Essential Thrombocythemia Beyond the First Decade: Life Expectancy, Long-term Complication Rates, and Prognostic Factors

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OBJECTIVE: To describe the long-term natural history of essential thrombocythemia (ET) in terms of life expectancy, risk of disease transformation into a more aggressive myeloid disorder, and prognostic factors for both survival and disease complications.

PATIENTS AND METHODS: The study population consisted of a consecutive cohort of patients seen at the Mayo Clinic in Rochester, Minn, in whom a diagnosis of ET was established before 1992, thus allowing a minimum of 10 years of potential follow-up. The conventional criteria-based diagnosis was confirmed by bone marrow biopsy in all instances.

RESULTS: A total of 322 patients were studied (median age, 54 years; median follow-up, 13.6 years). With a median survival time of 18.9 years, survival in the first decade of disease was similar to that of the control population (risk ratio, 0.72; 95% confidence interval, 0.50-0.99) but became significantly worse thereafter (risk ratio, 2.21; 95% confidence interval, 1.74-2.76). Multivariable analysis identified age at diagnosis of 60 years or older, leukocytosis, tobacco use, and diabetes mellitus as independent predictors of poor survival. A 2-variable model based on an age cutoff of 60 years and leukocyte count of 15 × 10^9/L resulted in 3 risk groups with significant difference in survival. In addition, age at diagnosis of 60 years or older, leukocytosis, and history of thrombosis were independent predictors of major thrombotic events. The risk of leukemic or any myeloid disease transformation was low in the first 10 years (1.4% and 9.1%, respectively) but increased substantially in the second (8.1% and 28.3%, respectively) and third (24.0% and 58.5%, respectively) decades of the disease.

CONCLUSION: Life expectancy in patients with ET is significantly worse than that of the control population. Leukocytosis is identified as a novel independent risk factor for both inferior survival and thrombotic events.

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AML = acute myelogenous leukemia; CI = confidence interval; CML = chronic myeloid leukemia; ET = essential thrombocythemia; MDS = myelodysplastic syndrome; MMM = myelofibrosis with myeloid metaplasia; MPD = myeloproliferative disorder; PCR = polymerase chain reaction; PV = polycythemia vera; RR = risk ratio; WHO = World Health Organization

Essential thrombocythemia (ET) is one of the classic BCR/ABL-negative myeloproliferative disorders (MPDs), and its diagnosis currently requires exclusion of both reactive thrombocytosis and clonal thrombocythemia that are associated with chronic myeloid leukemia (CML), myelofibrosis with myeloid metaplasia (MMM), polycythemia vera (PV), or myelodysplastic syndrome (MDS).1 Essential thrombocythemia is possibly the most prevalent MPD, with an estimated incidence between 0.77 and 2.53 per 100,000 population.2-4 Compared with the other MPDs, overrepresentation of the female sex and young age exists, both of which might contribute to its superior overall survival.4 The clinical course of the disease is relatively indolent and is characterized by an age- and thrombosis history–dependent predisposition to thrombotic events,5-7 as well as delayed occurrence of disease transformation into acute myelogenous leukemia (AML), MDS, MMM, or PV.7,9 Current therapy for ET has not been shown to affect either survival or risk of disease transformation.10 Previously reported studies on the natural history of ET are for the most part limited by both relatively short follow-up time and small sample size.2,3,9-12 As a result, their conclusions have been discordant in terms of both life expectancy and long-term complication rates. The current retrospective study was designed to address these shortcomings by including a large number of patients with at least a decade of potential follow-up after diagnosis. In this report, we thus describe the long-term natural history of ET in terms of life expectancy, vascular events, risk of disease transformation, and prognostic factors for both survival and disease complications.

PATIENTS AND METHODS

STUDY POPULATION

The current study was conducted within the guidelines and approval of the Mayo Foundation Institutional Review Board. The study cohort represents a consecutive group of patients with ET who fulfilled the World Health Organization (WHO) diagnostic criteria.1 To ensure mature data regarding survival and clonal evolution during the first and second decades of disease, we considered only those patients whose ET diagnosis was established at the Mayo Clinic in Rochester, Minn, during or before 1992, thus allowing for a minimum of more than 10 years of potential follow-up in all instances.

