Reduced renal function strongly affects survival and thrombosis in patients with myelofibrosis

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Title: Reduced renal function strongly affects survival and thrombosis in patients with myelofibrosis

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Abstract:

We retrospectively investigated a cohort of 176 myelofibrosis patients [128 primary-PMF; 48 secondary-SMF] from five hematology centers. Presence of chronic kidney disease (CKD) was determined in addition to other clinical characteristics.

CKD was present in 26.1% of MF patients and was significantly associated with older age (P<0.001), higher WBC (P=0.015) and its subsets [neutrophil, monocyte and basophil counts], higher platelets (P=0.001), lower albumin (P=0.018), higher serum uric acid (P=0.001), higher LDH (P=0.022), and presence of CV risk factors (P=0.011). There was no significant association with driver mutations, degree of bone marrow fibrosis, PMF/SMF or DIPSS risk categories (P>0.05 for all analyses).
Presence of CKD was significantly associated with shorter time to arterial (HR=3.49; P=0.041) and venous thrombosis (HR=7.08; P=0.030) as well as with shorter overall survival (HR 2.08; P=0.009). In multivariate analyses, CKD (HR=1.8; P=0.014) was associated with shorter survival independently of the DIPSS (HR=2.7; P<0.001); its effect being more pronounced in lower (HR=3.56; P=0.036) than higher DIPSS categories (HR=2.07; P=0.023).

MF patients with CKD should be candidates for active management aimed at improvement of renal function. Prospective studies defining optimal therapeutic approach are highly needed.

Keywords: myeloproliferative neoplasm; survival; thrombosis; renal function; JAK2

Introduction

Essential thrombocythemia (ET), polycythemia vera (PV) and primary myelofibrosis (PMF) are three classical Philadelphia chromosome (*bcr-abl*) negative myeloproliferative neoplasms (MPNs) developing due to acquired mutations in signal transduction pathways [1]. Constitutional activation of JAK-STAT signaling pathway results in chronic systemic inflammation, high cardiovascular (CV) disease burden and high risk of thrombotic incidents [2]. In contrast to ET and PV, patients with PMF and secondary post-ET/post-PV myelofibrosis (SMF) are exposed to stronger inflammatory atmosphere and substantially increased mortality due to bone marrow failure and disease transformation [3]. Risk scores in ET and PV are thus oriented at estimating the risk of thrombosis and risk scores in myelofibrosis (MF) are oriented at estimating the risk of death.

Dynamic International Prognostic Scoring System (DIPSS) [4] is a robust prognostic system enabling risk assessment in patients with MF by considering age >65 years, white blood cell count (WBC) >25 $x10^9$/L, hemoglobin <100 g/L, presence of peripheral blasts and presence of constitutional symptoms. Although it was inherited by more recent scores that take cytogenetic information and mutational status of specific genes into account, these data might not be readily available in the registries or at the bedside of a patient. Special score has been developed for SMF patients [5]. Besides DIPSS-contained factors, a variety of other factors like comorbidities and degree of bone marrow fibrosis might also influence survival in MF [6,7]. Thrombotic risk in myelofibrosis is underappreciated and risk factors for thrombosis in MF are less well defined [8]. Factors like age, CV risk factors, *JAK2* mutation and history of thrombosis as assessed through International Prognostic Score for thrombosis in Essential Thrombocythemia (IPSET) might be of use in patients with early/pre-PMF [9], and elevated WBC might contribute to estimation of thrombotic risk in established PMF [10].

Chronic kidney disease (CKD) defined as estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 is encountered in approximately one quarter to third MPN patients [11,12]. It is speculated that renal dysfunction might be a direct consequence of PMF and recent evidence implies the existence of the MPN related glomerulopathy [13-15]. Institution of cytoreductive therapy might prevent progression of renal dysfunction in PMF patients [16] and ruxolitinib in comparison to other therapies might be more potent in preserving renal function [17]. CKD has been recognized as a risk factor for thrombosis in PV and ET patients [12]. However, associations of CKD with survival and thrombotic risk in patients with MF has not been evaluated so far. Thus, we aimed to assess prognostic significance of CKD in patients with MF that we present in the current study.

