Spatial disparities in the reported incidence and survival of myeloproliferative neoplasms in Australia

Running title: Spatial disparities in myeloproliferative neoplasms

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Declarations

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Abstract

Myeloproliferative neoplasms (MPNs) are an uncommon group of blood cancers that, if untreated, result in an increased risk of haemorrhagic event or thrombosis. Unlike other cancer types, diagnosis of MPNs requires a combination of microscopic, clinical and genetic evidence, which provide unique challenges given the typical notification processes of cancer registries. This, and the relatively recent advances in diagnosis and revision of the World Health Organisation diagnostic criteria, may result in under-diagnosis or under-reporting of MPNs.

We used population-based cancer registry data from the Australian Cancer Database and modelled the incidence and survival of MPNs between 2007 and 2016 using generalised linear models and Bayesian spatial Leroux models.

Substantial evidence was found of spatial heterogeneity in the incidence of MPNs and significant differences in incidence and survival by state or territory. States with lower incidence tended to have poorer survival, suggesting that some less severe cases may not be diagnosed or notified to the registries in those states. Population rates of genetic testing and percentages of records diagnosed using bone marrow biopsies did not explain the differences in incidence by state and territory. It is important to determine the key drivers of these geographical patterns, including the need to standardise diagnosis and reporting of MPNs.

Key words

Myeloproliferative neoplasms; cancer; incidence; survival; diagnosis; registries; pathology; health geography; geographical disparities; spatial modelling; statistical modelling.
1 Introduction

Myeloproliferative neoplasms (MPNs) are a rare group of blood cancers caused by genetic mutations in hematopoietic stem cells and resulting in excess production of specific blood cells. MPNs, previously called myeloproliferative disorders, were first classified as neoplasms by the World Health Organisation (WHO) in 2008\(^1\),\(^2\) and the diagnostic criteria were subsequently revised in 2016.\(^3\),\(^4\) Under-reporting of these cancers may result from the recent reclassification and practical difficulties implementing the WHO diagnostic criteria.\(^5\),\(^6\)

MPNs are unique among cancers, in that diagnosis cannot be made simply by tissue histology, but require integration of clinical, haematological, genetic and biochemical findings.\(^6\) These requirements provide unique challenges to cancer registries compared to standard notification practices for other cancer types.

The term “classic MPNs” refers to a group of Philadelphia-negative MPNs consisting of polycythaemia vera (PV), essential thrombocytthaemia (ET), and primary myelofibrosis (PMF). Over 90% of MPN patients have a somatic mutation in one of three genes that activate JAK-STAT signalling: \textit{JAK2}, \textit{CALR} and \textit{MPL}.\(^7\) Almost all patients with PV have a \textit{JAK2} mutation, yet these mutations do not define a specific diagnosis since \textit{JAK2}, \textit{CALR} and \textit{MPL} mutations are found in, respectively, 50-60%, 20-30% and 5-10% of patients with ET and PMF.\(^8\),\(^9\) Furthermore, somatic mutations are found in the blood at increasing prevalence in healthy older individuals (clonal haematoipoiesis), further complicating the diagnostic pathway.\(^8\),\(^10\) Using highly sensitive testing, the common \textit{JAK2} V617F mutation was found in around 3% of adults in the general population aged over 40 years, although only a minority of these mutations would be detected in a routine diagnostic test with a typical detection limit of 1-5%.\(^10\)

MPNs have overlapping features, with a common predisposition to thrombosis, haemorrhage and leukaemic transformation, but vary in the incidence of these complications.\(^11\) Such events may precipitate diagnosis but frequently occur months or years prior to diagnosis.\(^12\)-\(^14\) The risk of a thrombotic event decreases rapidly following diagnosis and treatment.\(^13\),\(^15\) Therefore, delayed diagnosis or underdiagnosis pose an increased risk of morbidity or mortality.\(^12\),\(^14\),\(^15\)

Australia is a large land mass characterised by spatial diversity and low population density outside the capital cities. Population-based health systems that detect, diagnose and monitor the burden of cancer are administered by State or Territory governments. Since spatial mapping has a long history of informing the understanding of disease aetiology and burden,\(^16\) we used data from population-
based cancer registries to examine the spatial epidemiology of classic MPNs in Australia and quantify how the incidence and survival of the classic MPNs varied across the country.

