Hyperuricemia might promote thrombosis in essential thrombocythemia and polycythemia vera

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Title: Hyperuricemia might promote thrombosis in essential thrombocythemia and polycythemia vera

Running title: Hyperuricemia in ET and PV patients

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Essential thrombocythemia (ET) and polycythemia vera (PV) are hematopoietic stem cell disorders characterized by clonal myeloproliferation, strong inflammatory atmosphere and an increased cardiovascular (CV) burden. The main therapeutic objective in ET and PV is to prevent thrombotic complications. Age more than 60 years and history of thrombosis have been shown to be the most reliable risk factors for future arterial or venous events. Additionally, in ET patients, there is an increased risk of thrombosis in JAK2-mutated patients [1] .

In recent years, hyperuricemia has gained interest as a determinant of CV risk. Epidemiological and clinical data have shown that hyperuricemia might be associated with an increased risk of venous thromboembolism [2,3] and CV disease (CVD) in the general population, but the exact role of serum uric acid (SUA) as an independent risk factor for CVD, besides arterial hypertension, still remains controversial [4].

The association of hyperuricemia and secondary gout in ET and PV has been known for decades. Two mechanisms for hyperuricemia in ET and PV have been proposed; overproduction of SUA as a result of clonal myeloproliferation, and reduced SUA clearance caused by impaired renal function [5,6]. In everyday clinical practice, antiuricosuric treatment is prescribed to these patients on a case-to-case basis, as there are no evidence-based guidelines to support this decision. In this study, we aimed to investigate clinical correlations and the potential impact of hyperuricemia on thrombosis development in ET and PV.

This was a single-center, retrospective study. We analyzed a group of newly-diagnosed ET and PV patients who presented at General Hospital of Šibenik-Knin County, Croatia, in the period from 2001 to 2019. The diagnoses were reassessed according to the World

Health Organization 2016 criteria [7]. Baseline data regarding the patients' diagnosis, age, sex, mutational status, complete blood count, SUA, creatinine, C-reactive protein (CRP) and lactate dehydrogenase (LDH) levels, presence of palpable splenomegaly, history of thrombosis (arterial or venous), treatment modalities, and CV risk factors (arterial hypertension, diabetes or hyperlipidemia), were obtained at the time of diagnosis. Risk stratification of ET patients was made according to the R-IPSET criteria and PV patients were considered to be high risk if they were older than 60 years of age and/or had a history of thrombosis [1,8]. Glomerular filtration rate (eGFR) was estimated using the MDRD formula [9].

All statistical analyses were performed with MedCalc Statistical Software®, version 19.0.3. Categorical variables were compared using the chi-square test of Fisher's exact test, as appropriate. The differences between independent samples were assessed with Mann-Whitney U test or Kruskal-Wallis test. The Jonckheere-Terpstra trend test was used to test trends for increase in SUA accross R-IPSET risk categories. Spearman correlation coefficients were calculated to assess the correlations between SUA and different laboratory variables. Receiver operating characteristic (ROC) curve was constructed for specificity and sensitivity testing. Survival analyses were performed using the methods of Kaplan and Meier, the log-rank test and the Cox regression analysis. Thrombosis-free survival (TFS) was measured from the time of diagnosis, with failures defined as death from any cause and an ascertained thrombotic (arterial or venous) episode, whichever ocurred first. Data for surviving or thrombosis-free surviving were checked at the date of the last follow-up visit. Arterial thrombosis was defined as myocardial infarction, transitory cerebral ischemic attack, acute cerebral ischemic stroke or acute peripheral arterial occlusion. Venous thrombosis was defined as peripheral vein thrombosis,

pulmonary embolism or splanchnic vein thrombosis. P values <0.050 were considered statistically significant for all analyses. The study was performed in accordance to the Declaration of Helsinki and approved by the General Hospital of Šibenik-Knin County's Review Board.

We included 93 patients (52 ET and 41 PV). Median SUA was 333 μmol/L (range 111 – 673), and a total of 29/93 (31%) of patients had SUA above the laboratory reference range (>428.26 μmol/L for adult males, >356.88 μmol/L for adult females) [10]. There was no difference in SUA between ET [median 314 μmol/L (range 111-673)] and PV patients [median 348 μmol/L (range 156-592), p=0.093)]. Patient characteristics are shown in Table 1.