Patients and methods

Patients and methods

We retrospectively investigated a cohort of 176 MF patients diagnosed in or referred to five hematologic institutions in period from 2004 to 2020 that had stable and non-progressive serum creatinine levels for ≥3 months. All patients fulfilled 2016 World Health Organization (WHO) criteria for PMF [1] or 2008 International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) criteria for SMF [18]. Diagnoses in patients presenting prior to 2008 and 2016 were reassessed according to the aforementioned criteria. All patients provided written informed consent for molecular analyses. The study was approved by the Institutional review boards. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Since majority of our cohort was comprised of PMF patients, to prevent statistical power constraints due to rareness of events in particular subgroups, we decided to perform main analyses in an overall cohort of MF patients, thus using the DIPSS as a main risk assessment tool. Spleen size was assessed by palpation. Bone marrow fibrosis was graded according to the current European consensus [19]. CV risk factors were defined as the presence of arterial hypertension, hyperlipidemia, diabetes mellitus or smoking. 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, splanchnic or cerebral vein thrombosis for venous events. Kidney function was estimated using the Modification of Diet in Renal Disease (MDRD) formula [20], calculated as eGFR and expressed as mL/min/1.73 m^2. eGFR was derived from creatinine (μmol/L), sex and age (years) using the formula: eGFR = 175 × (standardized serum creatinine/88.4) − 1.154 × age − 0.203 × (0.742 if female) × (1.21 if black). All patients included in the study were Caucasians. CKD was defined according to the Kidney Disease Improving Global Outcomes (KDIGO) 2012 criteria [21] as eGFR < 60 mL/min/1.73 m^2 for ≥3 months. CKD stages 3–5 (moderate decrease; severe decrease and kidney failure) were accordingly defined as eGFR 30–59 mL/min/1.73 m^2, eGFR 15–29 mL/min/1.73 m^2, eGFR < 15 mL/min/1.73 m^2 or the need for hemodialysis, respectively.

Statistical methods

Normality of data distribution was assessed using the Shapiro Wilk test. All numerical variables had non-normal distribution and were presented as median and interquartile range (IQR) and were compared between groups using the Mann Whitney U test. Categorical variables were presented as ratio and percentage and were compared between groups using the X^2 test. Survival analyses were based on the Kaplan-Meier method. Overall survival (OS) was measured from the start of follow-up to the last visit or death of any cause. Time to thrombosis (TTT) was measured from the start of follow-up to the last visit or occurrence of arterial or venous thrombotic event. Survival curves were compared between groups using the Cox Mantel version of the log-rank test [22]. Multivariate survival analyses were performed using the Cox regression analysis. P values <0.05 were considered statistically significant. Data screening for associations with survival was performed using the custom-made MS Excel workbook [23]. Statistical analyses were performed using the MedCalc Statistical Software version 19.4 (MedCalc Software BVBA, Ostend, Belgium).

Results

Patients' characteristics and their relationship with eGFR

We evaluated renal function in a total of 176 patients with myelofibrosis. Median age was 67 years IQR (58-75) and 109/176 (61.9%) patients were males. There were 128/176 (72.7%) patients with PMF and 48/176 (27.3%) patients with SMF.

Median eGFR in overall cohort was 75.3 IQR (58.98 - 87.26) ml/min/1.73 m^2. A total of 46/176 (26.1%) MF patients had CKD, i.e. eGFR <60 ml/min/1.73 m^2 [41/176 (23.3%) had moderate decrease in eGFR, three patients had severe decrease in eGFR and two patients had kidney failure per definition].

Patients' characteristics and their relationship with eGFR status are shown in Table 1. Lower eGFR was significantly associated with older age (P<0.001), higher WBC (P=0.015) and higher absolute neutrophil- (P=0.008), monocyte- (P=0.007) and basophil- counts (0.009), lower albumin (P=0.018), higher serum uric acid (P=0.001), higher LDH (P=0.022), higher platelets (P=0.001), higher degree of anisocytosis as assessed through RDW (P=0.008) and presence of CV risk factors (P=0.011). Neither eGFR, nor CKD were significantly associated with sex, myelofibrosis type, grade of bone marrow fibrosis, *JAK2*, *CALR*, *MPL* mutational status (P>0.05 for all analyses). CKD did not show significant association with DIPSS risk categories (P=0.163).

