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Assessment of physician awareness and attitudes toward recognizing symptoms related to myeloproliferative neoplasms

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ABSTRACT

Background: The level of awareness and attitudes of primary care physicians toward diagnosing myeloproliferative neoplasms (MPNs) is widely unexplored and many physicians overlook the symptoms of MPNs. Identifying MPN related symptoms by the primary care physician can lead to early recognition of the disease and prevent MPN related complications. *Methods:* In this cross-sectional study data was collected via a survey questionnaire from 99 primary care physicians (family medicine, internal medicine, emergency medicine) within the Ministry of National Guard Health Affairs (MNGHA) facilities in Riyadh, Saudi Arabia. The aim is to assess the primary care physicians' awareness of MPN related symptoms. *Results:* There is a statistically significant difference in the level of awareness of MPN symptoms between physicians in each department. Emergency physicians scored the lowest mean score (3.21±0.22) and failed to identify most of the MPN-related symptoms whereas most Internal Medicine physicians (3.46±0.34) and Family Medicine physicians (3.45 ±0.34) were able to identify most of the symptoms. *Conclusion:* Many physicians failed to recognize disease specific symptoms but were able to identify "B" symptoms. A great proportion of physician failed to recognize splenomegaly related symptoms which are associated with poor disease outcome. Therefore, we emphasize the importance of educating primary care physicians of the presentation of these disorders which can prevent unnecessary hospital costs and achieve better patient outcomes.

Keywords: Myeloproliferative, neoplasms, cancer, awareness, primary care physicians

1. INTRODUCTION

Myeloproliferative neoplasms (MPNs), previously termed myeloproliferative disorders, are a group of bone marrow diseases characterized by myeloid

precursor regulatory impairment. There are three major subtypes of MPNs; namely, polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF). The prevalence of polycythemia vera and essential thrombocythemia is ten times higher than the prevalence of primary myelofibrosis; in the United States, the prevalence of PMF is four to six per 100,000 population compared to 45 to 57 per 100,000 for PV and 39 to 57 per 100,000forET (Mehta et al., 2014). PV is characterized by an increase in RBC count, splenomegaly, increased risk of thrombosis and the presence of JAK2V717F mutation (96%) with a high risk of transforming to MF or acute myeloid leukemia (AML) (Geyer & Mesa, 2017). On the other hand, ET usually presents with increased platelet count, arterial thrombotic events, hemorrhages, and vasomotor impairment (Geyer & Mesa, 2017). The most severe of all MPNs is myelofibrosis which is characterized by bone marrow fibrosis, severely decreased blood cell count parameters, and extramedullary hematopoiesis resulting in severe splenomegaly (Geyer & Mesa, 2017).

The importance of diagnosing and treating these neoplasms early is underscored by the low survival rate of untreated MPN patients compared to diagnosed and treated patients. For instance, the median survival in patients with PV undergoing treatment is approximately 14 years (24 years for patients younger than 60 years old); however, survival decreases to 1.5-3 years if they are not treated (Chievitz & Thiede, 1962; Tefferi et al., 2013). Nonetheless, no studies have been conducted in Saudi Arabia to assess the primary care physicians' knowledge of MPN symptoms, disease burden, or prevalence of these hematological disorders. These diseases are difficult to diagnose early because of their non-specific symptom profile and slow progression compared to hematological malignancies(Forsyth et al., 2018). Some of these symptoms include generalized fatigue (81%), early satiety (70%), pruritus (52%), night sweats (49%), bone pain (44%), fever (14%), and weight loss (13%) (Mesa et al., 2007). Symptoms associated with splenomegaly are the most prominent and were shown to compromise the quality of life for many MPN patients (Mesa et al., 2007).