Higher SUA was associated with older age (rho=0.250, p=0.015), JAK2 mutation (p=0.033), higher CRP (rho=0.263, p=0.010), presence of palpable splenomegaly (p<0.001), CV risk factors (p=0.037), history of thrombosis (p=0.006), higher creatinine (rho=0.551, p<0.001), lower eGFR (rho=-0.456, p=0.001), and the need for hydroxycarbamide therapy (p=0.036). These associations remained significant when ET and PV patients were analyzed separately (p<0.050 for all analyses), with the exception of advanced age that correlated positively with SUA only in ET patients (rho=0.338, p=0.015). Also, when two disorders were analyzed individually, higher SUA did not correlate with the presence of CV risk factors in both ET and PV patients (p≥0.050). Six patients (6.5%) had gout, nine (10%) received allopurinol at the time of diagnosis. As expected, these patients had higher SUA (p<0.050 for both analyses). In both ET and PV patients, SUA did not correlate with sex, leukocyte, granulocyte, erythrocyte and platelet counts, hemoglobin, hematocrit and LDH levels, allopurinol, acetylsalicylic acid or warfarin therapy.

Median follow-up of ET and PV patients was 62 months (range 3-219). Twenty-seven patients (29%) developed thrombosis during the follow-up; 11 (41%) were venous and 16 (59%) arterial (p=0.336). There was no difference in thrombosis frequency between ET (28.8%) and PV (29.2%) patients (p=0.919). When we classified patients according to current risk categories, there was a trend for increase in SUA accross R-IPSET categories in ET patients (p=0.002) (Figure 1). On the other hand, no difference was observed in SUA between low- and high-risk PV patients (p=0.233). However, PV patients had higher SUA when compared to very low- to intermediate-risk ET patients (p=0.005). Within the limitations of sample size and small number of thrombotic events, both prognostic systems in survival analyses were able to correctly identify ET and PV patients under increased risk of thrombosis (p=0.089 for the R-IPSET risk score, and p=0.003 for the PV risk score).

For the purpose of survival analyses, ROC curve with thrombosis as a classification variable was constructed to determine the optimal cut-off of SUA (>301 μmol/L). In univariate survival analyses, high SUA (HR 4.02, p<0.001) (Figure 2), history of thrombosis (HR 9.69, p<0.001), age >60 years (HR 5.47, p<0.001), and the presence of CV risk factors (HR 4.47, p=0.034), were associated with an increased risk of thrombosis. High SUA also had a negative prognostic impact on TFS when ET and PV patients were analyzed separately (HR 4.47, p=0.004 and HR 3.94, p=0.047, respectively). In the multivariate Cox proportional-hazards regression model, higher SUA remained independently associated with an inferior TFS, when adjusted for disease phenotype and classical ET and PV thrombosis-risk factors (Table 2.), showing it possesses good additional prognostic properties. We then created another Cox regression model to further test whether high SUA still had an independent effect on TFS when adjusted for variables

that differed at baseline (Table 1.). In this model, high SUA remained prognostic for inferior TFS (HR 5.04, p=0.024), when adjusted for JAK2 mutation (HR 7.13, p=0.007), age >60 years (HR 4.57, p=0.032), history of thrombosis (HR 7.01, p=0.008), CV risk factors (HR 0.58, p=0.446), hematocrit (HR 4.17, p=0.041), hemoglobin (HR 3.34, p=0.067), eGFR (HR 1.01, p=0.313), creatinine (HR 0.33, p=0.564), CRP (HR 0.12, p=0.720), gout (HR 0.15, p=0.699) and the presence of palpable splenomegaly (HR 1.00, p=0.316).

To the best of our knowledge, this is the first study to report independent prognostic properties of high SUA on thrombosis development in ET and PV patients. When interpreting our results, several interesting observations emerge from our study. First, SUA did not correlate with blood cell counts, which is in line with previously published observations [6]. Second, SUA correlated with the presence of JAK2 mutation, palpable splenomegaly, history of thrombosis, and the need for hydroxycarbamide therapy. These clinical and laboratory parameters are common indicators of the increased myeloproliferation. In addition, the association of SUA with the presence of JAK2 mutation might be explained with the fact that JAK2-mutated patients have been shown to have “more aggressive disease“ and are at significantly higher risk of thrombosis, when compared to their JAK2-unmutated counterparts [11,12]

