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Introduction

- There are several causes of macrocytosis, such as vitamin B12 or folic acid deficiency, alcoholism, drug-induced conditions such as hydroxyurea, and certain HIV medications such as zidovudine (AZT).
- The mean corpuscular volume (MCV) increased by a mean 3% at week 4, and 14% at 12 weeks after starting AZT. Macrocytosis (MCV >100 fl, normal 79 – 98fL) was present in 78% - 88% in HIV-infected patients treated with AZT.
- There is limited literature on duration of persistence of macrocytosis after AZT is discontinued.
- This study aims to characterize the duration and causes of persistent macrocytosis after discontinuation of AZT.

Method

This is a retrospective cohort study approved by our institution IRB. The inclusion criteria:

1. HIV-infected patient ≥18 years old, continuous exposure to AZT ≥ one year from Jan 01, 2004 to Dec 31, 2013, and availability of the laboratory parameter at least 3 to 6 months after discontinuation of AZT.
2. MCV and hemoglobin was recorded at the following time line: 1 year prior to discontinuation, at discontinuation, and 3-6 months, 1 year, and 2 years after discontinuation.
3. AST and ALT levels were recorded at 3-6 months after discontinuation. Chronic hepatitis B and C, TSH, folic acid, B12 level, and presence of fatty liver by ultrasound or CT scan of abdomen was also recorded if available at any time during the study period. There was no specific criterion for alcohol use.
4. The stop date of AZT was defined as one month after the last prescription date of available pharmacy dispense data at University of Kentucky or the documentation of date of clinic visit that AZT was stopped.
5. Anemia is defined as hemoglobin <13.5g/dL in males, <12g/dL in females.

Statistical Analysis

- Descriptive statistics were conducted for the entire study sample.
- Means, standard deviations, medians, ranges, and interquartile ranges (q1 and q3) were conducted for all continuous variables and frequencies, and percentages were conducted for all categorical variables.
- For analysis of the relationships of variables between MCV normalized group and MCV persistent group, bivariate analyses were performed using the chi-square test or the Fisher exact test for categorical variables, and the Wilcoxon tests for continuous variables.
- Kaplan Meier curves were produced to determine median time to normalize macrocytosis. SAS version 9.3 (SAS Institute, Cary, NC) was used for statistical analysis. The level of significance was defined as p <0.05 (2-sided) unless otherwise specified.

