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The prevalence of JAK2, CALR, and MPL mutations in BCR-ABL1 rearrangement negative Iraqi patients

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ABSTRACT

Purpose: To date, there is no enough data about the prevalence of JAK2, CALR, and MPL mutations in BCR-ABL1 rearrangement negative myeloproliferative neoplasms (MPN) patients in Iraq. This study was conducted to determine the prevalence of these mutations and to evaluate the clinical features of polycythemia vera (PV) and essential thrombocythemia (ET) patients in Iraq.

Methods: we evaluated the presence of JAK2, CALR, and MPL mutations in 158 patients. JAK2V617F mutation was assessed using either Allele specific PCR or quantitative PCR. JAK2 negative MPN patients were further assessed for the existence of CALR, MPL, or JAK2 exon 12 mutations by quantitative PCR.

Results: JAK2V617F mutation was detected in 97.9% and 61.7% of PV and ET patients respectively, while JAK2 exon 12 was found in 2.1% of PV patients. CALR mutation was identified in 38.3% of ET patients. PV patients had higher level of hemoglobin, hematocrit, WBC, and neutrophil counts, and had lower levels of platelet count when compared to ET. CALR mutation was more prevalent in younger age groups, while JAK2V617F mutation predominantly found in older age groups. Greater number of PV patients (34.7%) developed splenomegaly at diagnosis than ET (12.7%). More thrombotic events were observed in PV than ET patients, but the result did not reach statistical significance.

Conclusion: The incidence of JAK2V617F, JAK2 exon 12, and CALR mutations in Iraqi MPN patients was similar to the previously published literature. In addition, we reconfirmed some clinical features of PV and ET patients described in literature.

Keywords: *Myeloproliferative neoplasms; polycythemia vera; essential thrombocythemia; JAK2; CALR; MPL.*

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INTRODUCTION

Myeloproliferative neoplasm (MPN) is a rare heterogeneous group of disorders characterized by clonal over proliferation of haematopoetic stem cells in the bone marrow [1]. The American hematologist William Dameshek was the first to propose the concept of myeloproliferative disorder in 1951[2]. Dameshek described the disorder as an over production of fully differentiated blood cells.

In 2016 the World Health Organization classified the BCR-ABL1 rearrangement negative MPNs mainly into polycythemia vera (PV), essential thrombocythemia (ET), or primary myelofibrosis (PMF) [3]. The progression in genetic research had increased our understanding to the molecular basis of MPN.

At present, it is well-known that mutations in the tyrosine kinase receptor and other related genes lead to auto-activation of the receptor and lead to augmented activation of the JAK-Stat pathway, which in turn result in continues production of different blood cells regardless the presence of stimulus [4].

The diagnostic criteria of MPN have greatly improved after the discovery of JAK2V617F mutation in about 95% of patients with PV, 50-60% of ET, and 50% of PMF patients [5]. Shortly after this significant discovery, most JAK2V617F negative PV patients were found to have a gain of function mutations in JAK2 exon 12 [6] Subsequently, mutation in the thrombopoietin receptor (MPL) gene in exon 10 was identified in about 3-5% of ET, and 5-8% of PMF patients who are not carrying JAK2 mutation [7]. Lately, somatic mutations in CALR gene that encodes for the calreticulin protein were implicated in pathogenesis of MPN. CALR mutations, were identified in the majority of JAK2 negative ET and PMF patients [8,9]. A bout 70 types of CALR mutations were reported to occur in MPN patients. All of them are frameshift mutations (insertion or deletion) in the terminal sequence of exon 9 [9].

Advancing in the molecular diagnosis of MPN allow the incorporation of these mutations as molecular biomarkers in the WHO diagnostic criteria of MPN. The isotopic method used to detect the increase in red cell mass (RCM) was the main criterion for the diagnosis of PV. At the moment, the use of this method is limited to few centers. Besides, the hematocrit and hemoglobin levels are considered as a substitute marker of increase RCM [10]

Splenomegaly is considered as a major clinical manifestation of MPN, associated with disturbing symptoms, including early satiety, weakness, abdominal pain and even may progress into a more serious complication such as cytopenias as a result of splenic sequestration. A mild to moderate splenic enlargement was reported in about 5-20% of ET [11], and 20-75% of PV patients [12]. Less common symptoms associated with ET and PV is the hepatomegaly and the thrombotic events.

