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The Prevalence of Myeloproliferative Disorders in A Group of Iraqi Patients And Its Relation To Blood Indices Parameters

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Abstract

AIM: The aim of this study was to measure the prevalence of myeloproliferative disorders in a sample of Iraqi patients and to measure the changes in patients' blood parameters.

BACKGROUND: Myeloproliferative disorders are a group of neoplasms affecting the bone marrow progenitor cells characterized by excess cells with a risk of transforming to acute leukemia. There is a gap in knowledge about the prevalence of Iraqi population. Thus, we investigated the prevalence and distribution of different types of myeloproliferative disorders in a sample of Iraqi patients.

MATERIALS AND METHODS: Cross-sectional study is done at the National Center of Hematology from November 2019 till March 2020 on 75 patients who were diagnosed by a specialist hematopathologist to have one subtype of myeloproliferative disorders (MPDs). Blood samples were taken from them and analyzed to get complete blood count, blood film, bone marrow aspirate, and biopsy that were analyzed for each patient. Blood samples were taken from them and analyzed in terms of blood indices, which include red blood cells, white blood cells, and platelets.

RESULTS: The 75 patients were found to be comprising 35 chronic myelogenous leukemia (CML) patients (46.7%), myelofibrosis 22 patients (29.3%), essential thrombocythemia (ET) 9 patients (12%), and polycythemia vera (PV) 9 patients (12%). In terms of male/female ratios, they were as follows: Myeloproliferative neoplasms (MPNs) male-to-female ratio is 1.2, CML= 0.94, myelofibrosis= 2.14 and ET= 0.5 and PV male-to-female ratio is 2.

CONCLUSIONS: MPN male-to-female ratio in Iraq, which is 1.2, CML is the most common subtype. Regarding myelofibrosis, in our study, the male-to-female ratio is 2.14, which is much higher other countries. This could be attributed to high exposure to benzene and toluene which are well known to be causative agents for myelofibrosis. Regarding ET or PV, the male-to-female ratios were compatible with other countries.

Introduction

Myeloproliferative neoplasms (MPNs) are a category of bone marrow illnesses that contain excess cells, previously known as myeloproliferative disorders. They are connected to myelodysplastic syndrome and acute leukemia and can develop them, but overall myeloproliferative diseases have a far better prognosis.

This type of disease was changed from "myeloproliferative diseases" to "myeloproliferative neoplasms" in the World Health Organization's new classification of hematologic malignancies [1]. This reflects the clonally underlying genetic differences which are a central aspect of this disease group.

Classification: In 2016, MPD types were listed by the World Health Organization [2]:

1. Chronic myelogenous leukemia (BCR-ABL1–positive) (CML)
2. Chronic neutrophilic leukemia
3. Polycythemia vera (PV)
4. Primary myelofibrosis
5. Essential thrombocythemia (ET)
6. Chronic eosinophilic leukemia (not otherwise specified)
7. Mastocytosis.

Causes

All MPNs originate from the myeloid lineages precursors in the bone marrow. MPNs are attributed to DNA mutations. These mutations were studied thoroughly:

1. Philadelphia chromosome-negative cases have MPL or JAK2 mutation [1]
2. CALR mutations were found in [3] JAK2 and MPL-negative myelofibrosis and ET [4]
3. Others: Mutations in the genes LNK, CBL, TET2, ASXL1, IDH, and IKZF1 [5].

Diagnosis

Diagnostic tests may involve an assessment of red cell mass (for polycythemia), aspiration to the bone marrow, depending on the existence of MPN and trephine biopsy, levels of arterial oxygen, and carboxyhemoglobin, alkaline neutrophil, Vitamin B12, serum urate [6], or DNA sequencing [7].

Aim

The aims of this study were as follows:

1. To measure the prevalence of myeloproliferative disorders in a sample of Iraqi patients
2. To measure the changes in patients' blood parameters.

