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Higher serum uric acid is associated with higher risks of thrombosis and death in patients with primary myelofibrosis

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Summary
Background Serum uric acid (SUA) can promote inflammation and is associated with increased cardiovascular morbidity. Primary (PMF) and secondary myelofibrosis (SMF) are myeloproliferative neoplasms characterized by high cellular turnover and substantial risk of thrombosis and death.
Methods We have retrospectively investigated SUA in 173 patients with myelofibrosis (125 PMF; 48 SMF) and 30 controls.
Results The PMF patients had significantly higher SUA in comparison to SMF and controls. In both PMF and SMF higher SUA was significantly associated with arterial hypertension and decreased renal function. Among PMF patients, higher SUA was significantly associated with older age, larger spleen, higher white blood cell counts, higher lactate dehydrogenase, lower immunoglobulin G levels, allopurinol use and non-smoking. Among SMF patients, higher SUA was associated with male sex ($P<0.05$ for all analyses).

In PMF higher SUA was univariately associated with inferior survival (>427 μmol/L hazard ratio (HR) = 2.22; $P=0.006$) and shorter time to thrombosis (>444 μmol/L HR = 5.05; $P=0.006$), which could be shown separately for arterial (>380 μmol/L; HR = 4.9; $P=0.013$) and venous thromboses (>530 μmol/L; HR = 17.9; $P<0.001$). In multivariate analyses, SUA remained significantly associated with inferior survival independent of the Dynamic International Prognostic Staging System and with shorter time to thrombosis independent of age in PMF patients; however, the prognostic significance of SUA was diminished after including serum creatinine in the models. SUA was not prognostic in SMF patients.
Conclusion The PMF patients present with higher SUA levels, which are associated with features of more ad-

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vanced disease and higher risks of arterial and venous thrombosis and death.

Keywords Philadelphia chromosome negative myeloproliferative neoplasm · Osteomyelofibrosis · Thrombotic event · Mortality · Prognosis

Introduction

Primary (PMF) and secondary myelofibrosis (SMF) are Philadelphia chromosome negative myeloproliferative neoplasms (MPN) developing from clonal hematopoietic stem cells, either de novo or from previously present polycythemia vera (PV) or essential thrombocythemia (ET) [1, 2]. They share similar clinical presentations characterized by development of bone marrow fibrosis, splenomegaly and various numbers and degrees of cytoses or cytopenias; however, their molecular background differs [3] and various clinical parameters differently affect the prognosis in these two diseases [4–6]. In contrast to PV and ET, diseases with lower mortality where prognostication is aimed at assessing the risk of thrombotic events, prognostic scores in myelofibrosis are directed at assessing the risk of death. Nevertheless, myelofibrosis harbors substantial risks of thrombosis and bleeding [7]. With the exception of the *JAK2* V617F mutation, prognostic factors for thrombosis in myelofibrosis are inconsistent among different studies and are less well defined [8].

Serum uric acid (SUA) is a metabolic breakdown product of purine nucleotides and it is normally excreted through the kidneys into the urine. It can act as an inflammatory stimulus and induce inflammation in target tissues through nuclear factor (NF) kappa B signaling [9]. Increased SUA levels have been associated with arterial hypertension, diabetes mellitus and increased risk for cardiovascular morbidity and mortality [10, 11]. Hyperuricemia was reported to be associated with shorter thrombosis-free survival in patients with PV and ET [12], but the clinical and prognostic significances of SUA have not been investigated in patients with PMF or post-PV and post-ET myelofibrosis so far. Therefore, in this study we aimed to assess SUA levels, their relationship with clinical features of myelofibrosis and associations with thrombotic and mortality risks in patients with PMF and SMF.

