Original Article

Survival and Prognostic Factors of HIV-positive Patients after Antiretroviral Therapy Initiation at a Malaysian Referral Hospital

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Abstract

Background: Antiretroviral therapy (ART) has transformed the management of human immunodeficiency virus (HIV) infection and significantly improved survival rates, but there is lack of such survival data from Malaysia.

Objective: The objective was to determine the survival rates and prognostic factors of survival in HIV-infected adults treated with ART in Malaysia.

Materials and Methods: This retrospective cohort study considered all HIV-positive adult patients registered in Sungai Buloh Hospital, a major referral center in Malaysia, between January 1, 2007 and December 31, 2016. Then, patients were selected through a systematic sampling method. Demographic, clinical, and treatment data were extracted from electronic medical records. Person–years at risk and incidence of mortality rate per 100 person–years were calculated. The Kaplan–Meier survival curve and log-rank test were used to compare the overall survival rates. Cox proportional hazards regression was applied to determine the prognostic factors for survival.

Results: A total of 339 patients were included. The estimated overall survival rates were 93.8%, 90.4%, 84.9%, and 72.8% at 1, 3, 5, and 10 years, respectively, from ART initiation. The results of multiple Cox proportional hazard regression indicated that anemic patients were at a 3.76 times higher risk of mortality (95% confidence interval [CI]: 1.97–7.18; $P < 0.001$). The hazard risk was 2.09 times higher for HIV patients co-infected with tuberculosis (95% CI: 1.10, 3.96; $P = 0.024$).

Conclusion: The overall survival rates among HIV-infected adults in this study are higher than that from low-income countries but lower than that from high-income countries. Low baseline hemoglobin levels of <11 g/dL and tuberculosis co-infection were strong prognostic factors for survival.

Keywords: Antiretroviral therapy, human immunodeficiency virus, Malaysia, prognostic, survival

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INTRODUCTION

The first acquired immunodeficiency syndrome cases were reported in 1981. Since then, >77 million people worldwide have been diagnosed with the acquired human immunodeficiency virus (HIV), and 35 million have died of HIV-related illnesses.[1] In 2017, there were 36.9 million people living with HIV (PLHIV). Nonetheless, the global efforts to expand antiretroviral therapy (ART) coverage have reduced HIV-related mortality from 50.5% in 2005 to 2.5% in 2017. However, in Malaysia, the mortality rate was 5.1% in 2017 (4400 of 87,000 PLHIV), which is twice the global rate. In fact, the overall decrease in mortality in the country between 2005 and 2017 was only 13.7%.[2]

ART was introduced in Malaysia in 1997 but was not widely used because of its cost, and only patients who fulfilled selection criteria were provided subsidy for one antiretroviral drug. This policy was then upgraded to a two-drug subsidy in 2004, and in 2006, government hospitals and clinics provided free first-line ART to patients. To reach more PLHIV, in 2010, the threshold for starting ART was shifted from a CD4 count of 200 cells/μL to 350 cells/μL.[3]

The benefits of ART in reducing mortality are well established; however, the extent varies across regions.[4] In Malaysia, there is a lack of information on the prognostic factors for survival in antiretroviral-treated PLHIV. Few locally published studies have focused on the mortality rate and its determinants in PLHIV over a wide timeframe from as early as 1987 to 2009.[5,6] However, since then, antiretroviral drug availability and the provision policy in Malaysia have changed significantly. Therefore, the present study was conducted to determine the overall survival rates and identify the prognostic factors for survival in antiretroviral-treated PLHIV in Malaysia.

MATERIALS AND METHODS

Study design and population

This retrospective cohort study considered all PLHIV who were registered in Sungai Buloh Hospital, Selangor, Malaysia, between January 1, 2007 and December 31, 2016. This tertiary hospital is one of the centers of excellence for infectious disease in Malaysia.

Only ART-naive patients aged >15 years were included, while those discharged from the hospital without ART were excluded. The sample size was determined through the survival formula in the PS: Power and Sample Size Calculations software.[7] The significance level was 0.05, and the power was 80%. Considering that an estimated 10% of the sample might have 30% or more variables with incomplete data, an additional 10% of subjects would be sampled to achieve the final required sample size. Thus, based on the calculations, a total of 374 subjects were required for this study. Patients' data were assessed from the inclusion cutoff period up to 31 August 2018.

A large sample was available, but there were time constraints to process this data, thus systematic sampling method was adopted. The sampling interval (k) was 16 (calculated by dividing the total eligible patients with the required sample size). To initiate the first selection, "7" was randomly generated in Microsoft Excel using the formula: =RANDBETWEEN (1, 16). Accordingly, from the patients' list, which was sorted according to the date of ART initiation, patient number 7 was selected as the first subject, and every subsequent 16th patient was included (i.e., 7th, 23rd, 39th patient, and so on).

Data collection

Patient data were extracted from the hospital's electronic medical records at the Infectious Disease Clinic and then manually entered into the data collection form. A single researcher entered the data to avoid discrepancies in data entry. The data was cross-checked by another researcher to reduce the chances of error.

Primary event

The primary event of interest was death from all causes. For those lost to follow-up (LTFU) or alive at study closure, the observations were censored: on the date of the most recent follow-up visits for LTFU and on August 31, 2018, for those still alive. LTFU was defined as a patient missing the scheduled follow-up and not attending for 3 months since the appointment date. If a patient attended after 3 months, their final status at the study closure was recorded as the outcome for the analysis, and they were marked as having a history of default.

