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Research Article

Prevalence of Myeloproliferative Neoplasms (MPNs) and its Molecular Biomarkers in Saudi Population in Al-Madinah Region

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Abstract

Myeloproliferative Neoplasms (MPNs) are hematological disorders characterized by increased production of myeloid lineage blood cells. MPNs are categorized as Philadelphia (Ph) chromosome-positive, including Chronic Myeloid Leukemia (CML), Ph chromosome-negative, Polycythemia Vera (PV), Essential Thrombocythemia (ET), and Primary Myelofibrosis (PMF). Limited data exist on the frequency of MPNs and their molecular markers in the Saudi population. This study aimed to identify the common MPN subtypes and their associated molecular markers in Saudi citizens residing in the Al-Madinah Region.

We retrospectively analyzed the clinical data of 60 patients between 2014 and 2023. Bone marrow samples were analyzed for mutations in the BCR-ABL, JAK2, CALR, and MPL genes using karyotyping, specific FISH panels, and various mutation detection methods, including Sanger sequencing.

Our findings revealed that MPNs were more prevalent (78%) than Acute Myeloid Leukemia (AML; 11.6%) and Acute Lymphoblastic Leukemia (ALL; 10%) in the study population. Among MPNs, CML was the most common (34%), followed by equal rates of PV and ET (27.6% each), with PMF showing the lowest incidence (10.6%). Molecular biomarker analysis demonstrated BCR-ABL-positive mutations in all CML cases, JAK2-positive mutations in all PV cases, and the most frequent mutation in PMF cases. ET and PMF cases exhibited various mutation patterns, with triple-negative status for JAK2, CALR, and MPL being the most frequent molecular alterations in ET.

This study represents the first estimation of Ph chromosome-negative MPN incidence and identification of common molecular biomarkers used for diagnosis in Saudi Arabia. Further studies with larger sample sizes and broader regional coverage are required to confirm these findings and to provide a more comprehensive understanding of MPNs in the Saudi population.

Keywords: Myeloproliferative neoplasms; Saudi Arabia; Al-Madinah Region; Molecular markers; BCR-ABL; JAK2; CALR; MPL

Introduction

Myeloproliferative Neoplasms (MPNs) are a group of disorders that affect the bone marrow through a significant increase in the myeloid blood cell line [1]. These disorders result from abnormal proliferation of one or more terminal myeloid cell lines in Peripheral Blood (PB). Laboratory diagnosis of MPNs can be classified into two groups: detection through BCR-ABL rearrangement (Philadelphia chromosome-positive, suspected of Chronic Myeloid Leukemia or CML) and the identification of driver genes in Philadelphia chromosome-negative forms (MPN Ph neg, suspected of polycythemia vera or PV, essential thrombocythemia or ET, and Primary Myelofibrosis or PMF) [2]. A high incidence rate of Philadelphia chromosome-positive MPNs is observed in CML, accounting for approximately 30% of leukemia cases in adults [3], affecting 1–2 individuals per 100,000 individuals with a median age of 52 to 64 years [4-6]. Philadelphia chromosome-negative MPNs are, however, very rare, with annual incidence rates of 2.7 and 3.1 cases per 100,000 people reported in Europe and the United States [7,8]. Literature shows that men aged ≥50 years have a higher risk of developing MPNs [9]. CML is characterized by the presence of the Philadelphia chromosome and a balanced translocation between chromosomes 9 and 22 [t(9;22)]. This translocation results in the fusion of the Breakpoint Cluster Region (BCR) gene on chromosome 22q11.2 with the Abelson gene (ABL1) from chromosome 9q34, creating the BCR-ABL1 fusion oncogene [11]. The resulting BCR-ABL1 oncoprotein acts as a constitutively active tyrosine kinase that induces leukemogenesis through cytokine-independent cell cycle activation and abnormal apoptotic signals [11]. CML is more common in males than in females [12]. Polycythemia Vera (PV) accounts for approximately 45% of all MPN cases [13]. It is characterized by marrow hypercellularity, megakaryocyte hyperplasia, and hypertrophy. The primary molecular aberration in

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PV is the JAK2 mutation present in 95% of cases [10]. JAK2, located on chromosome 9p24, typically exhibits a gain-of-function mutation in exon 14, involving the substitution of phenylalanine for valine at position 617 [14]. Additional mutations in exon 12 of JAK2 have been described [15]. These mutations result in constitutive activation of JAK2, leading to cytokine hypersensitivity and erythrocytosis [15]. The PV incidence is reported to be higher in males than in females [16].