Patients, material and methods

Patients and methods

We retrospectively analyzed SUA levels and their clinical associations in a cohort of PMF and SMF patients newly diagnosed or referred to hematology departments of five hospitals in our country in the period from 2004 to 2019. All patients fulfilled 2016 World Health Orgnization (WHO) criteria for PMF [1] or 2008 International Working Group for Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) criteria for SMF [2]. Majority of patients were newly diagnosed at the time of study inclusion (153/173, 88.4%) and small proportion of patients started their follow-up at the time of referral (11.6%). All patients with available data were included without specific exclusion criteria. All patients provided written informed consent for molecular analyses. The study was approved by the institutional review boards. Patients were staged according to the Dynamic International Prognostic Scoring System (DIPSS) prognostic scoring system [6]. Spleen and liver size were assessed by palpation. Bone marrow fibrosis was graded according to the current European consensus [13]. The SUA levels were determined in addition to other standard hematological and clinical parameters at the study baseline (time of diagnosis or referral). The levels were also compared to 30 healthy control patients who underwent general systematic medical investigation. Controls were age and sex matched to match our myelofibrosis cohort as close as possible.

Thrombotic events were considered only if documented in medical records and evaluated by objective imaging methods. Thrombotic events were defined as myocardial infarction, transitory cerebral ischemic attack, acute cerebral ischemic stroke, splenic infarction or acute peripheral arterial occlusion for arterial events and peripheral vein thrombosis, pulmonary embolism, or splanchnic vein thrombosis for venous events.

Statistical methods

The normality of data distribution was tested using the Shapiro Wilk test. Most of the numerical variables were non-normally distributed and were presented as median and interquartile range (IQR) and were compared between three groups using the Kruskal-Wallis ANOVA test and post hoc test by Conover and between two groups using the Mann-Whitney U test. Normally distributed T values were presented as mean ± standard deviation and were compared between two groups using the t-test. Categorical variables were presented as ratios and proportions and were compared between the groups using the χ^2-test. Survival analyses were based on the Kaplan-Meier method [14], survival curves were compared between the groups using the Cox-Mantel version of the log-rank test [15] and the Cox regression analysis. Overall survival was measured from the start of follow-up to the last visit or death from any cause. Time to thrombosis was measured from the start of follow-up to the last visit or occurrence of arterial or venous thrombotic event. The receiver operating characteristic (ROC) curve analysis using survival status and thrombosis status as classification variables was performed for determining an optimal SUA cut-off value for survival analyses. P values < 0.05 were considered

statistically significant. Screening for associations with survival was performed using the custom-made MS Excel workbook [16]. Statistical analyses were performed using the MedCalc Statistical Software version 19.1.6 (MedCalc Software BVBA, Ostend, Belgium).

Results

Serum uric acid levels

We analyzed SUA levels in a total of 173 patients with myelofibrosis and 30 controls. There were 125 patients with PMF and 48 with SMF (29 post-PV SMF, 19 post-ET). Median age was 67 years, patients were mostly of male sex 108/173 (62.4%).

Median SUA levels in the unselected myelofibrosis cohort were 389 mcmol/L. Patients with PMF presented with significantly higher SUA levels in comparison to both SMF and control patients (median 407 vs. 341 vs 316 mcmol/L for PMF, SMF and controls; overall $P<0.001$; $P=0.001$ for both comparisons) as shown in the Fig. 1. There was no significant difference in SUA between post-PV, post-ET SMF and controls ($P=0.269$).

SUA associations with clinical characteristics

Patients' characteristics stratified according to the myelofibrosis type and their relationship with SUA stratified at median values are shown in Table 1. PMF patients presenting with higher SUA were significantly more likely to be of older age ($P=0.021$), have larger palpable spleen size ($P=0.007$), higher white blood cell counts (WBC; $P=0.008$), higher red cell distribution width (RDW; $P=0.004$), higher lactate dehydrogenase levels (LDH; $P=0.001$), higher urea ($P=0.008$), higher creatinine ($P=0.002$), lower immunoglobulin G levels (IgG; $P=0.021$), have arterial hypertension ($P=0.036$), use allopurinol ($P=0.017$) and were less likely to smoke ($P=0.044$).