CKD is associated with shorter time to thrombosis and shorter survival

Median follow up of our cohort was 61 months. A total of 21 patients experienced thrombotic event (14 arterial and 7 venous thrombotic events) and 73 patients died during follow-up period.

Presence of CKD was significantly associated with shorter **time to thrombosis** (HR=3.93; P=0.006) in overall MF cohort as shown in Figure 1A. This phenomenon could be demonstrated for both arterial (HR=3.49; P=0.041; Figure 1B) and venous thrombotic events (HR=7.08; P=0.030; Figure 1C) separately. Decrease in renal function remained significantly associated with shorter time to thrombosis (HR=3.24; P=0.011) independently of WBC >15 $x10^9$/L (HR=2.94; P=0.037) and history of thrombosis (HR=4.24; P=0.005) in the multivariate Cox regression model additionally adjusted for age >60 years (P=0.373), *JAK2* status (P=0.944) and CV risk factors (P=0.481). It should be noted that neither *JAK2* mutation, age nor CV risk factors showed significant univariate associations with shorter time to thrombosis in our cohort of patients, probably due to statistical power constraints (small number of events) and presence of competing risks (e.g. death due to disease progression or infections).

Presence of CKD was significantly associated with shorter **overall survival** (HR=2.08; P=0.009) in overall MF cohort as shown in Figure 1A. This phenomenon could be demonstrated in PMF (HR=2.53; P=0.004), and same trends of survival curves separation was present in SMF cohort although due to small number of events could not reach statistical significance (HR=1.62; P=0.090). We further investigated this phenomenon in the overall cohort where it persisted in the multivariate Cox regression model (HR=1.75; P=0.025) independently of all DIPSS contained factors (age >65 years, WBC >25 $x10^9$/L, presence of constitutional symptoms, presence of peripheral blasts, hemoglobin <100 g/L) as shown in Table 2. Accordingly, both CKD (HR=1.8; P=0.014) and DIPSS (HR=2.7; P<0.001) predicted shorter survival independently of each other and CKD was associated with inferior survival in both lower risk (DIPSS good and intermediate-1 risk; HR=3.56; P=0.036) and higher risk patients (DIPSS intermediate-2 and high risk; HR=2.07; P=0.023) as shown in Figure 2B-C.

Since CV risk factors showed both significant association with reduced eGFR (P=0.011) and shorter overall survival (P=0.019), we additionally investigated their relationship in the bivariate Cox regression model where both CKD (HR=1.64; P=0.049) and presence of CV risk factors (HR=2.37; P=0.017) remained independently associated with higher mortality. This supports the view that effects of reduced eGFR on survival are not entirely mediated by CV risk factors and other mechanisms also play a role in increased mortality.

Finally, we investigated relationship of CKD with other variables univariately associated with survival in our dataset (besides already mentioned CV risk factors and DIPSS contained variables these were: absolute monocyte and basophil count, transfusion dependence, blast phase disease, massive splenomegaly, platelet count, LDH, RDW, CRP, TIBC, ferritin, albumin and uric acid) using stepwise approach. CKD remained statistically significant and demonstrated robust association with inferior survival (HR=11.78; P=0.003) independently of CV risk factors (HR=5.05; P=0.027), blast phase disease (HR=22.91; P=0.001), LDH (HR=1.01; P=0.046), RDW (HR=1.21; P=0.033), CRP (HR=1.02; P=0.038) and TIBC (HR=0.82; P<0.001).

Discussion

To the best of our knowledge, our study is the first to demonstrate increased thrombotic and mortality risks associated with presence of CKD in patients with MF, which is being detrimental for survival in MF patients independently of the DIPSS risk. We would like to emphasize several important points.

