LETTER

CHRONIC MYELOPROLIFERATIVE NEOPLASMS

RBC distribution width predicts thrombosis risk in polycythemia vera

Dan Liu, Bing Li, Zefeng Xu, Peihong Zhang, Tiejun Qin, Shiqiang Qu, Lijuan Pan, Xiujuan Sun, Zhongxun Shi, Huijun Huang, Huijun Wang, Robert Peter Gale, Zhijian Xiao

© The Author(s), under exclusive licence to Springer Nature Limited 2021

Leukemia (2022) 36:566–568; https://doi.org/10.1038/s41375-021-01410-2

To the Editor

Thrombosis is a common complication and cause of death in persons with polycythemia vera (PV) with an lifetime incidence of 20–30 percent [1, 2]. Thrombosis risk correlates with age, prior thrombosis, hypertension, hyperlipidemia, leukocytosis, JAK2V617F allele burden and therapy in some, but not all, studies [1–5]. Only age and prior thrombosis are included in thrombosis risk stratification: persons age ≥ 60 years and/or with prior thrombosis are defined as high-risk and others, low-risk [6]. Recently, two studies reported RBC distribution width (RDW) predicts thrombosis in persons with PV but the data are inconsistent and these studies had few subjects and included subjects not newly-diagnosed [7, 8]. Several original findings in thrombosis of persons with PV are being reported in this study.

We interrogated data from 902 consecutive newly-diagnosed subjects >18 years with PV seen at the Blood Diseases Hospital, Chinese Academy of Medical Sciences from June 1, 2007 to Feb 28, 2020, and all subjects provided informed consent in compliance with the Declaration of Helsinki. PV was diagnosed according to 2016 World Health Organization (WHO) criteria [9]. Thrombotic events appearing ≥30 days after the date of diagnosis were considered post-diagnosis and others pre-diagnosis. Thrombosis-free survival (TFS) was defined as the interval from diagnosis to 1st post-diagnosis thrombosis, death or last contact. Survival was analyzed by Kaplan-Meier curves which were compared by the log-rank test. Cox proportional hazard regression model was used for multi-variable analyses. We used X-tile to determine the cut-offs of continuous variables for prognosing TFS. Data lock was October 31, 2020 with a median follow-up of 4.5 years (Inter-Quartile Range [IQR], 2–7 years).

Clinical and laboratory co-variates at diagnosis are displayed in Supplementary Table S1. 439 subjects (49%) were male. Median age was 57 years (IQR, 49–65 years). 843 (93%) and 21 (2%) had JAK2V617F and JAK2 exon12 mutations respectively. 2 subjects had JAK2V617F and JAK2 exon12 mutations. Median JAK2V617F variant allele frequency (VAF) at diagnosis was 56% (IQR, 35–73%).

274 subjects (32%) had ≥1 thrombotic event pre-diagnosis (Supplementary Table S2), 262 (96%) of which were arterial and 20 (7%), venous. These frequencies are higher than those reported in persons of predominately European descent (Fig. 1A) [2].

25 of 539 subjects (5%) had abnormal cytogenetics at diagnosis. 99 subjects had 112-gene panel next generation sequencing at diagnosis, 47 of whom (47%) had ≥1 mutated gene in addition to JAK2 (Fig. S1). The most common mutations were in TET2 (n = 18) and DNMT3A (n = 8).

Phlebotomy is recommended as initial therapy for low-risk PV [6]. However, only RBC apheresis is approved in China. Consequently, phlebotomy is used in few Chinese with PV. In our study, 837 (93%) subjects received cytoreductive treatment. 455 (50%), 155 (17%) and 213 (24%) initially received hydroxyurea, non-preglated interferon or combination of hydroxyurea with non-preglated interferon. 14 (2%) subjects received therapy(ies) other than hydroxyurea or interferon. 54 (6%) subjects underwent watching and waiting and 11 died without treatment details. 49 subjects (5%) had 56 thrombotic events post-diagnosis (rate 1.2% per year; 95% Confidence Interval [CI] [0.9, 1.6%]). Arterial and venous thrombosis occurred in 41 (percentage 5%, rate 0.9% per year; [0.6, 1.2]) and 9 subjects (percentage 1%, rate 0.2% per year; [0.1, 0.3%]; Supplementary Table S2), respectively.

