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ORIGINAL ARTICLE

Survival and prognosis among 1545 patients with contemporary polycythemia vera: an international study

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Under the auspices of an International Working Group, seven centers submitted diagnostic and follow-up information on 1545 patients with World Health Organization-defined polycythemia vera (PV). At diagnosis, median age was 61 years (51% females); thrombocytosis and venous thrombosis were more frequent in women and arterial thrombosis and abnormal karyotype in men. Considering patients from the center with the most mature follow-up information ($n = 337$ with 44% of patients followed to death), median survival (14.1 years) was significantly worse than that of the age- and sex-matched US population ($P < 0.001$). In multivariable analysis, survival for the entire study cohort ($n = 1545$) was adversely affected by older age, leukocytosis, venous thrombosis and abnormal karyotype; a prognostic model that included the first three parameters delineated risk groups with median survivals of 10.9–27.8 years (hazard ratio (HR), 10.7; 95% confidence interval (CI): 7.7–15.0). Pruritus was identified as a favorable risk factor for survival. Cumulative hazard of leukemic transformation, with death as a competing risk, was 2.3% at 10 years and 5.5% at 15 years; risk factors included older age, abnormal karyotype and leukocytes $\geqslant 15 \times 10^9$/l. Leukemic transformation was associated with treatment exposure to pipobroman or P32/chlorambucil. We found no association between leukemic transformation and hydroxyurea or busulfan use.

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INTRODUCTION

Over the past century, polycythemia vera (PV) has undergone substantive changes in its concept and diagnostic criteria. The disease was first described in 1882[1] by Louis Henri Vaquez (1860–1936) and further elaborated by William Osler (1849–1919) in 1903.[2] William Dameshek (1900–1969) included PV as one of the 'myeloproliferative disorders' in 1951.[3] In 1976, the clonal nature of PV was deciphered,[4] but it took another 20 years before William Vainchenker (*b*. 1947) discovered its signature mutation (*JAK2*V617F),[5] which is, however, neither specific to PV nor believed to constitute the disease-initiating event.[6]

Formal clinical research in PV started in 1967 with Louis Wasserman (1912–1999) establishing the Polycythemia Vera Study Group.[7] The Polycythemia Vera Study Group conducted a number of clinical trials in PV including its seminal contribution of drug leukemogenicity associated with chlorambucil and P32.[7] The Polycythemia Vera Study Group is also credited for the first consensus diagnostic criteria in PV,[7] which have since undergone substantial revisions by the World Health Organization (WHO) subcommittee for classification of myeloid malignancies. The most recent WHO document on PV underscores the diagnostic value of *JAK2* mutations and bone marrow morphology.[8]

This study is distinguished from previous studies in PV in its strict use of the 2008 WHO diagnostic criteria[9] and its main focus was survival and leukemic transformation. The large sample size enabled us to address a number of clinically relevant questions: (i) What is the contemporary disease presentation profile and is there a difference between men and women in this regard? (ii) How does life expectancy compare with that of the age- and sex-matched control population? (iii) What predicts overall and leukemia-free survival? (iv) Does exposure to certain drugs increase the likelihood of leukemic transformation?

PATIENTS AND METHODS

The International Working Group for Myeloproliferative Neoplasms (MPN) Research and Treatment (IWG-MRT) meets annually to organize clinical research projects and develop consensus criteria. The IWG-MRT recently published a series of papers that clarified the natural history of WHO-defined essential thrombocythemia (ET) and its distinction from prefibrotic myelofibrosis (MF).[10–19] During the 2010 IWG-MRT meeting in Florence, Italy, center and patient eligibility criteria for a large international study in PV were discussed and followed up by a request for participation. Study eligibility criteria included strict adherence to the 2008 WHO diagnostic criteria,[9] availability of clinical and laboratory information obtained within 1 year of diagnosis and before institution of cytoreductive therapy, diagnosis date after 1970 and age $\geqslant 18$ years old.

After approval from their respective institutional review board, seven centers from Italy, Austria and the United States collectively submitted diagnostic and follow-up information on 1818 patients, locally diagnosed with 'WHO-defined PV'. The two principle investigators (AT and TB)

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reviewed all submitted cases and, based on diagnostic accuracy[9] and the above stipulated eligibility criteria, selected 1545 patients for further analysis (Supplementary Table 1). Conventional criteria were used for diagnosis of post-PV acute myeloid leukemia (AML),[9] whereas post-PV MF was annotated by the coinvestigators from each center with recommendations of adherence to uniform criteria.[20] Conventional laboratory methods were used by each institution for *JAK2* mutation screening, measurement of serum erythropoietin level and detection of endogenous erythroid colonies.

