Survival of Patients with CML on Imatinib Experience with 44 Iraqi Patients

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Summary

Background: Chronic myeloid leukemia (CML) is a clonal stem disease with distinctive clinical course which is ultimately fatal. It is characterized by the presence of Philadelphia chromosome (t 9:22).Tyrosine kinase inhibitors like imatinib mesylate as targeted therapy had revolutionized the management of CML with significant prolongation of overall survival and decreased rate of blastic transformation.

Objective: This study will describe the experience of treating 44 Iraqi patients with chronic myeloid leukemia by imatinib at the National Hematology Centre in Baghdad.

Patients and Methods: This study included 44 Iraqi patients diagnosed in Chronic phase CML at the National Centre of Hematology in Baghdad from February 2003 till January 2006, all were pretreated with alfa interferon and hydroxyurea. All patients were started on imatinib mesylate 400 mg orally daily. The end points included overall survival (OS) and Blastic transformation free survival (TFS).The effect of age, gender, WBC count on starting Imatinib, presence of splenomegaly and duration of diagnosis of CML prior to starting imatinib, on the OS and TFS were studied.

Results: Median age was 35 years with 27 males and 17 females. The 3 year OS was 88.6% and the TFS was 79.5%.The only factor that had negative impact on OS and TFS was a diagnosis of CML more than 2 years before starting imatinib. The most common side effects were myalgia(75%) and peripheral oedema(65%). Neutropenia(20%),thrombocytopenia(12%) and elevated serum transaminases (2%) necessitated temporary cessation of treatment.No cytogenetic and molecular studies were available .

Conclusion: Imatinib is an effective therapy for Iraqi patients with CML with tolerable side effects and should be offered to newly dignosed CML patients as early as possible as frontline therapy to ensure better OS and TFS.Establishment of cytogenetic and molecular studies are crucial to optimize management.

Key Words: Chronic myeloid leukemia,CML,Imatinib.

Introduction :

Chronic myeloid leukemia(CML) is clonal myeloproliferative disorder that results from neoplastic transformation of the primitive hemopoietic stem cell ,the clinical picture is characterized by a chronic phase which ultimately progresses to an accelerated phase and finally ends in a terminal blastic phase [1].The hallmark of CML is the presence of a balanced translocation between the long arm of chromosomes 9 and 22 ,t(9;22)(q34;q11) known as Philadelphia chromosome [2]. Effective therapies that include alfa interferone, bone marrow transplantation , and tyrosine kinase inhibitors like imatinib mesylate(Glivec) have changed the natural history of CML.

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Certain patients characteristics on first diagnosis of chronic phase CML are useful in predicting the natural history and progression into accelerated and ultimately blastic phases, they have been incorporated in the Sokal CML score [3].

Imatinib has changed the current treatment approach. A complete cytogenetic response is achieved in 50-60% of patients treated with imatinib after failing alfa interferon therapy [4-6],and in 75-90 % of those treated with frontline imatinib therapy, and it is now considered as the standard frontline therapy for patients with newly diagnosed CML [7-9].

Patients and Methods

This study included 44 Iraqi CML patients in the chronic phase attending The National Center of Hematology in Baghdad from February 2003 to January 2006.

The diagnosis of CML was established according to a typical clinical presentation accompanied by

typical complete blood picture findings along with bone marrow aspirate and biopsy; no cytogenetic or molecular studies were available.

All patients were already pretreated with @INF and hydroxyurea. Treatment was started for all patients with imatinib mesylate 400 mg daily orally as single morning dose, blood counts were monitored after a week and later on every 4 weeks and liver enzymes were checked after 4 weeks and any side effect during therapy was recorded. Dose adjustment was done according to WBC count, Platelet count and other side effects. Patients with gaps in follow up more than 6 months were excluded from the evaluation. Blastic transformation was diagnosed if blast percentage in peripheral blood or bone marrow was=>20%. Sokal scoring was not possible at time of starting imatinib because the findings were modified by prior alfa interferon and hydroxyurea therapy.