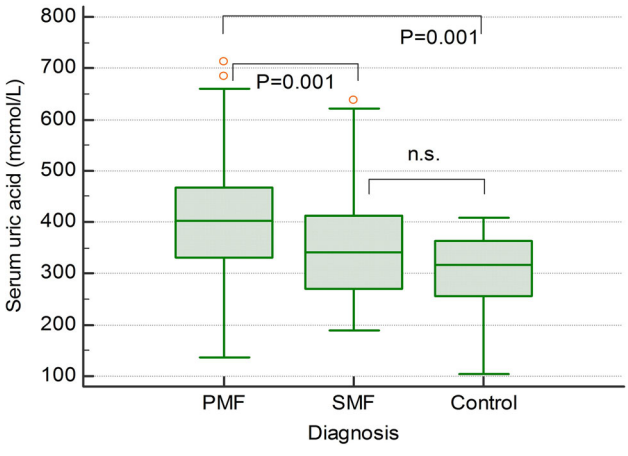

Fig. 1 Serum uric acid levels in comparison between primary (PMF), secondary myelofibrosis (SMF) patients and controls

SMF patients presenting with higher SUA were significantly more likely to be of male sex ($P<0.001$), have higher urea ($P=0.011$), higher creatinine ($P=0.019$) and arterial hypertension ($P=0.018$). There was no significant association of SUA with neither *JAK2, CALR, MPL* mutational status, degree of bone marrow fibrosis, nor with DIPSS risk category in neither PMF nor SMF patients ($P>0.05$ for all analyses).

Univariate SUA associations with the risks of thrombosis and death

Median follow-up of our cohort was 57 months. During follow-up a total of 59 deaths occurred (51 PMF and 19 SMF patients died). A total of 20 patients experienced a thrombotic event (13 PMF and 7 SMF patients experienced thrombosis), among them 9 arterial and 4 venous events in PMF and 4 arterial and 3 venous events in SMF patients. Median overall survival was 72 months and median time to thrombosis was not reached. The 5-year survival, arterial and venous thrombosis rates were 59%, 88% and 96%, respectively.

In the overall myelofibrosis cohort SUA as a continuous variable was significantly associated with higher mortality (hazard ratio, HR = 1.003; $P<0.001$), but not thrombosis risk ($P=0.147$). When stratified according to myelofibrosis type, higher SUA as a continuous variable showed significant association with both worse survival (HR = 1.003; $P<0.001$) and shorter time to thrombosis (HR = 1.004; $P=0.002$) among PMF patients, and no significant association with survival or thrombosis ($P>0.05$ for both analyses) among SMF patients.

Considering the PMF cohort, the ROC curve analysis defined optimal cut-off values for discrimination of patients with worse survival (>427 mcmol/L), thrombosis in general (>444 mcmol/L), arterial thrombotic events (>380 mcmol/L) and venous thrombotic events (>530 mcmol/L). PMF patients presenting with higher SUA (>427mcmol/L) had significantly shorter overall survival (HR = 2.22, 95% CI 1.25–3.95; $P=0.006$) in comparison to lower SUA patients (≤427 mcmol/L) as shown in the Fig. 2a. Also, PMF patients presenting with higher SUA (>444mcmol/L) had significantly higher risk of thrombotic events in general (HR = 5.05, 95%CI 1.57–15.96; $P=0.006$) in comparison to lower SUA patients (≤444 mcmol/L) as shown in the Fig. 2b. When stratified according to thrombosis type, high SUA was significantly associated with higher risks of both arterial (SUA >380 mcmol/L; HR = 4.9, 95%CI 1.40–17.53; $P=0.013$) and venous thromboses (SUA >530 mcmol/L; HR = 17.9, 95%CI 8.59–63.95; $P<0.001$) in PMF patients as shown in Fig. 2c, d.

Associations of SUA with overall survival, time to thrombosis in general, arterial and venous thrombosis were not statistically significant in SMF patients ($P>0.05$).