All analyses were conducted using The Stat View (SAS Institute, Cary, NC, USA), JMP (SAS Institute) or SAS version 9.2 (SAS Institute) statistical packages. Pre-receiver operating characteristic (ROC) plots were used to determine cutoff levels for continuous variables of interest.[21] Differences in the distribution of continuous variables between categories were analyzed by Mann–Whitney or Kruskal–Wallis test. Patient groups with nominal variables were compared by χ^2 test. Overall survival analysis was considered from the date of diagnosis to date of death (uncensored) or last contact (censored). Observed survival was compared with the expected survival of the age- and sex-matched US total population. The rate of post-PV AML was calculated as the cumulative incidence of transformation, accounting for the competing risk of death.[22] All survival curves were prepared by the Kaplan–Meier method and compared by the log-rank test. Cox proportional hazard regression model was used for multivariable analysis. *P*-values <0.05 were considered significant.

RESULTS

Presenting features

Table 1 provides all-inclusive and gender-stratified information on clinical and laboratory features at the time of diagnosis. Median age was 61 years (10% were below age 40 years) and gender distribution was close to 1:1. Palpable splenomegaly, pruritus and vasomotor symptoms were each expressed by about a third of the patients. Venous thrombosis (9.3% vs 5.4%; $P<0.01$) and thrombocytosis (60% vs 45.4%; $P<0.01$) were more frequent in women and arterial thrombosis (18% vs 14%; $P=0.02$) and palpable splenomegaly (40.3% vs 32%; $P<0.01$) in men. As expected, approximately 98% of the patients screened ($n=1268$) were positive for either *JAK2*V617F (95%) or other *JAK2* mutations (3%), whereas a subnormal serum erythropoietin level or endogenous erythroid colonies were documented in 81% and 73% of those tested, respectively. Less than 20% of the patients had undergone red cell mass measurement. Abnormal karyotype at diagnosis was documented in 12% of the patients examined ($n=631$) and was more frequent in men (15% vs 9%; $P=0.02$). Increased serum lactate dehydrogenase level and leukoerythroblastosis were, respectively, documented in 50% and 6% of patients evaluated.

Postdiagnosis events

At the time of this writing, 347 (23%) deaths, 50 (3%) leukemic transformations and 138 (9%) progressions to 'post-PV MF' were recorded (Table 2). Causes of death were reported on 164 (47.3%) patients and listed in Table 2. Follow-up time ranged from 0 to 39.3 years (median 6.9 years). The incidences of postdiagnosis arterial thrombosis, venous thrombosis and major hemorrhage were 12%, 9% and 4.2%, respectively. Treatment was according to individual physician discretion and cytoreductive drug or aspirin use was documented in 1129 (73%) and 1281 (84%) patients, respectively. Patients were assigned to operational treatment groups (Table 2) based on whether or not they were exposed to drugs that are generally believed to be leukemogenic (for example, radiophosphorus or chlorambucil),[23] were recently implicated to be leukemogenic (pipobroman)[24] or are controversial in terms of their leukemogenic potential (for example, hydroxyurea, busulfan).[23]

Table 1. All-inclusive and gender-stratified outline of presenting features in 1545 patients with PV