Our aim in this study is to describe the prevalence of major mutations in JAK2V617F, JAK2 exon 12, CALR, and MPL genes in Iraqi patients with BCR-ABL rearrangement negative MPNs. Additionally we inspected the clinical and hematological phenotypes at time of diagnosis of 48 patients with polycythemia vera and 47 patients with essential thrombocythemia.

METHODS

Patients and samples

Blood samples from 158 MPN suspected patients was collected in EDTA tubes at the Medical City, Baghdad Hospital, department of hematology, and the National Center of Hematology / Mustansiriyah University from December 2021 through May 2022. The diagnosis of 48 patients with PV and 47 patients with ET were established according to the 2016 World Health Organization (WHO) criteria for the diagnosis of MPN. This study was approved by the Ethical Committee of the institution. A verbal consent was obtained from the enrolled patients. Relevant clinical information was reported at time of diagnosis.

DNA was extracted from peripheral blood samples using QIAamp DNA Micro Kit (QIAGEN, Germany, cat. no 51304 and 51306) or ReliaPrep blood gDNA Miniprep system (Promega, USA, cat. No. A5081), collected in EDTA tubes and subsequently quantified using spectrophotometer (Qubit 4 flowmeter from thermo-fisher scientific).

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JAK2V617F mutation was assessed in all MPN suspected patients using either Allele specific PCR as described in previously published protocol [13] or JAK-2 quantitative real time PCR kit (SNP, TURKY, Cat. No: 21QR-10-01) according to the manufacturer's instruction. Patients with non-mutated JAK2 were assessed for the existence of CALR exon 9 (Type 1, Type 2 and other mutations), MPL exon 10 (W515L, W515K mutations), or JAK2 exon 12 mutations (between amino acids 530-547) using SNP biotechnology MPN screening kit (TURKEY, cat. No: 23R-20-10) according to the instruction protocol.

Statistical analysis

Statistical analysis of obtained data were performed using the Minitab statistical software. Anderson–Darling test was used to check data normal distribution. Numerical variables had been summarized as median and range and the categorical variables as count and relative frequency (%). Difference in the distribution of quantitative variables between groups were analysed using unpaired two sample T-test or the nonparametric Mann- Whitney test. Patients groups with qualitative variables were compared using the Fisher exact test. P values < 0.05 were considered to indicate statistical significance.

RESULTS

This is a cross sectional consecutive study, included 155 patients who were suspected to have BCR-ABL rearrangement negative MPNs and had their relevant clinical information available. Genetic studies confirmed the diagnosis for 95 patients (48 PV and 47 ET). This represents about 61 % of the recruited cohort as shown in (figure1).

Table 1 displays the mutation prevalence in MPN patients. We had noted that the frequency of JAK2V617F mutation in MPN patients was 80%; 61.7% in ET; and 97.9% in PV (P< 0.001). One PV patient had JAK2 exon 12 mutation and mutually exclusive with JAK2V617F mutation. Furthermore, 18 (38.3%) ET patients were found to have CALR mutation. We were not able to detect MPL mutation in the study population. In addition, we analysed the characteristics of MPN patients including the age, gender, and BMI. The median age of the study cohort was 59 years (range, 14-90). PV patients were significantly older than patients with ET (P<0.04). To further investigate the distribution of mutation types in MPN patients per age decades, we classified MPN patients into 9 age groups (figure 2). JAK2V617F mutation was more prevalent in the two oldest age groups in addition to the 60-69, and 20-29 age groups. However, the youngest age group contains one patient harboring CALR mutation.