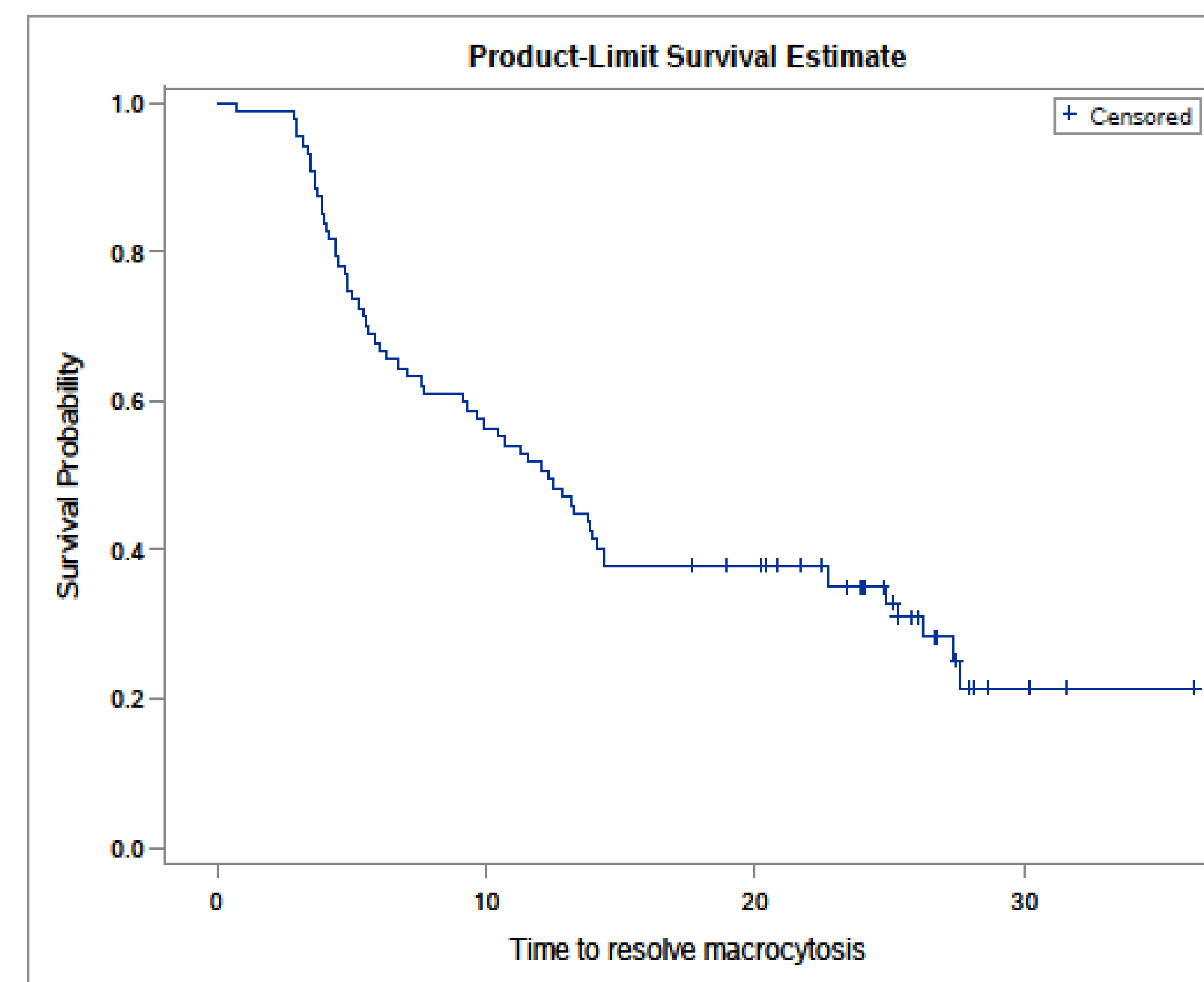
Table 1

Table 1. Comparison of resolved macrocytosis group and persistent macrocytosis group at 3 to 6 months after stopping AZT (N = 91)

	Total patients N=91	Resolved macrocytosis group (N=36)	Persistent macrocytosis group (N=55)	P Value
	Total N (%)	n (%)	n (%)	P ≥ 0.03
Average Age – mean (std)	46.6 (10.3)	45.7 (11.6)	47.2 (9.4)	0.58
Caucasian Race	73 (80.2)	27 (75.0)	46 (83.6)	0.31
Sex - male	76 (84.4)	30 (85.7)	46 (83.6)	0.79
Years on AZT – median (q1, q3)	4.0 (2.0, 6.0)	4.0 (2.0, 5.5)	4.0 (3.0, 6.0)	0.60
Anemia at 3 to 6 months	15 (16.7)	5 (14.3)	10 (18.2)	0.63
Smoking	56 (61.5)	18 (50.0)	38 (69.1)	0.07
Alcohol use	37 (40.7)	10 (27.8)	27 (49.1)	0.04
Chronic hepatitis B	10 (11.0)	3 (8.3)	7 (12.7)	0.73
Chronic hepatitis C	9 (9.9)	1 (2.8)	8 (14.6)	0.08
AST>40	17 (19)	5 (14)	12 (22)	0.42
ALT>41	32 (35)	12 (33)	20 (36)	0.77
TSH – median (q1, q3)	1.7 (1.2, 2.3)	1.75 (1.14, 2.20)	1.69 (1.26, 2.34)	0.89
B12 level – median (q1, q3)	502 (293, 766)	507.5 (280.5, 798.0)	424 (311, 675)	0.73
Folic acid level – median (q1, q3)	15.0 (9.9, 20.0)	18.1 (11.3, 20.0)	11.9 (9.1, 16.6)	0.03
Fatty liver on imaging*	13 (33)	6/18 (33)	7/22(32)	0.92
Macrocytosis at 1 year	34 (38.0)	0 (0)	34 (59.6)	<0.0001
Macrocytosis at 2 years	30 (39.5)	2 (7.1)	28 (58.3)	<0.0001

*n = 40

Figures:



Summary of the Number of Censored and Uncensored Values			
Total	Failed	Censored	Percent Censored
87	61	26	29.89

Note: 3 observations with invalid time or censoring values were deleted.

Figure 1. Time to resolve macrocytosis using the LIFETEST procedure.

