RESEARCH ARTICLE

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Physician Perceptions of the Clinical, Economic and Humanistic Burden of Disease and Unmet Needs in Myelofibrosis: Preliminary Findings from the MPN Landmark Survey in Indonesia

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Abstract

Background/ Objective: Myelofibrosis (MF) is a severe form of Myeloproliferative Neoplasms (MPNs). It is a rare disease in Indonesia and is reportedly associated with symptoms resulting in poor quality-of-life, pre-mature mortality, disability, and loss of productivity. As the disease is rare, there are limited published information around MF, particularly in Indonesia. **Methods:** A cross-sectional survey was designed and administered between November and December 2021 among practicing Haematologists-Medical Oncologists who are experienced in treating patients with MF. The objectives of the survey were to assess physician's understanding of the overall diagnosis of MF, the disease burden, current treatment practices and remaining unmet needs. Outcomes were analysed descriptively. **Result:** The survey was completed by 30 respondents. The findings suggest that symptom burden is high and has a significant negative impact on quality-of-life. Treatment burden is also high which can result in high healthcare resource utilisation. Physicians expressed need for novel therapeutic options and improved access and coverage for such options. There is also a need to improve access and coverage for JAK V617F testing locally and local hospital infrastructures should be upgraded to ensure MF is accurately diagnosed. Patient may benefit from information on MPN, which may result in earlier presentation, diagnosis and treatment which can improve outcomes. **Conclusion:** The findings align with previous international research reporting that symptoms and treatment burden are high, and that novel therapeutic options are needed. Additional patient research might be required to better understand the patient experience of MF and how this can be improved.

Keywords: Myelofibrosis- quality-of life- disease burden- unmet needs

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Introduction

Myeloproliferative Neoplasms (MPNs) represent a group of clonal hematopoietic disorders or blood cancers which involve, in a chronic phase, an overproduction of hematopoietic cells originating from the myeloid line (Nangalia et al., 2017). Though incidence of disease is low, patients are associated with an increased risk in pre-mature mortality, disability, and a loss of productivity. In Indonesia, incidence and prevalence rates of hematopoietic neoplasms are 1.35 per 100,000 population and 8.48 per 100,000 population respectively (IHME 2019). However, there is evidence that suggests an increase in incidence of MPNs, especially among older adults over 65 years of age (Mulatsih et al., 2019).

A wide number of diseases are classified as MPNs. However, most refer to the classic Philadelphia chromosome negative MPNs which include polycythemia vera (PV), essential thrombocythemia (ET), and myelofibrosis (MF) (Fowlkes et al., 2018). These diseases are characterized by the activation of the JAK-STAT signaling pathway and a lack of the BC-ACL fusion mutation gene, indicative of Philadelphia chromosome positive MPN chronic myeloid leukemia. Among the classic MPNs, Janus kinase 2 (JAK2) carries the most frequent mutations, while calreticulin (CALR) and/or

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myeloproliferative leukemia (MPL) gene mutations have also been identified among ET and MF patients negative for the JAK2 mutation (Ciboddo et al., 2018).

Myelofibrosis is a severe form of MPN, in which excessive extracellular fibers accumulate in the bone marrow and impair its ability to produce regular blood cells. Patients are diagnosed with either primary MF, if a preceding myeloproliferative neoplasm is not present, or secondary MF, if bone marrow fibrosis is observed in patients who were first diagnosed with ET or PV (Irhamsyah et al., 2018).

In Indonesia, MF remains a rare disease. However, the disease can cause a host of symptoms and complications, with about 70% of diagnosed Indonesian patients reporting symptoms (Rezkitha et al., 2018). Symptoms reported included tightness, fatigue, night sweats, cachexia, fever, and bleeding. Other serious complications associated with the disease include splenomegaly, thrombocytosis, anemia, progression to acute leukemia, and clotting complications (Anggraini et al., 2016).