Death status was verified by referring to the electronic medical records in the hospital's database e-HIS. For LTFU patients, outcome event status was matched with the National Registration Department database at Clinical Research Centre, Malaysia, which receives mortality data of the prior year from the National Registration Department every March. If any patient was confirmed dead based on the record, their LTFU status was changed to "died."

Study variables

The variables were patient-, clinical-, and treatment related. The patient-related characteristics at ART initiation were

age group, gender, ethnicity, HIV transmission mode, and history of illicit drug use.

The clinical-related characteristics were baseline CD4 cell count, baseline viral load, baseline hemoglobin level, World Health Organization (WHO) clinical staging, tuberculosis co-infection, hepatitis B co-infection, hepatitis C co-infection, opportunistic infection, and duration between first HIV positive test and ART initiation.

Treatment-related characteristics included the year of ART initiation (included because of changes in guidelines during the study period, with the first cutoff being due to a shift in CD4 threshold for starting ART in 2010 and the second cutoff due to the phasing-out of stavudine after 2014), first nonnucleoside reverse transcriptase inhibitor (NNRTI) background regimen and history of default. Based on expert opinions and previous studies, anemia was defined as a hemoglobin level <11 g/dL.[8,9]

As retention in care is crucial to achieve optimal outcomes in ART therapy, history of defaults was included as a covariate, along with associated factors such as mode of transmission and history of drug use. First NRTI background was included to reduce bias, as difference in survival is inevitable with the use of different drugs. Directed acyclic graphs were drawn [Figure 1]. Variables with >30% missing data were not included for analysis.

Ethical considerations

Ethical approval was obtained from the National Medical Research and Ethics Committee of the Ministry of Health, Malaysia, through the National Medical Research Registry and the Human Research Ethics Committee of Universiti Sains Malaysia (USM).

Data were entered into the analysis software in a password-protected computer with limited access and were kept strictly confidential. Furthermore, all forms were anonymized, with no unique identifiers of individual participants included.

Statistical analysis

The categorical data are presented as frequencies and percentages. The mean and standard deviation are provided for the normal numerical data. The median and interquartile range (IQR) are reported for the nonnormally distributed data. Normality of data was determined by reviewing the histogram, analyzing the skewness and kurtosis, and using Shapiro–Wilk and Kolmogorov–Smirnov tests.

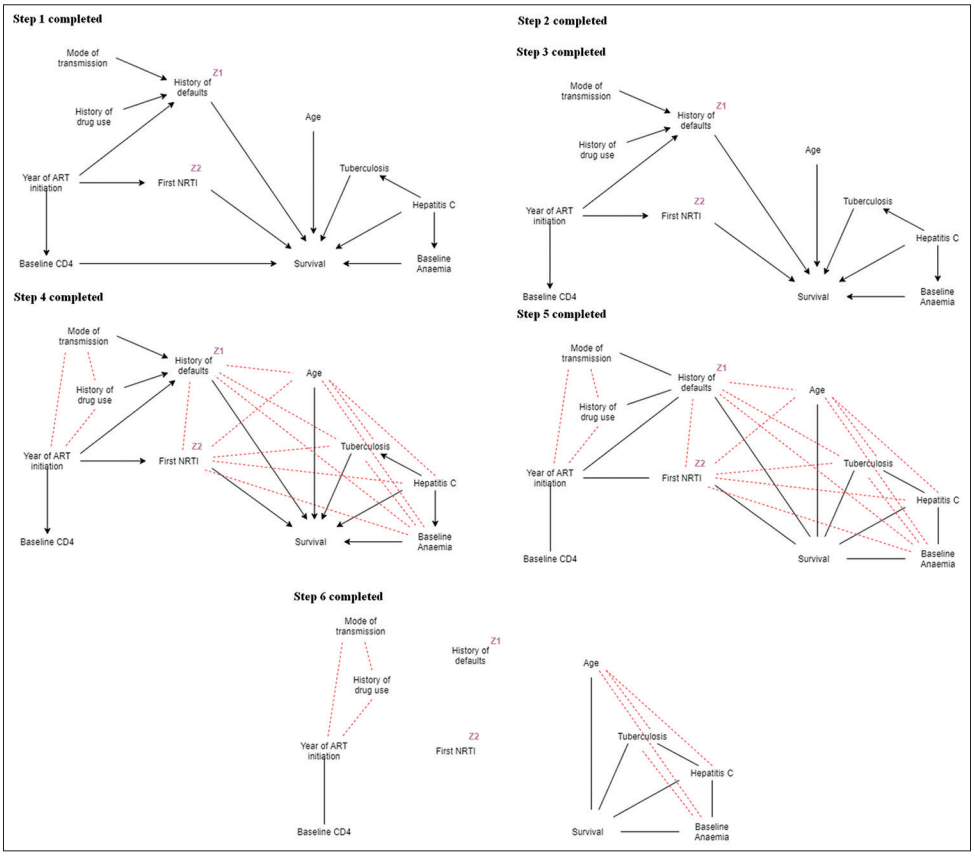

Figure 1: Directed acyclic graphs

Total person–years at risk and mortality rate per 100 person–years were calculated. Survival analysis including Kaplan–Meier survival curve and Cox proportional hazards regression were used owing to censored data. Survival time was defined as the period from ART initiation to the event. Kaplan–Meier method was used to estimate the survival rate after ART initiation and the log-rank test was used to determine statistical differences between survival rates in subgroups. Bonferroni correction was used in the event of multiple pairwise comparisons.[10]

Simple and multiple Cox proportional hazards regression were applied to model predictors of mortality following treatment initiation. The unadjusted and adjusted hazard ratios (HRs) with 95% CIs were estimated. Departure from the proportional hazard assumption was evaluated for Cox regression by tests of Schoenfeld residual plot and graphical inspection of log-minus-log plots and all the predictor variables satisfied the criterion of being asymptotic.