Symptomatic presentation of MPN disorders is usually variable and complicated, so physicians who are not acutely aware of these symptoms will not consider a diagnosis of MPN and carry out the necessary investigations on a timely manner. Undiagnosed MPN patients may mistakenly associate these symptoms with older age or other chronic illnesses and fail to describe them to the physician during consultations. On the other hand, physicians may not specifically ask the patients about each symptom during history taking, leading to inability for early identification and initiation of proper investigations. Delay in the diagnosis of MPNs leads to higher incidence of complications such as thrombosis and hemorrhages, leading to overall poor prognosis (Forsyth et al., 2018).

The MPN landmark survey showed that nearly half of the patients diagnosed with an MPN did not realize that they have a high disease-specific prognostic score (Harrison et al., 2017). The survey also showed that 27% of the patients surveyed experienced MPN-related symptoms for two years or more before being diagnosed with an MPN (Harrison et al., 2017). Disease-related symptoms were reported ≥1 year before diagnosis in 61% of patients with PV, 58% of patients with ET, and 49% of patients with MF (Mesa et al., 2016). This delineates the importance of awareness among physicians and patients of these symptoms. When searching in different databases, we could not find any study that assesses the general awareness of primary care physicians of MPN-related symptoms.

Many tools have been created and validated to assess the symptoms burden of MPNs. The MPN-Symptom Assessment Form - Total Symptom Score (MPN-SAF - TSS) is an easy and reliable tool that was validated in 2011 (Scherber et al., 2011). It contains the most frequent symptoms related to MPNs. The aim of this study is to investigate the level of awareness of MPN-related symptoms among primary care physicians within MNGHA and to understand their attitudes towards MPNs.

2. SUBJECTS AND METHODS

This quantitative, cross-sectional, questionnaire-based study was conducted at King Abdulaziz Medical City (KAMC) and other MNGHA clinics in Riyadh, Saudi Arabia in the period between January 2020 and July 2021. KAMC is a large tertiary center, which serves patients from all around the kingdom with a bed capacity of roughly 1500 beds. The participants were all physicians employed or training at KAMC. The three departments surveyed were Family Medicine, Internal Medicine and Emergency Medicine. The content experts exclusively chose these three departments because myeloproliferative neoplasms (MPN) patients typically present to a family physician, an internist or as an acute case in the ER (due to thrombosis, pancytopenia, bleeding… etc.).

The questionnaire was distributed during weekly morning meetings at various MNGHA-R facilities. Based on the availability of physicians and trainees at one time, the estimated sample size was calculated to be 100 physicians and the collected sample was 103 (95% CI, 10% margin of error and 50% response distribution). The study included interns, residents, fellows, and consultants. The exclusion criteria were limited to hematologists, oncologists, hematopathologists, students, and other healthcare staff. The questionnaire was developed with the help of three content experts in adult hematology and a biostatistician (Appendix 1). A

pilot study (n=33) was carried out at smaller hospitals outside the study population to avoid data contamination. The pilot study included physicians from Internal medicine, Family medicine, and Emergency medicine. The population of the pilot study included interns, residents, fellows, and consultants. Cronbach's alpha was calculated for each item for reliability and appropriate changes were made. The reliability of the questionnaire items was re-assessed after sample collection to ensure the integrity of the results.

Data was entered in Excel data sheet (MS Excel for Office 365 MSO, Version 16.0. Redmond, WA: MS Corp) and analyzed using IBM SPSS (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp). Categorical variables (department, experience, title… etc.) were described as frequencies and percentages and the continuous variable (knowledge score of MPN symptoms) was described as a mean and standard deviation. We devised a scoring system in which a correct answer "Agree" or "Strongly agree" equals one point, an incorrect answer "Disagree" or "Strongly disagree" equals minus one point, and a "Not Sure" answer equals zero. We reversed the scores for the negative symptoms which are not directly related to MPNs. The Likert scale was only used to analyze the descriptive statistics for questions 3 and 4.The independent sample *t*-test was used to compare the knowledge score between physicians and the independent one-way ANOVA test was used to compare different group means. For significant results, the Post hoc comparison was performed to determine which group was significantly different from other groups. The questionnaire also contained two questions regarding the attitudes and perceptions of physicians about MPNs (questions 3 and 4). For these questions, the Chi-square test was analyzed to compare different groups. For each statistical test, $P<0.05$ was considered significant and a confidence level of 95% was assumed.