2 Methods

2.1 Ethics

Ethical approval was granted by state or territory Data Custodians and some human research ethics committees. New South Wales, Victoria, Western Australia, South Australia, Tasmania approval was granted on the basis of approval from the NSW Population & Health Services Research Ethics Committee (EC00410, Reference: 2019/ETH01656). Approvals were obtained for each of the territories separately: the Australian Capital Territory Health Human Research Ethics Committee (EC00100, Reference: ETHLR.16.235) and the Human Research Ethics Committee for the Northern Territory Department of Health and from Menzies School of Health Research (EC00153, Ref: 2016-2720). QUT University Human Research Ethics Committee (EC00171, Reference: 1600000880) and the Griffith University Human Research Ethics Committee (EC00162, Reference:2018/280) provided approval for Queensland.

2.2 Data

All registered cases of classic MPN were obtained from the Australian Cancer Database using ICD-O-3 morphology codes 9950, 9960, 9961, 9962. Across Australia, medical facilities such as hospitals, nursing homes, pathology laboratories and death registrars are required to notify the relevant state/territory cancer registry of any instances of cancer. The state/territory cancer registry data are then combined within the Australian Cancer Database. Analyses of diagnoses used the data for persons aged 15 and over, while survival analyses included persons aged between 15 – 89 years old. For incidence results, 10 years of data were aggregated, spanning 2007 to 2016. For the survival analyses, the ‘at risk’ period was 2007 to 2016 and so included diagnoses between 2002 and 2016 to facilitate the calculation of five-year survival. Mortality status up to 31 December 2016 was obtained through routine annual linkage of cancer records with the Australian National Death Index. The data set included the residence of each patient at time of diagnosis, geocoded by Statistical Area 2, as defined in the Australian Bureau of Statistics’ (ABS) Geography Standard. Information about whether histological evidence was gathered for each diagnosis was also collected.

2.3 Statistical modelling

2.3.1 Summary statistics

Directly age standardised incidence rates were calculated using the Australian 2001 standard age distribution. Relative survival estimates were produced using the period approach. Poisson
generalised linear models were fitted to both the incidence and survival data to calculate age-adjusted, sex-specific rates for incidence and survival separately by three area-based factors: state or territory, remoteness and area-level socioeconomic index. Marginal incidence rates or survival were calculated for each category of the area-based factors by sex and sex-adjusted for all persons. The relative survival function was used as a link for the survival model.

The area-level quintiles of the Index for Relative Socioeconomic Advantage and Disadvantage, published by the ABS, were used as a measure of socioeconomic status. The remoteness areas were as defined by the ABS, with those living in remote and very remote areas grouped together. Since the remoteness variable did not improve model fit for either the incidence or survival data, it was omitted from subsequent modelling and reporting.

The percentages of MPN cases diagnosed based on histological evidence since 2012 were calculated. The probability of an MPN case having a histological basis for diagnosis was modelled using a logistic model, with variables selected via likelihood ratio tests from the following candidates: sex, age group, MPN subtype, year of diagnosis, whether the individual was diagnosed after 2011, state or territory, area-level socioeconomic quintile and remoteness category.

2.3.2 Spatial modelling
Bayesian spatial models were fitted to the incidence and survival data for males, females and persons at the Statistical Area 2 (‘small area’) level as per the Australian Cancer Atlas and as described in greater detail in the Supplementary material. The models estimate standardised incidence ratios (incidence) or excess hazard ratios (survival), smoothed over neighbouring areas, to distinguish real trends from noise, protect confidentiality and provide information on spatial patterns. The excess hazard ratios were also adjusted for the MPN subtype.

2.3.3 Test for spatial variation
Evidence of spatial variation between small areas was assessed using the Maximised Excess Events Test (MEET) by Tango, in which the modelled number of diagnoses or modelled number of excess deaths is compared with the expected counts of diagnoses or deaths.

