The mortality outcomes and survival pattern of patients of Myeloproliferative Neoplasms in Malaysia

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Abstract

Background: The prognostication of myeloproliferative neoplasm (MPN) has always been challenging even in the advent of Janus kinase 2 (JAK2 V617F) molecular studies. The survival pattern of MPN in a developing country such as Malaysia is still undetermined.

Materials and Methods: This was a retrospective study using information from 774 patients from the National MPN Registry conducted from the year 2009 to 2015 in Malaysia. Patients with the diagnosis of essential thrombocythaemia (ET), polycythaemia vera (PV), primary myelofibrosis (PMF) and unclassified MPN (MPN-U) were included. Survival data were traced until December 2018.

Results: The cohort consisted of 42.0% ET, 41.0% PV, 8.9% PMF and 8.1% MPN-U, with 48.8% Malay, 39.1% Chinese, 7.1% Indian, 5.0% Others. The subtypes analysis revealed that male MPNs was more than female MPNs except in ET. The Chinese ethnicity was associated with the highest incidence of ET. The mortality rate was the highest in PMF followed by MPN-U then PV and ET ($p < 0.0001$). Survival analysis revealed that the overall survival differed significantly according to characteristics such as sex, sub-types, JAK2 V617F mutation, bone marrow fibrosis, presence of splenomegaly, diabetes mellitus, hypertension, and bleeding manifestation. Cox regression analysis identified age, haemoglobin level, sex, and subtype as a significant risk factor for mortality outcome.

Conclusion: Patients with ET had the slightly better OS while PMF had the worst OS. This is in conjunction with low haemoglobin, worsening bone marrow fibrosis, splenomegaly, diabetes mellitus, hypertension and bleeding. JAK2 V617F mutation was seemingly resulting in inferior overall survival especially in ET and PMF. The survival outcome of the MPN registry is instrumental for future policy development of effective healthcare in Malaysia.

Introduction

Myeloproliferative neoplasm (MPN) has been reclassified by the World Health Organization (WHO) in the past few years signifying a paradigm shift in the diagnosis of myeloid neoplasms which includes the subsets like polycythaemia vera (PV), essential thrombocythaemia (ET) and primary myelofibrosis (PMF). The reclassification is based on clinical characteristics, morphologies, immunophenotyping and genetic studies [1]. The distinction between PV, ET and PMF in terms of prognosis is essential as patients with ET have been shown to have a significantly better prognosis than those with PMF and PV, while patients with PMF have the worst survival outcome [1].

The role of Janus Kinase 2 (JAK2 V617F) mutation or its allele burden in prognostication in MPN remains controversial. One retrospective study of 152 patients in the United Kingdom revealed that 83 patients with positive JAK2 V617F mutation were associated with poorer overall survival (OS) [2]. However, another prospective study of 174 patients in Italy stated that the presence of JAK2 V617F mutation was associated with larger spleen size requiring splenectomy and disease progression, to leukaemia

Loading [MathJax]/jax/output/CommonHTML/jax.js]. Similarly, another study from the United States of America

demonstrated that JAK2 V617F had no prognostic significance in survival outcome [4]. Similar results are also found in another larger study [5]. There are a number of other adverse prognostic factors identified such as old age, marked anaemia, leukocytosis or leukopenia, abnormal karyotypes, presence of constitutional symptoms and presence of circulating blasts [5]. Various vascular complications, including arterial or venous thrombosis and bleeding, might also affect the survival outcomes. There are quite a number of prognostic models derived from mainly clinical and hematologic parameters [6]. The International Prognostic Score for Essential Thrombocythemia (IPSET) which predicts thrombosis based on the major cardiovascular risk factor and JAK2 V617F mutation predicts survival based on age ≥ 60 years or thrombosis history and presence of JAK2 V617F mutation [6, 7]. The PV prognostic model is derived from conventional thrombosis score (European Leukemia Net recommendations) which includes older age, leukocytosis, venous thrombosis, abnormal karyotype and JAK2 V617F allele burden $> 50\%$ as adverse risk factors to survival [6, 8].

