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LETTER

CHRONIC MYELOPROLIFERATIVE NEOPLASMS

RBC distribution width predicts thrombosis risk in polycythemia vera

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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, $JAK2^{V617F}$ 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 $JAK2^{V617F}$ and $JAK2$ exon12 mutations respectively. 2 subjects had $JAK2^{V617F}$ and $JAK2$ exon12 mutations. Median $JAK2^{V617F}$ 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-pegylated interferon or combination of hydroxyurea with non-pegylated 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%]) in our. 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].

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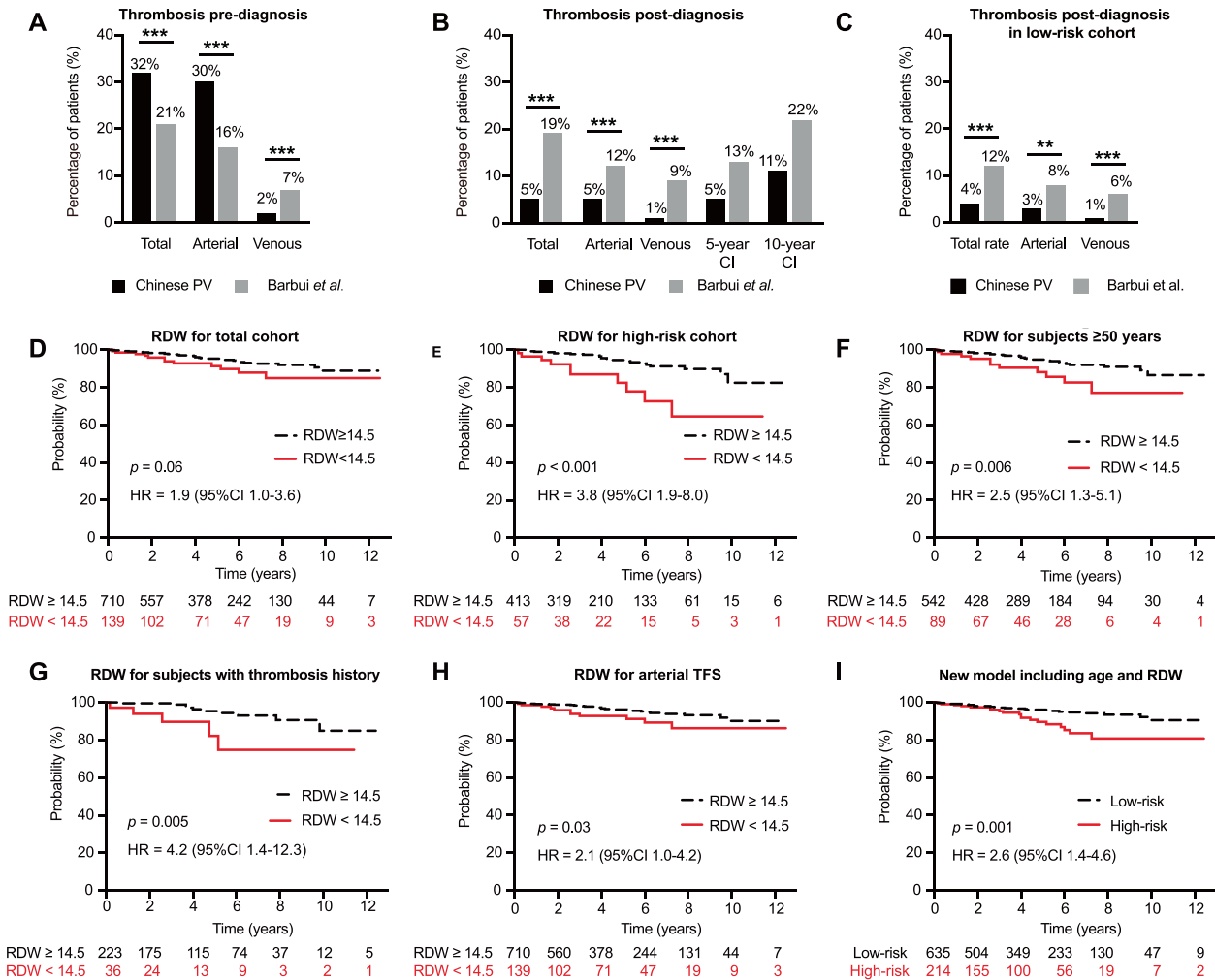
Fig. 1 Percentage of patients with thrombosis and thrombosis-free survivals. Comparison of percentage of patients with thrombosis between Chinese and persons of predominately European descent pre- (**A**) and post-diagnosis (**B**)[2] and in low-risk cohorts post-diagnosis (**C**)[15]. Prognostic value of RDW for TFS (**D**). RDW < 14.5% is associated with worse TFS in high-risk subjects defined by standard criteria (**E**), subjects ≥50 years (**F**) and with prior thrombosis (**G**). Predictive value of RDW for arterial TFS (**H**). New model for TFS including age ≥ 68 years (2 point), age 50–67 years (1 point) and RDW < 14.5% (1 point): low-risk (0 or 1 point; 5-year cumulative incidence [CI] of thrombosis: 3.9% [3.0, 4.8]); high-risk (≥2 points; 5-year CI of thrombosis: 10.4% [7.6, 13.2]) (**I**). Barbui et al. [2], median follow-up 6.9 years (range, 0–39 years; n = 1545). Barbui et al. [10], median follow-up 4.9 years (range, 0–34 years) in low-risk subjects treated by phlebotomy (n = 604). CI cumulative incidence, TFS thrombosis-free survival; **p < 0.01; *** p < 0.001.