3 Results
3.1 Incidence
3.1.1 Summary statistics
Between 2007 and 2016, an average of 958 diagnoses of classic MPNs were registered annually among persons aged between 15 and 89 years; 48% of these were females and 52% males. This
equates to age-standardised incidence rates of 4.9 (95% CI: 4.8-5.0) per 100 000 person-years for total persons, 4.4 (4.3-4.5) among females and 5.4 (5.3-5.6) among males. The age-standardised incidence rate ratio for males versus females was 1.24 (95% CI: 1.19-1.29).

Age-adjusted, sex-specific and total incidence rates by state and area-level socioeconomic index are presented in Figure 1. Note that these age-adjusted incidence rates are not comparable with the age-standardised rates above because different age weightings were used. Residential state was strongly associated with age- and sex-adjusted incidence rates (p < 0.0001). Age-adjusted incidence rates for Victoria and Queensland were higher than all other states and rates in Tasmania, Western Australia (WA) and the Australian Capital Territory (ACT) were lower than all other states and the Northern Territory (NT). The confidence intervals for the ACT and NT were broad because of the small populations in these territories. Sex-specific rates mirrored the pattern of the combined rates.

There was no evidence of a difference in the marginal incidence rates between area-level socioeconomic quintiles or remoteness categories. However, likelihood comparisons indicated that including area-level socioeconomic status improved model fit (p = 0.03) and so it was included in the generalised linear model for incidence, while remoteness category was not (p = 0.5). The results suggest that, while area-level socioeconomic status explained some of the variation in the data, the differences in the modelled estimates were negligible.

Age-standardised incidence rates for MPN subtypes varied by state or territory (Table 1) with patterns similar to those shown for all MPNs in Figure 1. Victoria and Queensland tended to have higher incidence rates and Tasmania and South Australia tended to have lower incidence rates for each subtype.

The percentage of MPNs that were diagnosed on the basis of histological evidence ranged from 79% in ACT to 34% in Victoria (Supplementary material Table S2). There was no evidence that the MPN incidence rates by state were associated with the percentage of records diagnosed based on histological evidence (correlation = -0.34, p = 0.4) and hence no indication that histological diagnosis accounted for the variation. With the exception of sex (p = 0.3) all the variables trialled explained some of the variation in the probability that a case had histological evidence (p < 0.0001 except remoteness where p = 0.003). There was also evidence of an interaction between MPN subtype and state (p < 0.0001), but no interaction between MPN subtype and remoteness category (p > 0.95). The modelled probability of having histological evidence varied by MPN subtype, state and area-level socioeconomic quintile, but not by remoteness category (Figure S6).
3.1.2 Spatial modelling

In the maps of smoothed standardised incidence ratios (SIRs) for classic MPNs, areas coloured creamy yellow have SIRs close to 1 and incidence rates similar to the Australian average, blue areas have low SIRs and incidence rates lower than the Australian average and orange areas have SIRs over 1 and higher than average incidence rates (Figure 2). There was strong evidence of spatial variation in SIRs for males, females and total persons according to the MEET statistical test (p < 0.001 for both sexes).

The model generated a probability distribution of potential values for the SIR of each area. The maps in Figure 2 show the median SIR (the most likely value), but the range of probable SIRs for each area is given by the credible intervals (CrIs). When the 80% CrIs for the SIRs are either entirely above one or entirely below one, this provides evidence that the incidence in that area is truly different from the Australian average. For persons, females and males, respectively, the models suggested that 26, 18 and 24% of geographic areas had incidence rates below the Australian average, and 19, 7 and 16% of geographic areas had incidence rates above the Australian average.

There were clear patterns in the distribution of the SIRs by state when the 80% CrIs for each small area were plotted in order of the magnitude of their median SIR (Figure 3). The majority of the small areas in Tasmania and WA had lower than average incidence rates. Some areas of Victoria, Queensland and NSW have SIRs greater than the national average and some areas of NSW have SIRs lower than the national average. Figure S1 in the Supplementary material describes Australian geography, including the states, the remoteness categories and the area-level socioeconomic percentile.