Along with an increasing trend of disease incidence and mortality, unmet needs associated with myelofibrosis treatment in Indonesia is evident. Geographical limitations in testing for JAK2 mutation represents a main diagnosis barrier and can be attributed to the lack of hospital equipment in specific regions (Irhamsyah et al., 2018; Anggraini et al., 2016). Additionally, difficulties in differentiating between ET, PV and MF subtypes exist due to overlapping phenotypes and similar cytogenic abnormalities. This is further exacerbated by the lack of specific diagnostic tests available in local care settings (Rezkitha et al., 2018; Saktini et al., 2015). In terms of MF treatment, autologous stem cell transplants (ASCT), the sole curative treatment for MF, poses a high risk of side effects for older patients and those with other health conditions. Hence, it may not be a viable treatment option for many patients (Irhamsyah et al., 2018).

Due to the rare nature of MF, there is limited published information assessing local epidemiology, clinical practice, disease burden, treatment guidelines, overall diagnosis, and unmet needs of MF in the Indonesian context. Hence, in this study we aimed to assess physician's understanding of the overall diagnosis of MPN, in particular MF, and to understand the clinical, economic, and humanistic burden of disease. Additionally, we aimed to determine how physicians currently treat MF, and explore the unmet needs associated with MF in Indonesia.

Materials and Methods

Questionnaire Design

A questionnaire was developed to assess the objectives described above. A multi-phase approach was used to develop the questionnaire to ensure that the objectives of the study were met. Firstly, a steering committee of 3 Haematologists-Medical Oncologists Key Opinion Leaders (KOLs) with in-depth knowledge of the MPN landscape in Indonesia were recruited. Focus group discussions with the KOLs were conducted and the questionnaire were developed based on inputs obtained during the focus group. The questionnaire was then disseminated to the KOLs to obtain feedback and comments and iterative changes were then made to the questionnaire and the final version was approved by all KOLs. Pilot surveys were also conducted in the initial phase to test the questionnaire and the feedback obtained was used to finalize the questionnaire.

The final questionnaire was refined based on the pilots and broadly contain 4 sections. The first section focused on physician demographics and caseload and the second section assessed patient disease burden, which include the clinical, economic, and humanistic burden of disease. The third section evaluated patient management and treatment decisions, and the last section investigated the physician perceptions of the challenges and unmet needs of treating MF. The final questionnaire administered is provided in the Appendix.

Questionnaire Administration

The quantitative questionnaire was administered through an online platform from November to December 2021. Qualified Haematologists-Medical Oncologists were recruited to participate and remained anonymous. Informed consent was obtained prior to the questionnaire administration. Ethics approval was not required as this was an anonymous survey, and no identifiable information, patient's data, nor personal information were obtained. Key inclusion criteria for participation included having seen MF patients in the last 24 months and spending more than half of their time in clinical patient care. A mix of participants from different cities, public and private settings were recruited to ensure wide representation and optimises external validity of the study.

Statistical Analysis

As this study is cross-sectional in nature, descriptive statistics were used in all analyses. No formal hypothesis testing was conducted. The reported statistics depended on the type of variable described. For categorical variables, percentages of responses are reported.

Results

Around 100 Haematologists-Medical Oncologists were screened for inclusion in the survey. Of the screened respondents, 30 met the inclusion criteria and were recruited into the study. Participants' demographics are summarized in Table 1. Physicians spent a significant amount of their time (42.8%) in the university/teaching hospitals and in private hospitals (50.5%), and most have appointments in large hospitals (more than 251 beds in university/teaching hospitals and more than 100 beds in private hospitals).

Physician's Caseload

Physicians reported that 65% of all their patients are classified as hematology cases, of which 48% are in-patient cases and 52% are out-patient cases. The majority of MPN patients are referred to them from internal medicine and primary care for specialist care, and only around 15% of patients present directly to them without a referral. Half (50%) of the physicians surveyed felt that discussion with

Table 1. Demographics of Haematologists-Medical Oncologists Interviewed (Participants)