Barbui et al. study enrolled 1545 patients with PV from 7 centers in Italy, Australia and the United States [2]. 73% patients received cytoreductive treatments, including hydroxyurea, interferon, anagrelide, chlorambucil, busulfan, pipobroman, P32 or other alkylating agents [2]. 19% patients had thrombosis post-diagnosis (rate 2.6% per year [2.3, 2.9]) [2]. Arterial and venous thrombosis occurred in 12% (1.6% per year [1.4, 1.8]) and 9% subjects (1.1% per year; [0.9, 1.3%]) [2].

The proportion of patients with post-diagnosis thrombosis was much lower in our study than reported in Barbui study (5% vs 19%, p < 0.001; Fig. 1B) [2]. The 5- and 10-year commutative incidences of thrombosis were 5.3% (4.4, 6.2%) and 11.0% (9.0, 13.0%) in our study, also lower than reported in Barbui study (Fig. 1B) [2].
In low-risk cohort, the proportion of patient with post-diagnosis thrombosis in our study was lower than reported in persons treated with phlebotomy in Barbui study (4% vs 12%; \( p < 0.001 \); Fig. 1C), similarly for thrombosis rate (0.8% per year [0.4, 1.2%] vs 2.0% per year [1.6, –2.5%]) [10].

Previous studies reported that PV receiving phlebotomy had higher thrombosis rate than those treated by chlorambucil, P32 or hydroxyurea [11–13]. The thrombosis rate post-diagnosis in our study was lower than that reported in Barbui study [2, 10], which might partly related to significantly less phlebotomies in Chinese than Western cohort.

Uni- and multi-variable analyses of TFS are displayed in Supplementary Table S3. Age \( \geq 50 \) years (HR = 2.6 [1.1, 6.0]; \( p = 0.03 \); Supplementary Fig. S2A), hypertension (HR = 2.0 [1.1, 3.7]; \( p = 0.03 \); Supplementary Fig. S2B) and RDW < 14.5% (HR = 1.9 [1.0, 3.6]; \( p = 0.06 \); Fig. 1D) were associated with worse TFS in univariable analyses. Age \( \geq 50 \) years (HR = 3.7 [1.1, 12.2]; \( p = 0.03 \)) and RDW < 14.5% (HR = 2.6 [1.3, 5.4]; \( p = 0.009 \)) were independently associated with TFS in multivariable analyses (Supplementary Table S3). JAK2V617F allele burden \( \geq 75 \% \) (HR = 0.8 [0.4, 1.7]; \( p = 0.54 \)) and WBC \( \geq 11 \times 10^9/L \) (HR = 1.0 [0.5, 1.7]; \( p = 0.80 \)) were not significant predictors of TFS (Supplementary Table S3). These data differ from prior studies [1, 2, 5].

Lower RDW correlated with worse TFS in subjects defined as high-risk using standard criteria (HR = 3.8 [95% CI 1.8–8.0]; \( p < 0.001 \); Fig. 1E) or with prior thrombosis (HR = 4.2 [95% CI 1.2–13.7]; \( p = 0.03 \); Fig. 1F). But lower RDW not significantly associated with TFS in subjects classified as low-risk (HR = 0.7 [95% CI 0.6–1.3]; \( p = 0.75 \)) or subjects without prior thrombosis (HR = 1.4 [95% CI 0.6–3.3]; \( p = 0.40 \)).

Arterial TFS was significantly correlated with age \( \geq 50 \) years (HR = 2.5 [95% CI 1.2–5.3]; \( p = 0.006 \); Fig. 1F) or with prior thrombosis (HR = 4.2 [95% CI 1.2–13.7]; \( p = 0.005 \); Fig. 1D). However, lower RDW not significantly associated with arterial TFS in subjects classified as low-risk (HR = 0.7 [95% CI 0.3–1.6]; \( p = 0.63 \)) [6], age <50 years (HR = 0.7 [95% CI 0.3–1.6]; \( p = 0.75 \)) or subjects without prior thrombosis (HR = 1.4 [95% CI 0.6–3.3]; \( p = 0.40 \)).