	N *evaluable*	*All patients* (N = *1545*)	*Females,* N = *785* *(51%)*	*Males,* N = *760* *(49%)*	P-*values*
Median age, years (range)	1545	61 (18–95)	62 (18–92)	59 (19–95)	**<0.01**
Ages below 40/50 years	1545	10/24%	10/23%	10/26%	0.58
Hemoglobin, median in g/dl (range)	1545	18.4 (15.1–26.5)	17.7 (15.1–24.5)	18.9 (17.1–26.5)	**<0.01**
Hematocrit (median and range)	1545	55 (36–78)	54 (36–76)	57 (42–78)	**<0.01**
Leukocyte count, median $\times 10^9$/l (range)	1545	10.4 (3–171.6)	10.3 (3–125.5)	10.5 (4.2–171.6)	0.85
Leukocytosis ($>10.5\times 10^9$/l), *n* (%)	1545	751 (49%)	375 (48%)	376 (49.5%)	0.5
Platelet count, median $\times 10^9$/l (range)	1545	466 (7–2370)	509 (7–2370)	419 (37–1410)	**<0.01**
Thrombocytosis ($\geqslant 450\times 10^9$/l), *n* (%)	1545	817 (53%)	472 (60%)	345 (45.4%)	**<0.01**
Extreme thrombocytosis ($\geqslant 1000\times 10^9$/l), *n* (%)	1545	58 (4%)	46 (6%)	12 (1.6%)	**<0.01**
Palpable spleen, *n* (%)	1477	534 (36%)	241 (32%)	293 (40.3%)	**<0.01**
Pruritus, *n* (%)	1349	485 (36%)	240 (35.4%)	245 (36.6%)	0.64
Vasomotor symptoms, *n* (%)	1412	403 (28.5%)	213 (30%)	190 (27%)	0.26
Arterial thrombosis before/at diagnosis, *n* (%)	1545	246 (16%)	108 (14%)	138 (18%)	**0.02**
Venous thrombosis before/at diagnosis, *n* (%)	1545	114 (7.4%)	73 (9.3%)	41 (5.4%)	**<0.01**
Major hemorrhage before/at diagnosis, *n* (%)	572	24 (4.2%)	16 (5.5%)	8 (2.8%)	0.11
↑ Lactate dehydrogenase, *n* (%)	732	368 (50%)	203 (54%)	165 (47%)	0.07
Leukoerythroblastic smear, *n* (%)	1056	63 (6%)	28 (5%)	35 (7%)	0.26
Abnormal karyotype, *n* (%)	631	77 (12%)	29 (9%)	48 (15%)	0.02
JAK2 mutation, *n* (%)	1268	1239 (98%)	626 (98%)	613 (97.3%)	0.68
V617F/other *JAK2* mutation (%)	1268	95%/3%	95.6%/2.5%	95%/3%	0.68
Serum Epo ↓/normal/↑ (%)	1058	81%/17%/2%	83%/15%/2%	79%/19%/1%	0.17
EEC, *n* (%)	454	331 (73%)	182 (76%)	149 (69.3%)	0.10
Increased red cell mass, *n* (%)	306	277 (91%)	149 (87.7%)	128 (94%)	0.06
Hemoglobin >18.5 g/dl (>16.5 ♀) *n* (%)	1545	1122 (73%)	652 (83%)	470 (62%)	**<0.01**
History of tobacco use, *n* (%)	1301	206 (16%)	74 (11.3%)	132 (20.4%)	**<0.01**
History of diabetes, *n* (%)	1149	97 (8.4%)	41 (7%)	56 (11%)	0.11
History of hyperlipidemia, *n* (%)	1073	196 (18.3%)	98 (18%)	98 (18.5%)	0.85
History of hypertension, *n* (%)	1388	638 (46%)	339 (48%)	299 (43.7%)	0.09

Abbreviations: EEC, endogenous erythroid colony; Epo, erythropoietin; PV, polycythemia vera. Bold numeral indicate differences that were statistically relevant.

Table 2. Events during the clinical course of 1545 patients with PV including age-stratified incidence rates

	All patients, n = *1545*	*Age >61 years*, N = *743*	*Age ≤61 years*, N = *802*	P-*value*
Median follow-up years (range)	6.9 (0–39)	5.8 (0–22)	8 (0–39)	<**0.0001**
Deaths, *n* (%)	347 (23%)	237 (32%)	110 (14%)	<**0.0001**
Causes of death				
Acute leukemia	36			
Second malignancies	36			
Thrombotic complications	32			
Heart failure	13			
Non-leukemic progressive disease	12			
Infection	7			
Respiratory failure	7			
Bleeding	5			
End-stage liver disease	3			
Cardiopulmonary arrest	3			
Other causes with incidences of 2 or less	10			
Unknown	183 (53%)			
Leukemic transformations, *n* (%)	50 (3%)	25 (3%)	25 (3%)	0.78
Progression to myelofibrosis, *n* (%)	138 (9%)	50 (7%)	88 (11%)	**0.004**
Arterial thrombosis	184 (12%)	86 (12%)	98 (12%)	0.70
Venous thrombosis	137 (9%)	63 (8%)	74 (9%)	0.61
Major hemorrhage	24/572 (4.2%)	13/281 (4.6%)	11/291 (3.8%)	0.61
Aspirin therapy	1281/1535 (84%)	599/739 (81%)	682/796 (86%)	**0.02**
Cytoreductive drug exposure, n *(%)*	1129 (73%)			
Leukemogenic[a] (single agent) ± non-leukemogenic	23	18 (78%)	5 (22%)	
Leukemogenic + pipobroman/busulfan/hydroxyurea	42	23 (55%)	19 (45%)	
Pipobroman alone ± non-leukemogenic	124	75 (60%)	49 (40%)	
Pipobroman + busulfan/hydroxyurea	41	14 (34%)	27 (66%)	<**0.0001**
Busulfan alone ± non-leukemogenic	35	26 (74%)	9 (26%)	
Busulfan + hydroxyurea	33	18 (55%)	15 (45%)	
Hydroxyurea alone ± non-leukemogenic	789	406 (51%)	383 (49%)	
Non-leukemogenic[b] or no cytoreductive drug therapy	458	163 (36%)	295 (64%)	

Abbreviations: PV, polycythemia vera. [a]Leukemogenic drugs included chlorambucil, P32 or other alkylating agents. [b]Non-leukemogenic drugs included interferon α and anagrelide. Bold numerals indicate differences that were statistically significant.