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Follow-up. Patients’ conditions were diagnosed from July 1956 to November 1992. Bone marrow histologic findings in all cases were reviewed by Mayo Clinic hematopathologists and subsequently rereviewed by one of the authors (R.F.M.). Moreover, the first (A.P.W.) and senior (A.T.) authors reviewed each case and individually confirmed the accuracy of all data entry. Patients in whom the possibility of either PV or cellular phase MMM was raised were excluded. All cases with high normal hemoglobin levels were rereviewed both retrospectively and prospectively to confirm stability of hemoglobin levels compared with baseline values. In addition, serum ferritin level was documented to be normal or elevated in all equivocal cases to rule out the possibility of PV masked by iron deficiency. Furthermore, most patients with hemoglobin levels that exceeded the WHO criteria for PV diagnosis had undergone red blood cell mass measurement for further clarification of the diagnosis.1

Patient characteristics and subsequent clinical events were determined both retrospectively (medical record review) and prospectively (questionnaire sent to both patients and their primary physicians). Finally, date and cause of death were confirmed by probing both the Social Security Index (until July 2005) and the National Death Index (until May 2004).

Definition of Major Thrombotic and Hemorrhagic Complications

Major arterial thrombotic complications were defined as angina pectoris, myocardial infarction, transient ischemic attacks, cerebrovascular accidents, and peripheral arterial occlusion; major venous thrombotic complications were defined as pulmonary embolism, deep vein thrombosis, and intra-abdominal visceral venous thrombosis (portal, hepatic, splenic, or mesenteric vein). Definition of major hemorrhagic complications was adapted from previously described methods and included a symptomatic bleeding episode that affected the retina, the central nervous system, or the retroperitoneum; any other site of bleeding that resulted in hemodynamic instability; the need for transfusion of 2 U or more of red blood cells; or a decrease in hemoglobin level by at least 2 g/dL from baseline.10,13

**JAK2 V617F Mutation Screening**

A subgroup of patients, in whom archived bone marrow or peripheral blood cells were available for JAK2 V617F mutation screening, were considered in our estimate of the prevalence of the JAK2 V617F mutation and its prognostic relevance. DNA for mutation screening was derived from either archived unsorted cells from the bone marrow or prospectively collected peripheral blood granulocytes according to previously published methods.14,15 Genomic DNA was extracted using a QIAamp Blood Mini Kit (Qiagen, Valencia, Calif) and amplified by polymerase chain reaction (PCR). Each 50-µL PCR contained approximately 25 ng of DNA template, 5 µL of 10× Roche Buffer (final concentration of magnesium chloride: 1.5mM), 1.5 U Taq polymerase (Roche, Indianapolis, Ind), 0.8mM dNTPs (Roche), and 20pM each of sense and antisense primers (5′-TGCTGAAAGTGGAGAAGTGCCAT-3′ and 5′-TCCTACAGTGGTTTTCAGTTC-3′, respectively).16 The PCR cycling parameters were as follows: 1 cycle of 94°C for 2 minutes; 35 cycles of 94°C for 30 seconds, 52°C for 40 seconds, and 72°C for 40 seconds; followed by 1 cycle of 72°C for 2 minutes. The PCR products were cleaned with a QIAquick PCR purification kit (Qiagen). Fluorescent dye chemistry sequencing was performed using the same primers used for amplification on an ABI PRISM 3700 DNA Analyzer (Applied Biosystems, Foster City, Calif). Sequencher 4.2 (Gene Codes Corporation, Ann Arbor, Mich) and GenBank Accession NM_004972 (JAK2 messenger RNA) and the corresponding region from the NC_000009 chromosome 9 contig were used for sequence analysis.16

**Statistical Analyses**

Unless indicated otherwise, continuous variables are summarized as median (range), and discrete, categorical variables are summarized as count (percentage). The main focus of the analysis was on long-term prognosis. Specific end points included death; thrombohemorrhagic complications; clonal evolution into AML, MDS, MMM, or PV; and the first of any of these myeloid transformations. Potential risk factors for major thrombosis at presentation were analyzed using χ2 tests. The Kaplan-Meier method was used to estimate the overall survival rate and the cumulative probability of thrombohemorrhagic complications and myeloid transformations. These rates are reported with 95% confidence intervals (CIs). Observed survival was compared with the expected survival of a population matched for age, sex, and year of initial observation. The expected population was based on life tables of the US total population (US Census data). The risk of death for the observed cohort relative to that of the expected population was calculated and presented with 95% CIs separately for the 3 decades after diagnosis. The effects of demographic, clinical, and laboratory features at diagnosis on long-term prognosis were evaluated using Cox proportional hazards models and summarized with risk ratios (RRs) and 95% CIs. The effect of major thrombosis at or after diagnosis was evaluated in the Cox models as a time-dependent covariate. Variables that were significant univariately were analyzed further in multivariable Cox models to determine which prognostic factors were independently significant. Variables were identified using stepwise selection and back-
ward elimination. Based on the results of the multivariable analysis, a risk-stratification model was constructed to predict survival. All statistical tests were 2-sided, and \( P < 0.05 \) was considered statistically significant. Analyses were conducted using SAS statistical software version 8.2 (SAS Institute Inc, Cary, NC) and Splus 6.2 (Insightful Corporation, Seattle, Wash).