PMF has three prognostic models, namely the International Prognostic Scoring System (IPSS), Dynamic International Prognostic Scoring System (DIPSS) and DIPSS-plus [5, 6]. All these are developed by the International Working Group for Myeloproliferative Neoplasm Research and Treatment (IWG-MRT). The DIPSS score encompasses age > 65 years (1 point), constitutional symptoms (1 point), hemoglobin (HB) < 10 g/dL (2 points), white blood cells (WBC) count $> 25 \times 10^9/L$ (1 point) and circulating blasts $\geq 1\%$ (1 point). The low risk (0 points) has median survival > 20 years; intermediate-1 risk (1 to 2 points) has a median survival of 14.2 years; intermediate-2 risk (3 to 4 points) has a median survival of 4 years, and high risk (5 to 6 points) has a median survival of only 1.5 years [6, 9]. The DIPSS-plus includes all DIPSS risk factors with additional factor included, for example, red cell transfusion-dependent (1 point), platelet (PLT) count $< 100 \times 10^9/L$ (1 point) and unfavourable karyotype (1 point). Low risk (0 point) had a median survival of 15 years; intermediate-1 risk (1 point) had a median survival of 6.6 years; intermediate-2 risks (2–3 points) had a median survival of 2.9 years and, high risk (4–6 points) had a median survival of 1.3 years [6, 10].

This research is the first study in Asian countries that reported the survival outcome of patients with MPN with the association to JAK2 V617F mutation, different patients' characteristics and demographics, based on the national registry for MPN. The MPN registry is valuable as it provides an insight into the outcome of MPN in our population in correlation with all the clinical, non-clinical and laboratory parameters.

Materials & Methods

The MPN registry

Malaysia provides accessible medical care for approximately 33 million people. The MPN registry was developed under the Malaysian Society of Haematology to understand the demographic and clinical characteristics of MPNs nationwide. The registry started from 2009 to 2015 and had successfully

country. The registry accepted both old and new cases with a confirmed diagnosis, resulting in a wide range for year of diagnosis from 1980 to 2015, with approximately 70% of MPN patients diagnosed between 2010 and 2014. The registry received its approval from the Medical Research & Ethics Committee in 2017 (registration number: NMRR-17-2250-37701).

The diagnosis of PV, ET and PMF were based on the Polycythemia Vera Study Group criteria. In accordance with the WHO classification 2016, we also included unclassified MPN (MPN-U) but removed hypereosinophilia syndrome (HES) from the analysis. We reported patient demographics such as gender, ethnicity, sub-types, and laboratory findings including degree of bone marrow (BM) fibrosis, presence of JAK2 V617F mutation, and presence of splenomegaly. We tabulated the age of diagnosis, mortality rate and mortality age according to patient demographics. Survival analysis was performed to estimate the 5-year and 15-year overall survival (OS) according to patient demographics and presence of diabetes, hypertension and bleeding episodes. Univariable and multivariable Cox regression model was performed to estimate the hazard ratio (HR) of abovementioned characteristics on the survival outcome. The assumption of proportionality for all categorical variables was assessed using plots of cumulative sums of Martingale residuals and Supremum test. Statistical analyses were performed using R version 3.6.1 at a significance level of 5% (2-sided) for all statistical tests.

Survival Outcome

Survival outcome of patients was traced and confirmed with the unique identification card (IC) number from the Malaysia National Registration Department up to the end of December 2018. All foreigners were excluded from the analysis as their survival outcome could not be traced without an IC number. The survival duration was calculated from the date of diagnosis until death or end of follow-up. The cumulative probability of OS was estimated using Kaplan-Meier method and difference in OS between subgroups was tested using the Log-rank test. Multiple comparisons were performed with adjusted significance level using the Tukey method.

Results

Table 1: See Supplementary File "Tables" for Table 1

The age of diagnosis, mortality rate differed significantly according to subtypes, as summarized in Table 1. As of December 2018, 201 deaths (26%) were recorded, with a mean mortality age of 54.8 ± 14.4 years. In overall, male MPNs was more than female MPNs. However, in the subtype ET, female significantly predominated in comparison to male. The ethnicity was mostly led by Malay followed by Chinese, Indian and Others. In the subtype ET, the Chinese had the most cases compared to other race ($p = 0.0097$). Table 2 demonstrated overall survival of patients with MPN according to characteristics and different subtypes. Male MPNs had a shorter OS in comparison to female MPNs ($p = 0.0069$). For MPN subtypes, the ET demonstrated the best OS of 76.4% in 10 years, followed by 75.6% in PV, 46.9% in MPN-U and 38.5% in PMF. Those with positive JAK2 V617F had demonstrated statistically significant inferior Loading [MathJax]/jax/output/CommonHTML/jax.js on in ET and PMF in 10 years ($p < 0.05$). Patients presented

with diabetes mellitus in PV, hypertension in ET and bleeding in ET were showing significant less favorable outcome compared to those without such manifestations.