Life expectancy

Median survival for the entire study cohort ($n = 1545$) was projected at 18.9 years and comparison with age- and sex-matched US population suggested a trend towards worse survival (Figure 1; $P = 0.1$). However, the particular comparison revealed significantly shortened life expectancy for patients with PV (Figure 2; $P < 0.001$) when the analysis was restricted to one of the seven participating centers (the Mayo Clinic cohort) with the most mature survival data ($n = 337$; 44% of patients followed to death; median survival 14.1 years). This phenomenon of survival overestimation as a result of immature survival data was further illustrated in Supplementary Figure 1, which showed significant intercenter differences in median survival projections (range 14.1 years to 'not reached') that correlated with the proportion of uncensored data in each center (range 5–44%). Mature survival data obtained from the Mayo Clinic cohort was also necessary to demonstrate inferior survival in both young and older patients in PV compared with the control population (Supplementary Figure 2); the cutoff levels for age stratification were determined by ROC plots.[21]

Prognostic factors

Each one of the parameters listed in Table 1 was evaluated for its survival prediction value and if significant was chosen for further multivariable analysis (Table 3). Higher leukocyte count, venous thrombosis, leukoerythroblastic blood smear and abnormal karyotype sustained an age-independent adverse prognostic value, whereas thrombocytosis and pruritus were associated with better survival. Karyotype-exclusive multivariable analysis confirmed the independent prognostic value of all of these variables (Table 3). The inclusion of cytogenetic information to the multivariable model reduced the number of fully informative cases from 964 to 383 and resulted in the loss of significance attached to thrombocytosis ($P = 0.09$) and leukoerythroblastosis ($P = 0.36$; Table 3). Incidentally, there was no difference in survival between patients with *JAK2*V617F vs other *JAK2* mutations ($P = 0.86$).

Prognostic models

Because of the maturity of its survival data, the Mayo Clinic cohort ($n = 337$) was used to prepare ROC plots to determine the best discriminant levels for age and leukocyte count.[21] Both early (10 years) and late (20 years) time points were considered in this regard and the respective optimal age cutoff levels were 67 years (area under the curve = 0.82) and 57 years (area under the curve = 0.89). A similar analysis resulted in a leukocyte cutoff value of 14.8×10^9/l (area under the curve = 0.64). Multivariable analyses for the entire study cohort ($n = 1545$) using these ROC-determined cutoff values confirmed their enhanced performance; karyotype-exclusive hazard ratio (HR) (95% confidence interval (CI)) were 8.5 (5.7–12.6) for age ⩾67 years, 2.9 (1.9–4.4) for age 57–66 years, 2.2 (1.6–3.0) for leukocyte count $\geqslant 15 \times 10^9$/l, 1.8 (1.1–2.8) for venous thrombosis and 0.7 (0.5–0.9) for pruritus (Supplementary Table 2).

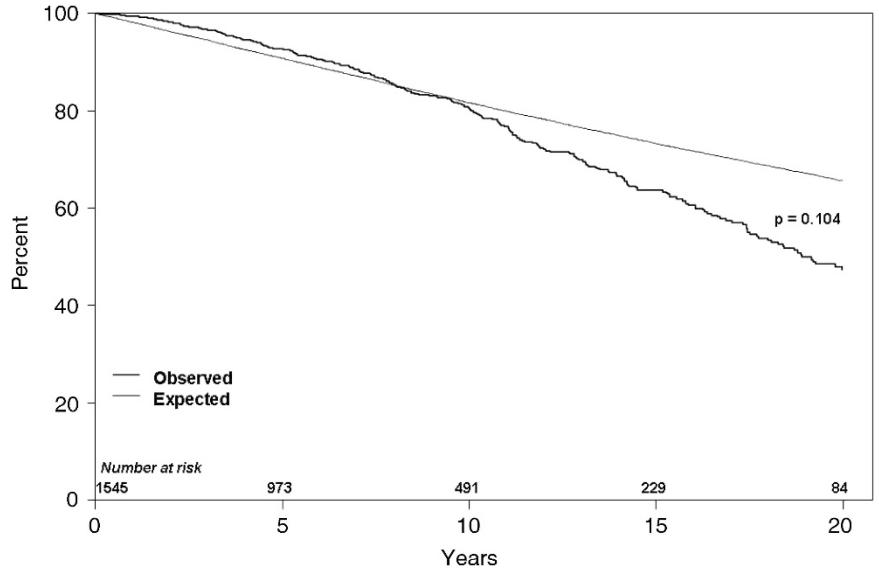

Figure 1. Survival in 1545 patients with PV (23% followed to death; median survival 18.9 years) compared with expected survival based on individuals of the same age and gender from the US total population.