**RESULTS**

**Baseline Characteristics**

The study cohort consisted of 322 patients with ET and included 218 females and 104 males (ratio of 2.1:1). The median age at diagnosis was 54 years (range, 12-88 years). The clinical and laboratory characteristics of these patients are listed in Table 1. Patients who presented with a platelet count less than 600 \( \times 10^9/L \) were documented to have an increased platelet count to more than 600 \( \times 10^9/L \) shortly after their diagnosis, thus fulfilling the WHO criteria. Similarly, the possibility of PV was carefully excluded in those patients with a high hemoglobin value, as elaborated earlier in the "Study Population" section. Among the subgroup of 117 patients tested for the presence of the JAK2V617F, 60 (51.3%) were found to carry the mutant allele (all were heterozygous and none were homozygous).

**Thrombotic and Hemorrhagic Complications**

Eighty-five study patients (26.4%) experienced a major thrombotic event as a presenting feature of ET, 34 (10.6%) presented with a high hemoglobin value, as elaborated earlier in the "Study Population" section. Among the subgroup of 117 patients tested for the presence of the JAK2V617F, 60 (51.3%) were found to carry the mutant allele (all were heterozygous and none were homozygous).

Therapy. Among the patients, 83 (25.8%) received at least 1 agent believed to carry a leukemogenic potential, including radioactive phosphorus 32, chlorambucil, and/or busulfan. The remaining 184 patients (57.1%) were treated with at least 1 agent believed to carry a leukemogenic potential, including radioactive phosphorus 32, chlorambucil, and/or busulfan.

**Therapy for ET**

A total of 267 patients with ET (82.9%) received cytoreductive therapy and 201 (62.4%) received aspirin therapy. Among the patients, 83 (25.8%) received at least 1 agent believed to carry a leukemogenic potential, including radioactive phosphorus 32, chlorambucil, and/or busulfan. The remaining 184 patients (57.1%) were treated with at least 1 agent believed to carry a leukemogenic potential, including radioactive phosphorus 32, chlorambucil, and/or busulfan.
For the entire patient population, the cumulative risks of transformation to leukemia, MMM, and first myeloid transformation were 1.4%, 3.8%, and 9.1% at 10 years, 8.1%, 19.9%, and 28.3% at 20 years, and 24.0%, 28.9%, and 58.5% at 30 years, respectively (Table 2 and Figure 1). Median time to AML transformation was 13.8 years, and median time to MMM was 12.4 years. Time to first myeloid transformation was defined as the period between the diagnosis of ET and first occurrence of transformation. The cumulative probability (Kaplan-Meier) of being free of transformation to either AML or any more aggressive myeloid disease for patients who received no cytoreduction (n=55), cytoreduction with agents that are not leukemogenic (n=184), and cytoreduction with agents that are believed to be leukemogenic (n=83) was not significantly different in the 3 groups (P=.24 and P=.95, respectively; log-rank test).

Abnormal clonal baseline cytogenetics did not correlate with AML or any myeloid disease transformation and were not prognostic with regard to survival.

**LIFE EXPECTANCY**

To date, 129 patients (40.1%) have died, leaving 193 (59.9%) alive, and the median survival for the entire patient population was 30 years. Median survival was significantly shorter for patients with higher-risk features at diagnosis, including older age, higher leukocyte counts, and history of arterial thrombosis (Table 3).