Furthermore, non-parametric tests were performed in addition to the independent sample *t*-test given the non-normal distribution of the data. The data was ensured to meet all the assumptions of the Mann-Whitney *U* test before the test was performed. The scores were converted into correct (one point) and incorrect (minus one point). Participants who answered "Not sure" were also considered incorrect (minus one point). Transforming the data to this new scale resulted in a non-normal distribution which required new analysis using non-parametric methods. Medians, ranks, percentiles, *P* values and the effect size were calculated and compared with the results of the independent sample *t*-test for each variable. The objective of modifying the scoring systems is to show the results in a different perspective.

A bi-lingual consent form was distributed along with the questionnaire to ensure the privacy of the participants. The form was self-developed and approved by the Ethical Committee at KAIMRC. For ethical concerns, no IDs or names were taken from any participant at any point. Each copy of the questionnaire was assigned a serial number to track the data source. The hard copies were stored and secured after transcribing the data into the Excel data entry sheet.

3. RESULTS

Of the 207 questionnaires distributed, 103 answered the questions (50% response rate) (N= 103). Four were not in the inclusion criteria; so the final sample was of 99 respondents. Another four respondents did not answer the demographic section, and fifteen respondents did not complete all questions of MPN symptoms scale. We included those questionnaires that were incomplete in our analysis and excluded those four respondents who were not in our inclusion criteria. The range of departments distribution in our questionnaire showed a slightly higher representation of internal medicine physicians 42 (46%) compared to family medicine 33 (36%) and emergency medicine 16 (17%). Also, residents 52 (63%) represented a higher percentage of the sample, followed by consultants 27 (33%). In addition, 53 (60%) of physicians surveyed have graduated for less than four years, and 59 (68%) have been in their current department for less than four years (Table 1).

Table 1 Demographic data of the study population (N=99)

	Demographic Variables	**n**	%
Dept. (n=92)	Family Medicine	33	36%
	Emergency Medicine	16	17%
	Internal Medicine	42	46%
	Other	1	1%
Title (n=83)	Intern	3	4%
	Resident	52	63%
	Fellow	1	1%
	Consultant	27	32%

Years since graduation (n=89)	0-4	53	60%
	5-9	8	9%
	10 and above	28	31%
Years in the Current Dept. (n=87)	0-4	59	68%
	5-9	7	8%
	10 and above	21	24%
Patients per day (n=87)	0-9	30	34%
	10-19	32	37%
	20-29	12	14%
	30 and above	13	15%

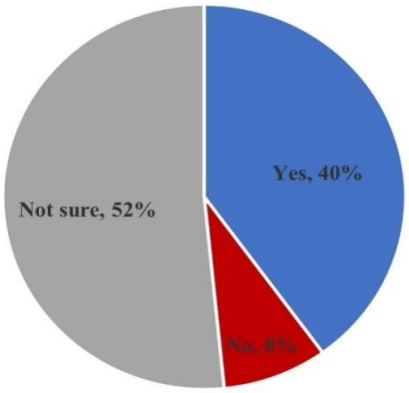

Figure 1 The percentage of physicians who believe they can identify MPN symptoms.