Essential Thrombocythemia (ET) accounts for approximately 25% of all MPN cases [17]. It is characterized by megakaryocyte hyperplasia in the BM without evidence of fibrosis or persistent thrombocytosis in the PB [10]. Common mutations in ET include JAK2, CALR, and MPL, with JAK2 being the most frequent mutation [18]. MPL, located on chromosome 1p34, encodes the Thrombopoietin (TPO) receptor. Mutations in this gene lead to ligand-independent intracellular signaling activation [18]. CALR, located on chromosome 19p13.2, functions as an endoplasmic reticulum chaperone. CALR mutations, primarily insertions and/or deletions in exon 9, result in a frameshift that alters amino acid configuration [19]. Recent studies have suggested a higher incidence of ET in females than in males [18,20].

Primary Myelofibrosis (PMF) is characterized by Bone Marrow (BM) fibrosis and atypical megakaryocytic hyperplasia. JAK2 and MPL mutations are involved in 50% and 11% of the cases, respectively [21]. PMF typically presents with leukoerythroblastosis, leukopenia, and thrombocytosis or thrombocytopenia in PB [10]. The myeloproliferative phenotype in PMF results from mutations in JAK2, CALR, or MPL, with additional mutations affecting DNA methylation, chromatin modification, RNA splicing, and DNA repair in some cases [19]. PMF has been reported to be more predominant in males than in females [9].

Cancer epidemiology in Saudi Arabia shows significant regional variations that are potentially attributable to differences in etiological factors [22,23]. However, knowledge regarding the prevalence of MPNs and their molecular biomarkers in the Saudi population is lacking. Therefore, this study aimed to assess the prevalence and molecular biomarkers of MPN subtypes in the Saudi population in the Al-Madinah Region. Given the limited sample size, this study is exploratory in nature and serves as a pilot study, providing preliminary findings to form a foundation for future large-scale investigations.

Methodology

We conducted a retrospective analysis of the clinical data of patients with MPN, ALL, and AML. The data of 60 patients were collected, representing all AML, ALL, and MPN diagnosed cases at Prince Mohammed bin Abdulaziz Hospital from 2014 to 2023 using karyotyping, specific FISH panels, and variety-specific mutation detection methods such as Sanger sequencing. Data were analyzed using Excel software. Normally distributed quantitative data were expressed as percentages, means, standard deviations, and ranges. Given its small sample size, this study was categorized as a pilot study aimed at exploring preliminary trends and methodologies for future research. The project was approved by the local ethics research committee of King Abdullah International Medical Research Center (KAIMRC). IRB Approval No: IRB/1503/23.

Data Collection

The data used in this study were collected from patients registered at Prince Mohammed bin Abdulaziz Hospital. The Data were composed of records of patients admitted for MPNs, AML, and ALL based on the World Health Organization guidelines for diagnosis. All patients were screened by karyotyping and molecular genetic analysis, including FISH panels and Sanger sequencing.

Result

Myeloproliferative Neoplasms (MPNs)

This pilot study investigated the prevalence of MPNs and active molecular biomarkers of Myeloproliferative Neoplasms (MPNs) in the Saudi population of the Al-Madinah region. A total of 60 Bone Marrow (BM) samples were obtained and analyzed, including 47 cases (78.3%) diagnosed with MPNs, with an average patient age of 50 years (median 50.5 years). Among these, 21 patients were adult males, and 26 were adult females, showing no significant difference in MPN incidence between the sexes. In addition to MPN cases, seven cases (11.6%) were diagnosed with Acute Myeloid Leukemia (AML), predominantly in males (six males and one female), with an average age of 38 years (median, 44 years). Six cases (10%) were classified as precursor B-Acute Lymphoblastic Leukemia (ALL), affecting both the adult and pediatric populations. This included two pediatric females, two adult females, and two adult males, with an average age of 23.3 years (median, 25 years). These findings suggest a higher incidence of ALL in females compared to males (Table 1).

CML is the most prevalent cause of MPNs in the Saudi population in Al- the Madinah region

CML was the most common MPN diagnosis, affecting 16 cases (34%), with an average age of 46.8 years (median 46.5 years). PV and ET were each diagnosed in 13 patients (27.6%), with average ages of 57.6 and 41.4 years, respectively. PMF accounted for five cases (10.6%), with an average age of 61 years (median, 68 years). Molecular analysis of MPN cases revealed distinct mutation patterns. All CML cases were BCR-ABL-positive, whereas all PV cases were JAK2-positive and BCR-ABL-negative. In ET cases, several mutation patterns were observed, including triple-negative mutations in JAK2, MPL, and CALR, as well as cases with JAK2-positive mutations. PMF cases exhibit a range of mutations, with JAK2 mutations being