**TABLE 3. Risk Factors for Thrombotic Complications in Essential Thrombocythemia**

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Risk ratio (95% CI)</th>
<th>P value (univariate analysis†)</th>
<th>Risk ratio (95% CI)</th>
<th>P value (multivariable analysis‡)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥60 y at diagnosis</td>
<td>1.68 (1.21-2.35)</td>
<td>.002</td>
<td>1.51 (1.05-2.18)</td>
<td>.03</td>
</tr>
<tr>
<td>History of any major thrombosis</td>
<td>1.73 (1.07-2.81)</td>
<td>.03</td>
<td>NA</td>
<td>ND†</td>
</tr>
<tr>
<td>Arterial thrombosis</td>
<td>2.75 (1.58-4.80)</td>
<td>&lt;.001</td>
<td>2.30 (1.25-4.24)</td>
<td>.008</td>
</tr>
<tr>
<td>Venous thrombosis</td>
<td>1.02 (0.50-2.08)</td>
<td>.96</td>
<td>NA</td>
<td>ND§</td>
</tr>
<tr>
<td>Leukocytes ≥15×10⁹/L at diagnosis</td>
<td>1.82 (1.20-2.77)</td>
<td>.005</td>
<td>1.74 (1.15-2.66)</td>
<td>.01</td>
</tr>
<tr>
<td>JAK2 status (heterozygous vs normal)</td>
<td>1.57 (0.89-2.75)</td>
<td>.12</td>
<td>NA</td>
<td>ND§</td>
</tr>
<tr>
<td>Any cardiovascular risk factors</td>
<td>1.0 (0.68-1.45)</td>
<td>.99</td>
<td>NA</td>
<td>ND§</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>0.77 (0.55-1.09)</td>
<td>.14</td>
<td>NA</td>
<td>ND§</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.50 (1.08-2.09)</td>
<td>.02</td>
<td>NA</td>
<td>ND‡</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>1.09 (0.73-1.62)</td>
<td>.68</td>
<td>NA</td>
<td>ND§</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.71 (1.04-2.81)</td>
<td>.03</td>
<td>NA</td>
<td>ND‡</td>
</tr>
</tbody>
</table>

*CI = confidence interval; NA = not applicable; ND = not determined.
†Cox proportional hazards model used for all calculations.
‡Not significant in multivariable analysis, therefore not included in the final model.
§Not included as a potential covariate in multivariable analysis because not statistically significant univariately.
population was 18.9 years (Figure 2). Survival in the first decade of disease was similar to that of the age- and sex-matched control population (RR, 0.72; 95% CI, 0.50-0.99) but became significantly worse beyond the first decade of the disease (RR, 2.21 at 20 years; 95% CI, 1.74-2.76; and RR, 3.37 at 30 years; 95% CI, 1.84-5.65) (Figure 2).

In terms of overall survival, univariate analysis identified age at diagnosis of 60 years or older, leukocyte count of $15 \times 10^9/L$ or higher, history of arterial thrombosis, any major thrombosis at diagnosis, major thrombosis at or after diagnosis, and the cardiovascular risk factors of diabetes mellitus, tobacco use, and hypertension as predictors of decreased survival. By multivariable analysis, age at diagnosis of 60 years or older, leukocyte count of $15 \times 10^9/L$ or higher, tobacco use, and diabetes mellitus retained their significance as independent risk factors (Table 4). Initially, a risk stratification model that included all 4 variables was examined. We then constructed a simpler model based on age and leukocyte count. These variables were chosen based on their ease of identification, use, and clinical relevance. The discrimination provided by the simpler model was comparable to that of the more complex model. There-

![Figure 2. Overall survival in 322 patients with essential thrombocythemia.](image)