Higher RDW has been recognized as a biomarker of ineffective erythropoiesis and inflammation [7], and was reported to have association with increased mortality in patients with COVID-19 infection [14]. Krečak et al. reported higher RDW was associated...
with inferior TFS in 92 patients with myeloproliferative neoplasms (51 essential thrombosis and 41 PV) [7], which is opposite to our study. Higher RDW correlates with older age, female sex, palpable splenomegaly, higher concentrations of WBC, RBC, hemoglobin and JAK2 (+) allele burden, but lower concentrations of eotinin, serum iron and serum ferritin in our study (Supplementary Table S4). However, the underlying mechanism of lower RDW correlated with worse TFS remains unknown.

A machine learning study reported that lymphocytes percentage <19.3% and RDW <14.05% were associated with higher thrombosis rate in the first year treatment of hydroxyurea for PV without history of thrombosis [8]. We found lymphocytes <1.2 × 10 E9/L was associated with worse TFS in subjects without prior thrombosis (HR = 2.8 [1.2, 4.9]; p = 0.01; Supplementary Fig. S2H). Lymphocytes ≥ 2.2 × 10 E9/L tend to associated with worse TFS in subjects with thrombosis history (HR = 2.6 [0.9, 4.4]; p = 0.06; Supplementary Fig. S2I).

We found no significant correlations between age >60 years (Hazard Ratio [HR] = 1.5 [0.8, 2.6]; p = 0.17) or prior thrombosis (HR = 1.1, [0.6, 2.0]; p = 0.74) and TFS, but standard thrombosis risk stratification still could predict thrombosis risk in our subjects (Supplementary Fig. S1G–I) [6].

As multivariable analysis yielded HR of 3.2 (1.1, 9.0) for age >67years, 2.4 (1.0, 5.9) for age 50 to 67 years, and 2.1 (1.0, 4.4) for RDW < 14.5%. We propused a new model including age > 67 years (2 points), age 50 to 67 years (1 point), and RDW < 14.5% (1 point), including low-risk (0 or 1 point) and high risk (≥2 points; HR = 2.7 [1.4, 4.6]; Fig. 1) cohorts. This new model had better likelihood ratio (20.6, p = 0.051) than standard thrombosis risk stratification (18.8, p = 0.16; Supplementary Fig. S1I) by multi-variable logistic regression model, suggesting a better prognostic value of the new model in our subjects.

Our study has limitations. It is retrospective, from one center and with relatively brief follow-up. As such our conclusions need external validation.

In summary, we found thrombosis rate post-diagnosis was lower in Chinese with PV compared with persons of predominately European descent [2, 10]. This could reflect a different phenotype, different therapy(ies), both or other factors [2, 10]. RDW < 14.5% at diagnosis was associated with worse TFS, especially for arterial thrombosis and subjects ≥50 years or with prior thrombosis.

REFERENCES

1. Cerquozzi S, Barraco D, Lasho T, Finke C, Hanson CA, Ketterling RP, et al. Risk factors for arterial versus venous thrombosis in polycythemia vera: a single center experience in 587 patients. Blood Cancer J. 2017;7:662.

2. Barbui T, Carobbio A, Rumi E, Finazzi G, Gisslinger H, Rodeghiero F, et al. In contemporary patients with polycythemia vera, rates of thrombosis and risk factors delineate a new clinical epidemiology. Blood. 2014;124:1822.

3. Landolfi R, Marchioli R, Kutta J, Gisslinger H, Tognoni G, Patrono C, et al. Efficacy and safety of low-dose aspirin in polycythemia vera. N Engl J Med. 2004;350:114–24.

4. De Stefano V, Rossi E, Carobbio A, Ghiaradi A, Betti S, Finazzi G, et al. Hydroxyurea prevents arterial and late venous thrombotic recurrences in patients with myeloproliferative neoplasms but fails in the splenic thrombotic venous district. Pooled analysis of 1500 cases. Blood Cancer J. 2018;8:112.

