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Full Length Article

High platelet count at diagnosis is a protective factor for thrombosis in patients with essential thrombocythemia

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ABSTRACT

To assess the role of platelet (PLT) count for thrombotic complications in Essential Thrombocythemia (ET), 1201 patients followed in 11 Hematological centers in the Latium region were retrospectively evaluated. At multivariate analysis, the following factors at diagnosis were predictive for a worse Thrombosis-free Survival (TFS): the occurrence of previous thrombotic events ($p = 0.0004$), age > 60 years ($p = 0.0044$), spleen enlargement ($p = 0.042$) and a lower PLT count ($p = 0.03$). Receiver Operating Characteristic (ROC) analyses based on thrombotic events during follow-up identified a baseline platelet count of 944×10^9/l as the best predictive threshold: thrombotic events were 40/384 (10.4%) in patients with PLT count > 944×10^9/l and 109/817 (13.3%) in patients with PLT count < 944×10^9/l, respectively ($p = 0.04$). Patients with PLT count < 944×10^9/l were older (median age 60.4 years. vs 57.1 years., $p = 0.016$), had a lower median WBC count (8.8×10^9/l vs 10.6×10^9/l, $p < 0.0001$), a higher median Hb level (14.1 g/dl vs 13.6 g/dl, $p < 0.0001$) and a higher rate of JAK-2-V617F positivity (67.2% vs 41.6%, $p < 0.0001$); no difference was observed as to thrombotic events before diagnosis, spleen enlargement and concomitant Cardiovascular Risk Factors. In conclusion, our results confirm the protective role for thrombosis of an high PLT count at diagnosis. The older age and the higher rate of JAK-2 V617F positivity in the group of patients with a baseline lower PLT count could in part be responsible of this counterintuitive finding.

What is known on this topic	What this paper adds
The finding of a counterintuitive protective role of very high PLT count in ET patients has been already incidentally reported: however, the role of PLT count has never been highlighted specifically in this context	In our study, we focused on the of PLT count at diagnosis as a thrombotic risk factor and used ROC analysis to determine the best PLT count to determine those at risk and those not at risk of thrombosis, confirming the protective effect of a higher PLT count
It is still unknown if ET patients with a higher PLT count at diagnosis constitute a different subtype with unique features	The subgroups of patients with lower and higher PLT count were characterized and we showed that these two populations had different clinical features
At present, no meaningful explanation has been provided for the protective role of a higher PLT count in ET patients with respect to thrombosis	Possible explanations for the protective effect of a higher PLT count with respect to thrombosis were advanced based on the different clinical features seen in patients with higher PLT counts

1. Introduction

The evaluation of thrombotic risk is very difficult in patients affected by Essential thrombocythemia (ET), due to a life expectancy closer to that of an age-adjusted normal population in the first ten years of observation [1,2]. Some prognostic factors for thrombotic complications and survival are well known: in particular, older age and previous

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Table 1
Main features of patients at diagnosis.

No. of cases	1201
Median age, years (range)	62.9 (19–96)
Gender, F/M (%)	765/436 (63.8–36.2)
Median follow-up, years	7.75
WBC $\times 10^9$/l, median (range)	8.8 (1.2–57.7)
Hb g/dl, median (range)	14.0 (6.0–20.5)
Plt ($\times 10^9$/l), median	813 (r. 457–3582)
JAK2 ^{V617F}, mutated/performed (%)	498/834 (59.7)
JAK2 ^{V617F} allele burden, median (range)	19.6 (0.2–99.9)
Spleen enlargement, no (%)	226 (18.7)
Previous thrombosis, no (%)	223 (17.9)
Arterial	176 (14.1)
Venous	47 (3.8)

thrombosis are recognized as increasing the risk for recurrent thrombosis during the follow-up [3–5]. On the contrary, there are controversial data concerning other putative risk factors as JAK-2 V617F positivity, leukocytosis and splenic enlargement at diagnosis [5–9].