Characteristic	Participants (n=30)
MF patient under care in past 24 months, mean (SD)	5.3 (4.2)
ET patient under care in past 24 months, mean (SD)	18.3 (12.5)
PV patient under care in past 24 months, mean (SD)	27.8 (24.9)
Percentage time spent in university/teaching hospital, mean (SD)	42.8 (30.6)
Percentage time spent in private hospital, mean (SD)	50.5 (27.4)
Number beds in main hospital: University/teaching hospital, n (%)	
No appointment in teaching hospital	8 (26.7)
≤500	12 (39.9)
>500	10 (33.3)
Number beds in main hospital: Private hospital, n (%)	
No appointment in private hospital	2 (6.7)
≤500	25 (83.4)
>500	3 (10.0)
Practice Area, n (%)	
Jakarta	13 (43.3)
Bandung	7 (23.3)
Surabaya	5 (16.7)
Semarang	3 (10.0)
Medan	2 (6.7)

other specialists before making a treatment decision for MPN patient was extremely important, while the other half felt that it was only somewhat important

Diagnostic challenges of MPN

Physicians surveyed were asked to describe some of the diagnostic challenges of MPN. 87% of them regard JAK2 V617F mutation testing to be extremely important for diagnosing MPN. However, they estimate that only 64% of symptomatic patients undergo JAK2 V617F mutation testing. When asked to rank the possible reasons behind the discordant, physicians indicated cost and lack of coverage as the most common reasons for patients not undergoing JAK2 V617F mutation testing (45% ranked as top reason), followed by patient request (32% ranked as top reason), a lack of hospital infrastructure (18% ranked as top reason), and difficulty of the procedure (8% ranked as top reason).

Similarly, 63% of physicians surveyed regarded bone marrow biopsy to be extremely important for diagnosing MPN but estimate that only 58% of symptomatic patients undergo bone marrow biopsy. When asked to rank the possible reasons behind the discordant, physicians indicated that patient request is the most common reason for patients not undergoing bone marrow biopsy (57% ranked as top reason), followed by cost and lack of coverage (27% ranked as top reason), and lack of hospital infrastructure (10% ranked as top reason).

MF Disease Burden

Physicians surveyed indicated that the disease burden for MF is high. 23% of physicians perceived that MF is the most burdensome of all the conditions they treat, and the remaining 77% perceived it to be somewhat burdensome. They also reported that 90% of MF patients are symptomatic at first visit and 74% remain symptomatic even after treatment.

Table 2. Physician Perception of MF Symptom Impact on Daily Activities

State of MF	Perception of MF symptom impact (% Hematologist-Medical Oncologists)		
	No impact (B2B)	Moderate Impact (M3B)	High impact (T2B)
Newly diagnosed	17%	40%	43%
Disease under control	24%	38%	38%

As shown in Table 2, 43% of physicians reported that MF has a high impact on daily life at diagnosis and 38% of physicians reported that MF continue to have a high impact on daily life even when the disease is under control. Abdominal pain (34% ranked as top symptom), fatigue (28% ranked as top symptom), dizziness (14% ranked as top symptom), headaches (10% ranked as top symptom) and early satiety (10% ranked as top symptom) are the most common symptoms reported by MF patients, and dizziness (92%), headaches (86%), fatigue (83%) and abdominal pain (79%) are reported to have a high negative impact on MF patient's quality of life.

The majority of physicians surveyed strongly agree that financial well-being (including concerns about cost of their care (67%), and inability to pay for their care (60%)) and physical well-being (pain (57%), as well as nausea (53%)) are top concerns for MF patients. Comparatively, social, and functional well-being are of lesser concerns. Most physicians agree that MF may progress to a more serious condition (90%), and that drug reimbursement plays a role in treatment choices (80%). Physicians reported that symptoms of MF reduce quality of life (70%), and MF patients may have an increased risk of cardiovascular diseases (70%). However, only 43% of physicians surveyed strongly agreed that MF is a rare blood cancer.

Shared Decision Making

Physicians surveyed were also asked about the treatment decision process among MPN patients. It was noted that only 37% of physicians perceived that MPN patients want to be highly involved in their treatment decisions while the remaining 63% perceived MPN patients only wanting to be moderately involved.

As shown on Table 3, physicians perceived that a majority of MPN patients (57%) sometimes disagree with treatment recommendations, and it is chiefly due to financial concerns (100%) and side effects of treatments (78%). In terms of patient and physician alignment on treatment goals, 34% of physicians perceived MPN patients to understand their treatment goals well, while the remaining 66% perceived MPN patients to understand their treatment goals only somewhat. However, most physicians (62%) felt that their MPN patients agreed with them on the treatment goals.