End points included overall survival (OS) and Blastic Transformation Free Survival (TFS), They were measured using the Kaplan Meier Survival curves and the difference between the results according to certain patient characteristics was studied using the log rank test. The effect of certain patient characteristics on OS and TFS were evaluated using univariate analysis. A P value < 0.05 was indicative of statistically significant difference. All Data were processed using SPSS 9 software.

Results

Table 1 shows some of the characteristics of the study group which included 44 patients, 27 males and 17 females with a median age of 35 years .Thirty two patients have been diagnosed for more than 2 years before starting imatinib, duration of follow up after starting imatinib was 3 years.

Table 2 shows the results of 3 year OS (88.6%) and TFS (79.5%), 9 patients had blastic transformation, and 5 of those patients died.

Table 3 shows univariate analysis of the effect of some variables on OS and TFS and it showed that duration of diagnosis of more than 2 years of CML before starting imatinib had been associated with negative impact on OS and TFS.

Figures 1-6 show the survival curve for OS and the results of comparison after splitting the patients into 2 groups according to sex, age, WBC count on starting Imatinib, presence of splenomegaly and duration of diagnosis of CML, all groups showed no statistically significant difference.

Figures 7-12 show the survival curves for TFS and the results of comparison for the same grouping parameters and only the duration of diagnosis of CML showed a statistically significant difference.

Table 4 shows some of the side effects of treatment with myalgia (75%) and peripheral oedema (65%) as the most common side effects while neutropenia occurred in 20% of cases, thrombocytopenia in 12% and transient elevation of serum transaminases in 2% of cases.

Discussion

From this study certain observation had been made. The median age of the study group was 35 years which differs from western studies in which the usual age is within the sixth and seventh decades[10].All patients were pretreated with alfa interferone and hydroxyurea. The 3 year OS and TFS were 88.6% and 79.5% respectively, in the 6 year update of IRIS trial(International Randomized Study of Interferon and STI571) the OS at 5 years was 91% and the EFS was 88% at 5 years [11].The difference in the results is probably related to the fact that many of our patients have some gaps in the treatment because of some difficulties in receiving the drug because of delayed patient attendance or gaps in the drug supply although patients with gaps in the treatment more than 6 months were excluded from the evaluation, also all these patients were pretreated. The effect of some of patient characteristics like WBC count, presence of splenomegaly, age ,gender and duration of diagnosis of CML prior to starting imatinib were evaluated and showed no statistically significant effect on both OS and TFS except for patients with a diagnosis of CML for more than 2 years before starting imatinib which may place these patients in a possibly high risk category. In an IRIS update, the OS at 42 months was better for patients with low risk Sokal score compared to patients with high Sokal score, but patients with high or low score once they achieve complete cytogenetic remission, they will have similar OS [12].

A drawback in this study was the lack of cytogenetic and molecular studies which did not allow us to evaluate the rate of cytogenetic and molecular responses in these patients. Side effects were tolerable and did not necessitate discontinuation of treatment, only temporary cessation of treatment for neutropenia, thrombocytopenia and elevated liver enzymes was adopted.

Conclusion

In spite of many limitations in Iraq, Imatinib is an effective therapy for this group of CML patients over three years of follow up. Starting Imatinib after more than two years of diagnosis has a negative impact on OS and TFS. Side effects were tolerable. Management can not be optimized without proper cytogenetic and molecular studies.

