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Original Article

Cardiovascular Risk in Essential Thrombocythemia and Polycythemia Vera: Thrombotic Risk and Survival

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Abstract. Thromboembolic and bleeding events pose a severe risk for patients with Polycythemia Vera (PV) and Essential Thrombocythemia (ET). Many factors can contribute to promoting the thrombotic event due to the interaction between platelets, leukocytes, and endothelium alterations. Moreover, a significant role can be played by cardiovascular risk factors (CV.R) such as cigarette smoking habits, hypertension, diabetes, obesity and dyslipidemia. In this study, we evaluated the impact that CV.R plays on thrombotic risk and survival in patients with PV and ET.

Keywords: Polycythemia Vera; Essential Thrombocythemia.

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Introduction. Diagnosis of PV requires as major criteria, the increase of hemoglobin/hematocrit ratio, whose threshold levels have been established by 2016 World Health Organization (WHO) revised criteria (>16.5 g/dL or >49% for males and >16 g/dL or >48% for females), the presence of *JAK2* mutation, the bone marrow tri- lineage proliferation with Pleomorphic mature megakaryocytes, and in the absence of a major criterium the presence of one minor.[1,2] Almost all patients with PV harbor a JAK2 mutation; approximately 96% and 3% of them display somatic activating mutations in exon 14 (JAK2-V617F) and JAK2 exon 12, respectively. Essential thrombocythemia (ET) is a chronic myeloproliferative neoplasm (MPN) characterized by persistently high platelet count and overall favorable prognosis with respect to the other MPNs (but Life-expectancy in ET is inferior to the control population).[2] Approximately 90% of patients with ET show a mutually exclusive JAK2, CALR, or myeloproliferative leukemia (MPL) mutation. In a recently published study conducted on 826 Mayo Clinic patients with ET, PV, or PMF, the respective median survivals were approximately 20 years for ET, 14 years for PV, and 6 years for primary myelofibrosis.[3] The increased risk of vascular complications over time is the main clinical feature of PV and ET. Concerning PV, two risk categories are defined. In particular, a low and high risk has been considered for patients without a history of thrombosis and younger than 60 years, and patients aged older than

60 or with a history of thrombosis. In ET, four risk categories are considered: very low (age ≤ 60 years, no thrombosis history, JAK2 wild-type), low (same as very low but presence of a JAK2 mutation), intermediate (age > 60 years, no thrombosis history, JAK2 wild-type) and high (thrombosis history present or age > 60 years with JAK2 mutation).[4] Current classifications of the thrombotic risk in patients with PV, as well as in those with ET do not predict cardiovascular risk (CVR), and this condition does not currently influence the choice of cytoreductive therapy. In this study, we considered evaluating the frequency of CVR in a cohort of patients with ET and with PV and the possible impact on the thrombotic risk on survival. This study was approved by our hospital's ethics committee.

Methods. From January 1997 to May 2019, 403 consecutive patients were followed with a median follow-up of 48,43 months (0.3 – 316 months). In particular, PV patients (n.165) had a median follow-up of 58,18 months (0.3 – 289.30 months), while the ET patients (n. 238) had a median follow-up of 44.60 months (0.4 - 316 months). We evaluated, with retrospective analysis, at diagnosis, the main characteristics of the study population such as gender, age, and mutational status along with CVR factors frequency such as cigarette smoking habits, hypertension, diabetes, obesity and dyslipidemia. In particular, patients with only one of these conditions were distinguished by those with more than one cardiovascular risk factor or without CVR factors. Moreover, the correlation of these cardiovascular risk conditions with the onset of thrombosis has been evaluated. The frequencies were calculated by using the chi-square method, and the comparison between medians was evaluated through the Kruskal-Wallis test. Furthermore, the survival has been evaluated by the Kaplan and Meyer method and the comparison between survival curves with the log-rank test.

Results. The main features, including sex, median age, and the mutational status, along with the cardiovascular risk factors of the cohort under examination (n. 403) were, respectively, summarized in **Table 1** and **Table 2**. In particular, 59 patients with ET (24.79%) and 37 PV patients (22.42) have no CVR, while 93 ET patients (39.07%) show only one CVR factor and 85 (35.71%) have more than one. Furthermore, 66 PV patients (49%) have only one cardiovascular risk factor, while 62 (37.57%) have more than one CVR.