Table 1 Patients' characteristics and their relationship with serum uric acid levels (SUA) stratified at median SUA levels and according to the myelofibrosis type (primary (PMF) and secondary myelofibrosis (SMF))

	PMF (total of 125 patients; median SUA 407 mcmol/L)			*SMF* (total of 48; median SUA 341 mcmol/L)		
	Low SUA	*High SUA*	*P value*	*Low SUA*	*High SUA*	*P value*
Number of patients	63	62	–	24	24	–
SUA (μmol/L)	334 IQR (289.5–374.5)	471.5 IQR (447.3–560.5)	–	271 IQR (229.3–316)	412.5 IQR (378.3–453.8)	–
Age (years)	65 IQR (57–71.5)	69.5 IQR (61.3–76.8)	***P*= 0.021 ***	62.2 ± 10.6	66 ± 11.4	*P*= 0.244
Sex						
Male	44/63 (69.8%)	40/62 (64.5%)	*P*= 0.526	5/24 (20.8%)	19/24 (79.2%)	***P*< 0.001 ***
Female	19/63 (30.2%)	22/62 (35.5%)		19/24 (79.2%)	5/24 (20.8%)	
BM fibrosis						
Grade 0–I	31/63 (49.2%)	22/62 (35.5%)	*P*= 0.121	0/24 (0%)	0/24 (0%)	*P*= 1.000
Grade II–III	32/63 (50.8%)	40/62 (64.5%)		24/24 (100%)	24/24 (100%)	
JAK2 mutated	35/61 (57.4%)	43/61 (70.5%)	*P*= 0.131	20/23 (87%)	19/24 (79.2%)	*P*= 0.701
CALR mutated	8/51 (15.7%)	5/51 (9.8%)	*P*= 0.373	0/20 (0%)	2/21 (9.5%)	*P*= 0.488
MPL mutated	3/51 (5.9%)	1/51 (2%)	*P*= 0.617	0/20 (0%)	0/21 (0%)	*P*= 1.000
Constitutional symptoms	23/63 (36.5%)	30/62 (48.4%)	*P*= 0.179	12/24 (50%)	14/24 (58.3%)	*P*= 0.562
Transfusion dependency	20/62 (32.3%)	16/59 (27.1%)	*P*= 0.537	3/24 (12.5%)	7/24 (29.2%)	*P*= 0.286
Massive splenomegaly	12/51 (23.5%)	19/55 (34.5%)	*P*= 0.213	6/20 (30%)	6/18 (33.3%)	*P*= 0.825
Blast phase disease	4/61 (6.6%)	1/59 (1.7%)	*P*= 0.365	3/24 (12.5%)	1/24 (4.2%)	*P*= 0.609
Spleen size under left costal margin (cm)	2 IQR (0–7)	5 IQR (2.5–10)	***P*= 0.007 ***	5 IQR (3–11)	5 IQR (1.8–10)	*P*= 0.977
WBC ($\times 10^9$/L)	9.9 IQR (5.6–14)	11.4 IQR (8.3–22.3)	***P*= 0.008 ***	10.8 IQR (5–18.8)	10.6 IQR (8.7–20.1)	*P*= 0.303
Circulatory blasts ≥ 1%	0 IQR (0–0)	0 IQR (0–0)	*P*= 0.534	0 IQR (0–0.5)	0 IQR (0–1)	*P*= 0.627
Abs. monocytes ($\times 10^9$/L)	0.4 IQR (0.2–0.6)	0.5 IQR (0.4–0.9)	*P*= 0.142	0.3 IQR (0.2–0.5)	0.6 IQR (0.2–0.7)	*P*= 0.168
Abs. lymphocytes ($\times 10^9$/L)	1.5 IQR (1–1.9)	1.6 IQR (1.2–2.4)	*P*= 0.304	1.2 IQR (0.9–1.4)	1.5 IQR (1.1–2.5)	*P*= 0.057
Hemoglobin level (g/L)	115 IQR (88.5–139)	113 IQR (89.5–132)	*P*= 0.743	105 IQR (99.5–128.8)	101.5 IQR (90.3–127.5)	*P*= 0.381
