Distinctive features of polycythaemia vera in New Zealand Polynesians

Merit Z Hanna, Maggie L Kalev-Zylinska, Sharon R Jackson, Gordon Royle, Hilary A Blacklock

ABSTRACT

AIM: The aim of this study was to examine a potential ethnic disparity in the phenotype of polycythaemia vera (PV) between New Zealand European and Polynesian patients.

METHOD: A retrospective review of medical records was conducted at Middlemore Hospital to identify adult patients with PV diagnosed between 1987 and 2007. Data extracted included diagnostic criteria, ethnicity, age, complications and survival.

RESULTS: Eighty-eight adult patients with PV were identified during 1987–2007, 49 (55.7%) were Europeans and 36 (40.9%) Polynesians. The most striking finding was that Polynesian patients presented almost 14 years younger than Europeans (mean age of 54 years versus [vs] 68, respectively; *P*<.001). The white cell and platelet counts were higher in Polynesians compared with Europeans (mean white cell count of $22x10^9$/L vs $13x10^9$/L; mean platelet count of $648x10^9$/L vs $512x10^9$/L, respectively; *P*<.05 for both). The rate of *JAK2 V617F* mutation in Polynesians was 96%, equivalent to other large cohorts of European patients. The rates of long-term complications were comparable between Polynesians and Europeans, but the predicted impact on life expectancy was more severe for Polynesians.

CONCLUSION: New Zealand Polynesian patients present with a distinctive PV phenotype. Their younger age at presentation suggests a different risk factor profile or a higher genetic susceptibility. We hope our observations initiate larger epidemiological and genetic studies to help elucidate the cause.

Polycythaemia vera (PV) is a chronic myeloproliferative neoplasm (MPN) that predominantly affects people over the age of 60 years.[1–5] Individuals presenting before the age of 50 years account for approximately 20%,[2] and before the age of 40 years for less than 10% of patients.[4,5] There is evidence to suggest that young patients present with a more aggressive PV phenotype, including more frequent vascular events and/or higher white cell and/or platelet counts.[6] In contrast, the long-term complications are similar to those in older patients. The risk of transformation to AML remains low and thrombotic events are comparable,[6–8] although some may be severe.[9] The overall life expectancy of young patients with PV is markedly shorter than that of the general population of the same age,[7] highlighting the need to identify mechanisms of disease development and age-adjusted therapies. Possible risk factors for MPN and PV include exposure to benzene,[10] smoking[11–13] and obesity,[14] but there is no evidence that these are more common in young patients.

In the 2013 Census, the New Zealand population consisted of 74% Europeans and 22.3% Polynesians, including 14.9% Māori and 7.4% Pacific Islanders.[15] Previous studies documented that New Zealand Polynesians have poorer health and a higher incidence of cancer overall;[16–18] increased rates of smoking, obesity and certain infections are thought to contribute.[18,19] There is also evidence that Māori have higher rates of acute leukaemia,[20] although varied data have been recorded.[21]

In French Polynesia, PV accounts for 3.8% of haematologic cancers.[22] In the US, Pacific Islanders have a higher incidence of PV than

non-Hispanic whites, suggesting inherent differences in disease susceptibility and/or different etiologies.[23] There are no published reports from New Zealand on differences seen in PV phenotype according to ethnicity, hence we compared clinico-pathologic features of PV between Polynesian and European patients managed in a New Zealand centre.

Methods

A retrospective review of medical records was conducted for the period 1987–2007 to identify consecutive patients with PV diagnosed at Middlemore Hospital, which serves a Polynesian-rich population. All study procedures were in accordance with the institutional ethics approvals. Diagnosis of PV was based on the diagnostic criteria applied at that time, including those issued by a PV study group until 2001,[24] World Health Organization (WHO) until 2005[25] and later, the algorithm incorporating the presence of the *Janus kinase 2 (JAK2) V617F* mutation.[26]

The following patient information was collected from the time of presentation: diagnostic criteria, full blood count, symptoms, ethnicity (self-reported), gender and age. Outcome data included arterial and venous thrombosis, major bleeding, progression to myelofibrosis (MF), acute myeloid leukaemia (AML) and death. The diagnoses of MF and AML were based on WHO definitions, including histopathologic confirmation of MF.[25] *JAK2 V617F* was tested using standard methods.[27]

Data are presented as mean ± standard deviation (SD), unless indicated otherwise. Statistical analysis was conducted using GraphPad Prism 5.0 software for Windows (San Diego, CA). Mean differences between groups were analysed using independent-samples *t*-test (two-sided), proportions employed Fisher's exact test. Median survival was estimated using a non-parametric Kaplan-Meier analysis with the log-rank test. *P* values less than .05 were considered statistically significant.