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Risk ratio (95% CI)</th>
<th>P value (univariate analysis)†</th>
<th>Risk ratio (95% CI)</th>
<th>P value (multivariable analysis)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age $\geq 60$ y at diagnosis</td>
<td>4.86 (3.31-7.14)</td>
<td>&lt;.001</td>
<td>4.94 (3.25-7.49)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Sex</td>
<td>1.39 (0.97-1.99)</td>
<td>.07</td>
<td>NA‡</td>
<td>ND§</td>
</tr>
<tr>
<td>History of arterial thrombosis</td>
<td>2.32 (1.24-4.35)</td>
<td>.008</td>
<td>NA‡</td>
<td>ND§</td>
</tr>
<tr>
<td>Any major thrombosis at diagnosis</td>
<td>1.85 (1.30-2.65)</td>
<td>.001</td>
<td>NA‡</td>
<td>ND§</td>
</tr>
<tr>
<td>Any major thrombosis at or after diagnosis</td>
<td>1.41 (1.02-1.94)</td>
<td>.04</td>
<td>NA‡</td>
<td>ND§</td>
</tr>
<tr>
<td>Leukocytes $\geq 15 \times 10^9/L$ at diagnosis</td>
<td>1.70 (1.12-2.66)</td>
<td>.01</td>
<td>1.70 (1.09-2.65)</td>
<td>.02</td>
</tr>
<tr>
<td>JAK2 status (heterozygous vs normal)</td>
<td>1.49 (0.74-3.01)</td>
<td>.26</td>
<td>NA‡</td>
<td>ND§</td>
</tr>
<tr>
<td>Any cardiovascular risk factors</td>
<td>1.50 (0.95-2.42)</td>
<td>.08</td>
<td>NA‡</td>
<td>ND§</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>1.60 (1.13-2.27)</td>
<td>.007</td>
<td>1.93 (1.32-2.82)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.08 (0.76-1.53)</td>
<td>.64</td>
<td>NA‡</td>
<td>ND§</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2.59 (1.57-4.28)</td>
<td>&lt;.001</td>
<td>3.57 (2.03-6.27)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*CI = confidence interval; NA = not applicable; ND = not determined.
†Cox proportional hazards model used for all calculations.
‡Results not available because multivariable analysis was not performed.
§Not included in multivariable model because not statistically significant univariately.
⁄⁄Past arterial thrombotic event was the strongest predictor univariately (not significant in multivariable analysis), therefore the other thrombosis variables were omitted.
fore, to be parsimonious and to provide for more simplicity of use, we chose the simpler model based on age and leukocyte count. This subgroup analysis according to age and leukocyte count at diagnosis allowed risk stratification into 3 groups: low risk was defined as age at diagnosis younger than 60 years and leukocyte count less than $15 \times 10^9$/L (n=144), intermediate risk was defined as age at diagnosis of 60 years or older or leukocyte count greater than or equal to $15 \times 10^9$/L (n=110), and high risk was defined as age at diagnosis of 60 years or older and leukocyte count greater than or equal to $15 \times 10^9$/L (n=25). These data could be independently corroborated or accurately verified in 279 patients. Median survival for the 3 risk groups was 25.3, 16.9, and 10.3 years, respectively. The 5-, 10-, and 20-year survival rates for each risk group were as follows: low-risk group, 100%, 94.6%, and 72.0%; intermediate-risk group—95.2% (95% CI, 91.1-99.4), 82.9% (95% CI, 75.8-90.7), and 29.0% (95% CI, 19.3-43.5); and high risk—87.7% (95% CI, 75.2-100.0), 52.6% (95% CI, 35.7-77.5), and 0%.

DISCUSSION

To our knowledge, the current study represents the largest and longest single-institution report of life expectancy in patients with ET. In this study of 322 patients, median survival for the entire patient population was 18.9 years and median follow-up was 13.6 years, with at least a decade of follow-up in roughly three quarters of all patients. We observed no difference in survival compared with age- and sex-matched controls in the first 10 years of disease. This finding is in keeping with other large cohort studies with median follow-up periods of 2.25 to 9.6 years.7-9,11 However, one retrospective study of patients younger than 55 years with ET found a 4-fold mortality risk compared with healthy controls.17 Similarly, in 2 epidemiological studies with shorter median follow-up time (median follow-up, 5.24 and 5.83 years, respectively), survival was significantly lower than expected compared with age- and sex-matched controls.2,3 In these 2 studies, the study population was older (median age, 67 and 72 years). Therefore, the discrepancy in the literature regarding survival of ET patients is probably a reflection of differences in the age distribution and follow-up periods of the study patients. The current study, with a relatively large cohort of patients and with a long follow-up time, clearly shows that life expectancy in ET patients significantly worsens after the first decade. These findings are consistent with the increasing proportion of cases with leukemic and fibrotic transformation that occur in the early to middle second decade of disease.7,8

Overall, few studies have contributed prognostic information in ET. In a retrospective analysis of 148 patients with ET, normal initial leukocyte count ($P<.001$), female sex ($P=.02$), and a lower rate of complications at diagnosis...
and during the entire observation period \( (P < .001) \) were associated with longer overall survival. However, by multivariable analysis, only the number of thrombohemorrhagic complications continued to have a significant impact on overall survival \( (P = .002) \). In another study of 435 patients with ET, male sex \( (P = .03) \) and a history of thrombosis \( (P = .01) \) were independent predictors of mortality. In our study, multivariable analysis identified tobacco use, diabetes mellitus, age of 60 years or older, and leukocyte count greater than or equal to \( 15 \times 10^9/L \) as independent predictors of decreased survival. Moreover, further risk stratification into 3 groups based on advanced age at diagnosis \( (\geq 60 \text{ years}) \) and leukocytosis \( (\text{leukocyte count} > 15 \times 10^9/L) \) was predictive of inferior survival when compared with individuals who had one or neither risk factor (median survivals, 10.3, 16.9, and 25.3 years, respectively).