Table 2: See Supplementary File "Tables" for Table 2

Different OS trends were observed among MPN patients with different characteristics, as illustrated (Fig. 1). Male MPN had an inferior OS compared to female ($p = 0.0201$). Patients with ET and PV had a better OS in comparison to MPN-U and PMF ($p < 0.0001$). Patients with JAK2 V617F mutation had a worse OS as compared to those without the mutation ($p = 0.0310$). Patients presented with splenomegaly did worse than those without splenomegaly ($p < 0.0001$). Survival outcome declined as the BM fibrosis grade increased from grade 0 to 4 ($p < 0.0001$). Patients with diabetes mellitus, hypertension and bleeding at presentation had worse OS than those without ($p < 0.05$), respectively.

The association of characteristics to survival outcome was estimated using a hazard ratio (HR), as summarized in Table 3. Simple Cox regression model identified all variables to be significant predictors for survival outcomes. For instance, a year increase in age was associated with a 6.3% increase in the risk of dying among MPN patients ($p < 0.0001$). In the multiple Cox regression model, we identified age, HB, sex, and sub-types as significant predictors for survival outcome (Fig. 2). Bone marrow fibrosis grade was excluded from the multiple regression model due to a large amount of missing data. Interestingly, the adjusted HR showed that male faced a higher mortality risk than female (HR = 1.492, $p = 0.216$). The HR increased from 1.388 in PV, 2.151 in PMF to 2.626 in MPN-U, as compared with ET.

Table 3: See Supplementary File "Tables" for Table 3

Discussion

The MPN registry was the largest collection specifically for patients with various sub-types of MPN in Malaysia. The mean mortality age of patients with MPN was 67.5 years, clearly shorter than the expected Malaysia life expectancy, ranged from 72–78 years. Patients who were diagnosed at an older age was associated with an unsatisfactory outcome. A similar result was also demonstrated in many studies. [11–13, 18]. The possible postulation for these findings is that elderly patients had likely more aggressive disease and with the presence of other co-morbidities, which resulted in a higher rate of hospitalization and treatment-related complications [11]. According to several myelodysplastic/myeloproliferative neoplasms studies in the United States, ageing is linked to the rising incidence of cancer as a result of immune senescence, autoimmunity, chronic inflammation and accumulating DNA damage [14–16].

We found similar gender distribution in our population with the rest of the world [14, 17]. The male MPN patients tend to do worse compared to female MPN patients. Female MPN patients tend to do better compared to their counterpart [11, 13]. The observed gender disparity possibly due to hormonal effect, occupational exposures, lifestyle factors [14, 19, 20].

The only peculiar thing that we discovered in our registry was Chinese ethnicity had a higher incidence of ET despite being a much smaller ethnic group compared to Malay. There is a similar finding to the previous paper of epidemiology of this MPN cohort in which Chinese seems to have a relatively higher incidence of death in MPN compared to Malay considering the racial distribution of 21.2% for Chinese and 61.8% for Malay in Malaysia.[41] Despite the statistical insignificance, geography and ethnicity are found to influence the survival in other countries [13]. Maynadie *et al.* revealed that the survival rates of 74% in Northern Europe in comparison to only 27% survival rates in Eastern Europe [21]. Another study from China also reported the Chinese MPN patients were significantly younger, had less splenomegaly or constitutional symptoms with significantly better survival when compared with the Caucasian MPN patients [22].

JAK2 V617F mutation was shown to have some influence on the survival outcome in our patient cohort. This is in contrast to the International Prognostic Scoring System (IPSS) of PMF in which the presence of JAK2 V617F did not influence the prognosis of PMF [23]. Nevertheless, several studies had demonstrated that there is an association between JAK2 V617F allelic burden with clinical phenotype and disease outcomes in PV patients [24, 25]. The suggestion of a possible link between the homozygous allele burden and older age, male gender, pruritus, splenomegaly, thrombosis and MF transformation [24]. Alvarez-Larrán *et al.* revealed that there was an increased risk of myelofibrotic transformation in association with high ($\geq 50\%$) or unstable JAK2 V617F burden during follow-up and a trend for a higher incidence of thrombosis than patients with allele burden $< 50\%$ [26]. Unfortunately, this information was not captured in our study.

Our study demonstrated that PMF had the worst OS in comparison to PV and ET. This is consistent with the findings from many studies [11, 13, 27, 28]. Low JAK2 V617F allele burden at diagnosis in patients with PMF is associated with shortened survival in PMF [28–30]. The inferior OS of PMF in our study can be possibly a result of leukaemic transformation and systemic infections which are documented in the Mayo Clinic study [29] and in the Italian study respectively [30].

The MPN-U was noted to have second-worst overall survival after the PMF. The MPN-U was associated with inferior survival of 12.4 months, compared to 16 months with MDS and 41.5 months with PMF ($p < 0.001$) in a study by DiNardo *et al.* [31]. This is further supported by Chaudhury *et al.* study stating that MDS/MPN-U is associated with poor outcomes in view of a variable disease course [32].