Platelets ($\times 10^9$/L)	304 IQR (140–543.5)	340.5 IQR (210.5–562.8)	*P*= 0.292	308.5 IQR (148.3–436.5)	288 IQR (223.3–535.8)	*P*= 0.404
RDW (%)	18.7 IQR (16.1–20.4)	20.3 IQR (17.8–22)	***P*= 0.004 ***	19.3 IQR (18.3–20.5)	19.6 IQR (18.5–20.8)	*P*= 0.831
LDH (U/L)	355 IQR (224–549)	563 IQR (340–758.5)	***P*= 0.001 ***	506.5 IQR (341.3–661.5)	460 IQR (348.3–729.5)	*P*= 0.885
CRP (mg/L)	3.7 IQR (0.8–10.8)	4.8 IQR (2–14.2)	*P*= 0.166	5.1 IQR (2.2–10.6)	6.8 IQR (1.9–9.8)	*P*= 0.752
Albumin (g/L)	43 IQR (40–46)	43 IQR (39.3–46)	*P*= 0.815	42 IQR (39–44)	40 IQR (38.6–44)	*P*= 0.530
Transferrin saturation	32 IQR (14.9–37.5)	27.4 IQR (13.9–34.2)	*P*= 0.541	21.1 IQR (12–31.6)	25.2 IQR (15.9–35.6)	*P*= 0.299
Ferritin (μg/L)	191 IQR (54.7–549)	217 IQR (78.5–402.5)	*P*= 0.932	132.5 IQR (24–654)	181.5 IQR (101–193.3)	*P*= 0.895
Creatinine (μmol/L)	82 IQR (72.3–99)	94.5 IQR (80–115)	***P*= 0.008 ***	76.6 ± 22.1	92.3 ± 18.5	***P*= 0.011 ***
Urea (mmol/L)	6.1 IQR (5–7.4)	7.3 IQR (6.2–9.6)	***P*= 0.002 ***	5.3 IQR (4.3–6.8)	6.7 IQR (5.7–7.1)	***P*= 0.019 ***
IgG (g/L)	10.1 IQR (9.2–11.8)	8.9 IQR (7.5–11)	***P*= 0.021 ***	9.5 IQR (7.6–11.1)	11.1 IQR (8.6–13.4)	*P*= 0.291
IgA (g/L)	2.1 IQR (1.5–2.9)	1.7 IQR (1.3–2.7)	*P*= 0.321	1.3 IQR (1–2.1)	1.9 IQR (1.7–2.2)	*P*= 0.235
IgM (g/L)	1.1 IQR (0.6–1.5)	0.9 IQR (0.6–1.5)	*P*= 0.782	1.2 IQR (0.8–1.5)	1.4 IQR (0.5–2.2)	*P*= 0.763
DIPSS						
Low risk	11/63 (17.5%)	8/62 (12.9%)	*P*= 0.667	5/24 (20.8%)	3/24 (12.5%)	*P*= 0.363
Intermediate-1 risk	25/63 (39.7%)	21/62 (33.9%)		11/24 (45.8%)	7/24 (29.2%)	
Intermediate-2	21/63 (33.3%)	27/62 (43.5%)		7/24 (29.2%)	13/24 (54.2%)	
High risk	6/63 (9.5%)	6/62 (9.7%)		1/24 (4.2%)	1/24 (4.2%)	
Allopurinol use	26/60 (43.3%)	39/60 (65%)	***P*= 0.017 ***	12/22 (54.5%)	14/23 (60.9%)	*P*= 0.668
Cytoreductive therapy	34/61 (55.7%)	35/60 (58.3%)	*P*= 0.773	19/23 (82.6%)	20/23 (87%)	*P*= 1.000
Aspirin	29/61 (47.5%)	26/60 (43.3%)	*P*= 0.642	9/22 (40.9%)	12/23 (52.2%)	*P*= 0.449
History of thrombosis	6/62 (9.7%)	9/60 (15%)	*P*= 0.371	5/24 (20.8%)	3/23 (13%)	*P*= 0.701
Oral anticoagulant therapy	4/52 (7.7%)	5/55 (9.1%)	*P*= 1.000	5/20 (25%)	6/20 (30%)	*P*= 0.723
Cardiovascular risk factors	36/49 (73.5%)	45/55 (81.8%)	*P*= 0.306	9/19 (47.4%)	15/20 (75%)	*P*= 0.076