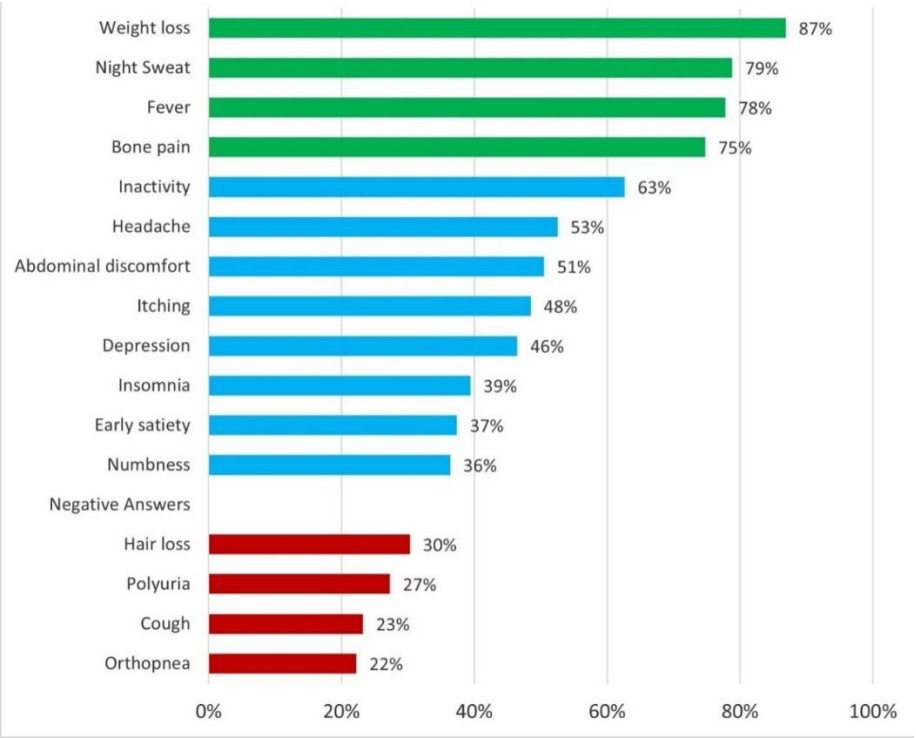

Figure 2 Bar chart showing overall percentages of physicians who agree with each symptom. Green color represents "B" symptoms, blue color indicates MPNs specific symptoms, and red color shows the negative symptoms which are unrelated to MPNs.

When asking physicians whether they can identify MPN-related symptoms or not, a high percentage of physicians 49 (52%) from the total respondents answered, "Not sure" (Figure 1). In addition, most physicians surveyed (87%) agreed that "weight loss" was one of the MPNs symptoms. However, more specific symptoms of MPNs such as insomnia and early satiety had inconsistent answers in which respectively 39 (39%) and 37 (37%) of physicians agreed that they were MPN-related symptoms. Symptoms not related to the disease processes of MPNs including hair loss, polyuria, cough, and orthopnea were also included in the questionnaire. For these negative symptoms, 30 (30%) considered "hair loss" as a symptom of MPNs (Figure 2).

The descriptive statistics associated with physicians' level of awareness toward MPNs are reported in Table 2. Emergency medicine physicians acquired the lowest mean score of level of awareness of MPN symptoms (3.21±0.22) whereas Internal Medicine physicians achieved the highest mean score (3.46±0.34). To test the hypothesis that the level of awareness of MPN-related symptoms between different departments (Family Medicine, Emergency Medicine, Internal Medicine) was statistically different, a one-way ANOVA comparison between the groups was performed. The independent one-way ANOVA yielded a statistically significant difference in the level of awareness between different medical departments (F (2, 88) = 3.94, P= 0.02). Thus, the null hypothesis of no difference between departments was rejected. Post hoc comparisons using the Tukey's test revealed that family medicine physicians were more aware of MPNs than emergency medicine (P=0.04, 95% CI 0.005 to 0.474), and comparing internal medicine to emergency medicine also showed that internal medicine physicians were more aware of MPN than emergency physicians (P= 0.02, 95% CI 0.03 to 0.482). However, the difference in knowledge of MPN between family medicine and internal medicine physicians was not statistically significant (P= 0.98, 95% CI -0.195 to 0.163).