Table 1: Clinical Characteristics of The patients

Characteristic	Number	%
Age in Years:		
Median	**35**	
Range	**15-56**	
Sex:		
Male	**27**	**61.3**
Female	**17**	**38.7**
WBC(x10^9/l) on starting Imatinib:		
Median	**24**	
Range	**6.2-318**	
Blasts in peripheral blood:		
Present	**24**	**54.5**
Absent	**20**	**45.5**
Splenomegaly:		
Present	**37**	**84.1**
Absent	**7**	**15.9**
Duration of CML Diagnosis:		
< 2 Y	**32**	**72.7**
=> 2 Y	**12**	**27.3**

Table 2 : Results of Treatment

Parameter	Number	%
Three Year OS	**39**	**88.6**
Three Year TFS	**35**	**79.5**
Blastic Transformation	**9**	**20.5**
Death	**5**	**11.4**

Table 3 :Univariate Analysis for The Influence of Some Factors on OS and TFS

Parameter	Number	TFS (P value)	OS (P value)
Age in Years:			
< 40	**30**	**NS**	**NS**
=> 40	**14**		
Sex:			
Male	**27**	**NS**	**NS**
Female	**17**		
WBC(x10^9/l) on starting Rx:	**6**		
< 11	**38**	**NS**	**NS**
=> 11			
Blasts in peripheral blood:			
Present	**24**	**NS**	**NS**
Absent	**20**		
Spenomegaly:			
Present	**37**	**NS**	**NS**
Absent	**7**		
Duration of CML Dx:			
< 2 Y	**32**		
=> 2 Y	**12**	**0.031***	**0.017***

NS= P value=>0.05

*=statistically significant

Table 4: Side Effects

Parameter	%
Neutropenia (ANC < 1000 / cmm)	**20**
Thrombocytopenia(PLAT< 50000/cmm)	**12**
Elevated Serum Transaminases	**2**
Peripheral Oedema	**65**
Myalgia	**75**