Table 3. Patient Disagreement with Treatment Decision

a. Proportion of patients that disagree with primary treatment recommendation

	Proportion of patients that disagree with primary treatment recommendation		
	Often	Sometimes	Never
% MPN patients	3%	57%	40%

b. Reasons why patients do not agree with recommended treatment decisions

	Reasons why patients do not agree with recommended treatment decisions (% MPN patients)
Financial concerns	100%
Concerns about SEs	78%
Impaired decision making	50%
Different treatment goal	44%
Frequency of hospital visit	33%
Lack of caregiver support	33%
Patients are misinformed	33%

MF Treatment

MF treatment decisions were also assessed in the survey. To assess for the progression of MF, the top 5 assessments used by physicians are change in haemoglobin (83%), change in platelets (83%), change in white blood cell (77%), change in spleen size (70%) and increasing weight loss (67%). When asked about MF symptoms that treatment is most likely recommended for, anaemia, splenomegaly and fever are ranked among the top 3, with 87% of physicians ranking anaemia as the top symptom they will recommend a drug treatment for. A range of treatments are prescribed by physicians for MF as described in Table 4, and a majority (77%) have prescribed transfusions and aspirin (53%). Physicians also indicated that the MF treatment burden is high, and patients require multiple therapies. Among the multiple therapies prescribed, the most common treatments include psychological therapy (55%), hydroxyurea (54%), transfusions (53%), or aspirin (51%) as highlighted on Figure 3. When asked to rank the top treatment goal, physicians ranked symptom improvement as the top treatment goal (53% ranked as top goal), followed by anaemia treatment (20% ranked as top goal), and better quality of life (13% ranked as top goal). Reduction in spleen size and reduction in frequency of blood transfusion are less important treatment goals according to physicians. Drug therapies may also evolve during the treatment course and most physicians reported that disease progression (83%), cytopenia (70%), side effects (70%), lack of efficacy (67%) and change of symptoms (60%) are the main reasons to change therapeutic strategy for MF patients.

MF Unmet Needs

There are several challenges and unmet needs in the treatment of MPN in Indonesia. As shown in Table 5, the majority of the physicians agree that MPNs are rare (57%) and difficult to diagnose (67%) and treat (53%). Patients often present late (60%), and diagnostic test access and coverage is low (53%). When asked to rank their top unmet needs, physicians felt that the ability to accurately diagnose (33% ranked as top), the lack of effective therapy (20% ranked as top) and the ability to diagnose MF early (13% ranked as top) are the top 3 unmet needs for MF (Figure 1). Consequently, they felt that improved diagnostic tools with greater specificity (40% ranked as top) and more effective drugs or therapies (27% ranked as top) are top solutions to overcome the unmet needs in MF patients.

Table 4. Treatments Currently Prescribed to MF Patients

	Treatments currently prescribed to MF patients (Average % of patients currently on treatment)
Psychological therapy	55%
Hydroxyurea	54%
Transfusion	53%
Aspirin	51%
Ruxolitinib	35%
Radiation therapy	32%
Bone marrow transplant or stem cell transplant	30%
Anticoagulants/ blood thinners	28%
Corticosteroids	28%
Thalidomide	24%
Removal of spleen	24%
Antihistamine	23%
Anabolic steroids	23%
Androgens	22%
Lenalidomide	21%
Epoetin alfa injection	21%
No treatment/ Watch and wait	20%
Iron preparations	17%
Antidepressants	17%

Table 5. Obstacles Faced by Physicians to Treating MPNs

	Treatments currently prescribed to MF patients (% Hematologist-Medical Oncologist)
Difficult to diagnose	67%
MPN patients present late	60%
MPN patients are rare	57%
Diagnostic test access/ coverage is limited	53%
Difficult to treat	53%
Treatment access/ coverage is low	43%
MPN patient prognosis is poor	13%
MPN patients often don't require treatment	13%