3.2 Survival

3.2.1 Summary statistics

Five-year relative survival for prevalent cases during 2007 to 2016 and aged 15 – 89 years old, was 78% (95% CI: 77-79) for all persons, 83% (81-84) among females and 74% (72-75) among males. Among the cohort of prevalent cases, there were annually on average 258 deaths among persons diagnosed less than 5 years previously, of which 171 deaths annually were in excess of that expected among the age- and sex-matched general population. Of these, 64 excess deaths were among females and 107 among males. The excess hazard ratio (EHR) for males versus females was 1.5 (95% CI: 1.3 – 1.6), calculated using relative survival and adjusting for age at diagnosis, MPN subtype and number of years since diagnosis.
Survival in Victoria and Queensland was higher than in NSW, WA and SA (Figure 4) after adjusting for age, sex, MPN subtype, risk year and area-level socioeconomic quintile. There was evidence that survival in the most affluent areas was higher than areas in the two most disadvantaged quintiles, although the difference may be small; persons in the most affluent areas had a survival of 82% (80-83) and persons in the most and second most disadvantaged groups had survival of 77% (75-78) and 75% (74, 77), respectively. Remoteness category did not improve model fit (p = 0.3) and so was not included in the model.

3.2.2 Spatial modelling
Maps of the results for the spatial survival models (Figure 6) show very little spatial variation in the small areas’ EHRs among males, females or both sexes combined, with excess mortality being close to the national average across the country. There was no evidence of heterogeneity in spatial EHRs for MPN for any sex, according to both the MEET statistical test (p = 0.4, 0.5 and 0.6 for persons, females and males, respectively) and the 80% CrIs (Supplementary material Figures S3 and S4).

4 Discussion
By describing the spatial differences in the incidence and survival of classic MPNs in Australia, this study highlighted the extent of geographical variation across the country. Both generalised linear regression and spatial modelling found marked variation in incidence rates of MPNs by state and territory. Incidence did not differ by remoteness or area-level disadvantage.

While the results of the spatial survival model suggested no variation in survival outcomes, the results of the generalised linear modelling, using broader geographical areas, provided some evidence that survival varied by state, most likely because of the increased statistical power in the generalised linear models. NSW, WA and SA had lower incidence as well as lower survival compared with Victoria and Queensland. This pattern is consistent with the hypothesis that some less severe cases remain undiagnosed or unreported in NSW, WA and SA, since this underrepresentation of less severe cases would reduce both the observed incidence rate and the observed survival. However, the lack of data on other clinical characteristics in the Australian Cancer Database precludes further examination in this study. It will be crucial in future studies to compare not only the incidence between jurisdictions, but also the clinical characteristics of MPNs diagnosed.

In Australia, cancer is a notifiable condition and so hospitals, pathology laboratories and other medical facilities are required by law to inform cancer registries of all suspected instances of cancer. However, most cancer types were defined prior to the establishment of the cancer registries in 1982. The relatively recent reclassification of MPNs as cancers and changes to the diagnostic criteria
may have impacted notification practices and subsequent enumeration of MPNs to the registries. Non-histological diagnosis of MPN may be a factor to account for the differences, especially for ET and PV; however, patterns between rates of having histological evidence, MPN subtype and state do not consistently explain the differences in incidence (Figure S6). Using data from the population-based cancer registries of each state and territory provides confidence that every case of MPN reported to the relevant cancer registry was included in the analysis. However, the results do not include any MPNs that either remain without a formal diagnosis or were not notified to the cancer registries.

Given that cancer registries in Australia are state- and territory-based, the differences in MPN incidence and survival according to these same jurisdictions, along with the paucity of clear differences by remoteness or area disadvantage, support the hypothesis that the state-specific differences are due to some inconsistency in diagnosis or registration practices. The WHO classification system requires histological proof to code an MPN and cancer registries in Australia adhere to this system to varying degrees. We found clear differences across the cancer registries in the percentages of cases diagnosed based on histological evidence, however these were not associated with the differences in MPN incidence. Given the complexities of diagnosing MPNs, not all patients have a bone marrow biopsy, and many patients are clinically diagnosed on the basis of blood cell counts and genetic tests.