Third, associations of SUA with older age, higher CRP, higher creatinine, lower eGFR, and the presence of CV risk factors, indicate that hyperuricemia, at least in part, might be induced by endothelial dysfunction, vascular aging, and subclinical inflammation that underlies CVD development in these disorders. Furthermore, chronic kidney disease (CKD) is an established risk factor for CVD in the general population [13]. It has been shown that approximately one third of ET and PV patients has CKD [14]. Moreover, a

term “MPN nephropathy“ has been proposed, due to associations of these disorders with CKD and undetermined glomerulopathies [15]. However, it is still unknown if CKD might be the cause of hyperuricemia, or hyperuricemia antecedents CKD. In this perspective, hyperuricemia, as a determinant of CV risk in ET and PV, might represent different patophysiological processes; stronger myeloproliferation, chronic inflammation, and reduced renal function. Further studies are needed to elucidate the patophysiological processes and the interplay between SUA and CKD in ET and PV.

Limitations of this study are its retrospective design, single-center experience, and small number of patients included. Due to small number of thrombotic events and limited number of patients receiving allopurinol, we were unable to analyze the impact of anturicosuric treatment on thrombosis development.

In summary, our data suggests that high SUA (>301 μmol/) at the time of ET and PV diagnosis might be JAK2, age and history of thrombosis independent risk factor for future CV events. Prospective controlled randomized trials are warranted to elucidate if more vigilant antiuricosuric treatment (i.e. with allopurinol or febuxostat) might improve outcomes in ET and PV patients.

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Tables and figures

Table 1. Patient characteristics. CV=cardiovascular, SUA=serum uric acid, CRP=C-reactive protein, LDH=lactate dehydrogenase, eGFR=estimated glomerular filtration rate, IQR=interquartile range. The chi-square and the Mann-Whitney U test were used.

Variable		SUA > 301 µmol/L	SUA ≤ 301 µmol/L	p value
ET / PV (%)	51 (56%) / 42 (44%)	27 (53%) / 29 (69%)	24 (46%) / 13 (31%)	0.116
Age, years	63 IQR (30-80)	64.5 IQR (31-80)	56 IQR (30-76)	**0.030**
Sex, male/female (%)	41 (44%) / 52 (56%)	28 (50%) / 28 (50%)	13 (35%) / 24 (65%)	0.159
JAK2 vs CALR/negative (%)	69 (74%) / 24 (26%)	45 (80%) / 11 (20%)	24 (65%) / 13 (35%)	0.096
Palpable splenomegaly, yes/no (%)	32 (34%)	25 (78%) / 7 (22%)	31 (51%) / 30 (49%)	***0.010***
CV risk factors, yes/no (%)	65 (70%)	44 (68%) / 21 (32%)	21 (57%) / 16 (43%)	***0.025***
History of thrombosis, yes/no (%)	23 (25%)	17 (30%) / 39 (70%)	6 (16%) / 31 (84%)	0.123
Gout, yes/no (%)	6 (6.5%)	6 (10%) / 50 (90%)	0 / 37 (100%)	***0.040***
Hydroxycarbamide, yes/no (%)	59 (63%)	38 (68%) / 18 (32%)	21 (57%) / 16 (43%)	0.279
Acetylsalicylic acid, yes/no (%)	68 (73%)	42 (75%) / 14 (25%)	26 (70%) / 11 (30%)	0.616
Warfarin, yes/no (%)	7 (7.5%)	4 (7%) / 52 (93%)	3 (8%) / 34 (92%)	0.863
Leukocytes ($x10^9$/L)	8.6 IQR (3.2-17.6)	8.6 IQR (4.2-16.6)	8.2 IQR (3.2-17.6)	0.872
Granulocytes ($x10^9$/L)	5.5 IQR (1.1-17.0)	5.4 IQR (1.9-12.7)	5.6 IQR (1.1-17)	0.848
Erythrocytes ($x10^{12}$/L)	4.7 IQR (3.0-7.9)	5.1 IQR (2.6-9.6)	4.6 IQR (3-7.9)	0.073
Platelets ($x10^9$/L)	546 IQR (142-1154)	527 IQR (142-1154)	573 IQR (181-321)	0.089
Hemoglobin (g/L)	138 IQR (87-202)	157 IQR (87-198)	141 IQR (89-202)	**0.032**
Hematocrit (%)	0.47 IQR (0.29-0.6)	0.47 IQR (0.29-0.60)	0.43 IQR (0.29-0.6)	**0.037**
Creatinine (µmol/L)	78 IQR (45-155)	86 IQR (56-155)	69 IQR (45-113)	**<0.001**

