Original Article

Predictive Factors of Early Mortality in HIV Patients with Co-existing TuberculosisAfterInitiating Antiretroviral Therapy: A Study From Northern India

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Abstract:

Background: In the era of Human immunodeficiency virus(HIV) pandemic, the initiation of highly active antiretroviral therapy (HAART) has dramatically improved the prognosis of AIDS patients. Nevertheless, mortality is high, particularly in the patientswith co-existing Tuberculosisafter initiating antiretroviral therapy. Thisstudy addresses these poorly understood factors as there is no similar study in northern India.

Methods: A total of 124 cases were taken consecutively who during a period of one year in the Department of Medicine in Nehru Chikitsalay of B.R.D Medical College, Gorakhpur from January 2009 to December 2009. Each case was followed up for 3 months to determine the mortality rate and identify the probable predictors using SASversion 9.1 software by multivariate binary logistic regression method.

Results: There were 17 (13.71%)deaths among 124 cases within the first 3 months of starting ART of which 12 were males and 5 were females.Mortality rate was high with CD4 count less than 50/µL (68.63%) but no mortality was seen with CD4 more than 200/µl.Mortality was significantly associated with low skin-fold thickness, leukocytosis, low serum albumin, high serum potassium and low serum phosphate levels.

Conclusion: In a newly registered HIV-infected patient with Co-existent tuberculosis, fewclinic-biochemicalparameters like skin-fold thickness, total leukocyte count, serum albumin,potassium and phosphate levels should be and looked for while initiating ART.Adequate and, if possible, intensive nutritional therapy of the patients is recommendedwith the initiation of antiretroviral therapyas most of the parameters indicate a deficient nutritional state. Hence we can say that Co-existent tuberculosis in HIV had significant impact on early ART mortality.

Introduction:

The introduction of highly active antiretroviral therapy (HAART) in decades of nineteen hundred ninty has dramatically improved the prognosis of human immunodeficiency virus(HIV)–infected (AIDS) patients. Nevertheless, mortality has remained high.[1-4]From all deaths that have occurred during ART, the highest death rate frequently occurs in the first three months of treatment[5,6]. Factors contributing to this high mortality are poorly understood, though multiple factors have been implicated[7-10].

In multivariate analyses, the independent predictors for mortality were unintentional loss of more than 10% body weight, bedridden functional status at baseline, CD4 cell count less than 200 /µl, and advanced WHO stage patients[10-14]. Several studies around the world proposed various parameters as the

predictors of early mortality which are male gender, age above 40 years, low body-mass index(BMI), severe malnutrition, low hemoglobin, thrombocytopenia, CD_4 count less than 50/µl, high HIV RNA load, raised Alanine aminotransferase(ALT), low serum phosphate, and Hepatitis B [10-23].

Methods:

This study was conducted at the ART Centre in a tertiary care hospital in northern part ofIndia, India after ethical review approval was granted by the ethics committee [24]. This was an analytical, prospective hospital based cohort study undertaken over a period of one yearin the Department of Medicine in Nehru Chikitsalay of B.R.D Medical College, Gorakhpur from January 2009 to December 2009.

All adult newly registered patients of HIV with co-existing Tuberculosisfor HAARTduring the study period who gave consent for the study were included in the study.[25]Severe co-morbidities like malignancy, heart diseases, renal failure, hepatic failure, etc. were excluded. Among 258 newly registered HIV/AIDS patients who met eligibility criteria, only 131 gave consent in this study of which 7 were lost to follow-up making the final study population of 124.

The studied parameters were —number of deaths in the first 3 months, age, gender, weight, height, body-mass index(BMI), skin-fold thickness, hemoglobin(Hb%), total leukocyte count(TLC), differential count(DC), erythrocyte sedimentation rate(ESR), bilirubin, albumin, globulin, urea, creatinine, Aspartate aminotransferase(AST), Alanine aminotransferase(ALT), alkaline phosphatase(ALP), fasting plasma glucose(FBS), serum sodium, serum potassium, serum phosphate, Hepatitis B virus(HBV) andHepatitis C virus(HCV).

A thorough physical examination was done. Height of the study subjects were measured using non-elastic measuring tape; body weight were taken using electronic weighting machine; skin-fold thickness were measured using Harpenden caliper (marketed in India by Industrial & Commercial Services); pulse rate was measured for a complete one minute in each patient; and blood pressure of every patient was measured by taking the mean of both arm blood pressures measured five minutes apart using mercury sphygmomanometer. The pulse rate and blood pressure were measured at least five minutes of taking rest after arriving at the ART Centre.

Blood was collected at the same sitting and sent for the different laboratory investigations. The hematological parameters were measured using Sysmax KX21 automated cell counter. CD4 cell count was measured with Becton Dickinson FACS Count machine (using CD4/CD3 BD FACS Count reagent) installed at the ART Centre. The biochemical parameters were measured using Erba XL600 autoanalyserand the kits used were marketed by Crest Biosystems, Goa, India for bilirubin (mod. Jendrassik&Grof's method) total protein (Biuret method), albumin (BCG method), urea (DAM method) and creatinine (mod. Jaffe's kinetic method). The metabolic parameters were measured using the same autoanalyser using kits for liver enzymes (Spectrascan UV 2600, Chemito), fasting glucose (GOD/POD method), serum sodium and potassium (colorimetric method) and phosphate (molybdate UV method).