Data analysis was performed in Stata SE version 14 (StataCorp, College Station, Texas, USA).[11] The two-sided $P < 0.05$ was considered as the level of significance.

RESULTS

A total of 6159 cases were eligible, from which 384 patients were selected through the systematic sampling method. Of these, 45 were excluded because they did not meet the inclusion criteria: 7 patients chose not to initiate ART, 8 were not treatment naïve and 30 were transferred. Therefore, the study reports the data of 339 patients [Figure 2].

Patients-, clinical- and treatment-related characteristics

The mean age of the patients at ART initiation was 37.0 (11.2) years, with the majority (85.3%) being male and 43.4% were of Malay ethnicity. Sexual transmission was the most common HIV transmission mode, and 18.0% of patients had a history of using illicit drugs.

The median baseline CD4 cell count was 157 cells/μL (IQR: 251): 50 cells/μL (IQR: 127) for those who died and 192 cells/μL (IQR: 248) for censored patients. A total of 78 (25.2%) patients were anemic [Table 1].

Eighty-five (25.1%), 27 (8.0%), and 50 (14.7%) patients were diagnosed with tuberculosis, hepatitis B, and C co-infections, respectively. Two (0.6%) were co-infected with both hepatitis B and C. Fewer than half (47.5%) of the patients experienced at least one episode of opportunistic infection, with the most common being candidiasis (21.9%), *Pneumocystis jiroveci* pneumonia (19.7%) and herpes (15.3%) [Table 1].

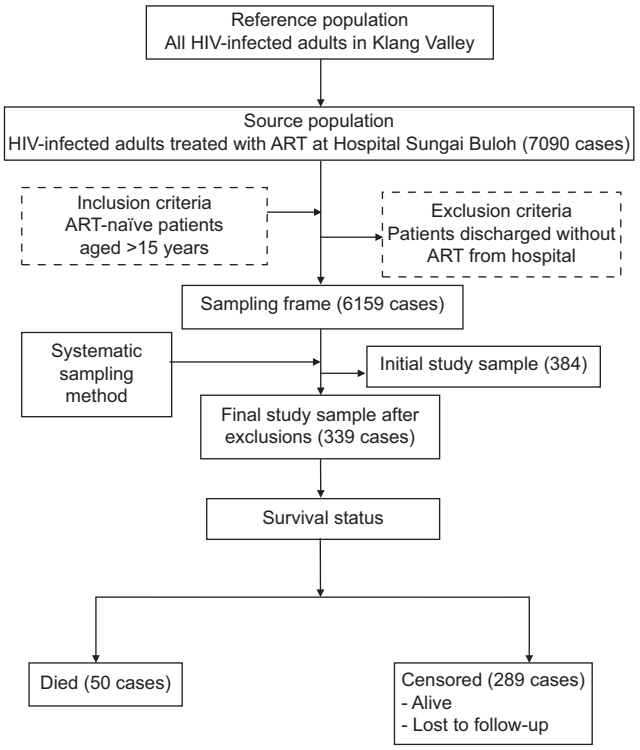

Figure 2: Flow diagram of the selection process

The overall median time from the first positive HIV test to ART initiation was 3.5 months (IQR: 20.8). A total of 63 patients (18.6%) had a history of defaulting from follow-up.

Survival rates

There were 50 deaths (14.7%) and 289 censored events (85.3%). In terms of deaths, majority (42.0%) were within the 1st year of ART initiation: 14 within 6 months and 7 were between 6 and 12 months. Of the within 6-month deaths, 6 were aged >50 years, 10 were anemic, 11 had CD4 counts <50 μL, and 8 had tuberculosis coinfection. In the censored observations, 241 (83.4%) patients were alive and 48 (16.6%) were LTFU. The overall median follow-up time was 4.3 (±4.1) years.

During the 1600 person–years of observation, the mortality rate was 3.12 (95% confidence interval [CI]: 2.37–4.12) per 100 person–years. The overall survival rates at 6 months, 1, 3, 5, and 10 years were 95.9% (95% CI: 93.1–97.5), 93.8% (90.6–95.9), 90.4% (86.6–93.2), 84.9% (80.0–88.8) and 72.8% (61.2–81.4). The Kaplan–Meier estimates for overall survival rates are presented in Figure 3.