Figure 1:Overall Survival(OS)for all patients

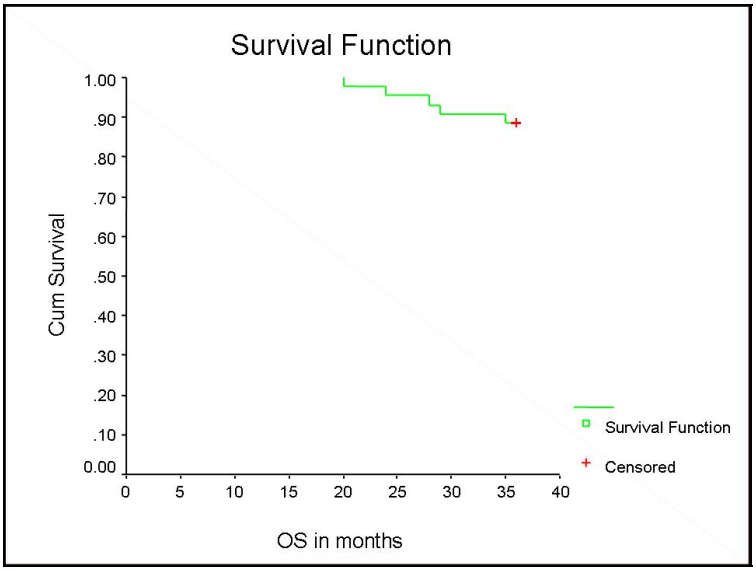


Figure 3: Overall Survival according to duration of diagnosis of CML

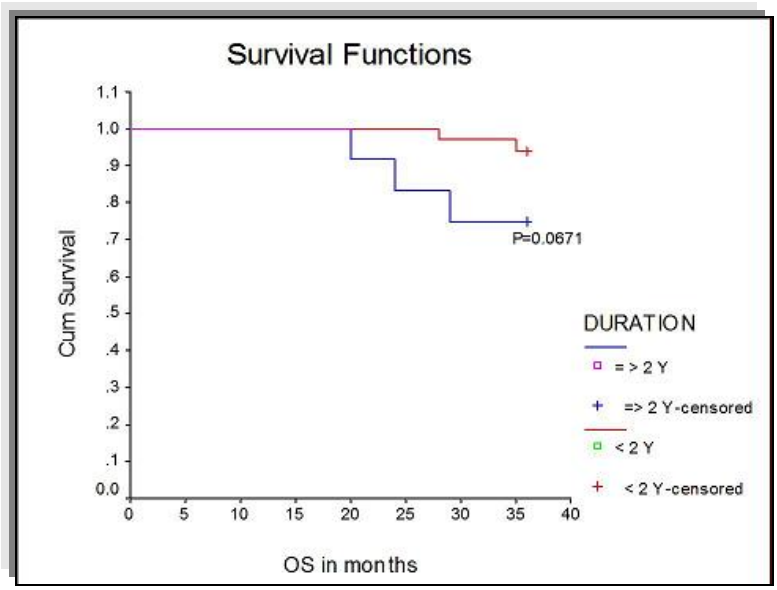


Figure 4: Overall Survival according to the presence of splenomegaly

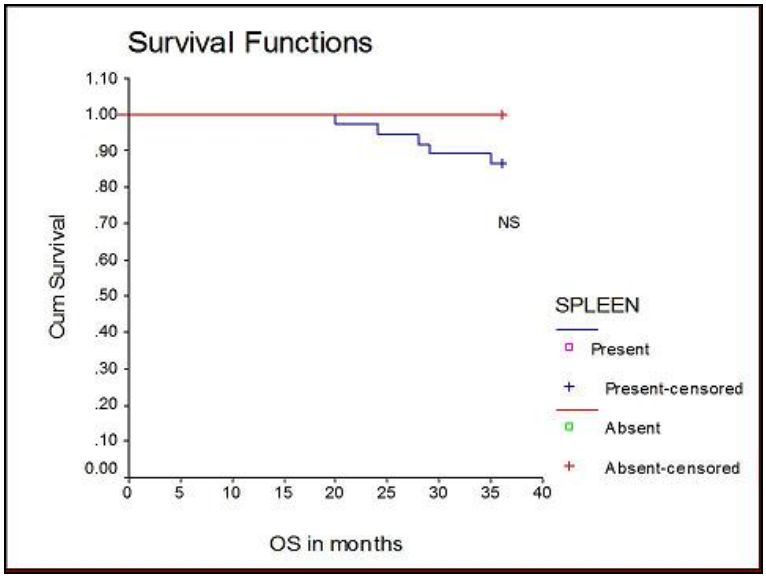


Figure 5: Overall Survival according to age

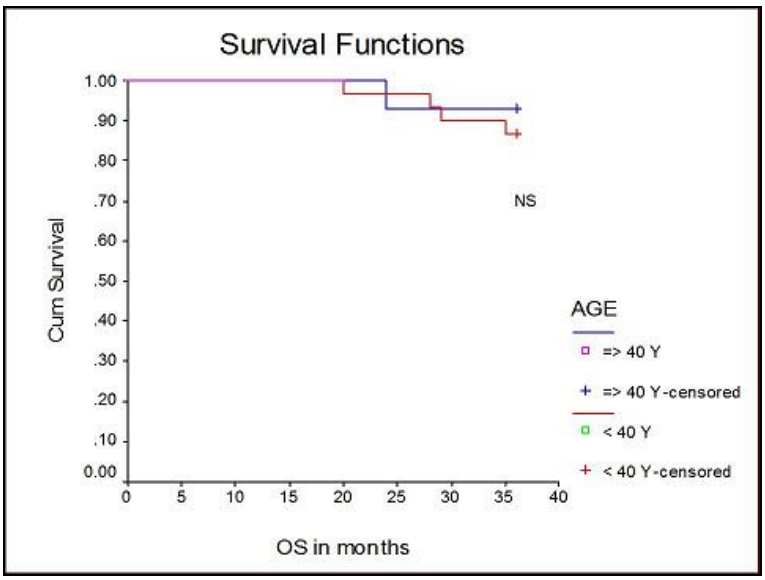


Figure 6: Overall Survival according to WBC count with a cutoff point of $11x10^9$/L