The collected data were entered in the Microsoft Office Excel Worksheet and the grand chart was prepared, from which data were managed and

analysed using SAS software for Windows. Mean and standard deviation (SD) were calculated for all continuous variables and independent sample t-test was subsequently applied with a probability cut-off value of 0.05. For binary logistic regression, the outcome (biostatus) at 24 weeks was taken as dependent variable (alive=0, expired=1) and the independent variables were the different parameters studied in this research as detailed above. Other variables assumed for statistical analyses were male=1, female=2, urban=1, rural=2, age grouping (<20=1, 20-29=2, 30-39=3, 40-49=4, ≥50=5) and CD4 count grouping (<50=1, 50-99=2, 100-199=3, 200-349=4, ≥350=5).

Results:

There were 100 (80.64%) males and 24 (19.35%) females, of which 70 (56.45%) patients were from rural and 54 (43.55%) were from urban areas. Mean age of the study population was 43.44±8.4 years. The mean BMI of the male population was 22.69±2.23 kg/m^2 whereas 21.38±2.59 kg/m^2 in females and that of the total population was 22.04±2.37 kg/m^2. Majority (61.13%) of the study population had CD4 count in between 100 and 199 cells/µL.

There was no mortality within 2 weeks of initiating ART, 8 (6.45%) mortalities in the first month and 9 more mortalities in the next 2 months, resulting in a total of 17 (13.71%) mortalities in the first 3 months of starting ART in HIV/AIDS patients[Fig. 1] of which 12 were male(14.46%) and 5 were female(12.2%). Most of the early ART mortalities (9) were in the age group 30-39 years (16.36%); the highest percentage of mortality was above 50 years of age (25%). The highest rate (68.63%) of mortality was with CD4 count <50/µL and also, there was no mortality with CD4 count above 200 cells/µL[Fig. 2].

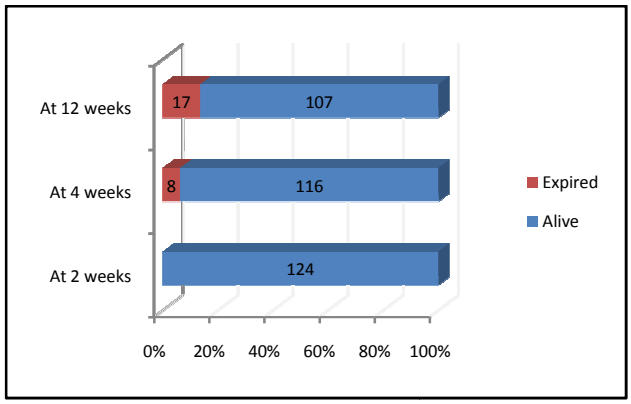

Fig. 1: *Mortality of the study population*

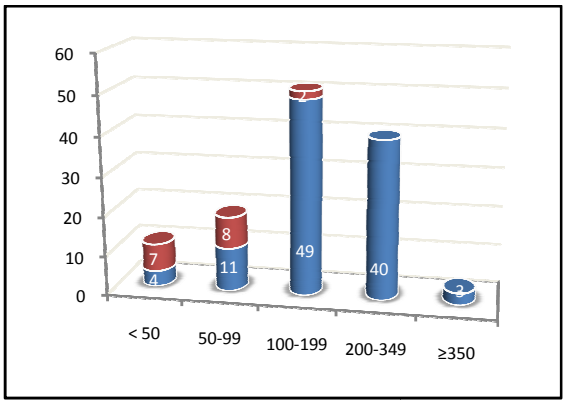

Fig. 2: *Mortality according to CD4 count*

There was significant positive correlation of early ART mortality with pulse rate, TLC, neutrophil count, ESR and serum urea level. There was significant negative association of mortality with body weight, skin-fold thickness, BMI, CD_4 count, Hb%, lymphocyte count, serum phosphate and serum albumin; strongest correlation being with skin-fold thickness, CD_4 count, phosphate level and hemoglobin. [Table 1]

Table 1.*Correlation of early mortality with the study parameters* (n=124)

Variables	Body Wt	Skin fold	BMI	Pulse	SBP	DBP	Hb%	TLC	Neutrophil	te	ESR	CD4	Bilirubin	Albumin	Globulin	Urea	Creatinine	AST	ALT	ALP	FBS	Na^+	K^+	Phosphate	TB	$HBsAg^+$	$AntiHCV^+$
Pearson correlation	**-0.222**	**-0.466**	**-0.239**	**0.404**	**0.021**	**-0.081**	-0.403	**0.279**	**0.451**	**-0.389**	**0.272**	**-0.495**	**0.030**	-0.229	-0.082	**0.187**	**0.103**	**-0.015**	**-0.035**	**0.143**	**-0.121**	**-0.138**	**0.150**	**-0.754**	**0.302**	**-0.112**	**-0.063**
P value	**0.013**	**0.000**	**0.008**	**0.000**	**0.820**	**0.373**	0.000	**0.002**	**0.000**	**0.000**	**0.002**	**0.000**	**0.741**	0.010	0.365	**0.037**	**0.254**	**0.868**	**0.700**	**0.113**	**0.182**	**0.126**	**0.095**	**0.000**	**0.001**	**0.218**	**0.489**

**correlation significant at 0.01 level (2-tailed)*

Logistic regression analysis showed that mortality was significantly associated with low skin fold thickness, high pulse rate, low CD4 count, and low serum phosphate levels. For infections, co-existent tuberculosis had significant impact. [Table2]. This indicates that incident nutritional status is very important for predicting short term mortality.