Although, there was different gender distribution among MPN subtypes with more men presented with PV than ET, this difference did not reach the statistical significance level. Moreover, no significant difference in BMI was observed between PV and ET patients. It is worth noting that the number of smokers, former smokers, and the non-smokers in PV and ET patients were not significantly different.

In this study, we investigated the hematological and clinical features of MPN patients (table 2). Unsurprisingly, hemoglobin and hematocrit levels were significantly (P<0.001) higher in PV than ET patients. The leukocyte, and absolute neutrophils counts were significantly (P<0.001) greater in PV patients, when compared to ET patients. In contrast, no significant differences were noted in eosinophil, basophil, and monocyte counts between patients with PV and ET.

Obviously, ET patients had significantly (P<0.001) higher levels of platelets than PV with a median of 856.6*109/L VS 562.5*109/L respectively. Next, we attempted to analyze the clinical manifestations of MPN in Iraqi patients and to detect which disease has more aggressive course. We found out that about 8.4% of MPN patients had hepatomegaly at diagnosis, 24.2% had splenomegaly, and 5.3% had hepatosplenomegaly. Fisher exact test revealed no difference in the fractions of PV and ET patients with hepatomegaly, and hepatosplenomegaly. Alternatively, greater (P<0.01) proportion of patients with PV developed splenomegaly at diagnosis (35.4%) than ET (12.5%).

In addition, the current results showed that the thrombotic events were more common in PV patients than ET, although no statistical significance was reached (figure 3).

DISCUSSION

The understanding of the myeloproliferative neoplasms has greatly developed since the first description by Dr. Dameshek [2]. Despite the consecutive discoveries in the molecular bases of MPN, differentiating subtypes is still a complicated matter which needs thorough cooperation between clinical and laboratory data. The discovery of JAK2V617F [14], CALR [8,9], MPL [15], and JAK2 exon 12 [6] somatic driver mutations was the most exciting progression in the molecular diagnosis of BCR- ABL rearrangement negative MPN. Testing for the presence of these mutations are mandatory in MPN patients, as they represent diagnostic and prognostic markers in addition to their potential of becoming a therapeutic target in the treatment of MPN patients.

In the present study cohort, we analyzed the prevalence of JAK2 V617F, CALR, MPL, and JAK2 exon 12 mutations in Iraqi patients. These results are supporting the suggestion of inclusion JAK2V617F, CALR, and JAK2 exon 12 mutations as major criteria for the diagnosis of BCR-ABL rearrangement negative MPN [3]. In our study, JAK2V617F mutation represent the overwhelming type of mutation affected about 80% of MPN patients, 97.9% of PV patients, and 61.7% of ET patients. These results are comparable to previous publications in which JAK2V617F mutation was identified in about 80-95% of PV patients and 20-70% of ET patients [13,16,17]. Similar to previously published reports, JAK2 exon 12 mutation has been described in 3.1% of PV patients [18,6]. No other types of tested mutations were detected in PV patients [8]. Therefore, patients carrying mutation in CALR or MPL genes should be excluded from the diagnosis of PV. As reported in previous literatures, CALR exon 9 mutations are the second most common type of mutations in MPN after JAK2V617F [8,19]. In the current study cohort, the prevalence of CALR mutation was 18.95% in MPN, and 38.3% in ET patients. MPL mutation could not be detected in the current cohort. This result is similar to a recently published systemic review and meta-analysis who showed that the prevalence of MPL mutation in PV patients was 0% [20]. Meanwhile, the relatively small number of ET patients included in the current study cohort and the rare occurrence of the mutation in ET patients (0.9-12.4%) [20] might be the reason as to why we were not able to detect the MPL mutation in the present cohort of patients.

By evaluating the age of MPN patients carrying different kind of mutations, we found that CALR mutations tend to be more prevalent in the younger age groups while, JAK2V617F mutation predominantly found in the older age groups. Likewise, patients with polycythemia were older than patients with ET, this may be due to high prevalence of JAK2V617F mutation among PV patients. Our results are in the general line with the work published by Lin et al (2015) [19] who suggested that CALR mutant patients were younger than patients harboring JAK2V617F mutation. Pietra et al (2011) [21] found that JAK2 exon 12 mutation predominantly found in the middle and young age patients. This was similar to the result from our study, as we detected JAK2 exon 12 mutation in one middle age patient.