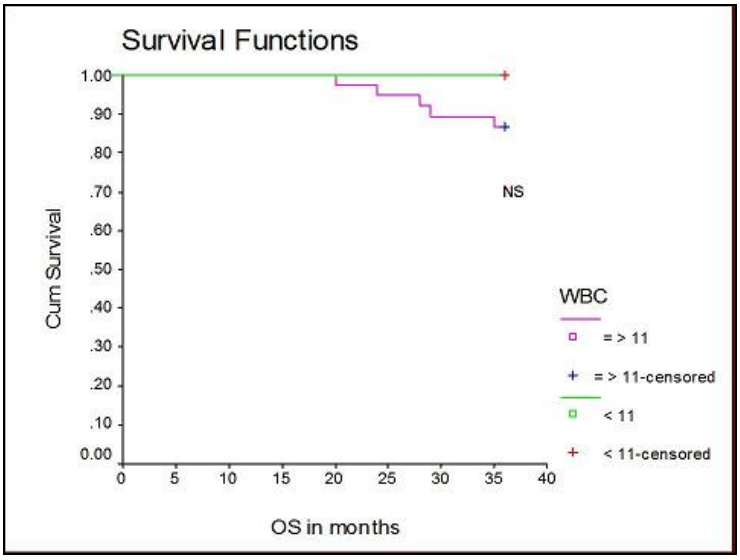


Figure 7: Transformation Free Survival (TFS) for all patients

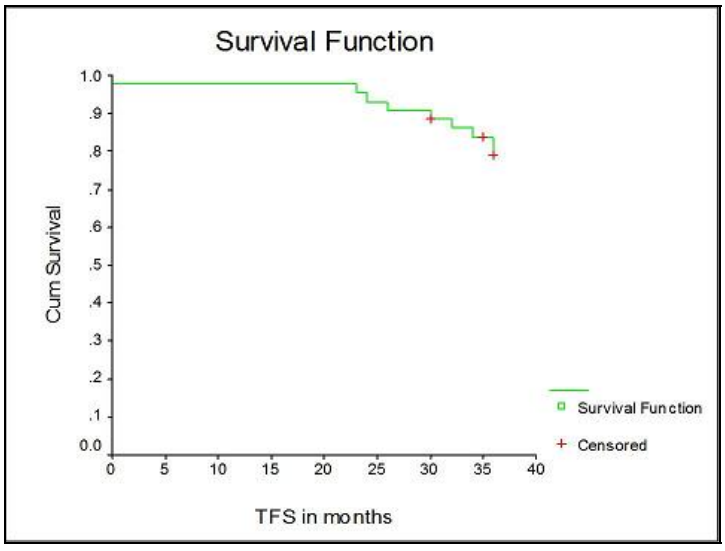


Figure 8: TFS according to sex

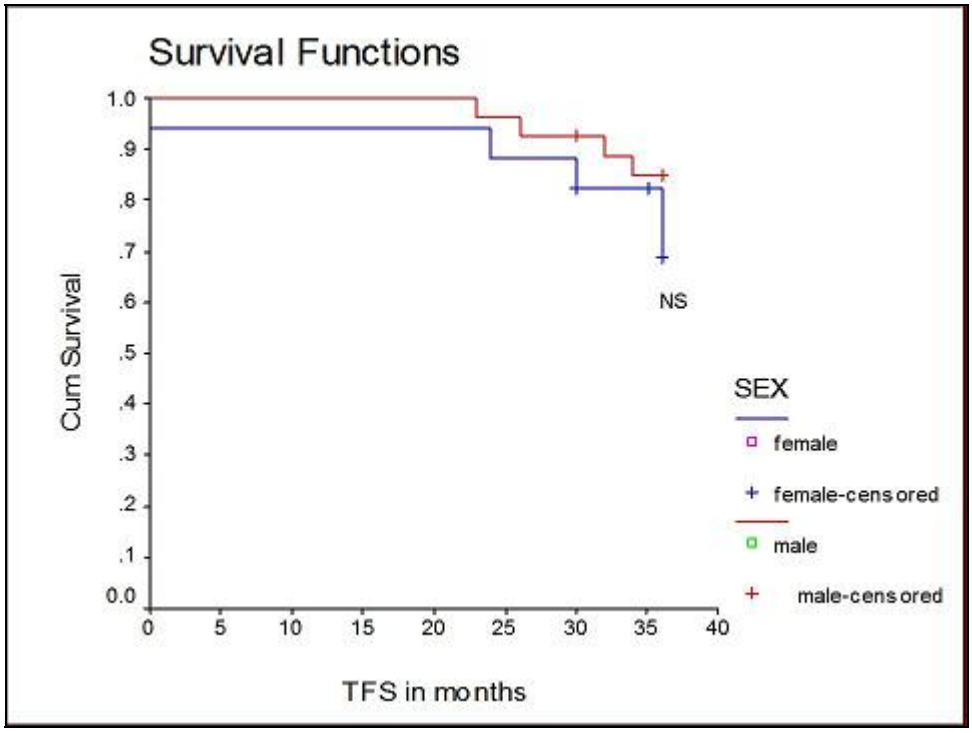