The results of the log-rank test indicated varying levels of significance in the overall survival rates by age group ($P < 0.001$), employment status ($P < 0.001$), HIV transmission mode ($P = 0.003$) and illicit drug use

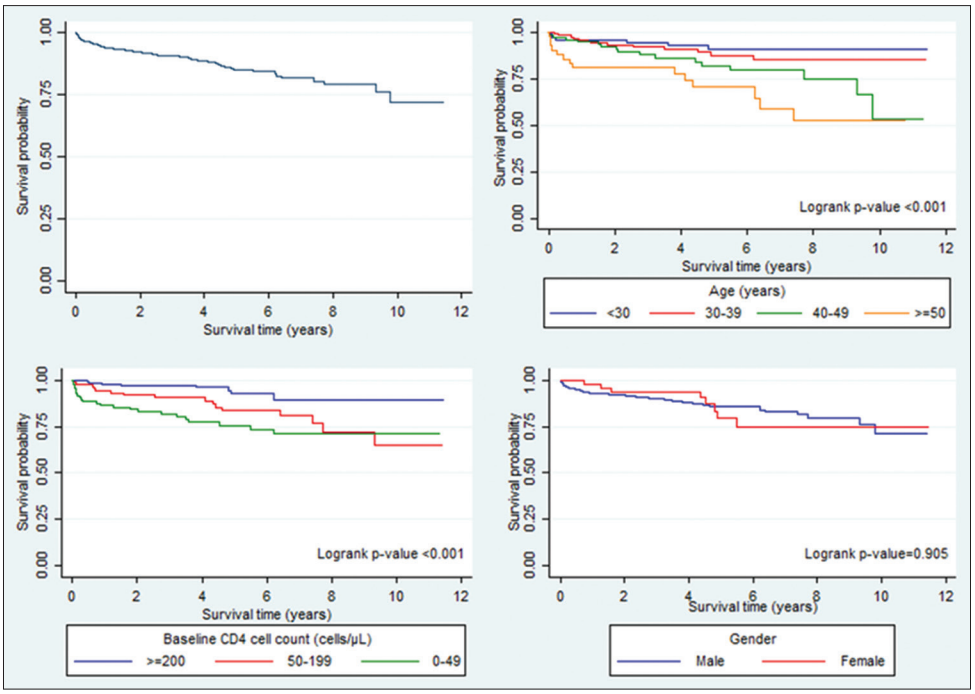

Figure 3: Kaplan–Meier estimates for (i) overall survival rates of HIV-infected adults as well as overall survival rates based on (ii) age group, (iii) baseline CD4 cell count, and (iv) gender

history (P = 0.017). There was a significant difference in survival rates based on patients' age group. Pairwise comparison with Bonferroni correction (α = 0.008) showed that patients aged ≥50 years had lower survival rates (51.5%, 95% CI; 28.9–70.2) than those aged <30 years (91.0%; 95% CI: 81.5–95.8; P < 0.001) and 30–39 years old (85.2%, 95% CI: 64.8–91.6; P < 0.001). Regarding employment status, patients who were employed had higher survival rate (84.2%; 95% CI: 72.4–91.2) than those unemployed (41.1%; 95% CI: 17.3–63.7).

Patients infected through the parenteral route had the lowest survival rates (53.1%; 95% CI: 27.3–73.5) compared with those infected through heterosexual (71.0%; 95% CI: 58.6–80.3) and homosexual/bisexual (92.9%; 95% CI: 85.9–96.5) mode of transmission. Pairwise comparison with Bonferroni correction (α = 0.017) showed a significant difference in survival rate between homosexual/bisexual versus heterosexual (P = 0.006) and homosexual/bisexual versus parenteral route (P < 0.001). The survival rate was lower in those with a history of illicit drug use (57.8%; 95% CI: 30.4–77.7) compared to those with no such history (79.1%, 95% CI 57.8–90.4).

Patients with baseline CD4 counts of 0–49 cells/μL and 50–199 cells/μL had lower overall survival rates (70.6%, 95% CI: 58.0–80.1; 63.6%, 95% CI: 39.6–80.1, respectively) than those with ≥200 cells/μL (89.6%; 95% CI: 77.3–95.4). The difference in survival rate was statistically significant (P = 0.015 and P < 0.001, respectively) based on *post hoc* analysis with Bonferroni correction (α =0.017). Patients without anemia had higher survival rate (95.9%, 95% CI: 90.1–98.3) than anemic patients (58.8%, 95% CI: 41.7–72.4). Likewise, there were significant differences in overall survival rates between patients with and without tuberculosis (49.9%, [95% CI: 26.2- 69.8] and 81.4%, [95% CI: 68.6–89.3], respectively; P < 0.001) and hepatitis C co-infections (50.7% [95% CI: 27.0–70.2] and 81.9% [95% CI: 74.4–87.5], respectively; P = 0.008).

Regarding treatment-related characteristics, the overall survival rates were significantly influenced by the first NRTI background regimen (P < 0.001) and history of default (P = 0.021). Patients started with the combination of stavudine and lamivudine (d4T/3TC) as the first ART had lower overall survival rates (52.7%; 95% CI: 36.2–66.7) than those in the other groups [Table 2]. Pairwise comparison with Bonferroni correction (α = 0.008) found significant differences in overall survival rates between d4T/3TC versus AZT/3TC (P < 0.001) and d4T/3TC versus TDF/FTC (P = 0.006). History of follow-up defaults was also associated with overall survival rates: patients with no default history (79.0%; 95 CI: 67.1, 87.0) survived longer than those who defaulted at least once (51.5%; 95% CI: 22.2–74.6).