Results

Presenting features

This review identified 88 adult patients with PV diagnosed at Middlemore Hospital during 1987–2007; 49 (55.7%) were European, 36 (40.9%) Polynesian (Māori or Pacific Islanders), two (2.3%) Asians and one (1.1%) black African. Disease features displayed by New Zealand Polynesians were compared against all other patients combined, 94.2% of whom were European; the latter group was used as the European reference in this study.

The mean age at presentation for all patients was 63 years. Intriguingly, Polynesian patients presented approximately 10 years earlier, at the mean age of 54 versus (vs) 68 years for Europeans (*P*<.001; Table 1, Figure 1A).

Four patients were younger than 30 years at presentation, all were Polynesians; a further two Polynesians presented before the age of 40 years. Overall, 6 of 36 (17%) Polynesians were diagnosed before the age of 40 years, compared with only one European. Most Europeans were diagnosed over the age of 60 years (41/52, 79%), compared with 14/36 (39%) Polynesians (*P*<.05). The female:male ratio was similar for Polynesian (1.1:1) and European (1:1) patients.

The presenting white cell counts were higher in Polynesians, mean 22 x 10^9/L compared with 13x10^9/L in Europeans (*P*<.001). Similarly, mean platelet counts were higher in Polynesians, 648x10^9/L vs 512x10^9/L in Europeans (*P*=.018). In contrast, mean haemoglobin levels and splenomegaly rates were similar (Table 1).

Most patients in this study were diagnosed before the discovery of *JAK2 V617F* in MPN, hence had not been tested for this mutation at presentation. Retrospectively, 28 Polynesian patients were tested for *JAK2 V617F* and the mutation was detected in 27 (96%) cases. This frequency of *JAK2 V617F* is comparable to that reported in previous larger cohorts of predominantly European patients.[27–30]

Table 1: Clinical and laboratory features of patients with polycythaemia vera diagnosed at Middlemore Hospital during 1987–2007.

	Polynesians n=36	**Europeans[a] n=52**	***P* value**
Presenting features			
Age at presentation mean (SD) years	54 (17.2)	67.5 (12.7)	<.001[b]
Numbers of patients aged <40 years n (%)	6 (16.7 %)	1 (1.9 %)	.017[c]
Male / female (ratio)	17/19 (1.1:1)	26/26 (1:1)	.831[c]
Mean haemoglobin level (g/L) (SD)[d]	185.5 (23.1)	183.1 (16.5)	.566[b]
Mean white cell count (x10^9/L) (SD)	21.5 (17.0)	12.6 (5.3)	<.001[b]
Mean platelet count (x10^9/L) (SD)	647.8 (331.01)	511.8 (196.2)	.018[b]
Splenomegaly n (%)	15 (41.6%)	19 (36.5%)	.645[c]
Thrombotic events n (%)	4 (11.1%)	6 (11.5%)	>.999[c]
Follow-up events n (%)			
Patients with thromboembolic events	11 (30.6%)	19 (36.5%)	.650[c]
Total thromboembolic events	16	22	0.251[c]
arterial thrombotic events	13 (81.3%)	17 (77.3%)	>.999[c]
venous thrombotic events	3 (18.8%)	5 (22.7%)	>.999[c]
Major bleeding	0 (0%)	3 (5.8%)	.266[c]
Progression to myelofibrosis	3 (8.3%)	2 (3.8%)	.396[c]
Transformation to acute leukaemia	1 (2.8%)	2 (3.8%)	>.999[c]

[a] 94.2% Europeans.
[b] Independent-samples *t*-test.
[c] Fisher's exact test.
[d] Patients who had iron deficiency were excluded from this analysis.
Abbreviation: SD, standard deviation.