Table2. *Logistic regression model for predicting mortality at the end of the study* (n=124)

Variables	Body Wt	Skin fold	BMI	Pulse	SBP	DBP	Hb%	TLC	Neutrophil	Lymphocyte	ESR	CD4	Bilirubin	Albumin	Globulin	Urea	Creatinine	SGOT	SGPT	ALP	FBS	Na^+	K^+	Phosphate	TB	$HBsAg^+$	$AntiHCV^+$
B	**0.003**	**-1.145**	**-0.182**	**0.241**	**0.081**	**0.065**	**-1.184**	**0.002**	**0.346**	**0.022**	**0.017**	**-0.125**	**0.426**	**-1.250**	**-0.551**	**0.048**	**1.363**	**-0.022**	**-0.144**	**0.038**	**-0.004**	**-0.319**	**10.094**	**-7.012**	**1.780**	**-19.135**	**-19.135**
p value	**0.976**	**0.001**	**0.506**	**0.003**	**0.079**	**0.513**	**0.086**	**0.043**	**0.354**	**0.938**	**0.406**	**0.026**	**0.667**	**0.024**	**0.201**	**0.190**	**0.500**	**0.695**	**0.287**	**0.070**	**0.967**	**0.139**	**0.011**	**0.004**	**0.005**	**0.999**	**0.999**

**The overall predictivity of this model is 86.3%. *Cox and Snell R Square - 0.086 & Nagelkerke R Square - 0.157.*

Discussion:

Similar studies from the Sub-Saharan Africa found mortality rates of around 20% which is much higher than what we found in this study(13.71%), probably because of improved support system of the current setup[17,18,19]. It was found that 21.82% of the urban population expired within the first three months of initiating ART, but only 7.25% of the rural population expired in the early period, the precise cause or significance could not be decoded.

Independent predictors for mortality inthe Vietnam study, were age above 40 years, male gender, CD4 count ≤100 cells/μL, HBsAg positivity, HBV/HCV co-infection, ALT>40 IU/L and co-existent

tuberculosis[12].Two studies from South Africa and Singapore indicate CD4cell count <50/µL, a low hemoglobin concentration (≤ 8 g/dl), a history of oral candidiasis and history of cryptococcal meningitisas strong predictors of mortality[9-11]. According to the Tanzanian cohort, the strong predictors of mortality were anemia, thrombocytopenia and severe malnutrition[13], while from Zambian cohort, low serum phosphate at ART initiation was an independent predictor of early mortality[14].Low baseline BMI and Hb% are both related to poor nutritional status and a decline of immunity[15]. Individuals who were severely malnourished [BMI <16.0 kg/m^2] had six times higher risk of dying in the first 3 months than those with a normal nutritional status[16-20]. Also, low absolute lymphocyte count which is an indirect marker of CD4 count, was associated with increased mortality [21-23].

The findings of the present study are corroborating with those from the above mentioned studies. The highest mortality rate (68.63%) was found with CD4 count less than 50/µL. There was no mortality when CD4 count > 200/µL. There was significant negative impact of serum albumin (p=0.01) and phosphate (p<0.001) levels on mortality. Serum phosphate level was found to be an independent predictor of early ART mortality [14]. Coexistent tuberculosis was also associated with increased mortality (p=0.001).

Independent factors associated with early mortality in a meta-analysis of 30 studies included low baseline CD4 cell count, male gender, advanced World Health Organization clinical stage, low BMI, anemia, age above 40 years, and pre-ART quantitative HIV RNA[17]. One study from India, which found pulmonary tuberculosis (TB) as a significant risk factor for mortality, along with Pneumocystis pneumonia, Cyptococcal meningitis and Toxoplasmosis, also support our findings[4].

Thelist of mortality predictors in different countries among different ethnic groups is different. Accordingly, it is necessary to validate the studies with the countries' real context before endorsing the raw evidence from different clinical setups.

Conclusion:

In a newly registered HIV-infected patient with Co-existent tuberculosis, fewclinic-biochemical parameters like skin-fold thickness, total leukocyte count, serum albumin, potassium and phosphate levels should be and looked for while initiating ART. Adequate and, if possible, intensive nutritional therapy of the patients is recommendedwith the initiation of antiretroviral therapyas most of the parameters indicate a deficient nutritional state. Hence we can say that Co-existent tuberculosis in HIV had significant impact on early ART mortality.

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