Table 1 (Continued)

	PMF (total of 125 patients; median SUA 407 mcmol/L)			*SMF* (total of 48; median SUA 341 mcmol/L)		
	Low SUA	*High SUA*	*P value*	*Low SUA*	*High SUA*	*P value*
Arterial hypertension	30/58 (51.7%)	41/58 (70.7%)	***P*= 0.036 ***	7/23 (30.4%)	15/23 (65.2%)	***P*= 0.018 ***
Diabetes mellitus	8/58 (13.8%)	11/59 (18.6%)	*P*= 0.477	5/23 (21.7%)	2/22 (9.1%)	*P*= 0.414
Hyperlipidemia	8/55 (14.5%)	11/54 (20.4%)	*P*= 0.423	2/21 (9.5%)	5/22 (22.7%)	*P*= 0.412
Smoking	12/46 (26.1%)	5/49 (10.2%)	***P*= 0.044 ***	1/20 (5%)	0/20 (0%)	*P*= 1.000

SUA serum uric acid, *PMF* primary myelofibrosis, *SMF* secondary myelofibrosis, *IQR* interquartile range, *BM* bone marrow, *JAK2* Janus kinase 2, *CALR* calreticulin, *MPL* myeloproliferative leukemia virus oncogene, *WBC* white blood cells, *Abs.* absolute, *RDW* red cell distribution width, *LDH* lactate dehydrogenase, *CRP* C reactive protein, *IgG* immunoglobulin G, *DIPSS* dynamic international prognostic scoring system
*statistically significant at $P<0.05$