CKD seems to affect a substantial proportion of MF patients, but its prevalence might not be more frequent than in other MPN subtypes (26.1% for MF in the current study vs 26.3% for PV [12] vs 27.6% for ET [12]). Some author groups reported lower prevalence of CKD in their MPN cohorts [24], whereas other groups found similar frequency [11,12]. Presence of CV risk factors, which are the most common cause of CKD in general population, is associated with higher frequency of CKD in our cohort of MF patients as well. However, CKD may negatively affect prognosis irrespectively of CV risk factors as suggested by our data. Presence of CKD was also associated with features of stronger myeloproliferation like higher WBC and its subsets (higher absolute neutrophil, monocyte and basophil counts), higher platelets, higher LDH and higher serum uric acid, linking the CKD with stronger proliferative potential of the malignant disease. These findings are similar to previously published MPN cohorts where similar associations of CKD and loss of renal function with higher blood cell counts and LDH were found [24,12]. Recent evidence suggests that MPN related glomerulopathy (characterized by mesangial expansion and hypercellularity, features of chronic thrombotic microangiopathy and intracapillary extramedullary hematopoiesis in absence of immune-mediated glomerulonephritis) might be the most common cause of renal dysfunction in PMF patients [13-15]. A number of MPN-related pathophysiologic mechanisms like platelet-leukocyte aggregates, elevated levels of inflammatory cytokines, accumulation of reactive oxygen species and intrarenal extramedullary hematopoiesis could contribute to renal disease [25].

There is no established treatment of MPN related glomerulopathy [25]. Cytoreductive therapies and aspirin might diminish aggregation of platelets and leukocytes and reduce inflammatory burden associated with the malignant disease. Cytoreductive therapy was shown to slow down the loss of renal function in PMF patients [26,16]. According to one retrospective study, ruxolitinib could be the most potent among current therapeutic choices [17]. Ruxolitinib decreases the production of major inflammatory cytokines, reduces spleen size with possible hemodynamic repercussions on renal perfusion and it was suggested to better improve renal function in comparison to other non-ruxolinitib based therapies [17]. Aggressive control of CV factors and reduction of serum uric acid may also play important role in preserving renal function [16]. It should be noted that presence of CV risk factors was associated with higher adjusted hazard for death (HR=2.37) than CKD (HR=1.64) when analyzed in the bivariate context in the current study, emphasizing the importance of control over CV risk factors for reasons surpassing quality of renal function. Drug classes like statins and ACE inhibitors are beneficial for CV risk factor control and provide direct nephroprotective effects [27,28]. However, their role in MPNs has not yet been fully elucidated.

CKD is associated with increased thrombotic risk for both arterial and venous thromboses in MF patients. This is in line with the recent report in ET and PV patients [12], but with smaller magnitude of effect (HR=8.78 in composite PV and ET cohort; HR=3.93 in our PMF cohort). As we show, hazard seems to be higher for venous than arterial thromboses and CKD remained significantly associated with the risk of thrombosis independently of leukocytosis and history of thrombosis after adjusting for clinically relevant parameters. Thrombotic risk and CV disease burden in MF are often underappreciated but must not be ignored as thrombotic incidents may result in higher functional dependency of patients and also affect mortality from non-CV causes.

Our most important finding is that CKD is associated with inferior overall survival in MF patients independently of the DIPSS. Besides WBC and older age, there was no significant association of CKD with other DIPSS-contained factors and CKD patients did not distribute differently across DIPSS risk categories. When stratifying analyses according to lower and higher DIPSS categories, it becomes evident that lower DIPSS risk patients might be even more affected by reduced renal function (HR=3.56) than higher DIPSS risk patients (HR=2.07). Therefore, especially lower DIPSS risk patients with CKD should be candidates for active management aimed at improvement of renal function. Prospective studies in independent cohorts of patients are highly needed to evaluate this issue. Question also remains whether recovery of renal function would affect clinical outcomes in these patients.

Limitations of our study are retrospective study design, heterogeneity of our MF cohort regarding MPN disease duration (PMF vs SMF) and exposure to different therapies and inability to assess other features of renal disease (proteinuria, albuminuria, urine sediment analysis, morphologic features, urolithiasis etc.). Extra renal factors might affect eGFR calculations in MF patients, like plasma volume expansion due to splenomegaly and muscle wasting due to cachexia. Also, some analyses were limited by loss of statistical power due to small number of events in specific subgroups and the issue of death as a competing risk for time to thrombosis evaluation. Nevertheless, our multicentric study identified CKD as an important risk factor for both thrombosis and survival with potential therapeutic implications for patients that would otherwise not be candidates for cytoreductive therapy.