The non-parametric tests reveal similar results. Comparison between departments shows similar differences with the Kruskal-Wallis test (P= 0.001). A significant difference in the score of physicians who see more patients per day and physicians with more experience was observed. Also, the comparison between the scores of physicians based on the number of years since graduation from medical school using the Man-Whitney U test shows a significant increase in the mean score favoring physicians who have more experience (P= 0.008 and effect size of 0.32). Furthermore, physicians who see 20 or more patients per day achieved a significantly higher mean score compared to physicians who see less patients (P= 0.004 and effect size of 0.37). These findings might indicate the need for an expert physician to identify MPN related symptoms.

When asked about the types of barriers that affected the process of diagnosing MPNs, 61% of consultants believed that little time allocated to hematology during rotations was a barrier that prevented them from having a good knowledge of MPNs. Also, 15 (54%) of fellows/consultants agreed that the lack of local epidemiological data made them less knowledgeable about MPNs. For factors that might contribute to the delay of diagnosis of MPNs, 75% of fellows/consultants and 64% of interns/residents believe that the ambiguity of the symptoms of MPNs to be the main factor. Also, 27 (49%) of interns/residents believe that low prevalence of this group of diseases was one of the factors making them unable to identify MPN patients early (Table 3 and 4).

Table 2 Comparison of means for MPN symptom score and SD between different demographic groups.

	Demographic Variables	Total, n	Mean Score for MPN Symptoms			P
Title	Intern / Resident	55	3.39	±	0.33	0.99
	Fellow / Consultant	28	3.38	±	0.36	
Years since graduation	0-9	61	3.40	±	0.32	0.92
	10 and above	28	3.40	±	0.35	
Years in Current Dept.	0-9	66	3.40	±	0.31	0.89
	10 and above	21	3.39	±	0.40	
Dept.	Family Medicine	33	3.45	±	0.34	**0.02**
	Emergency Medicine	16	3.21*	±	0.22	
	Internal Medicine	42	3.46	±	0.34	

Patients per day	0-9	30	3.40	±	0.27	0.84
	10-19	32	3.37	±	0.38	
	20 and above	25	3.42	±	0.33	

* Significantly lower than the other two categories

Table 3 Physicians of different titles have significantly different beliefs when considering knowledge barriers of MPNs.

		Title		
		Intern / Resident (n=55)	Fellow / Consultant (n=28)	*P*
Little time allocated to hematology during rotation during training	Disagree	7 (13%)	8 (28%)	0.01
	Not sure	23 (42%)	3 (11%)	
	Agree	25 (45%)	17 (61%)	
Lack of epidemiological data of MPNs locally	Disagree	2 (4%)	6 (21%)	0.01
	Not sure	27 (49%)	7 (25%)	
	Agree	26 (47%)	15 (54%)	
Lack of general knowledge and interest in hematology field	Disagree	16 (29%)	11 (41%)	0.43
	Not sure	14 (26%)	4 (15%)	
	Agree	25 (45%)	12 (44%)	
Poor access to medical library and lacking up to date references in the hospital	Disagree	31 (56%)	16 (57%)	0.47
	Not sure	17 (31%)	6 (21%)	
	Agree	7 (13%)	6 (21%)	
Not enough continuous education sessions during department activities	Disagree	12 (22%)	9 (32%)	0.59
	Not sure	13 (24%)	6 (21%)	
	Agree	30 (54%)	13 (46%)	

Table 4 Physicians of different titles have different ideas about the factors that might delay the diagnosis of MPNs.