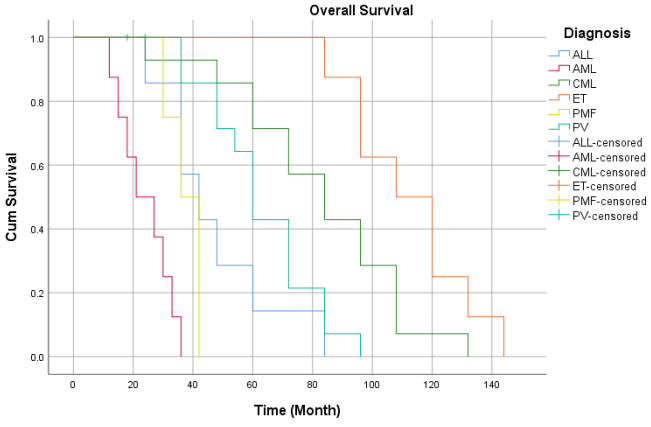

Figure 1: Overall Survival of the MPN patients.

Table 1: Summary of the myeloproliferative neoplasm (MPN) cases and related hematologic disorders, including Acute Myeloid Leukemia (AML), Acute Lymphoblastic Leukemia (ALL), Chronic Myeloid Leukemia (CML), Polycythemia Vera (PV), Essential Thrombocythemia (ET), and Primary Myelofibrosis (PMF).

Diagnosis	Cases (n)	Average Age (Years)	Median Age (Years)	Male (%)	Female (%)	Mean Survival (Months)	Median Survival (Months)
MPN (Total)	47	50	50.5	44.7	55.3	N/A	N/A
AML	7	38	44	85.7	14.3	24	21
ALL	6	23.3	25	50	50	47.143	42
CML	16	46.8	46.5	50	50	82.286	84
PV	13	57.6	61	61.5	38.5	63	60
ET	13	41.4	40	30.8	69.2	112.5	108
PMF	5	61	68	20	80	37.5	36

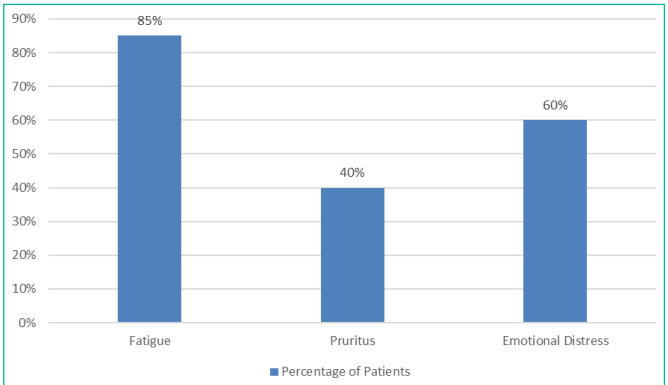

Figure 2: Common Symptoms in MPN patients.

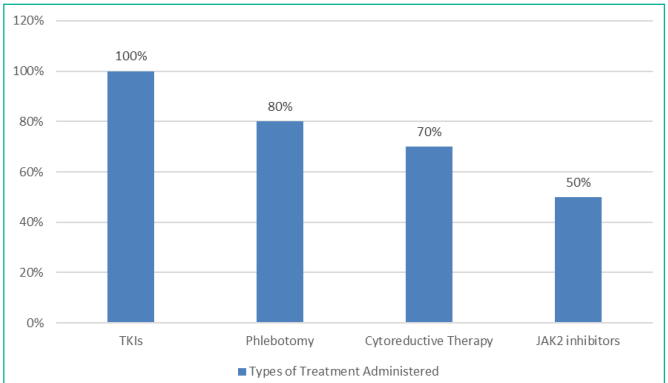

Figure 3: Types of Treatment Administered on MPN Patients.

the most frequent. Overall, triple-negative cases for JAK2, CALR, and MPL were most common in ET, whereas JAK2 mutations were prevalent in PMF (Table 1).

Survival Analysis of MPN Subtypes

Survival time analysis revealed significant differences in survival across the various MPN subtypes. Chronic Myeloid Leukemia (CML) had the highest mean survival of 82.3 months (median, 84 months), whereas ET had a mean survival of 112.5 months (median, 108 months). AML patients exhibited the lowest mean survival of 24 months (median, 21 months).

Primary Myelofibrosis (PMF) and Polycythemia Vera (PV) had mean survival times of 37.5 and 63 months, respectively (Figure 1). Overall, the mean survival across all diagnoses was 65.7 months (median, 60 months), with statistical tests confirming significant differences in survival distributions across the different types of MPNs ($p < .001$).