In conclusion, CKD is associated with shorter time to arterial and venous thrombosis in MF patients. CKD affects survival of MF patients independently of CV risk factors and DIPSS, with hazard of death being more pronounced in lower DIPSS risk categories. MF patients presenting with CKD or rapid loss of renal function might be candidates for start of cytoreductive therapy even if being in lower DIPSS risk categories. However, optimal therapeutic approach is yet to be prospectively defined.

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References:

1. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, Bloomfield CD, Cazzola M, Vardiman JW (2016) The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 127 (20):2391-2405. doi:10.1182/blood-2016-03-643544
2. Hasselbalch HC, Bjørn ME (2015) MPNs as Inflammatory Diseases: The Evidence, Consequences, and Perspectives. Mediators of inflammation 2015:102476. doi:10.1155/2015/102476
3. Hultcrantz M, Kristinsson SY, Andersson TM, Landgren O, Eloranta S, Derolf AR, Dickman PW, Bjorkholm M (2012) Patterns of survival among patients with myeloproliferative neoplasms diagnosed in Sweden from 1973 to 2008: a population-based study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 30 (24):2995-3001. doi:10.1200/JCO.2012.42.1925
4. Passamonti F, Cervantes F, Vannucchi AM, Morra E, Rumi E, Pereira A, Guglielmelli P, Pungolino E, Caramella M, Maffioli M, Pascutto C, Lazzarino M, Cazzola M, Tefferi A (2010) A dynamic prognostic model to predict survival in primary myelofibrosis: a study by the IWG-MRT (International Working Group for Myeloproliferative Neoplasms Research and Treatment). Blood 115 (9):1703-1708. doi:10.1182/blood-2009-09-245837
5. Passamonti F, Giorgino T, Mora B, Guglielmelli P, Rumi E, Maffioli M, Rambaldi A, Caramella M, Komrokji R, Gotlib J, Kiladjian JJ, Cervantes F, Devos T, Palandri F, De Stefano V, Ruggeri M, Silver RT, Benevolo G, Albano F, Caramazza D, Merli M, Pietra D, Casalone R, Rotunno G, Barbui T, Cazzola M,