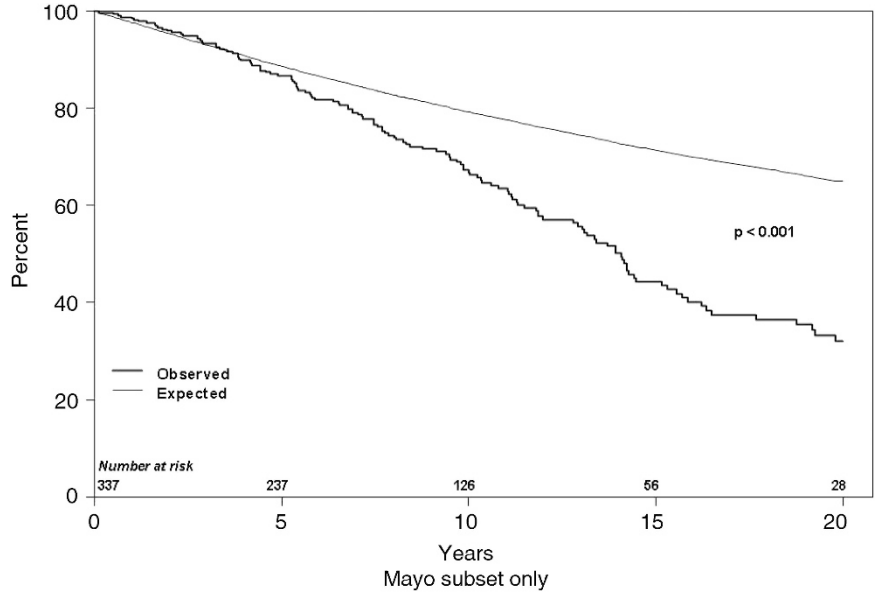

Figure 2. Survival in 337 Mayo Clinic patients with PV (44% followed to death; median survival 14.1 years) compared with expected survival based on individuals of the same age and gender from the US total population.

To develop a widely applicable prognostic model with objective parameters, we chose the ROC-determined three-tired age categories (age $\geqslant$67, 57–66 and $<$57 years old), leukocytosis (below or $\geqslant 15 \times 10^9$/l) and venous thrombosis (present or absent) as important variables. We used the Mayo Clinic cohort ($n = 337$) as the training set where multivariable analysis yielded HR (95% CI) of 10.3 (6.3–16.7) for age $\geqslant$67 years, 3.9 (2.4–6.5) for age 57–66 years, 2.3 (1.3–4.0) for leukocyte count $\geqslant 15 \times 10^9$/l and 1.6 (1.1–2.2) for venous thrombosis. Consequently, HR-weighted adverse points were assigned to age $\geqslant$67 years (5 points), age 57–66 years (2 points), leukocyte count $\geqslant 15 \times 10^9$/l (1 point) and venous thrombosis (1 point), to devise a prognostic model that included low-risk (0 points), intermediate-risk (one or 2 points) and high-risk ($\geqslant$3 points) categories.

The new prognostic model applied to the training set (the Mayo Clinic cohort) displayed excellent discrimination between high-risk ($n = 155$; median survival = 8.3 years; HR, 11.1; 95% CI: 6.3–19.6), intermediate-risk ($n = 100$; median survival = 15 years; HR, 3.5; 95% CI: 1.9–6.2) and low-risk ($n = 82$; median survival = 26 years) patient groups and was subsequently validated in the entire study cohort ($n = 1545$; Figure 3). Supplementary Figure 3 illustrates the influence of karyotype information on survival data shown in Figure 3.

Leukemic transformation

A total of 50 (3%) cases of post-PV AML were documented and occurred at a median of 10.8 years (range 0.5–22.3) from diagnosis. Figure 4 illustrates the cumulative incidence of post-PV AML, with death as a competing risk: 2.3% at 10 years, 5.5% at 15 years and 7.9% at 20 years. For purposes of visual comparison, this cumulative incidence curve was overlaid with a separate curve representing the cumulative probability of

Table 3. Predictors of overall and leukemia-free survival among 1545 patients with PV