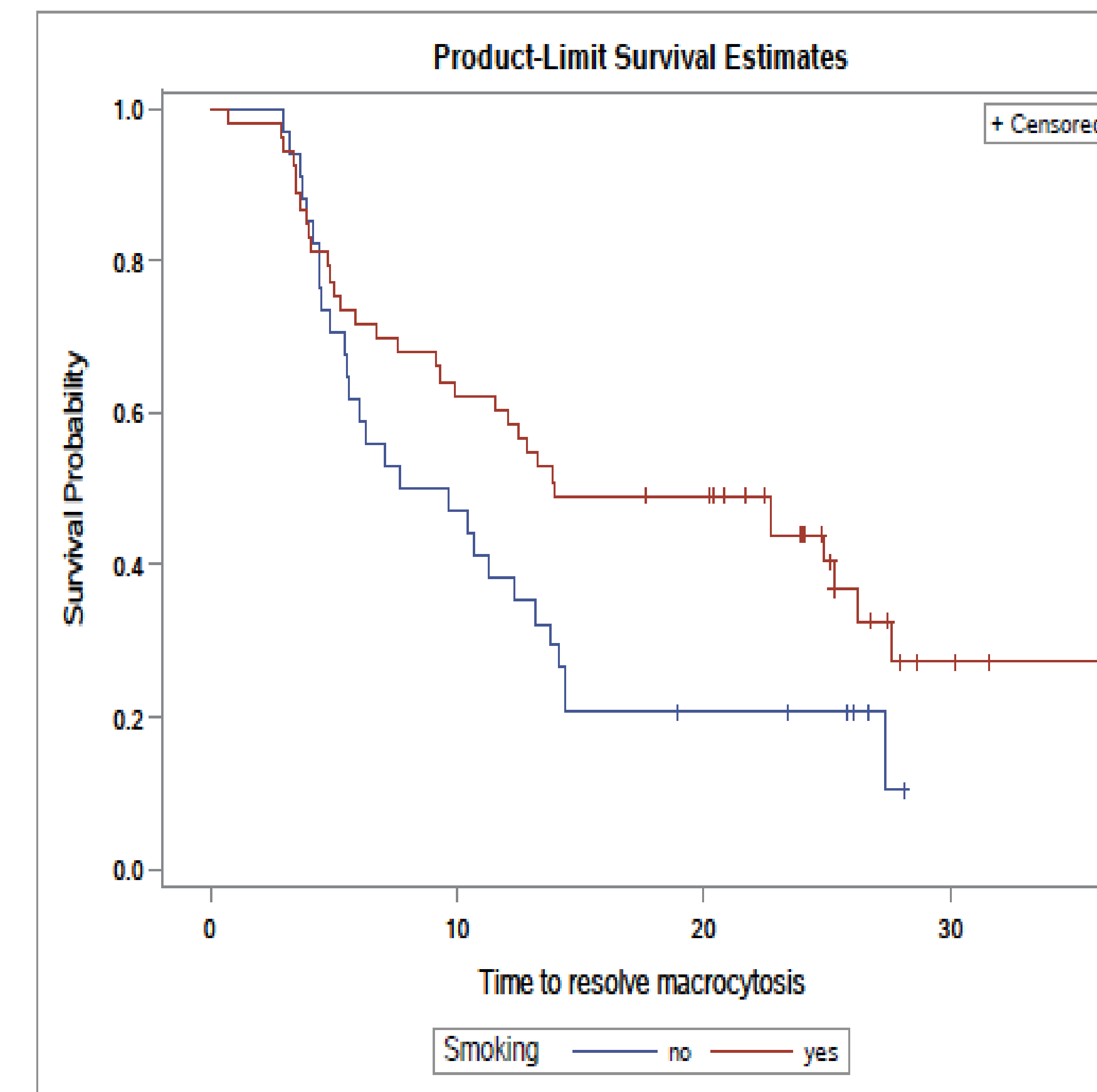


Figure 2. Time to resolve macrocytosis by smoking status using the LIFETEST procedure

Discussion

- Patients taking AZT were switched to an alternative regimen primarily because of its toxicities including macrocytosis and bone marrow toxicity, lipodystrophy, lactic acidosis, myopathy, and liver toxicity.
- AZT is still used in the US as part of a preferred regimen for prevention of perinatal HIV transmission in antiretroviral-naïve pregnant women and in resource limited countries.
- The median treatment duration of AZT in our study population was 4.0 years (range, 1– 14 years).
- The duration of AZT use did not affect the persistence of macrocytosis.
- Nine patients who were on AZT ≥ 10 years normalized MCV within 3 to 6 months after stopping AZT.
- The higher the number of MCV at the time of stopping AZT, the more likely the patient was to develop persistent macrocytosis up to two years later.
- In comparison between the resolved macrocytosis group and persistent macrocytosis group, alcohol use, smoking, and lower folic acid level were statistically significant for persistence of macrocytosis. There were no patients with folic acid deficiency in the persistent macrocytosis group; their folic acid levels were lower normal limit (median 11.1ng/mL).
- The duration of AZT, anemia, TSH, B12 level, elevated transaminases and presence of fatty liver was not statistically significant. Five patients with abnormal thyroid stimulating hormone test (2 low TSH and 3 high TSH, normal 0.5 – 4) had normal MCV at 3 months, 6 months, one year, and two years of study period.
- Macrocytosis could be persistent up to 2 years if there was macrocytosis at 3 to 6 months after stopping AZT.
- Several limitations of this study require consideration. First, this is a retrospective study; laboratory data were not obtained with consistency or at regular intervals. Second, duration of AZT was recorded from the chart if they were transferred from another clinic. Third, there is no specific definition for alcohol use, which was recorded from chart.

Conclusion

- There is a persistence of macrocytosis in 60% of HIV-infected patients at 3 – 6 months, 37% at one year, and 39% at two years after discontinuation of AZT.
- Duration of AZT has no effect on persistence of macrocytosis. The median time for MCV to be normalized was 12.5 months after stopping AZT.
- Alcohol use, smoking, and low folic acid is related to persistence of macrocytosis.