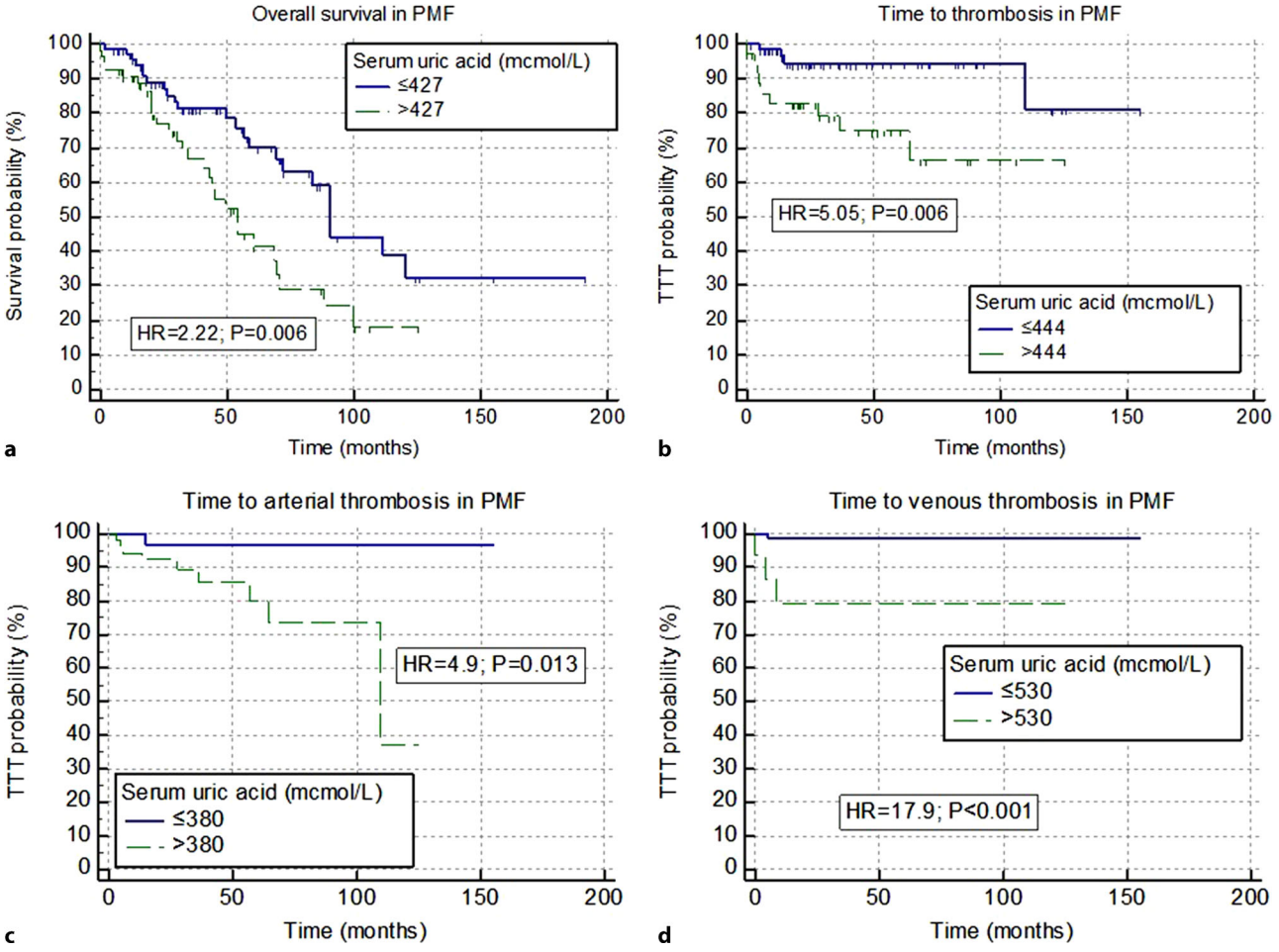

Fig. 2 **a** Overall survival, **b** time to thrombosis (TTT) in general, **c** time to arterial and **d** time to venous thrombosis in PMF patients stratified by serum uric acid levels. *HR* hazard ratio

Multivariate Cox regression analyses in PMF cohort

Regarding overall survival, in the multivariate Cox regression analysis adjusted for age, sex and DIPSS, both higher SUA (HR = 1.8, 95% CI 1.0–3.22; $P=0.048$) and higher DIPSS (HR = 3.07, 95% CI 1.98–4.78; $P<0.001$) predicted inferior survival in PMF patients independently of each other. Prognostic properties of SUA were weakened but not completely diminished after further adjusting the model for serum creatinine and higher SUA retained borderline statistical significance (HR = 1.74, 95% CI 0.97–3.13; $P=0.062$) whereas DIPSS remained statistically significant (HR = 3.09, 95% CI 1.99–4.81; $P<0.001$).

Regarding time to thrombosis, in the multivariate Cox regression analysis adjusted for age, sex, *JAK2* status, cardiovascular risk factors and history of thrombosis, higher SUA (HR = 4.56, 95% CI 1.22–16.96; $P=0.024$) and older age (HR = 1.08, 95% CI 1.0–1.16; $P=0.037$) remained significantly associated with the higher risk for thrombotic event. After further adjusting the model for serum creatinine and WBC,

SUA lost statistical significance. Subanalyses for time to arterial and time to venous thrombosis were not attempted due to small number of events.

Discussion

Our data suggest that PMF patients present with significantly higher SUA levels in comparison to both controls and SMF patients, whereas SUA levels do not significantly differ between SMF and controls. This unexpected difference might reflect the fact that SMF patients are experienced patients who progressed after being followed for prior MPN for many years with more intensive supervision of metabolic deflections and cardiovascular risk factors, potentially being exposed to SUA lowering and cytoreductive therapies during this prolonged period. This could also reflect the potential selection of patients as only PV and ET patients with lower SUA, who have lower risk of thrombosis [12], might have lived long enough and reached the myelofibrosis stage. Same observations apply for difference in prognostic properties of SUA in PMF (where it performed well) and SMF (where it performed weakly as a prognostic marker). It should be noted that frequency of oral anticoagulation therapy was significantly higher and proportions of patients with prior thrombosis, exposure to aspirin and allopurinol were insignificantly higher among SMF patients, which might also affect the association between SUA and outcomes in SMF cohort.