	N *evaluable*	*Univariate* P-*values*	*Age-adjusted* P-*values*	*Multivariable* P-*values*[a] *(HR; 95% CI)* N = *964*	*Multivariable* P-*values*[b] *(HR; 95% CI)* N = *383*
Overall survival					
Age	1545	<0.0001			
Age >median (that is, >61 years)	1545	<0.0001		<0.0001 (5.6; 4.1–7.8)	<0.0001 (7.4; 3.9–14.1)
Leukocyte count	1545	0.02	<0.0001	<0.0001	0.001
Leukocytosis (>10.5×10^9/l)	1545	<0.0001	<0.0001	<0.0001 (1.9; 1.4–2.6)	0.0001 (3.3; 1.8–6.1)
Thrombocytosis (⩾450×10^9/l)	1545	0.003	0.006	0.03 (0.7; 0.6–0.98)	0.09
Extreme thrombocytosis (⩾1000×10^9/l)	1545	0.04	0.48		
Arterial thrombosis (at or before diagnosis)	1545	0.0007	0.28		
Venous thrombosis (at or before diagnosis)	1545	0.008	0.0006	0.007 (1.9; 1.2–3.0)	0.0002 (3.9; 1.9–8.2)
Hypertension	1388	<0.0001	0.91		
Diabetes	1149	0.003	0.11		
Leukoerythroblastic blood smear	1056	0.002	0.0003	0.003 (2.1; 1.3–3.4)	0.36
Pruritus	1349	0.04	0.02	0.02 (0.7; 0.5–0.95)	0.004 (0.4; 0.2–0.8)
Abnormal karyotype	631	<0.0001	0.0005		0.0005 (3.1; 1.6–5.8)
Leukemia-free survival					
Age	1545	0.0002			
Age >median (that is, >61 years)	1545	0.005		0.007 (2.2; 1.3–4.1)	0.004 (6.3; 1.8–22)
Abnormal karyotype	631	0.03	0.03		0.03 (3.9; 1.2–13.1)
Leukocyte count ⩾15×10^9/l	1545	0.0003	0.0002	0.0004 (2.9; 1.6–5.2)	0.01 (3.9; 1.3–11.6)

Abbreviations: CI, confidence interval; HR, hazard ratio; PV, polycythemia vera. [a]Karyotype excluded as a covariate. [b]Karyotype included as a covariate.

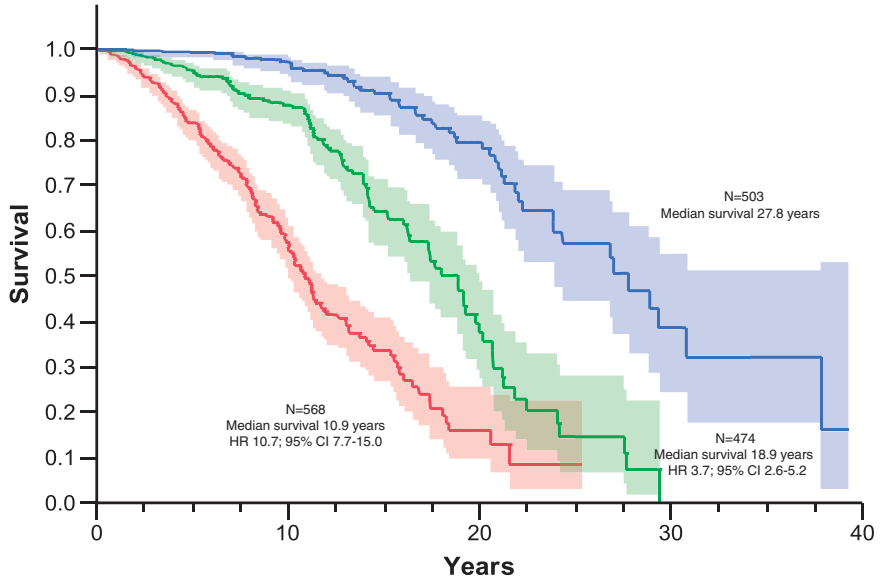

Figure 3. Risk-stratified survival in 1545 patients with PV. Adverse points are assigned to age ⩾67 years (5 points), age 57–66 years (2 points), leukocyte count ⩾15×10^9/l (1 point) and venous thrombosis (1 point): low-risk (0 points), intermediate-risk (1 or 2 points) and high-risk (⩾3 points).

transformation to AML in which patients who died were censored (that is, ignoring the competing risk of death). Both univariate and multivariable analyses of parameters at diagnosis identified older age (HR, 6.3; 95% CI: 1.8–22.0), abnormal karyotype (HR, 3.9; 95% CI: 1.2–13.1) and leukocyte count ⩾15×10^9/l (HR, 3.9; 95% CI: 1.3–11.6) as independent risk factors for leukemia-free survival (Table 3). We used the particular leukocyte cutoff level based on our previously reported observation regarding its association with leukemic transformation in PV.[25]

Univariate analysis revealed significant associations between leukemic transformation and (i) anytime exposure to P32 or chlorambucil alone ($P = 0.007$), (ii) anytime exposure to pipobroman alone ($P = 0.008$) and (iii) anytime exposure to pipobroman + hydroxyurea or busulfan ($= 0.03$) (Supplementary Figure 4). Multivariable analysis that included age as a covariate confirmed these associations; HR (95% CI) were 2.1 (1.1–3.9) for age, 4.8 (1.2–18.4) for P32/chlorambucil alone, 3.9 (1.2–12.3) for pipobroman alone and 4.1 (1.2–14.2) for pipobroman + hydroxyurea/busulfan. These significant associations were sustained when leukocyte count ⩾15×10^9/l was added to the multivariable model, but the small number of informative cases did not allow additional analysis with karyotype as a covariate. Similar results were obtained when analysis considered only the initial cytoreductive agents used (Figure 5). The association