Discussion

This preliminary study on MF is the first survey to evaluate physician understanding of MF and explore unmet needs associated with MF in Indonesia. The study findings

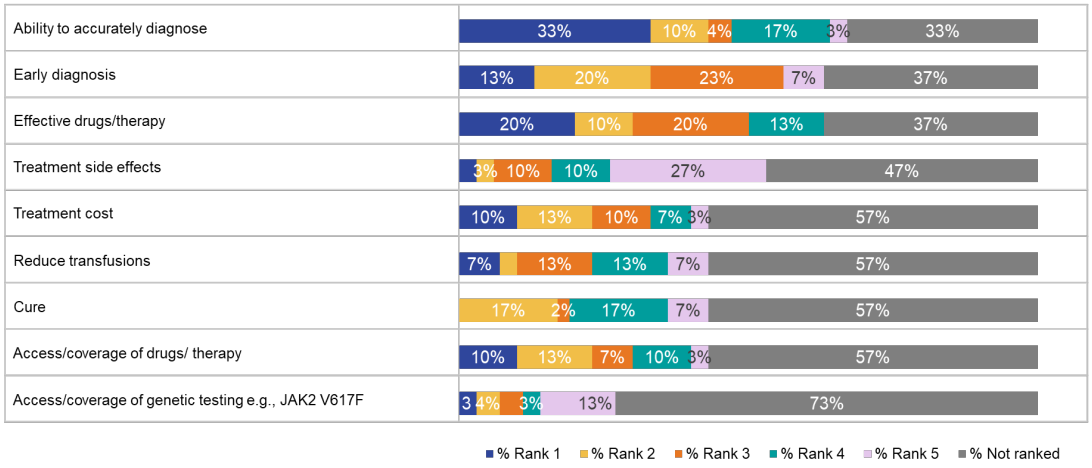

Figure 1. Perceived Physician Unmet Needs for MF

suggest that symptom burden is high, and symptoms have a significant impact on patient quality of life, most notably on their physical and financial well-being. This finding is in line with other landmark surveys done internationally, in the US and the UK (Harrison et al., 2019; Harrison et al., 2017; Mesa et al.,2016) and other global studies which reports significant symptom burden and negative impact on quality of life (Taher er al., 2018; Ionova et al., 209; Palandri et al., 2018). This study also reports significant treatment burden of MF, with high levels of co-prescribing, and high prescribing of treatments such as psychological therapy, hydroxyurea, and transfusions, which may potentially result in high healthcare resource utilisation and costs. This supports other studies conducted in the United States that reported the annual healthcare expenditure of MF patients to be three to five times higher than a matched comparator (Mehta et al., 2014; Bankar et al., 2020). Identifying the full disease burden associated with MF will allow us to better understand unmet needs and design interventions and strategies to improve patient care and outcomes.

Interestingly, our study showed that most physicians felt that their patients agreed with them on treatment goals. This differs from the international and Taiwanese landmark study (Harrison et al., 2017; Chang et al., 2021) which revealed a lack of alignment between physician and patient in terms of their treatment goals. Possible reasons may be due to more patients wanting to be involved in their treatment or better patient-physician communication in Indonesia. Patient research can be conducted to understand the true extent of alignment which is important in shaping and improving the management of these patients.

Like various studies reported worldwide, physicians expressed a need for novel therapeutic options and improved access and coverage for such options to address patient symptoms and reduce the burden of disease (Scotch et al., 2017, Waksal et al., 2022). Currently, there are limited curative treatment options available for MF, especially for older adults unfit for ASCT, and treatment goals are mainly aimed at improving symptoms (Waksal etl al., 2022). With financial concerns being the primary reason patients stop or decline receiving treatment, this study highlights the need for patient financial assistance or patient assistance programs to support patient access to treatments.