		Title		
		Intern / Resident (n=55)	Fellow / Consultant (n=28)	*P*
Ambiguity of the symptoms of these diseases	Disagree	3 (5%)	5 (18%)	0.02
	Not sure	17 (31%)	2 (7%)	
	Agree	35 (64%)	21 (75%)	
Lack of interest and knowledge of the field of hematology	Disagree	11 (20%)	15 (54%)	0.004
	Not sure	23 (42%)	4 (14%)	
	Agree	21 (38%)	9 (32%)	
Low prevalence for these diseases	Disagree	5 (9%)	9 (32%)	0.03
	Not sure	23 (42%)	10 (36%)	
	Agree	27 (49%)	9 (32%)	

4. DISCUSSION

The findings of this study show that most physicians surveyed at MNGHA-R are not sure if they can correctly identify MPN-related symptoms. Despite the lack of epidemiological data of MPNs in Saudi Arabia, we postulate that this result is due to the low overall prevalence and the limited exposure of primary care physicians to hematological disorders in general. In 2001 the WHO established a criteria to classify and diagnose MPNs based on molecular genetic testing (Tefferi & Vardiman, 2008). However, a clear guideline for identifying MPNs clinically is not yet established. Multiple large-scale studies have investigated the prevalence of each MPN symptom (Vannucchi et al., 2009). In the last two decades, studies about MPNs began to mount and many studies focused on the perception of patients rather than physicians. Mesa et al., (2017) specifically measured patient perceptions of MPN symptoms and disease burden. To our knowledge, this is the first study which solely focuses on the attitudes, perceptions, and awareness of primary care physicians of MPNs. The difficulty to identify MPN-related symptoms is common due to the variety and ambiguity of the symptoms which differ in each type of MPN (ET, PV and PMF) and differ from patient to patient depending on the comorbidities. A study by Zefeng and Zhijian, (2020) surveyed MPN patients and physicians in China and found that 90% of physicians accurately classified their patients as per the prognostic risk score. Their results do not mention whether these physicians are specialists (i.e. hematologists or oncologists) or primary care physicians. Zefeng and Zhijian, (2020) also report a high patient satisfaction (89%) with the physician communication and treatment plan which could be related to the high success rate in the diagnostic process.

Most physicians who participated in this study were able to recognize the general "B symptoms" that are associated with malignancy, such as weight loss, night sweats, bone pain, and fever. Yet, these symptoms are not related to MPNs only and they are common to many other non-hematological disorders. Despite being prevalent symptoms in MPN patients, they are non-specific and do not point the primary care physician in the right direction. The same pattern was noticed with the negative symptoms such as cough, hair loss, and polyurea. Many physicians were not able to recognize the specific symptoms related to MPNs such as itching, early satiety, and insomnia.

Emergency department physicians scored the lowest when identifying MPN-related symptoms. This result was expected since MPNs are considered chronic disorders and rarely present with acute complications. On the other hands, Internal medicine and Family medicine physicians achieved higher scores in identifying MPN-related symptoms. Since the majority of the participants reported that they are not sure if they can identify MPN-related symptoms, we grouped them into two groups based on years of experience to explore their perceptions of the barriers contributing to their lack of awareness of MPN symptoms. Most of the physicians with more than 10 years' experience believe that the main reason is that lack of local epidemiological studies and short time allocated to hematology rotation during residency.

On the other hand, physicians with low experience believe that lack of interest in the field of hematology, and shortage in continuous education activities are major barriers. Surprisingly, most of the participants claim that they have access to good medical libraries and up to date data on hematology despite the fact that only few hematology journals are offered at MNGHA-R medical library. Delayed diagnosis is a major factor in the outcome of the disease and might be a major factor in the overall patient survival rate and Quality of Life (QOL). The ambiguity of the symptoms plays a major role in the delayed diagnosis of MPNs which was agreed upon by the majority of participants in this study. The second factor leading to the delay of diagnosis in the opinion of most participants is the lack of epidemiological studies on MPNs in Saudi Arabia.

One of the limitations is the place of the study. The study was conducted in MNGHA in Riyadh, which is a large tertiary center in which physicians are familiar with complex cases and therefore this study only reflects the awareness and perception of the physicians at MNGHA-R. This study may not accurately reflect the awareness and perception of physicians in other cities in different regions in Saudi Arabia.