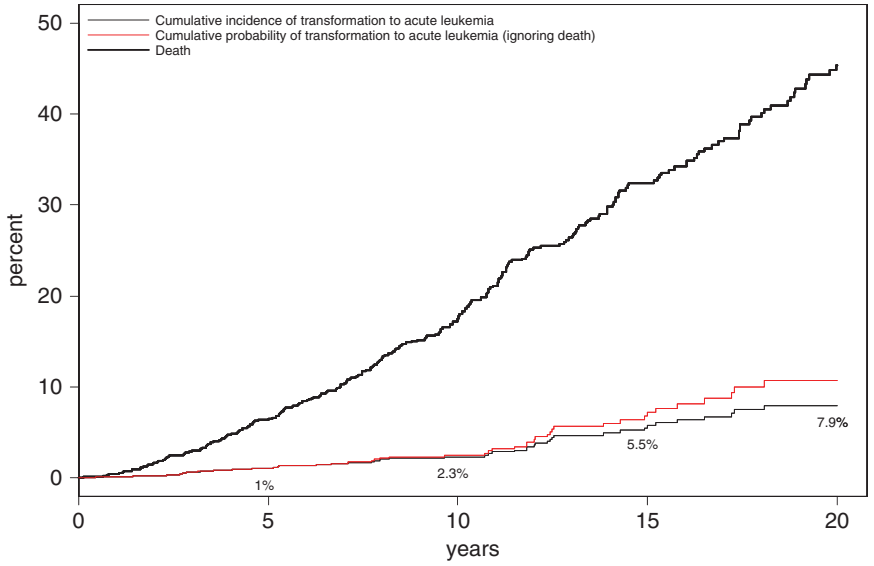

Figure 4. Cumulative incidence of leukemic transformation (LT) in 1545 patients with PV (thin black line), accounting for death as a competing risk (thick black line = cumulative incidence of death). The red line is the cumulative probability of LT ignoring death because of other causes.

between pipobroman exposure and leukemic transformation became apparent at a later time point compared with that seen with P32/chlorambucil (Figure 5 and Supplementary Figure 4). Exposure to single-agent busulfan ($P = 0.91$), single-agent hydroxyurea ($P = 0.23$) or both busulfan and hydroxyurea ($P = 0.44$) was not associated with leukemic transformation (Figure 5 and Supplementary Figure 4).

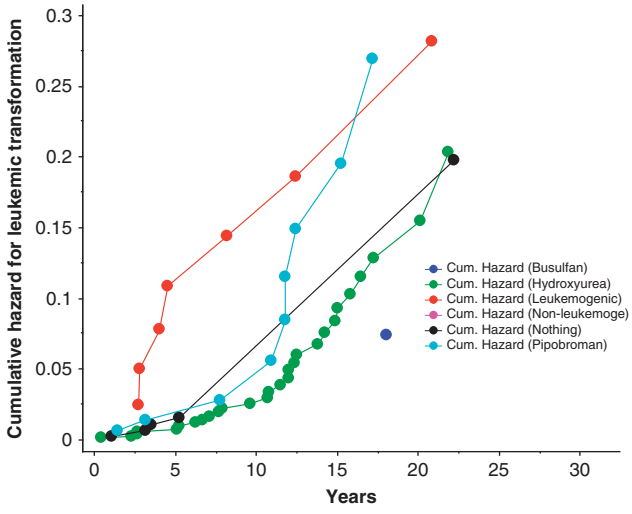

Figure 5. Cumulative incidence and time to event for leukemic transformation of PV among 1545 patients stratified by the first cytoreductive drugs they were exposed to. 'Leukemogenic' drugs include chlorambucil, P32 and other alkylating agents; 'Non-leukemogenic', for the purposes of Figure 5, signifies the use of interferon α or anagrelide, only; 'Nothing' refers to patients who were not exposed to any cytoreductive agent.