Due to the wide geographical distribution and decentralized healthcare system in Indonesia, there are still significant regional disparities in the quality, availability, and capacity of health services (Mahendradhata et al., 2017). Findings from the survey suggest that in the local context, there is a need to improve access and coverage of JAK V617F testing to ensure MPNs are being accurately diagnosed and that local hospital infrastructures and equipment will need to be improved to minimise difficulties in performing diagnostic procedures and reduce lead time to obtain results. This allows the physician to make a prognostic assessment and decide on the targeted treatment therapies earlier, which can improve patient outcomes (Baumeister et al., 2021; Reilly et al., 2012). Additionally, patients may also benefit from educational resources on MPN symptoms which may allow for earlier presentation and diagnosis due to increased public awareness. Information on JAK V617F testing can also potentially encourage uptake among patients, and information on treatment goals, which according to our survey findings, is perceived to be only somewhat understood by patients can be useful in addressing concerns about treatment and reduce instances when patient declines diagnostic tests or treatments. Another interesting survey finding is that only a minority of physicians strongly agree that MF is a blood cancer, and it is inconsistent with the World Health Organization (WHO) classification system which classifies MF as a category of MPN defined under haematolymphoid tumours (Khoury et al., 2022). The steering committee felt that this may be due to MF having a different progression as other blood cancer such as leukaemia and reflects a disparity in education on MF amongst physicians across Indonesia. Therefore, physicians may also benefit from educational resources to align on disease classification and understanding which can improve treatment strategies and consequently patient outcomes.

There are several limitations to this study, primarily the small sample size, descriptive study design and

self-reported nature of the survey. As this is a preliminary study and MPN is a rare disease, there are limited experienced physicians in the local clinical setting, resulting in the small sample size included in the study. Additionally, the study was also designed to be analysed descriptively and reported as descriptive analyses. Hence, there were no formal hypothesis testing and statistical comparison of the data. All results were also self-reported by respondents and were not validated by real-world data, which may result in reporting bias. Nonetheless, this was the only feasible methodology for assessing a rare disease in a developing healthcare system. Since this survey only includes the physician's perspective, future research may assess the patient's perspective and qualitative interviews may be conducted to explore patient's experience of MF to provide a better understanding of how this can be improved with the goal of improving patient care and outcomes in Indonesia.

Our study also had several strengths. Firstly, it is the first study in Indonesia to evaluate the physician understanding of overall diagnosis and unmet needs of MF at the time of diagnosis and will serve as a basis for further research in this rare disease area. Next, a steering committee to guide research development was formed with KOLs with deep understanding of the MPN landscape in Indonesia. Inclusion criteria were also intentionally tightened so that only experienced physicians who have good knowledge of MF were recruited to ensure quality data. Finally, pilot surveys were also completed, and changes were made based on the feedback prior to actual implementation. This served as an additional quality assurance step to ensure that adequate and accurate data were collected from the surveys.

In conclusion, consistent with other studies worldwide, this study suggests that in Indonesia, MF has a high symptom burden with significant negative impact on patients' QoL especially regarding physical and financial well-being. MF patients are faced with significant treatment burden which may be associated with high healthcare utilization and costs. There is a need for improved access and coverage of JAK V617F mutation testing, which is important for diagnosis, improved hospital infrastructure and access to novel therapy options. Patients may also benefit from increased knowledge of the disease. Additional research from the patient's perspectives should be undertaken to enhance understanding of MF in Indonesia and improve the overall health outcomes of patients living with MF.

Author Contribution Statement

All authors read and approved the final manuscript for submission. PIF, MSH, TDA, contributed to the design of the study and reviewing and revising the manuscript. WR contributed to the design and coordination of the study and analysis of data from the study. LH, KMT, AG contributed to the design and coordination of the study, analysis of data and development of manuscript draft..

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Approval

Informed consent was obtained prior to the questionnaire administration. Ethics approval was not required as this was an anonymous survey, and no identifiable information, patient's data, nor personal information were obtained.

Ethical Declaration

Individual patient data/ information was not collected, nor utilized at any point during this research, and all survey data was anonymized, with no personal information collected. Additionally, GDPR compliant participant information sheets and consent forms were utilized to ensure informed consent. All surveys were conducted in line with ESOMAR guidelines.

Conflict of Interest

PIF, MSH, TDA: Novartis: consultant or advisory role WR: Novartis: previous employment LH, KMT, AG: Ipsos Healthcare Singapore: employment.

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