Vannucchi AM (2017) A clinical-molecular prognostic model to predict survival in patients with post polycythemia vera and post essential thrombocythemia myelofibrosis. Leukemia 31 (12):2726-2731. doi:10.1038/leu.2017.169
6. Lekovic D, Gotic M, Perunicic-Jovanovic M, Vidovic A, Bogdanovic A, Jankovic G, Cokic V, Milic N (2014) Contribution of comorbidities and grade of bone marrow fibrosis to the prognosis of survival in patients with primary myelofibrosis. Medical oncology 31 (3):869. doi:10.1007/s12032-014-0869-8
7. Newberry KJ, Naqvi K, Nguyen KT, Cardenas-Turanzas M, Florencia Tanaka M, Pierce S, Verstovsek S (2014) Comorbidities predict worse prognosis in patients with primary myelofibrosis. Cancer 120 (19):2996-3002. doi:10.1002/cncr.28857
8. Kc D, Falchi L, Verstovsek S (2017) The underappreciated risk of thrombosis and bleeding in patients with myelofibrosis: a review. Annals of hematology 96 (10):1595-1604. doi:10.1007/s00277-017-3099-2
9. Guglielmelli P, Carobbio A, Rumi E, De Stefano V, Mannelli L, Mannelli F, Rotunno G, Coltro G, Betti S, Cavalloni C, Finazzi MC, Thiele J, Cazzola M, Vannucchi AM, Barbui T (2020) Validation of the IPSET score for thrombosis in patients with prefibrotic myelofibrosis. Blood cancer journal 10 (2):21. doi:10.1038/s41408-020-0289-2
10. Barbui T, Carobbio A, Cervantes F, Vannucchi AM, Guglielmelli P, Antonioli E, Alvarez-Larran A, Rambaldi A, Finazzi G, Barosi G (2010) Thrombosis in primary myelofibrosis: incidence and risk factors. Blood 115 (4):778-782. doi:10.1182/blood-2009-08-238956
11. Christensen AS, Moller JB, Hasselbalch HC (2014) Chronic kidney disease in patients with the Philadelphia-negative chronic myeloproliferative neoplasms. Leukemia research 38 (4):490-495. doi:10.1016/j.leukres.2014.01.014
12. Krečak I, Holik H, Martina MP, Zekanović I, Coha B, Gverić-Krečak V (2020) Chronic kidney disease could be a risk factor for thrombosis in essential thrombocythemia and polycythemia vera. International journal of hematology. doi:10.1007/s12185-020-02898-7
13. Said SM, Leung N, Sethi S, Cornell LD, Fidler ME, Grande JP, Herrmann S, Tefferi A, D'Agati VD, Nasr SH (2011) Myeloproliferative neoplasms cause glomerulopathy. Kidney international 80 (7):753-759. doi:10.1038/ki.2011.147
14. Alexander MP, Nasr SH, Kurtin PJ, Casey ET, Hernandez LP, Fidler ME, Sethi S, Cornell LD (2015) Renal extramedullary hematopoiesis: interstitial and glomerular pathology. Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc 28 (12):1574-1583. doi:10.1038/modpathol.2015.117
15. Strati P, Glass WF, Abdelrahim M, Selamet U, Tchakarov A, Workeneh BT, Verstovsek S, Abudayyeh A (2019) Renal complications of primary myelofibrosis. Leukemia & lymphoma 60 (2):507-510. doi:10.1080/10428194.2018.1474525
16. Fukuda Y, Araki M, Yamamoto K, Morishita S, Inano T, Misawa K, Ochiai T, Edahiro Y, Imai M, Yasuda H, Gotoh A, Ohsaka A, Komatsu N (2019) Evidence for prevention of renal dysfunction associated with primary myelofibrosis by cytoreductive therapy. Haematologica 104 (11):e506-e509. doi:10.3324/haematol.2018.208876
17. Strati P, Abdelrahim M, Selamet U, Page VD, Pierce SA, Verstovsek S, Abudayyeh A (2019) Ruxolitinib therapy is associated with improved renal function in patients with primary myelofibrosis. Annals of hematology 98 (7):1611-1616. doi:10.1007/s00277-019-03708-9
18. Barosi G, Mesa RA, Thiele J, Cervantes F, Campbell PJ, Verstovsek S, Dupriez B, Levine RL, Passamonti F, Gotlib J, Reilly JT, Vannucchi AM, Hanson CA, Solberg LA, Orazi A, Tefferi A, International Working Group for Myelofibrosis R, Treatment (2008) Proposed criteria for the diagnosis of post-polycythemia vera and post-essential thrombocythemia myelofibrosis: a consensus statement from the International Working Group for Myelofibrosis Research and Treatment. Leukemia 22 (2):437-438. doi:10.1038/sj.leu.2404914

19. Thiele J, Kvasnicka HM, Facchetti F, Franco V, van der Walt J, Orazi A (2005) European consensus on grading bone marrow fibrosis and assessment of cellularity. Haematologica 90 (8):1128-1132
20. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D (1999) A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Annals of internal medicine 130 (6):461-470
21. Levin A, Stevens PE (2014) Summary of KDIGO 2012 CKD Guideline: behind the scenes, need for guidance, and a framework for moving forward. Kidney international 85 (1):49-61. doi:10.1038/ki.2013.444
22. Lucijanic M, Skelin M, Lucijanic T (2017) Survival analysis, more than meets the eye. Biochem Med 27 (1):14–18
23. Lucijanic M (2016) Survival analysis in clinical practice: analyze your own data using an Excel workbook. Croatian medical journal 57 (1):77-79. doi:10.3325/cmj.2016.57.77
24. Baek SW, Moon JY, Ryu H, Choi YS, Song IC, Lee HJ, Yun HJ, Kim S, Jo DY (2018) Chronic kidney disease in the BCR-ABL1-negative myeloproliferative neoplasm: a single-center retrospective study. The Korean journal of internal medicine 33 (4):790-797. doi:10.3904/kjim.2016.263
25. Maruyama K, Nakagawa N, Suzuki A, Kabara M, Matsuki M, Shindo M, Iwasaki S, Ogawa Y, Hasebe N (2019) Novel Detection of CALR-Mutated Cells in Myeloproliferative Neoplasm-Related Glomerulopathy With Interstitial Extramedullary Hematopoiesis: A Case Report. American journal of kidney diseases : the official journal of the National Kidney Foundation 74 (6):844-848. doi:10.1053/j.ajkd.2019.05.016
26. Christensen AS, Møller JB, Hasselbalch HC (2014) Chronic kidney disease in patients with the Philadelphia-negative chronic myeloproliferative neoplasms. Leukemia research 38 (4):490-495. doi:10.1016/j.leukres.2014.01.014
27. Afzali B, Goldsmith DJA (2004) Beneficial effects of statins on the kidney. Journal of clinical pathology 57 (7):673-674. doi:10.1136/jcp.2003.014282
28. Orth S, Nowicki M, Wiecek A, Ritz E (1993) Nephroprotective effect of ACE inhibitors. Drugs 46 Suppl 2:189-195; discussion 195-186. doi:10.2165/00003495-199300462-00029