Figure 9: TFS according to duration of diagnosis of CML

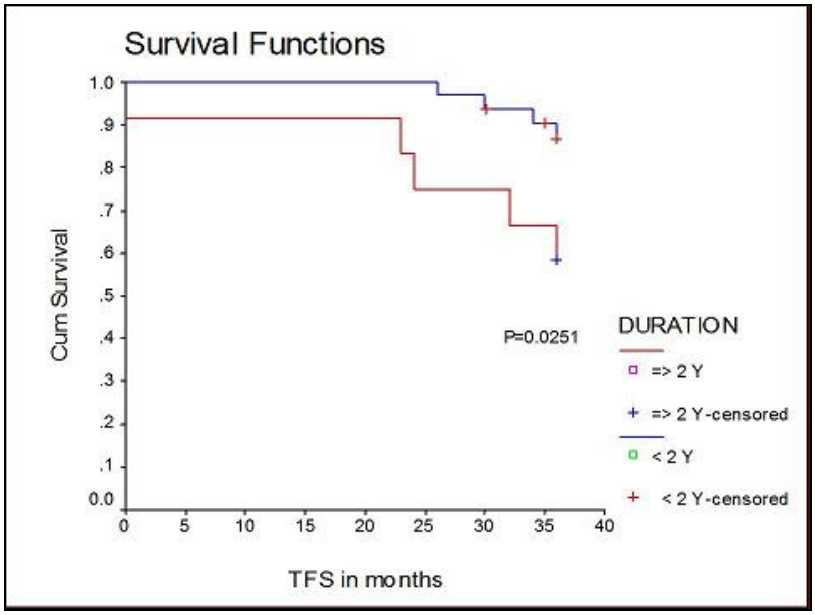


Figure 10: TFS according to presence of splenomegaly

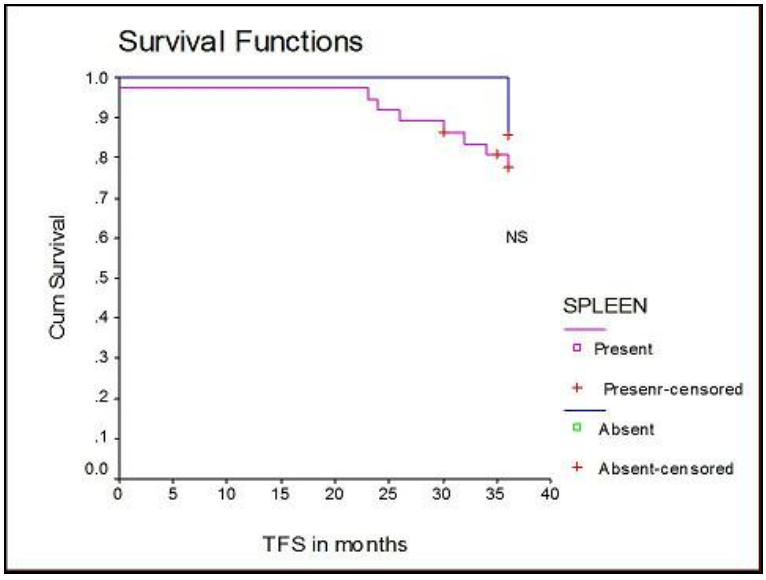


Figure 11: TFS according to the age