Despite the equivalent gender distribution in the study population, we noted a remarkable gender discrepancy between patients with PV, with more male being diagnosed with PV (male 62.5% and female 37.5%) [22]. In contrast, no significant difference was observed in the gender distribution among ET patients (male 46.8% and female 53.2%), this is different from earlier results that support higher prevalence of female among ET patients [18]

The shared mutation type and the overlapping laboratory and clinical characteristics made it difficult to distinguish between early PV and ET patients especially when iron deficiency cannot be excluded or the red cell mass is unapproachable. Discriminating these diseases in the early stages has clinical significance. The diagnosis of PV and ET in most hematology centers is based on the criteria defined by the WHO. In the current study, we compared the laboratory and clinical characteristics of patients with ET and PV diagnosed according to the WHO criteria. PV patients appeared to have higher hemoglobin, and hematocrit levels allowing clear distinction between PV and ET. Although, about 71% of PV patients had platelets count more than 450*10^9/L, but still the median platelets count was higher in ET patients with a marginal overlap. Moreover, the total leukocytes, and absolute neutrophil counts were higher in PV patients than ET patients. These findings are similar to the previous observation on ET and PV patients [23].

Pearson and Wetherley- Mein (1978) [24] had demonstrated that hematocrit level directly affect the frequency of thrombotic events in PV patients. This is similar to what we observed in this study, PV patients had higher frequency of thrombotic events which were the consequences of high hematocrit level.

Splenomegaly is a major clinical manifestation in MPN patients. It causes discomfort and affect the quality of life of those patients. In our study, 34.7% of PV patients and 12.7% of ET patients developed splenomegaly at diagnosis. Our results are consistent with previous publications. In a large study including 587 patient with PV revealed that 31% of them had splenomegaly at diagnosis [25]. Another study included 238 patients with ET showed that 15.54% of them had splenomegaly at diagnosis [26].

The most important limitation in the present study was the absence of MPL mutation status in MPN patients. The possible reasons were the small number of patients in our study cohort and low frequency of MPL mutation in MPN patients [15,27].

In conclusion, in the current study we reconfirmed some of the distinctive laboratory and clinical features of PV and ET patients described in prior publications. Furthermore, we showed that the incidence of JAK2V617F, JAK2 exon 12, and CALR mutations was similar to previously published literature.

Statements and declarations

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TABLE 1: Baseline characteristics of PV and ET patients at diagnosis.

	All MPNs N (95)	PV N (48)	ET N (47)	P value
Age (years) median (Range)	59 (14-90)	64 (24-83)	52 (14-90)	<0.04
Gender (%):				
Male	52 (54.7%)	30 (62.5%)	22 (46.8%)	NS
Female	43 (45.3%)	18 (37.5%)	25 (53.2%)	NS
BMI (kg/m²) (range)	27.4 (17.3-42.3)	27.6 (17.3-32.7)	27.2 (20.3- 42.3)	NS
Smoking status (%):				
Never	77 (81%)	38 (79.2%)	39 (83%)	NS
Current	6 (6.3%)	4 (8.3%)	2 (4.2%)	NS
Former	12 (12.6%)	6 (12.5%)	6 (12.8%)	NS
Mutation Status (%):				
JAK2V617F	76 (80%)	47 (97.9%)	29 (61.7%)	<0.001
JAK2 exon12	1 (1.05%)	1 (2.1%)	0 (0%)	NS
CALR	18 (18.95%)	0 (0%)	18 (38.3%)	<0.001
MPL	0 (0%)	0 (0%)	0 (0%)	NS

BMI, body mass index; MPN, myeloproliferative neoplasm; PV, polycythemia vera; ET, essential thrombocythemia. Data is expressed as median and range, or as relative frequencies. NS = Not significant.

TABLE 2: The Hematologic and Clinical characteristics of MPN Patients.