Prognostic factors

The results of the simple Cox proportional hazards regression indicated that age group, HIV transmission mode, illicit

Table 1: Patients-, clinical-, and treatment-related group of HIV-infected adults treated with antiretroviral therapy

Variables	Frequency, *n* (%)		
	Death (*n*=50)	Censored (*n*=289)	Total (*N*=339)
Age (years)			
<30	7 (7.3)	89 (92.7)	96 (28.3)
30-39	13 (10.6)	110 (89.4)	123 (36.3)
40-49	16 (20.5)	62 (79.5)	78 (23.0)
≥50	14 (33.3)	28 (66.7)	42 (12.4)
Gender			
Male	42 (14.5)	247 (85.5)	289 (85.3)
Female	8 (16.0)	42 (84.0)	50 (14.7)
Ethnicity			
Malay	23 (15.7)	124 (84.4)	147 (43.4)
Chinese	17 (13.4)	110 (86.6)	127 (37.5)
Others	10 (15.4)	55 (84.6)	65 (19.1)
Mode of transmission			
Homosexual/bisexual	8 (6.0)	126 (94.0)	134 (39.5)
Heterosexual	26 (19.1)	110 (80.9)	136 (40.1)
Injection drug use	13 (28.9)	32 (71.1)	45 (13.3)
Unknown	3 (12.5)	21 (87.5)	24 (7.1)
History of illicit drug use			
No	21 (9.8)	193 (90.2)	214 (63.1)
Yes	14 (23.0)	47 (77.1)	61 (18.0)
Unknown	15 (23.4)	49 (76.6)	64 (18.9)
Baseline CD4 cell count (cells/μL)			
≥200	8 (5.6)	134 (94.4)	142 (41.9)
50–199	16 (18.0)	73 (82.0)	89 (26.3)
0–49	23 (24.0)	73 (76.0)	96 (28.3)
Unknown	3 (25.0)	9 (75.0)	12 (3.5)
Median (IQR) baseline CD4 cell count (cells/μL)	50 (11-138)	192 (46-294)	157 (35-286)
Baseline viral load (copies/ml)			
<10,000	4 (11.4)	31 (88.6)	35 (10.3)
10,000-100,000	4 (5.6)	67 (94.4)	71 (20.9)
≥100,000	17 (16.4)	87 (83.7)	104 (30.7)
Unknown	25 (19.4)	104 (80.6)	129 (38.1)
Median (IQR) baseline viral load (copies/ml)	182,941 (59,809-424,144)	82,546 (20,800-322,910)	89,589 (22,875-340,547)
Baseline hemoglobin level (g/dL)			
No anemia	17 (7.4)	214 (92.6)	231 (68.1)
Anemia	24 (30.8)	54 (69.2)	78 (23.0)
Unknown	9 (30.0)	21 (70.0)	30 (8.9)
WHO clinical staging			
Class I	7 (6.2)	106 (93.8)	113 (33.3)
Class II	2 (8.0)	23 (92.0)	25 (7.4)
Class III	4 (12.9)	27 (87.1)	31 (9.1)
Class IV	1 (6.7)	14 (93.3)	15 (4.5)
Unknown	36 (23.2)	119 (76.8)	155 (45.7)
Tuberculosis			
No	25 (9.8)	229 (90.2)	254 (74.9)
Yes	25 (29.4)	60 (70.6)	85 (25.1)
Hepatitis B			
No	46 (14.7)	266 (85.3)	312 (92.0)
Yes	4 (14.8)	23 (85.2)	27 (8.0)
Hepatitis C			
No	35 (12.1)	254 (87.9)	289 (85.3)
Yes	15 (30.0)	35 (70.0)	50 (14.7)
Opportunistic infection			
No	22 (12.4)	156 (87.6)	178 (52.5)
Yes	28 (17.4)	133 (82.6)	161 (47.5)
Duration of first HIV-positive test to ART initiation (days)*	145 (1621)	104 (527)	106 (623)
Year of ART initiation			
2007–2010	25 (28.4)	63 (71.6)	88 (26.0)
2011–2013	17 (14.8)	98 (85.2)	115 (33.9)
2014–2016	8 (5.9)	128 (94.1)	136 (40.1)
First NRTI background			
TDF/FTC	8 (8.3)	89 (91.8)	97 (28.6)
ZDV/3TC	18 (9.9)	164 (90.1)	182 (53.7)
d4T/3TC	23 (41.1)	33 (58.9)	56 (16.5)

Contd...

Table 1: Contd...

Variables	Frequency, *n* (%)		
	Death (*n*=50)	Censored (*n*=289)	Total (*n*=339)
ABC/3TC	1 (25.0)	3 (75.0)	4 (1.2)
History of defaults			
No	33 (12.0)	243 (88.0)	276 (81.4)
Yes	17 (27.0)	46 (73.0)	63 (18.6)

*Median, IQR; right skew. WHO – World health organization; HIV – Human immunodeficiency virus; ART – Antiretroviral therapy; NRTI – Nonnucleoside reverse transcriptase; IQR – Interquartile range

Table 2: Mortality distribution among HIV-infected adults treated with antiretroviral therapy