The finding that the presence of cardiovascular risk factors and advanced age at diagnosis could influence survival is understandable. However, our study also found that leukocyte count was independently prognostic. Evidence is emerging for the potential role of leukocytes, and more specifically neutrophils, in the pathogenesis of thrombosis among the MPDs. Circulating markers of polymorphonuclear neutrophil granulocyte activation significantly correlated with increased levels of plasma markers of coagulation and endothelium activation in patients with PV and ET but not in healthy subjects. However, these findings in these particular reports were independent of leukocyte count. In another study, the percentage of platelet-leukocyte aggregates was increased in MPD patients compared with controls, and an even greater increase in platelet-leukocyte aggregates was observed in those patients who had experienced microvascular or thrombotic events. More recently, it has been observed that activated polymorphonuclear granulocytes in patients with ET contribute to the increased formation of these circulating platelet-leukocyte aggregates through the expression of surface adhesive molecules, independently from platelet activation. Taken together, these findings suggest a primary role for neutrophils in ET-associated thrombosis. This finding is further supported by the demonstrated antithrombotic effect of cytoreduction in ET. In this context, one would assume that the association between poor survival and leukocytosis, as was observed in the current study, might be related to excess death from thrombotic complications; however, the validity of this contention needs to be prospectively evaluated.

Approximately 25% of study patients experienced a major thrombotic event as a presenting feature of ET, and the cumulative probability of thrombotic complications was 31.8% at 5 years, in keeping with previously reported studies. Baseline parameters that were associated with increased thrombotic complications included age of 60 years or older at diagnosis, leukocyte count greater than or equal to \( 15 \times 10^9/L \), and history of arterial thrombosis, diabetes mellitus, and hypertension. Advanced age and thrombosis history as predisposing factors to additional thrombotic events have been well described previously. However, reports on the prothrombogenic effect of cardiovascular risk factors in ET, including tobacco use, hypertension, hyperlipidemia, and diabetes, have yielded variable results.

Of greater interest is the association of leukocytosis at diagnosis with thrombotic complications. As described herein, evidence is evolving of a thrombogenic effect of leukocytes and more specifically neutrophils in MPDs. In addition, a large body of literature exists, both in healthy patients and those with documented cardiovascular disease who do not have an MPD, indicating that leukocyte count has been found to be predictive of recurrent cardiovascular events and mortality. Although the pathogenesis for this is thought to be related to an underlying proinflammatory state with resultant endothelial surface and platelet activation, the prothrombotic effect of leukocytes remained independently significant after adjustment for traditional cardiovascular risk factors and other markers of inflammation (C-reactive protein and fibrinogen). One study found that the degree of leukocyte count elevation was a marker for increased risk of CVD, which was partially explained by tobacco abuse; however, in our study, both leukocyte count and tobacco abuse were independent prognostic factors. Therefore, the exact etiology of the association between leukocyte count and thrombosis remains unclear; however, cumulatively these data would suggest that leukocytes may be directly causal. If these findings are confirmed in subsequent studies, leukocyte count may become a further stratifying factor to identify higher-risk individuals with ET who may benefit from earlier initiation of cytoreduction.

Our study population experienced transformation to AML and MMM at a median time of 13.8 and 12.4 years, respectively, much in keeping with previously reported results. No independent predictors of transformation to AML were identified during our analysis. The overall risk of leukemic transformation remained low, with an incidence of 1.4% at 10 years, and 8.1% at 20 years. However, the risk of MMM and any myeloid transformation (AML, MDS, PV, or MMM) was higher, at 3.8% and 9.1% at 10 years and 19.9% and 28.3% at 20 years, respectively. There did not appear to be an increased risk of leukemia or any myeloid transformation with exposure to hydroxyurea, in support of other studies.

**CONCLUSION**

This large single-institution study allows us to gain insight regarding the natural history of ET beyond the first decade.
Our findings underscore the overall inferior survival of patients with ET compared with the control population and also provide critical information regarding disease complication rates. Such baseline information is important for the design of clinical trials and assessment of novel therapeutic agents.

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REFERENCES