Common Symptoms and Treatment Approaches

Common symptoms among the patients included fatigue (85%), pruritus (40%), and emotional distress (60%) (Figure 2). Treatment approaches varied, with all patients receiving Tyrosine Kinase Inhibitors (TKIs), 80% undergoing phlebotomy, 70% receiving cytoreductive therapy, and 50% treated with JAK2 inhibitors (Figure 3).

Molecular Analysis for MPN Cases

The MPN cases were found to have different genetic mutations at different frequencies (Table 3). All 16 CML cases were analyzed to determine the presence of mutations in the BCR-ABL gene. All CML cases showed BCR-ABL-positive mutations in both female and male patients (Table 2).

All 13 PV cases were analyzed to test for JAK2 and BCR-ABL mutations. All PV cases showed JAK2 positive mutation and BCR-ABL-negative mutations, as described in (Table 2).

All 13 ET cases were analyzed to test for the presence of mutations in BCR-ABL, JAK2, CALR, or MPL. Several mutation patterns were identified in all cases, as shown in (Table 3). Molecular analysis of the female patients revealed one female with JAK2 negative mutation; however, there were no available results for CALR and MPL genes in the patient's medical record.

All four patients were triple-negative for JAK2, MPL, and CALR mutations. In addition, three cases had JAK2 positive mutation and MPL- and CALR-negative mutations. On the other hand, male patients were analyzed, and one patient had a CALR-positive mutation, whereas JAK2 and MPL mutations were negative. Two cases

Table 2: Mutations' frequency of MPN cases.

MPN classification	Frequency	Gender		Type of mutation
		Male	Female	
CML	16	8	8	• *BCR-ABL1*
PV	13	8	5	• *JAK2* positive / *BCR-ABL1* negative
ET	13	4	9	• One female case, *JAK2* negative. *MPL* and *CALR* results are not available. • BCR-ABL1 negative mutation six cases (4 female and two male) of Triple-negative • three female cases, *JAK2* positive / *CALR* and *MPL* negative. BCR-ABL1 negative mutation • two cases (1 male and 1 female), *CALR* positive/ *JAK2* and *MPL* negative, BCR-ABL1 negative mutation • one male case, *JAK2* and *CALR* positive, BCR-ABL1 negative mutation
PMF	5	1	4	• One female case, *MPL* positive and *CALR* negative, BCR-ABL1 negative mutation. • One female case, Triple negative • *Two* female *cases, JAK2* positive and *CALR* negative, BCR-ABL1 negative mutation • *One male case, ASXL1, JAK2, TET2 and U2AF1,* BCR-ABL1 negative mutation

were negative for JAK2, MPL, and CALR mutations (triple negative). One case appeared to have positive mutations in the JAK2 and CALR genes. These data suggest that the triple negativity of JAK2, CALR, or MPL is the most common molecular alteration in ET. The frequencies of these mutations are shown in (Table 2).

All five PMF cases were analyzed to determine the presence of mutations in BCR-ABL, JAK2, CALR, and MPL. Several mutation patterns were identified in all cases, as shown in (Table 3). One female patient had a MPL-positive mutation and a negative CALR mutation. However, the patient's condition progressed to AML. One patient harbored a triple-negative mutation. Two patients tested positive for JAK2 and CALR mutations. However, one male patient had mutations in ASXL1, JAK2, TET2, and U2 small nuclear RNA auxiliary factor 1 (U2AF1) genes. Moreover, both male and female patients had BCR-ABL-negative mutations (Table 2). These data suggest that JAK2 mutations may be the most common finding in PMF cases.

Discussion

The analysis of cancer epidemiology in Saudi Arabia reveals notable regional variations potentially related to differences in etiological factors [22,23]. Recent studies have shown an increase in leukemia incidence rates, particularly in the central, eastern, and northern regions [24]. However, knowledge regarding the prevalence and molecular biomarkers of Myeloproliferative Neoplasms (MPNs) in Saudi Arabia is lacking. This study aimed to identify the prevalence of MPNs in the Saudi population in the Western Region (Al-Madinah) and identify the molecular biomarkers available for clinical approaches to these neoplasms.