Variables	Overall deaths	Total person-years at risk	Incidence mortality rate per 100 person-years	Overall survival rate at 10 years, % (95% CI)
Age (years)				
<30	7	431	1.6	91.0 (81.5-95.8)
30-39	13	584	2.2	85.2 (74.8-91.6)
40-49	16	401	4.0	58.8 (33.3-77.4)
≥50	14	184	3.5	51.5 (28.9-70.2)
Gender				
Male	42	1354	3.1	72.2 (28.7-82.0)
Female	8	246	3.3	74.9 (54.7-87.0)
Mode of transmission				
Homosexual/bisexual	8	586	1.4	92.9 (85.9-96.5)
Heterosexual	26	676	3.8	71.0 (58.6-80.3)
Injection drug use	13	235	5.5	53.1 (27.3-73.5)
History of illicit drug use				
No	21	1062	2.0	79.1 (57.8-90.4)
Yes	14	252	5.6	57.8 (30.4-77.7)
Baseline CD4 cell count (cells/μL)				
≥200	8	641	1.2	89.6 (77.3-95.4)
50-199	16	440	3.6	63.6 (39.6-80.1)
0-49	23	434	5.3	70.6 (58.0-80.0)
Baseline viral load (copies/ml)				
<10,000	4	180	2.2	86.4 (67.2-94.7)
10,000-100,000	4	326	1.2	86.6 (64.4-95.3)
≥100,000	17	435	4.0	78.6 (66.2-86.8)
Baseline hemoglobin level (g/dL)				
No anemia	17	766	2.2	88.0 (79.1-93.3)
Anemia	24	633	3.8	48.8 (26.7-67.7)
Tuberculosis				
No	25	1227	2.0	81.4 (68.6-89.3)
Yes	25	323	7.7	49.9 (26.2-69.8)
Hepatitis C				
No	35	1339	2.6	81.9 (74.4-87.5)
Yes	15	261	5.7	50.7 (27.0-70.2)
First NRTI background				
TDF/FTC	8	333	2.4	91.6 (83.9-95.7)
ZDV/3TC	18	884	2.0	86.5 (78.4-91.7)
d4T/3TC	23	373	6.2	52.7 (36.2-66.7)
ABC/3TC	1	11	9.1	75.0 (12.8-96.1) c
History of defaults				
No	33	1265	2.6	79.0 (67.1-87.0)
Yes	17	335	5.1	51.5 (22.2-74.6)

NRTI – Nonnucleoside reverse transcriptase; CI – Confidence interval

drug use history, baseline CD4 cell count and hemoglobin level, tuberculosis and hepatitis C co-infection, ART initiation year, first NRTI background regimen, and history of default were significantly associated with overall survival.

The results of the multivariable analysis showed that baseline hemoglobin level and tuberculosis co-infection were significant prognostic factors for survival among HIV-infected patients. A preliminary main effect model was obtained. Anemic patients were at a 3.76 times higher risk of mortality (95% CI: 1.97–7.18; $P < 0.001$) and patients co-infected with tuberculosis were at a 2.09 times higher risk of mortality (95% CI: 1.10, 3.96; $P = 0.024$).

Checking assumptions of the model

Both baseline hemoglobin level and tuberculosis followed proportionality assumption [Supplementary Figures 1–3 and Supplementary Table 1].

Final model

In this study, being anemic increased the mortality risk by 3.76 times(95% CI: 1.97–7.18; $P < 0.001$) compared with those who were not anemic, after adjusting for tuberculosis co-infection. The hazard risk was 2.09 times higher (95% CI: 1.10–3.96; $P = 0.024$) among those with tuberculosis co-infection than those without, after adjusting for baseline hemoglobin level [Table 3].

DISCUSSION

The findings of this study are nationally representative, as it was conducted at one of the largest tertiary hospitals under the Ministry of Health in Malaysia. Further, mortality data were obtained from a trusted source (i.e., the National Registration Department). Finally, all patients in this study were treatment naive, and thus there was no confounding effect of previous ART.

The demographic data of this study are consistent with previous local studies. The mean age of HIV patients remained similar to that previously reported in a study from the same hospital.[6] Between 2007 and 2016, more than half of the new HIV cases in Malaysia were in those aged 30–49 years.[12] Similarly, about 65% of the patients in the current study were in this age group. The vast majority of PLHIV in Malaysia were previously found to be males,[12] which is also the case in this study.

The current study had a higher survival rate than that of a previous study from Malaysia.[5] However, it should be noted that while all participants in the current study received ART treatments, the previous study included patients who were started with single-, double- or triple-drug regimens, and those receiving ART were chosen on narrower selection criteria because of limited government subsidy before 2006.[6] In terms of global comparison, the survival rates of this study were lower than those in England and Wales[13,14] and higher than those in Tanzania, Nepal and Ethiopia.[15,16] The 1-year survival rates of the current study were lower than those in China, a middle-income country, but the 3-year survival rates were almost the same.[17]

Table 3: Prognostic factors for survival

Variables	Regression coefficients (b)	Adjusted hazard ratio (95% CI)	*P*
Baseline hemoglobin level			
No anemia	-	1.00	-
Anemia	1.33	3.76 (1.97-7.18)	<0.001
Tuberculosis			
No	-	1.00	-
Yes	0.74	2.09 (1.10-3.96)	0.024

Forward stepwise Cox proportional hazards regression model applied. Multicollinearity and interactions were checked and not found. The preliminary final model was properly specified. Hazards function plots, log-minus-log plots, Schoenfeld partial residual plots, scaled and nonscaled Schoenfeld residuals test and C-statistic were applied to check the assumption of the model. CI – Confidence interval