In patients with PV, we highlighted 49 (29.69%) cases of thrombosis at diagnosis or before diagnosis and 16 (9.69%) cases of thrombosis after diagnosis, while in patients with ET, respectively 49 (20.61%) and 17 cases (6.72%). Overall, PV patients show a thrombosis frequency of 39.39% if compared to 27.39% of ET patients (p = 0.014).

Table 1. Characteristics of patients with ET and PV.

	ET	PV
N°	238	165
Female	162	60
Male	76	105
Age (Years)	65.9 (19.2 – 92.3)	62.8 (18.4 – 97.2)
JAK2 V617F	172 (72.27%)	153 (92.72%)
JAK2 Ex12	-	5 (3.03%)
CALR	22 (9.24%)	-
MPL	4 (1.68%)	-
NEGATIVE	40 (16.81%)	7 (4.24%)

Table 2. Cardiovascular risk in 403 ET and PV patients.

CVR factor	ET # (%)	PV # (%)
Smoke	34 (14.16)	25 (15.0)
Hypertension	152 (63.94)	105 (63.75)
Obesity	23 (9.44)	12 (7.5)
Dyslipidemia	59 (24.89)	47 (28.75)
Diabetes	34 (14.16)	28 (16.87)

In patients with PV and ET, the frequency of thrombotic episodes is strictly correlated with cardiovascular risk factors; in fact, the frequency of thrombosis is much lower in patients without CVR. In ET patients without CVR, the thrombotic event is present in 10/59 cases if compared to patients with only one CVR factor (18/93) and to patients with more than one CVR factor (37/85). In PV patients, thrombosis is present, respectively, in 11/37 cases, 20/66 cases and 24/62 cases. Our data also show a significant correlation between cardiovascular risk factors and survival both in the cohort of patients with PV and ET, distinguished by the number of cardiovascular risk factors (see **Figure 1**).

Discussion. Patients with myeloproliferative neoplasms (MPNs) have an increased risk of thrombotic events if compared with the general population, adding the latter a higher risk of morbidity and mortality MPNs-associated.[5,6] A recent single-center study conducted on 526 patients with MPNs with an overall study period of 3497.4 years, reported an incidence rate of 1.7% of venous thrombosis per patient/year.[7] Overall, 38.4% of all venous thrombosis occurred before or at diagnosis of MPNs, with 55.6% occurring at uncommon sites such as splanchnic or cerebral veins. Polycythemia Vera (PV) and Essential Thrombocythemia (ET) are myeloproliferative neoplasms respectively characterized by erythrocytosis