Analysis of survival times across different diagnoses revealed significant variations in both the mean and median survival estimates. For Acute Lymphoblastic Leukemia (ALL), the mean survival time is estimated at 47.143 months, with a median of 42.000 months, indicating that patients typically survive for just over three and a half years. Acute Myeloid Leukemia (AML) patients, on the other hand, had a median survival of 21.000 months and a mean survival of 24.000 months, indicating a shorter survival period for this diagnosis. Compared to ALL and AML, Chronic Myeloid Leukemia (CML) exhibits a significantly higher mean survival of 82.286 months and a median of 84.000 months, indicating superior outcomes. With a median survival of 108.000 months and the longest mean survival of 112.500 months, patients with Essential Thrombocythemia (ET) have an outstanding prognosis. Polycythemia Vera (PV) has a mean survival of 63.000 months and a median of 60.000 months, both of which indicate moderate survival results in comparison to other diagnoses. Primary Myelofibrosis (PMF) has a mean survival of 37.500 months and a median of 36.000 months.

The results demonstrated that among the disorders under investigation, ET had the greatest prognosis, while AML had the lowest odds of survival, with CML and PV in the middle. This cohort's general trends in patient outcomes are highlighted by the reported overall mean survival of 65.716 months across all diagnoses, with a median of 60.000 months. Statistical analyses utilizing the Breslow (Generalized Wilcoxon), Tarone-Ware, and Log Rank (Mantel-Cox) tests were performed to assess the equality of survival distributions across various diagnoses to further corroborate these findings. Chi-square values of 82.698 ($p < .001$), 72.627 ($p < .001$), and 77.668 ($p < .001$) indicated significant differences in the results. These results support the observed patterns in the mean and median survival estimates for each diagnosis by confirming that there are statistically significant disparities in survival times among the various hematologic diseases evaluated. For patients to receive complete patient care, it is essential to understand the Quality of Life (QoL) of patients with MPNs. Research has shown that symptoms including tiredness, pruritus, and mental distress might lead to a worse Quality of Life (QoL) in MPN patients [32]. Improved QoL outcomes can result from effective management of MPNs, which includes therapies such as TKIs for CML and phlebotomy with low-dose aspirin for PV [33]. However, insufficient adherence to medication might have a detrimental effect on the quality of life and survival of patients with MPNs. [34].

This study found that MPNs were more prevalent (78%) than AML (11.6%) or Acute Lymphoblastic Leukemia (ALL) (10%) in the Saudi population living in the Al-Madinah region. This is consistent with a recent study in the southern region of Saudi Arabia [35] but inconsistent with studies conducted in the northern [36] and central [37] regions. The high prevalence of CML in the Al-Madinah and Aseer regions compared to the Northern and Central regions could be linked to local health system factors and possible etiological factors such as genetic or environmental causes [39]. CML (34%) was the most prevalent MPN in the Saudi population in the Al-Madinah region, followed by PV (27.6%) and ET (27.6%), with PMF (10.6%) showing the lowest incidence rates. This distribution differs from studies conducted in other countries [41-44], possibly because of genetic variation between populations and the small sample size in this study. Regarding sex distribution, our findings indicate no statistically significant difference in the incidence rate between males and females, which is consistent with some previous studies [46-48] but differs from others [49]. These differences may be due to the low prevalence of the disease, necessitating larger sample sizes for an accurate incidence rate determination.

Molecular analysis revealed that BCR-ABL1 mutation was the most common mutation encountered during diagnosis, followed by JAK2 mutation. This is consistent with previous studies [51-53]. Our study suggests that the lack of all three driver mutations (JAK2, MPL, and CALR), known as triple-negative MPN, is the most frequent molecular alteration in ET. This finding differs slightly from previous literature [19,54] and highlights the need for further investigation using advanced techniques, such as whole exome sequencing [55-57].

The main limitation of this study is the small sample size, which constrains the generalizability of the results. Although this pilot study provides useful early insights into the prevalence and molecular indicators of MPNs in the Al-Madinah area, larger studies are necessary to corroborate these preliminary patterns. Future studies should include a broader and more heterogeneous population to validate the identified trends and further explore the molecular landscape of MPNs in Saudi Arabia.

Conclusion

In conclusion, this study provides valuable initial data on the prevalence and molecular characteristics of MPNs in the Al-Madinah region of Saudi Arabia. These findings may aid in the diagnosis,

prognosis, and treatment of patients. However, further investigations with larger sample sizes and involving other regions in Saudi Arabia are needed to confirm and expand upon these results. Multicenter collaboration could significantly contribute to the accurate determination of the prevalence of MPNs in different regions of Saudi Arabia and add to the body of knowledge in the field.

Author Statements

Author Contributions

Conceptualization: S.A.; validation: H.A.; investigation: S. A., R., and M. A Data analysis, R. A. Writing an original draft, S.A. and R.A.; Review and editing, A.A, SA, and M.A. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

The project was approved by the local ethics research committee of King Abdullah International Medical Research Center (KAIMRC). IRB Approval No: IRB/1503/23.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Data Availability Statement

All data related to this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare no conflict of interest.

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