The bone marrow fibrosis grade 2 to grade 4 was associated with worse overall survival in our study. The accurate evaluation of bone marrow fibrosis has been highlighted to be a key point to predict prognosis in PMF [33]. Guglielmelli *et al.* showed that there was a correlation between the higher grades of fibrosis and survival despite the IPSS variables and mutational status [34]. The median survival was significantly reduced in patients with grade 2 and 3 fibrosis in comparison to grade 1 in a multivariate analysis [34, 35]. The bone marrow fibrosis of grade 2 and above is linked to a more advanced clinical presentation encompassing constitutional symptoms, cytopenias, larger splenomegaly, a higher IPSS risk category and more frequent adverse mutations (ASXL1 and EZH2) [35].

The patients presented with vasomotor symptoms such as headache, dizziness, tinnitus, syncope, tingling, visual changes, acrocyanosis or erythromelalgia were not significantly associated with adverse survival outcome in our study. Twenty-five per cent (25%) to 35% of patients were asymptomatic, and the thrombocytosis were incidental findings [36]. The presence of vasomotor symptoms resulted in patients seeking medical attention and treatment early, hence better OS. Whereas, bleeding episodes as an initial clinical presentation was seemingly linked to worse OS in our study. This was evidenced by the causes of mortality in which the bleeding events were the most frequent reason for death due to underlying disease.

Older age and the presence of diabetes mellitus were the risk factors found to have statistical significance for mortality in this study. According to Gangat *et al.* age, haemoglobin level, leukocyte count, smoking, diabetes mellitus, thrombosis, male sex and the absence of microvascular symptoms are independent predictors of inferior survival [37]. Advanced age, leukocytosis and thrombosis are the risk factors for survival in ET and PV. [38–40]

The ET patients seemingly had a similar OS in comparison to PV patients within the first ten years in which conventionally ET is believed to be doing much better compared to other subtypes. The reason maybe there was a possibility of “prefibrotic” MF mimicking ET in its presentation. This was probably missed as many patients did not undergo bone marrow biopsy. The revised 2016 WHO classification system categorized “prefibrotic” MF from “overtly fibrotic” PMF and it is prognostically relevant to differentiate between the two.[42] The presence of JAK2 V617F mutation was statistically significant for OS in ET and PMF in this study could possibly related to the “prefibrotic” MF.

The PMF had the worst overall survival in this study. The molecular landscape of the MF has evolved in recent years beyond the identification of driver mutations in JAK2, CALR and MPL resulting in the development of genetically based prognostic scoring systems (MIPPS70, MIPSS70 + version 2.0 and GIPPS).[43] GIPPS (Genetically inspired prognostic scoring system) is tabulated from mutations and karyotype which offers a more simplified prognostic tool while MIPSS70 + version 2.0 (Mutation and karyotype-enhanced international prognostic scoring system) is formed based on genetic and clinical risk factors.[42]

Based on the model assumption in proportionality and linearity, effective sample size and clinical significance, age, JAK2 V617F mutation, Ethnic groups, MPN sub-types, Jak 2 V617F, splenomegaly, BM fibrosis, bleeding episodes, hypertension, diabetes mellitus, smoking and obesity were included into the multivariable Cox PH model for assessment of variable predictability in patient’s survival outcome (Table 3). The multivariable model showed that patient’s age at diagnosis, Male, MPN subtypes, especially PMF and MPN-U, might independently predict the survival outcome of MPN patients.

There is a number of limitations in this study which includes loss of data, lack of treatment data and inability to determine the cause and effect. The MPN registry included prevalent cases instead of incident cases hence the long survivors would be overrepresented in the registry whereas those who passed away prior to year 2009 would not be included. However, this is the only registry for MPN patients in Malaysia

that can provide us with many informative findings which can be utilized to improve the management of MPN patients in the future.

Conclusion

The presence of JAK2 V617F mutation did show a negative impact on the overall survival of MPN patients in Malaysia especially in ET and PMF. Low haemoglobin, worsening bone marrow fibrosis with splenomegaly, diabetes mellitus, hypertension and bleeding were associated with reduced overall survival. Patients with ET was found to have slightly better OS, followed by PV while PMF had the worst OS. The MPN-U was associated with inferior outcome after PMF which should be researched further in the future. The survival outcome of these patients is instrumental for future policy development of effective healthcare system in Malaysia.

Declarations

Competing interests: The authors declare no competing interests in this research.

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Figures

Figure 1

Survival outcome of MPN patients with different characteristics.

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