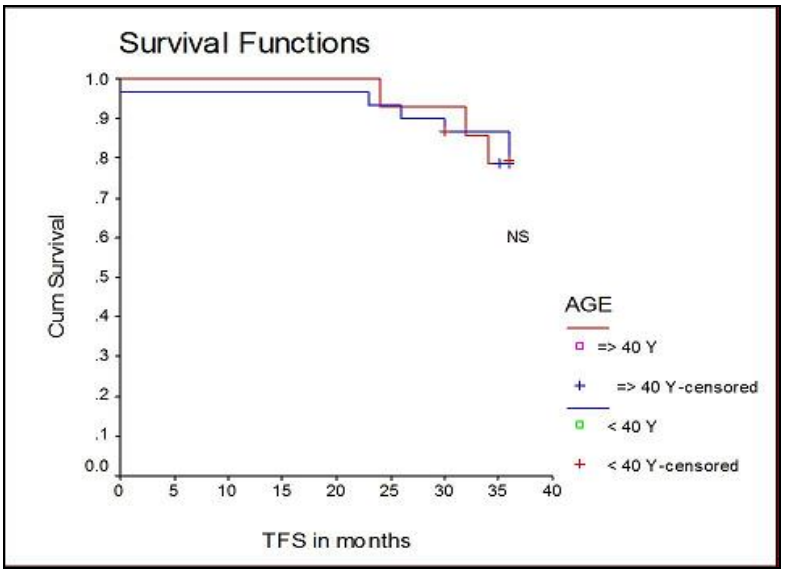
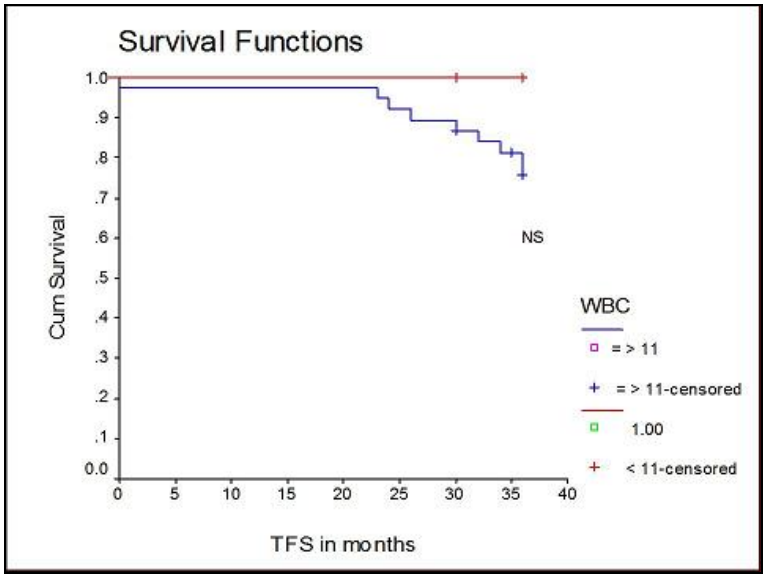


Figure 12: TFS according to WBC count with a cutoff point of $11x10^9/L$



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