5. Vannucchi AM, Antonioli E, Guglielmelli P, Longo G, Pancrazzi A, Ponziani V, et al. Prospective identification of high-risk polycythemia vera patients based on JAK2V617F allele burden. Leukemia. 2007;21:1952–59.

6. Guideline of myeloproliferative neoplasms on National Comprehensive Cancer Network (NCCN) (Version 2020). 2020.

7. Kreca k I, Krecak F, Gveric-Krecak V. High red blood cell distribution width might predict thrombosis in essential thrombocytemia and polycythemia vera. Blood Cells Mol Dis. 2020;80:102368.

8. Srdan V, Valerio DS, Florian HH, Mike Z, Michael Z, Kenneth B, et al. Interactions of key hematological parameters with red cell distribution width (RDW) are associated with incidence of thromboembolic events (TEs) in polycythemia vera (PV) patients: a machine learning study (PV-AIM). Blood. 2020;136:45–46.

9. Arber DA, Orazi A, Hasserjian R, Theile J, Borowitz MJ, Le Beau MM, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127:2391–405.

10. Barbui T, Vannucchi AM, Carobbio A, Rumi E, Finazzi G, Gisslinger H, et al. The effect of arterial hypertension on thrombosis in low-risk polycythemia vera. Am J Hematol. 2017;92:E5–E6.

11. Berk PD, Goldberg JD, Donovan PB, Fruchtman SM, Berlin NL, Wasserman LR. Therapeutic recommendations in polycythemia vera based on polycythemia Vera Study Group protocols. Semin Hematol. 1986;23:132–43.

12. Barbui T, Vannucchi AM, Finazzi G, Finazzi MC, Masciulli A, Carobbio A, et al. A reappraisal of the benefit-risk profile of hydroxyurea in polycythemia vera: a propensity-matched study. Am J Hematol. 2017;92:1131–36.

13. Barbui T, De Stefano V, Ghiaradi A, Masciulli A, Finazzi G, Vannucchi AM. Different effect of hydroxyurea and phlebotomy on prevention of arterial and venous thrombosis in polycythemia vera. Blood Cancer J. 2018;8:124.

14. Foy BH, Carlson JCT, Reintersen E, Padros IVR, Pallares Lopez R, Palanques-Tost E, et al. Association of red blood cell distribution width with mortality risk in hospitalized adults with SARS-CoV-2 infection. JAMA Netw Open. 2020;3:e2002058.

ACKNOWLEDGEMENTS

Supported in part by National Natural Science Funds (No. 81530008,81870104,82070134), Tianjin Natural Science Funds (18JCZDJC4900,16JCQNJC11400,19JQCNOC9400), CAMS Initiative Fund for Medical Sciences (No. 2016-I2M-1-001,2020-I2M-C67-A-020,2020-I2M-C67-B-090). RPG acknowledges support from the National Institute of Health Research (NIHR) Biomedical Research Centre funding scheme. Prof. Tiziano Barbui (Oespedale Papa Giovanni XXIII, Bergamo) kindly reviewed the typescript.

AUTHOR CONTRIBUTIONS

ZJX designed the study, DL and ZFX collected and analyzed the data. PHZ analyzed the bone marrow histology. TJQ, SQQ, LJQ and XJS recruited subjects and collected the data. DL prepared the typescript with contributions from ZJX, ZFX, BL, RPG, ZXS, HJJH and HJWW. All authors reviewed the typescript, approved this version and agreed to submit for publication.

COMPETING INTERESTS

RPG is a consultant to BeiGene Ltd., Fusion Pharma LLC, LaJolla NanoMedical Inc., Mingsight Pharmaceuticals Inc. and CStone Pharmaceuticals; advisor to Antegene Biotech LLC, Medical Director, FFF Enterprises Inc.; partner, AZAC Inc.; Board of Directors, Russian Foundation for Cancer Research Support; and Scientific Advisory Board: StemRad Ltd. The remaining authors declare no competing interests.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41375-021-01415-2.

Correspondence and requests for materials should be addressed to Zhijian Xiao.

Reprints and permission information is available at http://www.nature.com/reprints

Publisher’s note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.