A study from China found poorer survival rates with poor baseline patient characteristics, as also observed in the current study. The authors had suggested that early diagnosis and treatment within the first 6 months of ART were important for improving the survival outcomes of HIV-infected patients.[18]

Anemia, which was determined by the baseline hemoglobin level, is a well-recognized predictor for the survival of HIV patients. The current study also found that anemia is one of the most important factors in mortality in these patients, consistent with those of previous studies. An Ethiopian study reported that HIV patients with baseline hemoglobin levels of <11 g/dL had an increased hazard risk of 3.06.[8] In Tanzania, moderate and severe anemia were reported to increase the hazard risk by 7.50 and 9.20 times, respectively.[12] Vietnam, the neighboring country of Malaysia, reported a lower hazard ratio. HIV patients with baseline hemoglobin levels <10 g/dL had a 1.9 times mortality risk than those with hemoglobin levels were ≥10 g/dL.[19] A previous study in Malaysia found the same inverse relationship between mortality and baseline hemoglobin levels (analyzed as a continuous variable), with the hazard risk decreasing by 16% for every 1 g/dL increase in hemoglobin level.[6]

Baseline hemoglobin levels were predictive of long-term mortality and have been shown to be significantly associated with early mortality during the first 6 months of ART. The same study also found that the long-term mortality risk beyond 6 months of ART increased by 4.9 times with the presence of persistent anemia.[20] The concept of lifelong therapy for HIV treatment may be deterrent in some patients from starting care or in their retention.[21] However, clinicians should use the results of this and similar studies to highlight increased mortality resulting from low baseline hemoglobin levels.

Although anemia is known to increase the mortality risk, the possibility of reverse causality should be considered. Anemia at the baseline could be the result of HIV disease, particularly at an advanced stage. A common hematologic complication in HIV-infected patients, anemia has a multifactorial etiology. Anemia could result from bone marrow suppression, micronutrient deficiency, impaired erythropoiesis, systematic fungal and mycobacterial infection, malignancy, or chronic disease.[22] Anemia, which results from co-infection, could lead to a longer recovery

time or poor recovery prognosis. Thus, these patients have a higher mortality risk.[19] Nonetheless, anemia can be improved with ART. However, certain antiretroviral drugs, such as zidovudine, have been known to cause bone marrow toxicity, which leads to anemia.[23] Therefore, the periodic monitoring of hemoglobin levels, in accordance with the national guidelines, is important if zidovudine is the drug of choice in an ART regimen.

Another prognostic factor for survival in this study was tuberculosis co-infection. The results of the current study were comparable with those of studies in countries such as China, Ethiopia, Myanmar and Iran.[16,24-26] A study found that smear-positive and smear-negative extrapulmonary tuberculosis patients were not prognostic for a higher likelihood of mortality.[27] Similarly, in a study from Myanmar, pulmonary tuberculosis was not found to be a predictor for death.[24]

HIV and tuberculosis accelerate disease progression reciprocally, creating a lethal combination. Tuberculosis is the leading cause of death in HIV patients.[28,29] Disease management of HIV patients co-infected with tuberculosis is complicated by the interactions of drugs used in HIV and tuberculosis treatment.

Antiretroviral drugs such as NNRTIs and protease inhibitors are inducers or inhibitors of drug-metabolizing enzymes. Antituberculosis drugs such as rifampicin, are potent inducers of metabolizing enzymes and transporters. The consequences of the interactions include therapeutic failure and increased toxicity, which can increase the mortality risk of HIV/tuberculosis co-infected patients. However, the mortality rates in this group of patients could be reduced by a systematic approach to the identification and management of individual drug regimens. The WHO recommends starting ART in all HIV/tuberculosis co-infected patients regardless of their CD4 cell counts. Because tuberculosis is the most common co-infection in HIV patients, the coordination of HIV and tuberculosis care services for this group of patients is important.[21,30]

It was expected that the CD4 cell count would be a significant predictor of survival; however, the results of the Cox multiple regression showed otherwise. This could be explained by the small proportion of patients within the event group in this current study.

Limitations

A limitation of this study was that systematic sampling was applied and an additional number of patients were excluded based on them not meeting the inclusion criteria, whereas ideally, only those meeting the inclusion criteria should have been subjected to this sampling method. This unforeseen limitation was due to a lack of update in the MATCH database beyond December 31, 2017; the hospital medical records were then used to exclude those incorrectly selected.

As patients were included retrospectively, five important variables (namely, alcohol intake, smoking status, viral load, WHO clinical staging, and advanced clinical staging) were excluded from the survival analysis. This could have introduced bias in the assessment of the progression to mortality. In addition, the study did not account for ART adherence because it had not been consistently included in the medical records. Adherence assessments were also not standardized, and exclusion of this information might have led to bias in the identification of the prognostic factors for survival.

CONCLUSION

The overall survival rates in the present study were 93.8%, 90.4%, 84.9% and 72.8% at 1, 3, 5 and 10 years, respectively. Low baseline hemoglobin levels and tuberculosis coinfection were strong prognostic factors for survival. The mortality was highest in the 1st year of ART initiation, further highlighting the importance of early treatment initiation, especially in those with low hemoglobin levels or tuberculosis co-infections.