Table 1: Patients' characteristics stratified according to presence of CKD.

	eGFR <60 ml/min/1.73 m^2	**eGFR ≥60 ml/min/1.73 m^2**	**P value**
Number of patients	46/176 (26.1%)	130/176 (73.9%)	-
Age (years)	73 IQR (67 - 78.5)	65 IQR (57 - 72)	**<0.001 ***
Sex Male Female	 24/46 (52.2%) 22/46 (47.8%)	 85/130 (65.4%) 45/130 (34.6%)	0.113
Myelofibrosis type PMF SMF	 37/46 (80.4%) 9/46 (19.6%)	 91/130 (70%) 39/130 (30%)	0.172
BM fibrosis Grade 0-I Grade II-III	 14/46 (30.4%) 32/46 (69.6%)	 41/130 (31.5%) 89/130 (68.5%)	0.890
***JAK2* mutated**	32/46 (69.6%)	86/126 (68.3%)	0.870
***CALR* mutated**	2/36 (5.6%)	13/108 (12%)	0.357
***MPL* mutated**	1/36 (2.8%)	3/108 (2.8%)	1.000
Constitutional symptoms	25/46 (54.3%)	56/130 (43.1%)	0.187
Transfusion dependency	14/43 (32.6%)	32/129 (24.8%)	0.320
Massive splenomegaly	9/37 (24.3%)	36/110 (32.7%)	0.337
Blast phase disease	4/44 (9.1%)	5/128 (3.9%)	0.236
Spleen size under left costal margin (cm)	4 IQR (0 - 8)	4 IQR (1 - 10)	0.329
WBC (x10^9/L)	12.3 IQR (8.98 - 17.98)	9.6 IQR (5.8 - 15.85)	**0.015 ***
Circulatory blasts ≥1%	16/46 (34.8%)	45/130 (34.6%)	0.984
Abs. mono. (x10^9/L)	0.6 IQR (0.4 - 0.99)	0.4 IQR (0.21 - 0.69)	**0.007 ***
Abs. basophils (x10^9/L)	0.2 IQR (0.1 - 0.33)	0.1 IQR (0.01 - 0.2)	**0.009 ***
Abs. lymphocytes (x10^9/L)	1.6 IQR (1.2 - 2.47)	1.4 IQR (1 - 1.9)	0.111
Hemoglobin level (g/L)	103 IQR (91.25 - 123.25)	112.5 IQR (92.25 - 134.75)	0.209
MCV (fL**)**	88 IQR (82.5 - 94.9)	87.1 IQR (81.83 - 93)	0.691
RDW (%)	20.4 IQR (18.88 - 21.85)	19.3 IQR (17.2 - 20.73)	**0.008 ***
Platelets (x10^9/L)	423.5 IQR (258.75 - 938)	290.5 IQR (160.25 - 473.25)	**0.001 ***