Among PMF patients, SUA levels >427 mcmol/L seem to be good DIPSS-independent prognostic factor for survival. Patients with higher SUA had 80% higher hazard for death in comparison to lower SUA PMF patients after adjusting for age, sex and DIPSS, providing additional prognostic information to DIPSS staging. Regarding time to thrombosis, SUA levels >444 mcmol/L were significantly univariately associated with 5-fold higher hazard for thrombotic events which also remained statistically significant (HR 4.56) in the multivariate model adjusted for age, sex, *JAK2* V617F status, prior thrombosis and cardiovascular risk factors. Further adjusting the models for serum creatinine diminishes significance of SUA association with outcomes suggesting that SUA has overlapping prognostic properties with parameters measuring renal function. Risk for thrombosis in PMF is generally underappreciated with only few established risk factors, most notably *JAK2* V617F mutation and comorbidities [8, 17–20]. Chronic kidney disease (CKD) which can be present in one quarter of MPN patients was recently shown to be associated with higher thrombotic risk in all three classical MPN subsets (PV, ET and myelofibrosis) [21, 22]. Elevated SUA is a feature of CKD and thus might be partially responsible for its detrimental effects.

In both PMF and SMF cohorts higher SUA was present in patients with arterial hypertension and higher urea and creatinine levels, which are well known clinical associations [23]. In PMF patients, hyperuricemia was also associated with features of more advanced disease and high cellular turnover (higher WBC, larger spleen, higher LDH, pronounced anisocytosis), which could lead to higher SUA production. Most interestingly, PMF patients with higher SUA were more likely to have lower IgG levels, suggesting possible higher susceptibility to infections. Mechanisms behind observed associations are not defined. It is unclear whether SUA is elevated as a secondary response to arterial hypertension and renal impairment or it might play a causative role in these disorders [24]. Hyperuricemia induces endothelial dysfunction [25] and lowering SUA through xanthine oxidase inhibition by allopurinol was shown to improve endothelial function in different clinical contexts [26–28]. Also, hyperuricemia activates NF-kappa B signaling cascade in the liver and leads to NLRP3 inflammasome (Nucleotide binding oligomerization domain, Leucine rich Repeat and Pyrin domain containing 3 inflammasome) mediated interleukin (IL)-1β production and higher mRNA expression of acute phase reactants (CRP, complement components, ferritin, fibrinogen) [29]. Therefore, hyperuricemia can promote systemic inflammation and has a potential to actively support pathogenesis of myelofibrosis.

Our study is limited by retrospective design, number of patients, number of thrombotic events and inability to assign direct cause of death to thrombosis or infections to directly investigate associations with higher SUA. High number of statistical tests performed increase the chance of false positive findings. Also, we do not have available data on follow-up SUA levels to assess SUA dynamics over time and whether they reflect on prognosis of myelofibrosis patients; however, our findings are based on data from several hematological centers and supported by large numbers of survival events. They identify higher SUA as a prognostically relevant parameter in patients with PMF. Association of SUA with thrombotic and mortality risks is biologically plausible and prompts a provoking question of SUA-oriented therapeutic interventions and whether could they affect prognosis in PMF. Currently there is no evidence that would support such approaches, but there is a need for both preclinical and larger prospective clinical studies further defining role of SUA in pathogenesis of PMF.

In conclusion, PMF patients experienced significantly higher SUA levels than SMF patients and controls. Higher SUA was associated with arterial hypertension and decreased renal function in both PMF and SMF patients. In PMF, higher SUA was associated with features of more advanced disease with stronger proliferative potential, lower IgG levels and significantly increased hazard for thrombotic events and death. SUA was not prognostic for thrombosis and death in SMF patients. Whether therapies for lowering SUA could improve prognosis of PMF patients remains to be elucidated in future studies.

Compliance with ethical guidelines

Conflict of interest M. Lucijanic, I. Krecak, D. Galusic, M. Sedinic, H. Holik, V. Perisa, M. Moric Peric, I. Zekanovic, T. Stoos-Veic, V. Pejsa, and R. Kusec declare that they have no competing interests.

Ethical standards All procedures performed in studies involving human participants or on human tissue were in accordance with the ethical standards of the institutional and/or national research committee and with the 1975 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the institutional review boards. All subjects in whom molecular studies were performed provided written informed consent.

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