Complications and survival

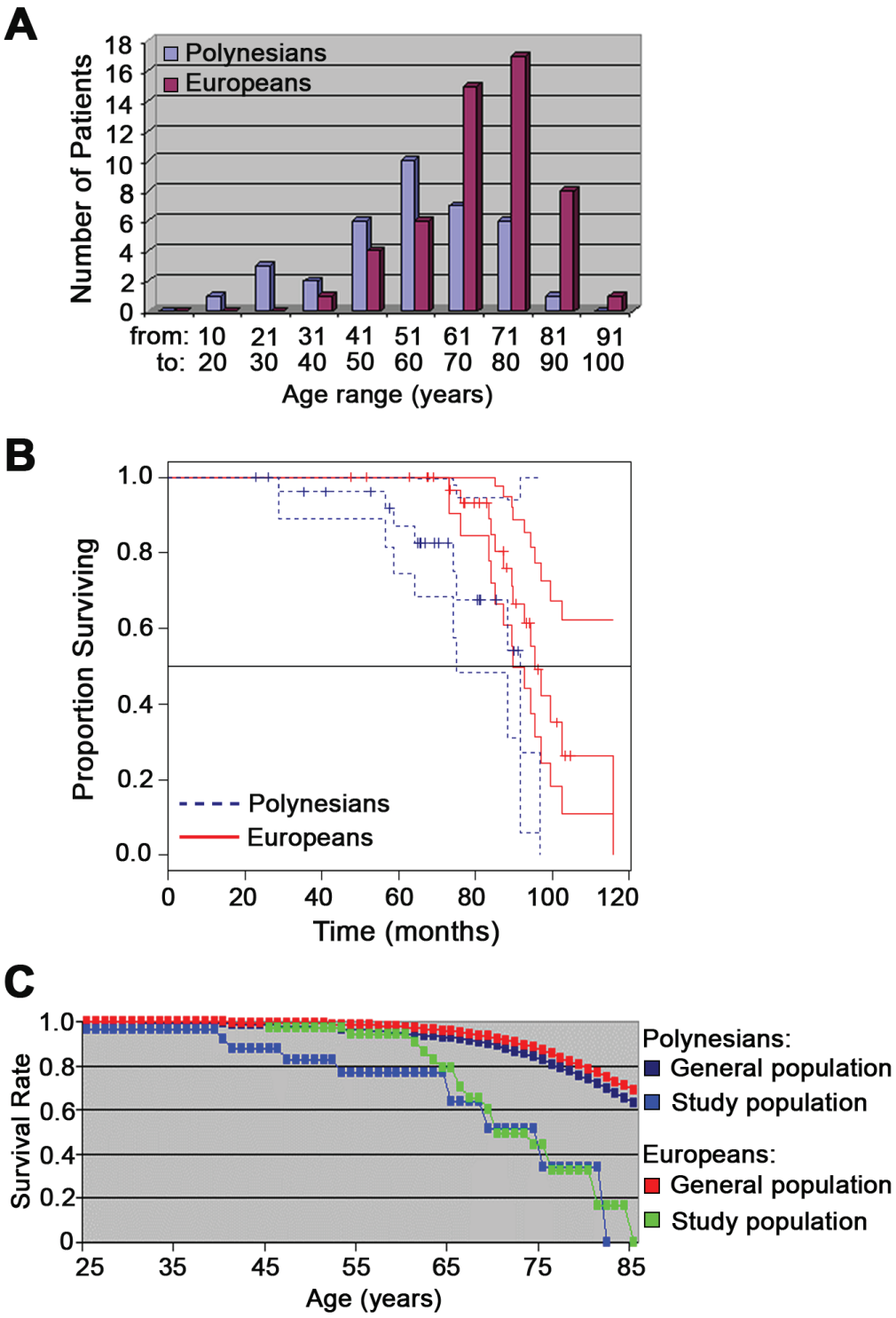
The rates of long-term complications were similar between Polynesians and Europeans (Table 1). Thromboembolic events (in particular arterial) were most common but occurred at similar frequencies in Polynesian and European patients.

Other complications, including major bleeding and transforming events were rare. MF occurred in five patients, two Europeans and three Māori. Two Māori who developed myeloid metaplasia were initially diagnosed before the age of 30 years. They were managed with venesections and hydroxyurea (HU) and progressed 7 and 13 years later respectively.