DISCUSSION

A number of novel observations and important confirmations are born out of this study. We show, for the first time, the prognostic relevance of karyotype, which is in line with the experience in most myeloid malignancies, including primary (PMF) and post-PV MF.[26,27] The reason why this was not evident in previous PV studies might be related to inadequate sample size and follow-up time.[28,29] Unlike the case with PMF,[26,30,31] the number of patients with cytogenetic abnormalities was too small to further query differential prognostic effect associated with specific cytogenetic abnormalities. Regardless, our findings signify the potential value of obtaining cytogenetic information in patients with PV and warrant additional studies to determine if the acquisition of an abnormal karyotype carries a similar significance. It also points out the need to examine the prognostic contribution of submicroscopic genetic changes, as has been the case in PMF.[32,33]

Another novel observation from this study was the association between pruritus and superior survival. This might simply reflect a lead-time bias stemming from symptom-driven earlier diagnosis. However, it is also possible that pruritus in PV is a marker of an underlying favorable biology, as suggested by its previously reported association with a lower incidence of arterial thrombosis.[34] Regardless, considering the negative effect on quality of life,[35] the particular observation is consoling for patients with pruritus. The only other disease variable that was associated with good prognosis was thrombocytosis, although its significance was less pronounced in the presence of cytogenetic information. It is to be recalled that extreme thrombocytosis in WHO-defined ET was associated with a lower incidence of arterial thrombosis.[11] Taken together, these observations should serve to lessen the pressure to take therapeutic action in patients with PV or ET, based simply on platelet count.

One of the core objectives of this study was to identify independent predictors of poor survival and develop a prognostic model; the IWG-MRT has previously accomplished this in WHO-defined ET.[10] To that effect, both karyotype-exclusive and karyotype-inclusive multivariable analyses were performed. In the first instance, older age, leukocytosis, venous thrombosis and the presence of a leukoerythroblastic blood smear were found to be significant. The first three remained significant when karyotype was added as a covariate. A prognostic model based on these three parameters and karyotype generated operational risk

categories with median survivals ranging from 5.8 to 29.4 years. Advanced age and leukocytosis are also important risk factors in ET[10,15] and PMF.[36–38] Regarding the former, the observations from this study favor a three-tiered rather than two-tiered age categorization. Leukocytosis is a common marker of aggressive disease biology in myeloid malignancies; however, prospective controlled studies are needed to determine if current management should be modified based on leukocyte count. The adverse survival impact of otherwise unspecified 'thrombosis' have previously been reported in both ET[10] and PV,[39] and based on the results from this study, it would be important to further clarify if the specific association involves arterial or venous thrombosis.

There is an ongoing controversy about the contribution of certain drugs to leukemic transformation in MPN. Controlled prospective studies have implicated treatment with chlorambucil,[7] P32[7] or pipobroman[24] as being leukemogenic in PV, whereas large retrospective and population-based studies have repeatedly shown the absence of such an association with hydroxyurea.[25,39,40] The results from this study are consistent with these assertions and, in addition, exonerate busulfan from such liability.[41] This is comforting news for physicians who, respectively, use hydroxyurea and busulfan as first- and second-line cytoreductive drugs of choice in PV. Our study also confirmed the association between leukemic transformation and older age, leukocyte count $\geqslant 15 \times 10^9$/l and also identified abnormal karyotype as an additional risk factor for the same.

Another important observation from this study involves the inherent flaw associated with life expectancy projections based on immature survival data. In other words, longevity in relatively indolent diseases such as PV and ET might be exaggerated in the absence of adequate number of uncensored events. In this study, 44% of the patients in the Mayo Clinic cohort ($n = 337$) were followed to death, whereas the corresponding value for the entire study cohort ($n = 1545$) was only 23%. We believe that this was the main underlying reason for the substantially different median survival projections for the two cohorts (14.1 vs 18.9 years, respectively) and the fact that survival comparisons with the age- and sex-matched control population showed a significant difference for the former ($P < 0.001$) but not the latter ($P = 0.1$).

In conclusion, this study contains information that is both practically useful and provides context for the design and interpretation of clinical trials in PV. Considering the retrospective study design, our findings must be interpreted with caution, but we are comforted by similar observations from a recent population-based study ($n = 327$) where age >70 years, leukocyte count $>13 \times 10^9$/l and thrombosis were identified as independent predictors of poor survival.[39] Based on our large multicenter study, we are inclined to advocate the inclusion of cytogenetic studies during the initial evaluation of patients with PV and underscore the relative safety of treatment with either hydroxyurea or busulfan. The comparatively mature survival data from the Mayo Clinic cohort allows us to conclude that life expectancy in both young and older patients with PV is significantly shorter than expected in the absence of disease. Whereas the age-independent detrimental effect of leukocytosis, venous thrombosis and abnormal karyotype is duly recognized, we are particularly intrigued by the biology behind the favorable survival effect of pruritus. Finally, considering our novel observation regarding the prognostic relevance of karyotype, it is important to find out if the same holds true for submicroscopic genetic changes, including mutations recently shown to affect outcome in PMF and other myeloid malignancies.[32,33,42–46]

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supplementary Information accompanies this paper on the Leukemia website (http://www.nature.com/leu)