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 ≥ 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 uni-variable analyses. Age ≥ 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 multi-variable analyses (Supplementary Table S3). JAK2^{V617F} allele burden ≥ 75% (HR = 0.8 [0.4, 1.7]; $p = 0.54$) and WBC ≥ 11 x 10E + 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].

A lower RDW correlated with worse TFS in subjects defined as high-risk using standard risk criteria (HR = 3.8 [1.8, 8.0]; $p < 0.001$; Fig. 1E) [6], subjects ≥ 50 years (HR = 2.5 [1.3, 5.1]; $p = 0.006$; Fig. 1F) or with prior thrombosis (HR = 4.2 [1.4, 12.3]; $p = 0.005$; Fig. 1G). But lower RDW not significantly associated with TFS in subjects classified as low-risk (HR = 0.7 [0.2, 3.1]; $p = 0.63$) [6], age <50 years (HR = 0.7 [0.1, 6.1]; $p = 0.75$) or subjects without prior thrombosis (HR = 1.4 [0.6, 3.3]; $p = 0.40$).

Arterial TFS was significantly correlated with age ≥ 50 years (HR = 4.9 [1.1, 21]; $p = 0.03$; Supplementary Table S3 and Supplementary Fig. S2C) and RDW < 14.5% (HR = 3.1 [1.4, 6.9]; $p = 0.004$; Fig. 1H) in multi-variable analyses. Prior venous thrombosis was the only predictor for future venous thrombosis (HR = 7.9 [1.0, 64.2]; $p = 0.02$; Supplementary Table S3 and Supplementary Fig. S1D).

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 corelates with older age, female sex, palpable splenomegaly, higher concentrations of WBC, RBC, hemoglobin and JAK2^{V617F} allele burden, but lower concentrations of epoetin, serum iron and serum ferritin in our study (Supplementary Table S4). However, the underlying mechanism of lower RDW corelated 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 E + 9/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 E + 9/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 > 67 years, 2.4 (1.0, 5.9) for age 50 to 67 years, and 2.1 (1.0, 4.4) for RDW < 14.5%. We propursed 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. 1I) 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 multivariable 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.

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AUTHOR CONTRIBUTIONS

ZJX designed the study. DL and ZFX collected and analyzed the data. PHZ analyzed the bone marrow histology. TJQ, SQQ, LJP and XJS recruited subjects and collected the data. DL prepared the typescript with contributions from ZJX, ZFX, BL, RPG, ZXS, HJH and HJW. 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 Parmaceuticals 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

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