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Ethical considerations

Ethical approval was obtained from the National Medical Research and Ethics Committee of the Ministry of Health, Malaysia, through the National Medical Research Registry [Ref: KKM. NIHSEC. P18-1703 (6) and NMRR-18-2100-42257(IIR)] on September 6, 2018. Approval was also obtained from the Human Research Ethics Committee of USM (Ref: USM/JEPeM/18060287) on September 17, 2018. Requirement of patient consent was waived due to use of anonymized data.

Peer review

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Conflicts of interest

There are no conflicts of interest.

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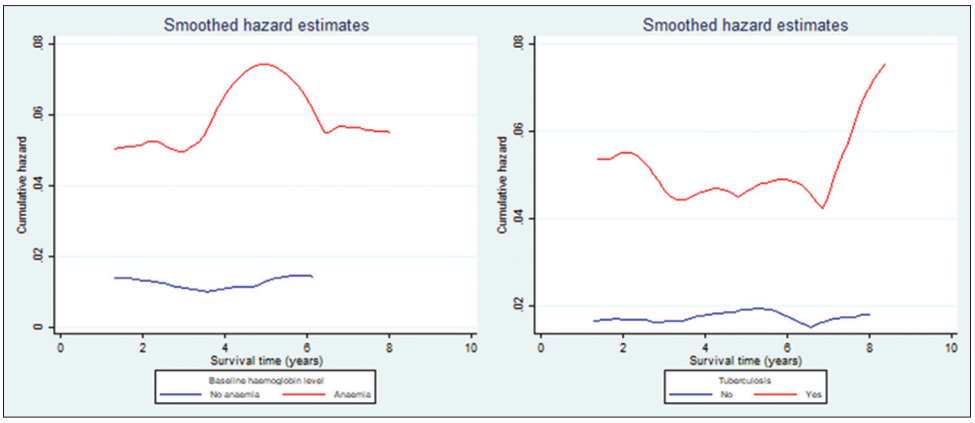
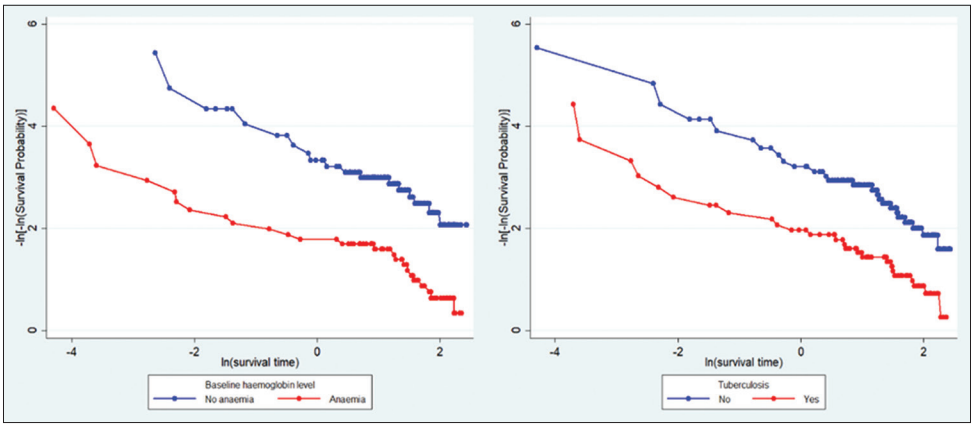
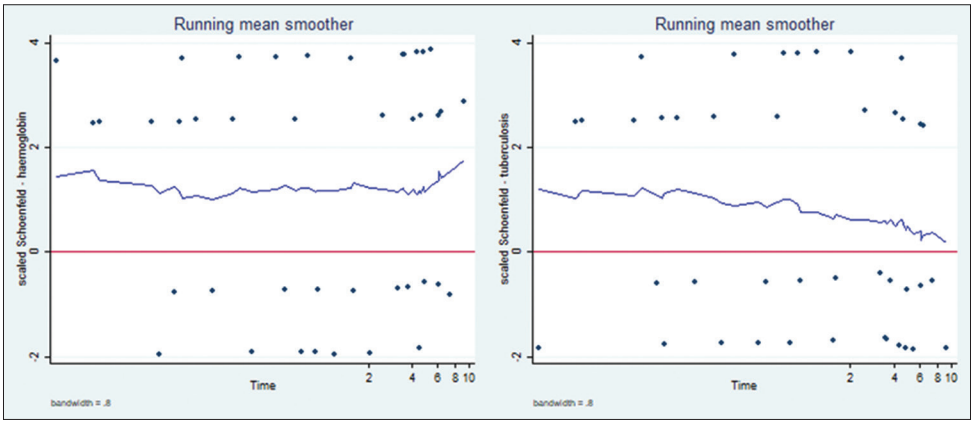


Supplementary Figure 1: Hazard function plot for baseline hemoglobin level and tuberculosis co-infection



Supplementary Figure 2: Log-minus-log plot for baseline hemoglobin level and tuberculosis co-infection



Supplementary Figure 3: Schoenfeld residual plot for baseline hemoglobin level and tuberculosis co-infection

Supplementary Table 1: Test of proportional hazard assumption based on scaled Schoenfeld and unscaled Schoenfeld

Variables	Scaled Schoenfeld (*P*)	Unscaled Schoenfeld (*P*)
Baseline hemoglobin level	0.968	0.380
Tuberculosis	0.184	