AML developed in three patients. Two older European men, aged 77 and 82 years, were treated with radioactive phosphorus-32 (^{32}P) and progressed to acute leukaemia eight and two years after the initial presentation. The third patient, a 38-year-old Māori woman who presented with PV at the age of 24, was treated with venesections and HU (but not ^{32}P) and transformed to AML 14 years later.

The median follow-up time in this study was eight years. There was no statistical difference in median survival between Polynesian and European patients (88 vs 109 months; *P*=.522; Figure 1B). Nevertheless, the reduction in expected life-expectancy compared with the general population was greater for Polynesians (*P*<.05; Figure 1C).

Figure 1: Age at diagnosis and outcomes of patients with polycythaemia vera diagnosed at Middlemore Hospital during 1987–2007.



(A) Bars indicate numbers of Polynesian (n=36) and European[a] (n=52) patients according to age.
(B) Survival curves of Polynesian (blue lines) and European[a] patients (red lines), together with their 95% confidence intervals.
(C) Survivor rates of patients compared to the New Zealand general population (derived from Abridged Life Table, Statistics New Zealand 1996–2000).

Discussion

This study demonstrates a racial disparity in the PV phenotype between New Zealand Polynesian and European patients. The most significant differences were seen at presentation, when Polynesian patients were younger and had higher white cell and platelet counts. Other disease characteristics were similar, including comparable rates of *JAK2 V617F* mutation, long-term complications and survival; however, the predicted impact on life expectancy was more severe in Polynesians.

While patients below the age of 40 years comprised 4–7% of previous large European PV cohorts,[2,5] we found that 17% of New Zealand Polynesian patients were younger than 40 years. Our study was not population-based but most patients in the region would have been captured, thus this percentage suggests a higher incidence of PV in young New Zealand Polynesians.

The higher white cell and platelet counts in Polynesian patients were unlikely to be due to a delay in presentation, as haemoglobin levels and splenomegaly rates were similar to those in Europeans. Instead, we speculate that higher counts in Polynesians may indicate a more proliferative PV phenotype, previously shown linked with a high allele burden of *JAK2 V617F*.[31,32] Unfortunately, we were unable to measure the *JAK2 V617F* allele burden nor cell proliferation in these patients, and future studies will need to follow.

Similar rates of thrombotic complications and disease progression in Polynesians and Europeans are in agreement with previous studies.[6–8] Nevertheless, this seems in conflict with the higher counts found in Polynesians. Leukocytosis is an established risk factor for thrombosis,[33,34] including in young patients.[35] The regular use of HU may have attenuated the long-term impact of leukocytosis in this study. Also, there is a known lower rate propensity to thrombosis in Polynesians.[36] Our centre followed treatment guidelines previously proposed to reduce the risk of vascular events in the younger age group.[6]

Leukocytosis is also an independent predictor of leukaemic transformation.[37] Other risk factors include advancing age,[5] smoking, obesity[38,39] and genotoxic drugs, including ^{32}P.[40] The use of ^{32}P may have contributed to the development of secondary AML in two older Europeans in our study but not in the young Māori individual. Despite the lack of statistical difference, we were concerned that the most severe transformations developed in three of four young Māori patients diagnosed before the age of 30 years. It is possible that as young patients age, transformation events may become more apparent.

Small numbers of events limit conclusions from this study; other limitations include a retrospective and a single-centre approach. Larger, multi-centre studies will be required to confirm our observations. The reason for an earlier onset of PV in Polynesians requires elucidation. Māori and Pacific Islanders smoke more tobacco and have higher rates of obesity,[18,19] which increases the risk of certain cancers, including PV.[11–14] Future studies should therefore record lifestyle and environmental risk factors in the PV cohorts. Modern molecular examination to determine germline and somatic variants/mutations and epigenetic changes will also be of importance, as such lesions influence susceptibility, phenotype and prognosis of PV.[41–43] Genetic studies in Māori can raise challenges. Our results indicate that such studies are important to undertake to advance the understanding of PV pathogenesis in general, and also to improve health outcomes of New Zealand patients.

In summary, we found an intriguing ethnic disparity in the PV phenotype in New Zealand Polynesians, which adds to the increasing recognition of ethnic differences in haematological malignancies.[44] Our results suggest that the pathway to PV development may differ in Polynesians, elucidation of which will require larger, racially inclusive epidemiological and genetic studies.

Competing interests:
Nil.

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