Federal government (Medicare) funded genetic tests have been available since July 2011 for mutations in JAK2 and MPL. Additional tests for mutations in CALR and other MPN-associated genes may be funded privately or by state governments or individual hospitals, and those results are not captured here. Per capita rates of the Medicare-funded genetic tests by state between 1 January 2012 and 31 December 2016 (Supplementary material Table S1) suggest that while the low rates of genetic testing in WA, Tasmania and ACT are consistent with the low MPN incidence rates in these states, the extremely low genetic testing in NT is not consistent with its moderate incidence rates, nor is the low genetic testing rate in Victoria consistent with its relatively high MPN incidence rates. Rates of testing have increased in many jurisdictions since 2016 (Supplementary material Figure S5), when the WHO guidelines were updated and since the end of our study period, which was determined by the most recent available data on cancer diagnoses. Note that the rates from the Medicare data include persons under 15 years of age, while the other analyses do not.

The results potentially also reflect a true difference in incidence. This is difficult to ascertain, given the poorly understood aetiologies of MPNs and that they differ by type. For example, ET has been associated with exposure to benzene, body mass, lack of high intensity physical activity and
diabetes, PV has been associated with smoking, and both PV and PMF have been associated with farming and occupation in the rural sector.\(^{29}\) The lack of clear MPN incidence patterns by remoteness and socioeconomic disadvantage, by which some of the above risk factors are known to vary,\(^{29}\) suggests other drivers are behind the spatial difference. Persons in regional and remote areas are referred to haematologists in larger cities for diagnosis. The travel required may seem unnecessary to patients who do not feel unwell. However, there was no evidence that registered cases living in regional or remote areas were less likely to have histological evidence. While the geographical patterns for MPN had some similarities with those for leukaemia,\(^{27}\) the patterns were not consistently similar and the MPN patterns were much more distinctive. Regardless of the true cause, definitive evidence is lacking, and it is hoped that these results will provide further incentive to investigate reasons for the marked differences in incidence between the states and territories.

Disease mapping can be used to identify the aetiology of disease\(^ {16}\) or spatial disparities in incidence and outcomes, as demonstrated in this study. Previous studies have compared regional incidence rates of MPNs using meta-analysis\(^ {30,31}\) or calculated and mapped crude incidence rates for PV.\(^ {32}\) The findings of our study should motivate spatial analyses of MPNs internationally. The method of spatial smoothing, as used in this study allows reporting of geographical differences using small geographical areas while maintaining confidentiality and helps distinguish the underlying patterns from normal random variation in the data. A comprehensive guide to fitting spatial models for cancer data can be found online at the Australian Cancer Atlas.\(^ {33}\) Aetiological studies aimed at identifying environmental factors that predispose to MPN, and population-level outcome studies aimed at understanding the effectiveness of diagnosis and treatment can only be performed if the cancer registry data are complete and consistent.

5 Conclusions

This study found clear evidence of jurisdictional differences in MPN incidence, and some evidence of differences in survival. Understanding the reasons for these differences will require details on the clinical characteristics of notified cases to test for jurisdictional differences in severity, as well as detailed descriptions of how the diagnostic and notification processes, including genetic testing, vary by state and territory. Much of this information is currently not being collected on a population basis. By quantifying the extent of the differences in incidence and survival for MPN across Australia, the results of this study should stimulate efforts to collect and report these data using consistent methods. These efforts will require dedicated funding to develop and implement the best-practice processes. Until this is done, initiatives to reduce disparities in diagnosis and management practices
for MPNs will not be evidence-based, reducing the potential for these activities to reach best practice throughout the country.
Figure 1; Age-adjusted marginal incidence rates (/100 000 person-years) and 95% confidence intervals for classic myeloproliferative neoplasms by sex and state or area-level index of relative socioeconomic disadvantage quintiles. The states and territories include New South Wales (NSW), Western Australia (WA), South Australia (SA), Australian Capital Territory (ACT) and the Northern Territory (NT).
Figure 2: Maps of the standardised incidence ratios (SIRs) for classic myeloproliferative neoplasms by geographic area for all persons combined (centre), with maps of the state and territory capital cities for detail. Note that the map for Canberra includes the boundary between the Australian Capital Territory and New South Wales. An SIR with value 1 indicates incidence is equal to the Australian average.
Figure 3: The 80% credible intervals for the standardised incidence ratios (SIRs) for classic myeloproliferative neoplasms by sex and state, with a horizontal line indicating an SIR of 1 representing the Australian average. The states and territories include New South Wales (NSW), Western Australia (WA), South Australia (SA), Australian Capital Territory (ACT) and the Northern Territory (NT).
Figure 4: Age-adjusted, five-year relative survival and 95% confidence intervals for classic myeloproliferative neoplasms by sex and state or area-level index of relative socioeconomic disadvantage quintile. The states and territories include New South Wales (NSW), Western Australia (WA), South Australia (SA), Australian Capital Territory (ACT) and the Northern Territory (NT).
Figure 5: Maps of excess hazard ratios (EHRs) by geographic area for classic myeloproliferative neoplasms for all persons combined (centre), with maps of the state and territory capital cities for detail. Note that the map for Canberra includes the boundary between the Australian Capital Territory and New South Wales. An EHR with value 1 indicates survival is equal to the Australian average.
Tables