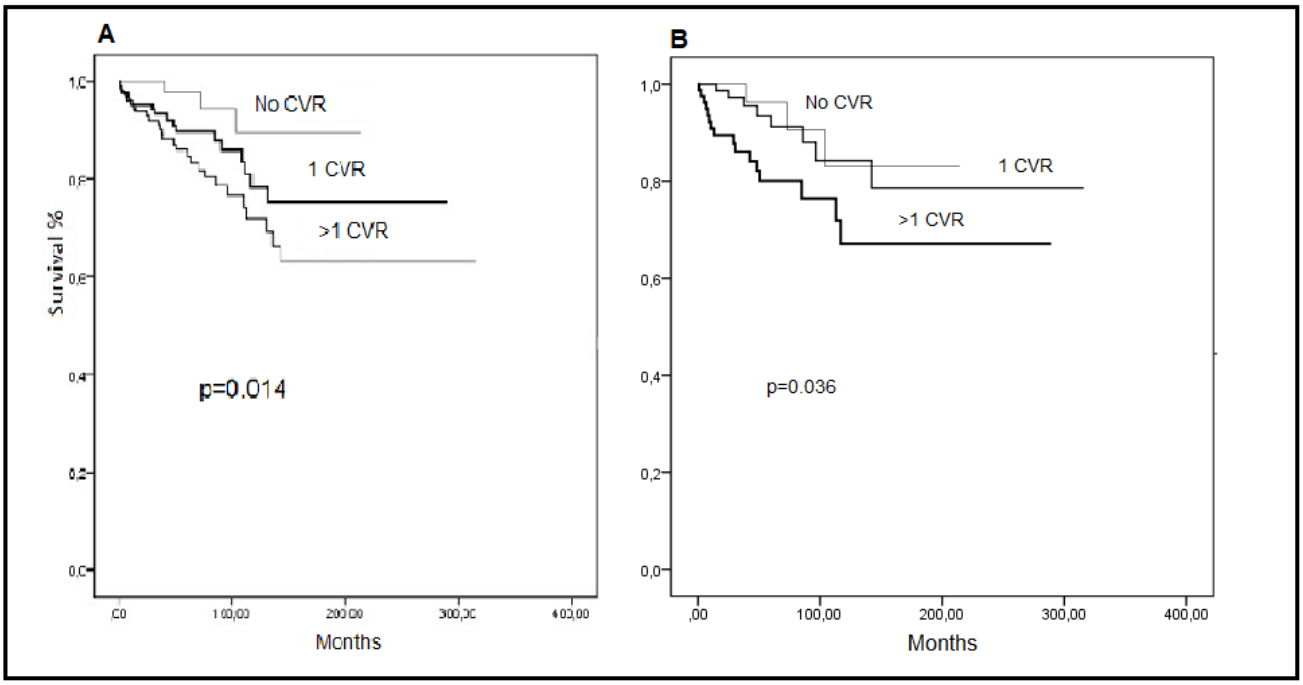

Figure 1. Survival and CVR factors in PV (A) and ET (B) patients.

and thrombocytosis; other clinical features include leukocytosis, splenomegaly, thrombosis, bleeding, microcirculatory symptoms, pruritus, and risk of leukemic or fibrotic transformation; moreover, thrombosis and cardiovascular disease are more prevalent in PV than in the other MPNs. It has been estimated that 30% to 50% of PV patients have minor and major thrombotic complications, and vascular mortality accounts for 35% to 45% of all deaths.[8] Also, in ET, thrombotic complications and cardiovascular events are very frequent. In a recent study, thrombotic events before or at the time of ET diagnosis were reported in 231 (17.8%) of 1,297 patients.[9] Determining the thrombotic risk in the PV and ET is pivotal for the proper therapeutic choice. In PV, two risk categories are generally considered: high risk (age > 60 years or thrombosis history present) and low risk (absence of both risk factors). The IPSETt classification of the thrombotic risk contemplates the assignment of 2 points for previous thrombotic events in patients aged greater than 60 years and the presence of JAK2-V617F mutation, 1 point for age greater than 60 years and a point for the presence of CVR factors. The low-risk is defined by a score lower than 2, the intermediate-risk by a score equal to 2 and the high-risk by a score greater than 2.[10] A new classification for the thrombotic risk describes four risk categories: very low, low, intermediate and high (as described in the introduction) but, unfortunately, cardiovascular risk factors are not yet considered. In a previously proposed thrombotic risk classification model, at the traditional high and low risk category was added an intermediate risk category specific for all the patients aged under 60 years, with no history of thrombosis but with the presence of cardiovascular risk factors.[11] This thrombotic risk classification model was not followed. Cerquozzi et al. explored the association of cardiovascular risk factors with the occurrence of arterial or venous events at or following diagnosis; they found that older age (≥ 60 years), hypertension, diabetes, hyperlipidemia, and normal karyotype were associated with arterial events, whereas younger age (< 60 years), female sex, palpable splenomegaly, and history of major hemorrhage were associated with venous events.[12] Today for patients with PV or ET with less than 60 years and with one or more cardiovascular risk factors, there is no indication for cytoreductive therapy, but only for antiplatelet drugs prophylaxis. Only for ET, the IPSET-thrombosis system that includes age, previous thrombosis, cardiovascular risk factors, and JAK2-V617F mutation is the recommended prognostic system, and it should be scored in all patients at diagnosis. This implies that general risk factors for thrombosis, including smoking habits, diabetes mellitus, arterial hypertension, and hypercholesterolemia, should also be considered even if the absence of specific therapeutic indications remains.[13] According to our experience, it should be useful to carry out prospective studies for the characterization of the influence of cardiovascular risk factors in the thrombotic event and on survival in order to evaluate the opportunity to develop specific therapeutic recommendations for patients with PV and ET with less than 60 years and cardiovascular risk factors.

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