5. CONCLUSION

This study attempted to investigate the level of awareness and explore attitudes of primary care physicians toward MPN-related symptoms. This was done by constructing a cross-sectional, questionnaire-based study. The main findings suggest that there is a significant difference in level of awareness between family medicine, internal medicine and emergency medicine. As expected, emergency medicine physicians have the lowest mean of knowledge score in comparison to internal medicine and family medicine. Analyzing the data through applicable statistical tests shows this difference as statistically significant. There are two suggestions that this study can provide in order to increase the accuracy of diagnosing MPNs. First, increase the exposure of primary care physicians to patients with hematological disorders such as MPNs by increasing the duration of hematology rotation in their fields. Second, providing a validated tool that primary care physicians can use to recognize ambiguous symptoms will improve the

identification of MPN patients and prevent the development of serious complications. Hopefully, this study will encourage researchers to focus more on knowledge aspects of primary care physicians about MPNs and similar chronic disorders that can improve the outcome for patients.

Ethical approval

The study was approved by the Medical Ethics Committee of King Abdullah International Medical Research Center (KAIMRC) (Ethical approval code: SP19/348/R).

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Appendix 1

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KAIMRC APPROVED IRB

Demographic Data:

Department name: ☐ Family Medicine ☐ Emergency Medicine ☐ Internal Medicine
☐ Other (Please Specify): …… ……
Title: ☐ Intern ☐ Resident ☐ Fellow ☐ Consultant
Years of practice since graduation: ☐ 0-4 ☐ 5-9 ☐ 10 and above
Years of practice in the current department: ☐ 0-4 ☐ 5-9 ☐ 10 and above
Number of patient seen in one day: ☐ 0-9 ☐ 10-19 ☐ 20-29 ☐ 30 and above

Research Questions:

1. Do you think that you can identify symptoms related to Myeloproliferative neoplasms (MPN)?
☐ Yes ☐ No ☐ Not sure

2. When considering a diagnosis of a Myeloproliferative neoplasms (MPN), patients usually present with the following symptoms (rate whether you agree or disagree with each):

Symptoms	Strongly Disagree	Disagree	Not sure	Agree	Strongly Agree
Early satiety	☐	☐	☐	☐	☐
Night Sweat	☐	☐	☐	☐	☐
Polyuria	☐	☐	☐	☐	☐
Hair loss	☐	☐	☐	☐	☐
Itching	☐	☐	☐	☐	☐
Bone pain	☐	☐	☐	☐	☐
Cough	☐	☐	☐	☐	☐
Headache	☐	☐	☐	☐	☐
Depression	☐	☐	☐	☐	☐
Orthopnea	☐	☐	☐	☐	☐
Numbness	☐	☐	☐	☐	☐
Fever	☐	☐	☐	☐	☐
Insomnia	☐	☐	☐	☐	☐
Weight loss	☐	☐	☐	☐	☐
Abdominal discomfort	☐	☐	☐	☐	☐
Inactivity	☐	☐	☐	☐	☐

3. The following is a list of barriers that you may encounter while diagnosing MPNs. Please rate whether you agree or disagree with each.

	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
Little time allocated to hematology during rotation during training.	☐	☐	☐	☐	☐
Lack of epidemiological data of MPNs locally	☐	☐	☐	☐	☐
Lack of general knowledge and interest of hematology field	☐	☐	☐	☐	☐
Poor access to medical library and lacking up to date references in the hospital.	☐	☐	☐	☐	☐
Not enough continuous education sessions during department activities.	☐	☐	☐	☐	☐

4. In your opinion, which of the fallowing factors may contribute to the delayed diagnosis of MPNs?

	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
Ambiguity of the symptoms of these diseases	☐	☐	☐	☐	☐
Lack of interest and knowledge of the field of hematology	☐	☐	☐	☐	☐
Low prevalence for this class of diseases.	☐	☐	☐	☐	☐

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Conflicts of interest

The authors declare that there are no conflicts of interests.

Data and materials availability

All data associated with this study are present in the paper.

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