	eGFR <60 ml/min/1.73 m^2	eGFR ≥60 ml/min/1.73 m^2	P value
MPV (fL)	9.5 IQR (8.38 - 10.15)	9.3 IQR (8.35 - 10.3)	0.948
LDH (U/L)	549 IQR (347 - 853)	422.5 IQR (301.75 - 672.5)	**0.022 ***
CRP (mg/L)	5 IQR (1.1 - 15.3)	4.4 IQR (1.6 - 10.95)	0.717
Albumin (g/L)	40 IQR (37.5 - 44.25)	43 IQR (40 - 46)	**0.018 ***
Uric acid	451 IQR (378.25 - 582.75)	367.5 IQR (310.25 - 445.5)	**0.001 ***
Fe (mcmol/L)	12 IQR (4.5 - 16.4)	14 IQR (8.4 - 18.15)	0.125
TIBC (mcmol/L)	49.5 IQR (41.9 - 55.45)	50.9 IQR (44.4 - 57.7)	0.444
Transferrin saturation (%)	22.8 IQR (7.9 - 36.31)	28.5 IQR (15.95 - 35.58)	0.476
Ferritin (μg/L)	202 IQR (44.3 - 492.75)	187 IQR (78 - 407)	0.921
CV risk factors	34/38 (89.5%)	74/108 (68.5%)	**0.011 ***
History of thrombosis	6/45 (13.3%)	17/127 (13.4%)	0.993
DIPSS (PMF)			
Low risk	3/46 (6.5%)	24/130 (18.5%)	0.163
Intermediate-1 risk	16/46 (34.8%)	50/130 (38.5%)	
Intermediate-2 risk	22/46 (47.8%)	47/130 (36.2%)	
High risk	5/46 (10.9%)	9/130 (6.9%)	

*statistically significant at level P<0.05

Table 2: Cox regression model for overall survival investigating prognostic properties of CKD in the context of DIPSS-contained variables.

	HR and 95% Confidence interval	P value
MDRD <60 ml/min/1.73 m^2	1.75 (1.07-2.87)	**0.025 ***
Age >65 years	2.14 (1.14-4.04)	**0.018 ***
WBC >25 $x10^9$/L	2.56 (1.4-4.69)	**0.002 ***
Hemoglobin <100 g/L	1.61 (0.99-2.63)	0.055
Peripheral blasts	2.17 (1.29-3.66)	**0.003 ***
Constitutional symptoms	1.76 (1.05-2.95)	**0.031 ***

*statistically significant at level P<0.05

Figure 1: Time to thrombosis stratified according to the presence of chronic kidney disease **A)** with both arterial and venous thromboses considered as an endpoint, **B)** considering arterial thromboses only, and **C)** considering venous thromboses only.

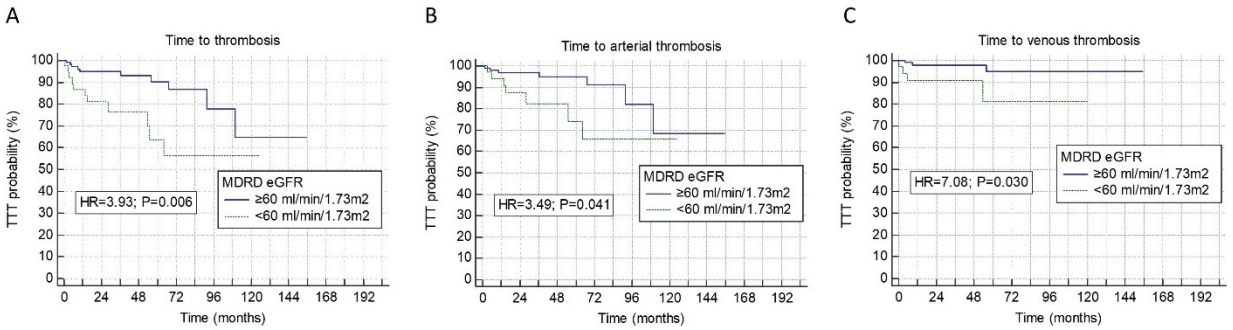

Figure 2: A) Overall survival of the whole cohort, **B)** lower DIPSS categories patients and **C)** higher DIPSS risk categories patients stratified according to the presence of chronic kidney disease.