In addition, the impact of platelet (PLT) number at diagnosis on the risk of thrombosis remains a matter of debate. To address this question, we retrospectively analyzed the influence of PLT count on Thrombosis-free Survival (TFS) using a database of 1249 ET patients followed in the Latium region of Italy.

2. Patients and methods

2.1. Patient population

A global cohort of 1201 patients with ET collected in the database of the Latium cooperative group for Ph-negative Chronic Myeloproliferative Syndromes and followed in 11 hematological centers in our region was retrospectively analyzed. The diagnosis of ET was made between January 1978 to December 2010 according to PVSG, WHO 2001 and 2008 criteria, based on the year of presentation. The main features at diagnosis are described in the Table 1.

2.2. Definition of thrombotic events

The following events were considered as thrombotic complications in the present analysis;

- Arterial thrombosis: acute myocardial infarction (AMI), angina pectoris, ischemic stroke, transient ischemic attack (TIA), peripheral arterial occlusion
- Venous thrombosis: pulmonary embolism, peripheral or splanchnic venous thrombosis, cerebral venous sinus thrombosis.

2.3. Variables for the analysis of thrombotic risk

The following variables at diagnosis were considered in univariate and multivariate models to find prognostic factors for thrombosis: age, sex, white blood cell count (WBC), hemoglobin level, PLT count, spleen size, history of previous thrombosis (before and at diagnosis) and cardiovascular risk factors (CVRF) defined as the presence of at least one of arterial hypertension, diabetes, smoking attitude and hypercholesterolemia. JAK2-V617F mutation and the allele burden were evaluated at onset in patients diagnosed after 2006 and during follow-up in patients diagnosed before that year.

2.4. Statistical analysis

Data were expressed as mean ± standard deviation (SD) (normally distributed data), median and range (non-normally distributed data) or as percentage frequencies, and within-patient comparisons were made by paired *t*-test and χ^2 test, as appropriate, at significance levels of $p < 0.05$.

The Kaplan-Meier product-limit method was used to estimate univariate survival curves, and the log-rank test was adopted to compare the survival curves. Cox proportional hazards regression was used to carry out multivariate survival analyses. TFS was calculated from the date of diagnosis to the occurrence of any event above defined as thrombotic complication. Receiver Operating Characteristic (ROC) analysis was applied to PLT count to find the best discriminating cut-off [10].

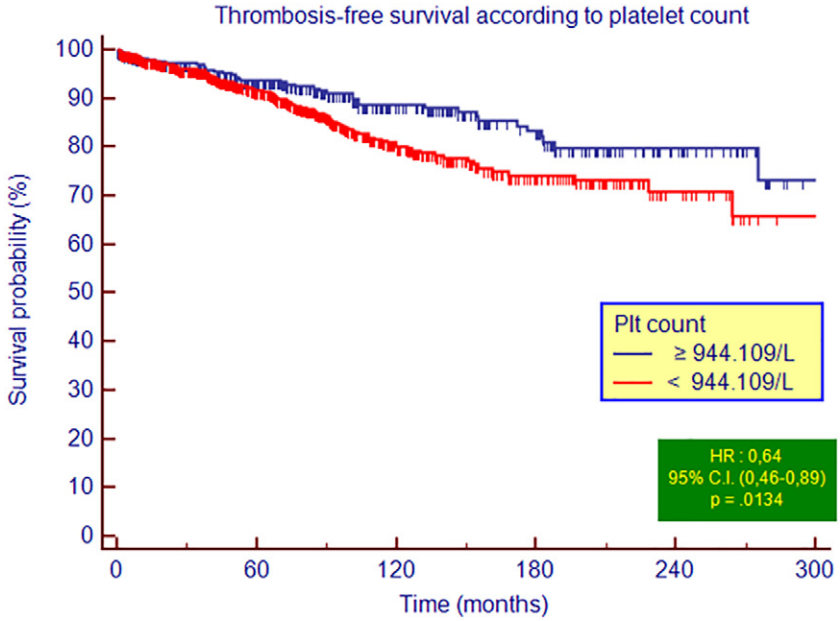

Fig. 1. Thrombosis-free Survival according to different PLT count at diagnosis.