic infections and correlates with more severe clinical stages of HIV/AIDS.[13]

Interestingly, our study also found that employed patients had a 3.06 times higher risk of death compared to unemployed individuals. Previous research has suggested that PLWHA with precarious employment, such as day laborers, may face higher mortality risks due to factors like income instability and limited access to healthcare.[14] However, our study only captured whether patients had a job or not, without detailed occupational data, so these findings should be interpreted cautiously.

In the multivariate analysis, the associations between CD4+ count, TB status, and employment with mortality were no longer significant, primarily due to the strong effect of the clinical stage variable. Patients in clinical stages 3 and 4 had a 30.65 times higher risk of mortality than those in stages 1 or 2. In advanced stages of HIV, other prognostic factors may become less influential as severe complications—such as opportunistic infections, organ failure, and metabolic disorders—play a more dominant role in determining outcomes. This suggests that while CD4+ count and TB status remain important for managing HIV, their impact on mortality risk diminishes in severe clinical stages.[1]

The survival analysis in this study aligns with prior research from Ethiopia, which reported survival probabilities of 93% at 20 months and 83% at 60 months.[6] Our study demonstrated slightly lower survival at 20 months (89%) but a higher five-year survival probability (87%), suggesting improved long-term outcomes in our cohort.

This study's strengths include the large cohort size and the extended study period (January 2008 to December 2021), which enabled robust analyses of factors associated with mortality in HIV/AIDS patients. The integration of data from HIV/AIDS clinics and hospital medical records enhanced data integrity and helped address the limitations of using secondary data alone. However, several limitations should be acknowledged. First, the study lacked detailed information on medication adherence, including the specific number of drugs consumed and prescribed, as this was not available in the medical records. Data completeness also posed challenges; CD4+ and viral load measurements were often missing due to governmental shortages of reagents. Additionally, patients from earlier years of the study had lower data completeness because electronic medical record-keeping had not yet been implemented at RSUP Dr. Sardjito. Mortality data for patients who died outside the hospital were sometimes lost due to a lack of reporting by family members. Moreover, because occupational data were limited to employment status without specific job type, further analysis to determine which types of occupations might increase mortality risk could not be conducted. Future studies should focus on collecting more comprehensive data on medication adherence, enhancing electronic medical record systems to improve data completeness, and investigating the specific occupational risks associated with increased mortality in PLWHA.

CONCLUSION

Clinical stage of HIV infection, CD4+ count, and employment status were identified as the key factors independently associated with HIV-related mortality among patients receiving ART therapy. Of these, advanced clinical stages (3 and 4) had the most significant impact on mortality risk, highlighting the critical need for early diagnosis and timely initiation of ART therapy to improve survival outcomes. These findings underscore the importance of targeted interventions, particularly for high-risk groups, to enhance the management and prognosis of PLWHA.

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CONFLICT OF INTERESTS

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AUTHOR CONTRIBUTIONS

H.H. and Y.W.S. conceived the study design. H.H. and D.P.W. developed the theory and performed the computations. Y.W.S. and D.P.W. verified the analytical methods. All authors discussed the results and contributed to the final manuscript.

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DISCLAIMER

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