eGFR (mL/min/1.73m2)	72.5 IQR (35.6-144)	65.3 IQR (35.6-136.2)	91.3 IQR (45-144)	**<0.001**
LDH (IU/L)	231 IQR (94-696)	231 IQR (94-512)	237 IQR (130-696)	0.591
CRP (mg/L)	2.2 IQR (0.2-15.3)	2.4 IQR (0.2-15.3)	2.1 IQR (0.6-8.8)	**0.046**
SUA (µmol/L)	326 IQR (111-673)	/	/	/

SUA=serum uric acid, ET=essential thrombocythemia, PV=polycythemia vera, JAK2=Janus Kinase 2, CALR=calreticulin, CV=cardiovascular, eGFR=estimated glomerular filtration rate, LDH=lactate dehydrogenase, CRP=C-reactive protein, IU/L=international units per liter, IQR=interquartile range

Table 2. Higher SUA in essential thrombocythemia and polycythemia vera was associated with an increased risk of thrombosis in the multivariate Cox regression model.

Variable	HR	95% CI	p
SUA > 301 µmol/L	8.43	[2.07-43.41]	***0.003***
JAK2 mutation	7.14	[0.09-0.69]	***0.007***
History of thrombosis	5.34	[1.16-6.33]	***0.020***
Age > 60 years	6.97	[2.04-124.38]	***0.008***
CV risk factors	0.48	[0.21-2.79]	0.702
PV phenotype	0.61	[0.16-2.34]	0.486

SUA=serum uric acid, HR=hazard ratio, CI= confidence interval, JAK2-Janus Kinase 2, CV=cardiovascular, PV=polycythemia vera

Figure 1. SUA=serum uric acid. There was trend for increase in SUA accross R-IPSET risk categories in essential thrombocythemia patients. The Jonckheere-Terpstra trend test was used.

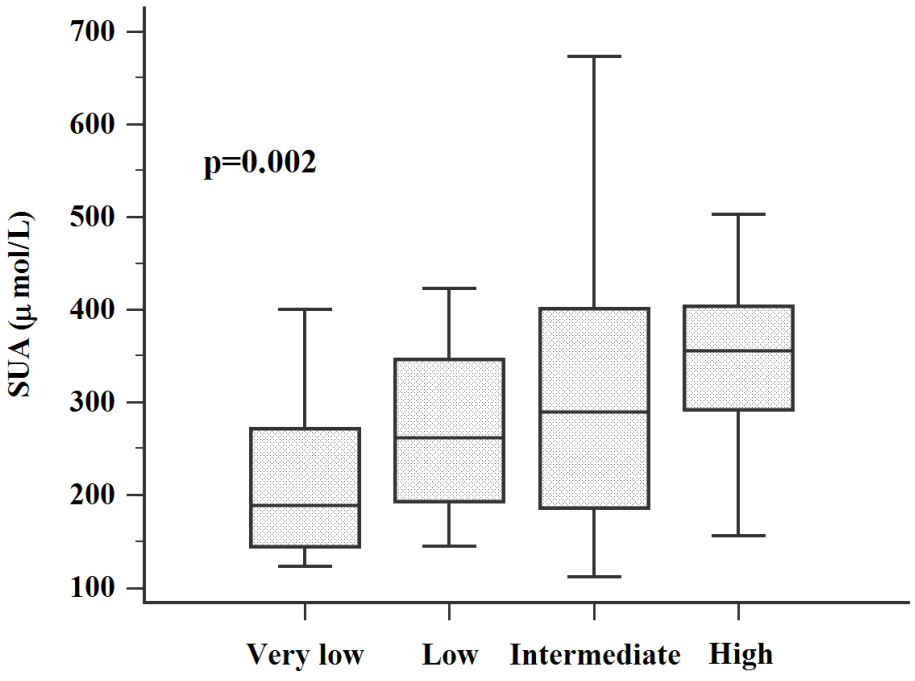

Figure 2. SUA=serum uric acid, TFS=thrombosis-free survival. Higher SUA in essential thrombocythemia and polycythemia vera patients was associated with an inferior TFS.