	All MPNs N (95)	PV N (48)	ET N (47)	P value
Hemoglobin (g/dL)	16.2 (9.99-23)	17.3 (16.2-23)	12.53 (9.99-15.2)	<0.001
Hematocrit (%)	48 (30.8-72)	54.65 (45.8-72)	39 (30.8-49.3)	<0.001
Leukocyte (*10³/µL)	11.69 (5.07-47.1)	13.63 (7.55-47.1)	10.09 (5.07-22.29)	<0.001
neutrophils (*10³/µL)	8.1 (2.39-32.9)	10.38 (3.69-32.9)	6.93 (2.39-16.16)	<0.001
Eosinophils (*10³/µL)	0.25 (0.01-1.49)	0.287 (0.01-1.09)	0.22 (0.04-1.49)	NS
Basophils (*10³/µL)	0.13 (0.02-1.18)	0.142 (0.02-0.76)	0.10 (0.22-1.18)	NS
Monocytes (*10³/µL)	0.56 (0.01-8.42)	0.64 (0.01-8.42)	0.47 (0.04-1.51)	NS
Platelets (*10^3/µL)	731 (168-1928)	562.5 (168-1500)	856.6 (435-1928)	<0.001
Hepatomegaly (%)	8 (8.4%)	6 (12.5%)	2 (4.2%)	NS
Splenomegaly (%)	23 (24.2%)	17 (35.4%)	6 (12.7%)	<0.01
Hepatosplenomegaly (%)	5 (5.3%)	4 (8.3%)	1 (2.1%)	NS

MPN, myeloproliferative neoplasm; PV, polycythemia vera; ET, essential thrombocythemia. Data is expressed as median and range. NS = Not significant.