Table 1: Incidence rates per hundred thousand persons of MPN subtypes by state and 95% confidence intervals.

<table>
<thead>
<tr>
<th>State or territory</th>
<th>ET</th>
<th>PV</th>
<th>PMF</th>
<th>NOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSW</td>
<td>2.0 (1.9, 2.1)</td>
<td>1.1 (1.0, 1.2)</td>
<td>0.7 (0.6, 0.8)</td>
<td>0.7 (0.7, 0.8)</td>
</tr>
<tr>
<td>Victoria</td>
<td>1.9 (1.7, 2.0)</td>
<td>1.8 (1.6, 1.9)</td>
<td>1.2 (1.1, 1.3)</td>
<td>0.6 (0.6, 0.7)</td>
</tr>
<tr>
<td>Queensland</td>
<td>2.1 (2.0, 2.3)</td>
<td>1.7 (1.6, 1.9)</td>
<td>0.9 (0.8, 1.0)</td>
<td>1.3 (1.2, 1.4)</td>
</tr>
<tr>
<td>WA</td>
<td>1.7 (1.5, 1.9)</td>
<td>1.2 (1.1, 1.4)</td>
<td>0.9 (0.8, 1.1)</td>
<td>0.4 (0.3, 0.6)</td>
</tr>
<tr>
<td>SA</td>
<td>1.1 (1.0, 1.3)</td>
<td>1.0 (0.8, 1.1)</td>
<td>0.6 (0.5, 0.7)</td>
<td>0.7 (0.6, 0.9)</td>
</tr>
<tr>
<td>Tasmania</td>
<td>0.8 (0.6, 1.1)</td>
<td>0.5 (0.3, 0.8)</td>
<td>0.5 (0.3, 0.7)</td>
<td>0.6 (0.4, 0.8)</td>
</tr>
<tr>
<td>ACT</td>
<td>2.3 (1.5, 3.3)</td>
<td>1.0 (0.4, 2.1)</td>
<td>1.0 (0.4, 1.9)</td>
<td>0.7 (0.3, 1.3)</td>
</tr>
<tr>
<td>NT</td>
<td>1.7 (1.3, 2.3)</td>
<td>0.7 (0.5, 1.1)</td>
<td>0.7 (0.5, 1.1)</td>
<td>0.3 (0.1, 0.6)</td>
</tr>
<tr>
<td>Total</td>
<td>1.8 (1.8, 1.9)</td>
<td>1.4 (1.3, 1.4)</td>
<td>0.8 (0.8, 0.9)</td>
<td>0.8 (0.8, 0.8)</td>
</tr>
</tbody>
</table>

1. The states and territories are NSW: New South Wales, WA: Western Australia, SA: South Australia, ACT: Australian Capital Territory, NT: Northern Territory.
2. The subtypes are essential thrombocythaemia (ET, ICD-O-3 morphology code 9962), polycythaemia vera (PV, 9950), primary myelofibrosis (PMF, 9961) and MPN not otherwise specified (NOS, 9960).

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References