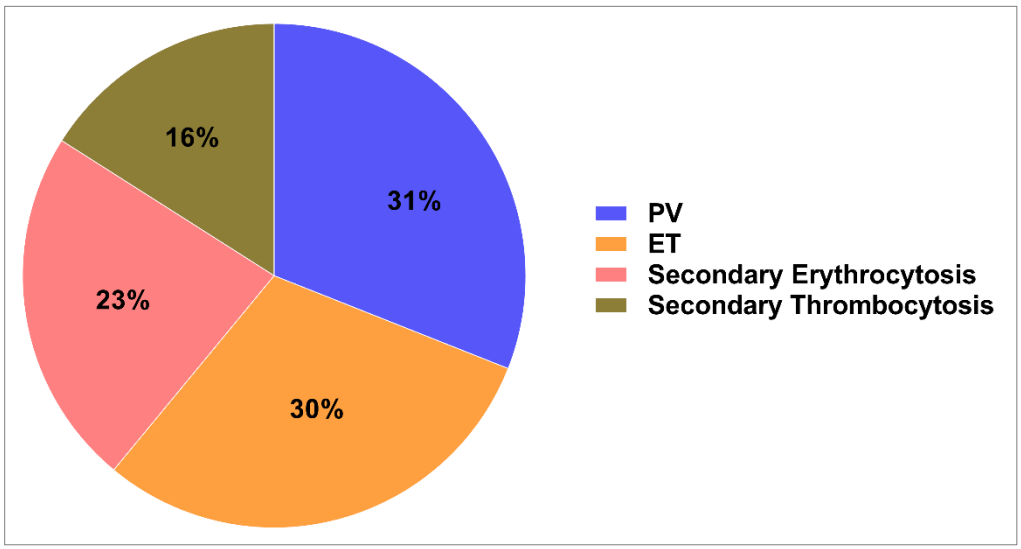

FIGURE 1: Diagnosis distribution of patients

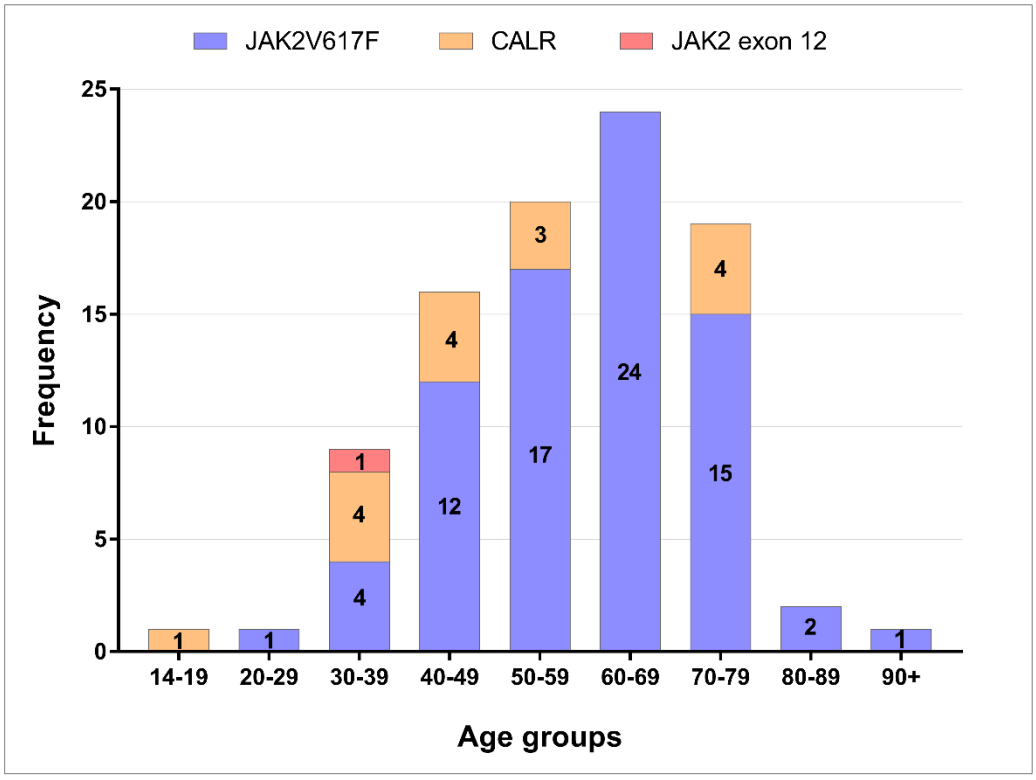

FIGURE 2: Frequency distribution of mutations at different age groups

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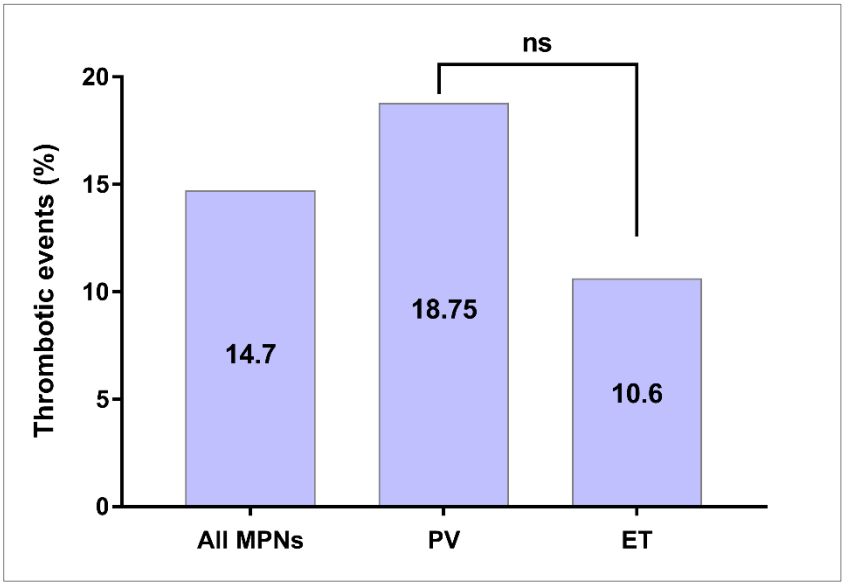

FIGURE 3: Thrombotic events in MPN patients.

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