Materials and Methods

A cross-sectional study was done at the National Center of Hematology/Baghdad/Iraq from November 2019 till March 2020 on 75 patients who were diagnosed by a specialist hematopathologist to have one subtype of MPDs. Inclusion criteria: Any patient with MPD, regardless of age and gender, was included in the study. Exclusion criteria: None.

Blood samples were taken from them and analyzed to get a complete blood count using an automated electronic counter (hematology auto-analyzer - BECKMAN COULTER, ACT. 5 diff. USA). Blood samples were taken from them and analyzed in terms of blood indices which include red blood cells (RBCs), white blood cells (WBCs), and platelets.

Blood film, bone marrow aspirate, and biopsy were analyzed for each patient.

The study protocol was approved by our Institutional Review Board and conformed to the principles of the Declaration of Helsinki. After obtaining formal written consent from each patient, data were prepared as frequencies, relative frequencies.

Data were presented in frequencies and percentages and analyzed using Student T-test and ANOVA test when applicable using Graph pad 8 software and p = 0.05 as the significance level.

Results

Seventy-five patients were enrolled in this study, males 41 (54.7%) and females 34 (45.3%) with their blood indices, as shown in Table 1.

Then, patient samples were analyzed in-depth for blood indices according to sex (Table 2).

Blood film samples analysis is shown in Table 3, showing the prevalent hematologic phenotypes. The most common are CML (13 cases) and leukocytosis with the left shift (12 cases).

Table 1: Absolute blood indices of recruited patients in terms of mean and standard deviation and range

Parameters	Mean ± SD	(Range)
WBC count (×10^3)/µl	62.35 ± 71.91	(2.06–243.96)
Neutrophils (×10^3)/µl	52.23 ± 62.72	(0.66–218.1)
Lymphocytes (×10^3)/µl	5.73 ± 5.59	(0.68–25.45)
Monocytes (×10^3)/µl	1.48 ± 2.16	(0.03–11.72)
Eosinophils (×10^3)/µl	0.68 ± 0.99	(0–4.47)
Basophils (×10^3)/µl	2.25 ± 4.46	(0–20.94)
RBC count (×10^6) /µl	4.54 ± 1.86	(0.1–8.5)
Hb g/l	12.16 ± 3.25	(3.7–22.5)
HCT l/l	34.79 ± 11.28	(9.8–66.4)
MCV Fl	77.73 ± 13.21	(28–125.1)
MCH Pg	29.69 ± 10.32	(14.8–75.7)
MCHC g/l	36.65 ± 9.02	(26.5–79.5)
RDW %	19.26 ± 5.87	(10.9–42)
Platelets count (×10^3)/µl	402.60 ± 285.21	(15.4–1184)

RBC: Red blood cells, WBC: White blood cells.

Table 2: Absolute blood indices of recruited patients (males and females) in terms of mean and standard deviation and range (in brackets)

Parameters	Male (n=41)	Female (n=34)	p-value
WBC count (×103)/µl	55.5 ± 69.6 (2.51-212.23)	70.6 ± 74.9 (2.06-243.96)	0.370
Neutrophils (×103)/µl	46.4 ± 59.3 (0.66-187.4)	59.3 ± 66.9 (1.07-218.1)	0.381
Lymphocytes (×103)/µl	5.22 ± 5.49 (0.68-20)	6.34 ± 5.73 (0.77-25.45)	0.391
Monocytes (×103)/µl	1.29 ± 2.03 (0.04-10)	1.69 ± 2.31 (0.03-11.72)	0.427
Eosinophils (×103)/µl	0.51 ± 0.77 (0-3.45)	0.88 ± 1.18 (0.01-4.47)	0.101
Basophils (×103)/µl	2.10 ± 4.44 (0-20.94)	2.43 ± 4.54 (0-18.23)	0.750
RBC count (×106) /µl	4.79 ± 1.94 (0.1-8.2)	4.23 ± 1.73 (1.6-8.5)	0.198
Hb g/l	12.58 ± 3.62 (3.7-22.5)	11.66 ± 2.72 (5.3-19.3)	0.225
HCT l/l	36.57 ± 12.01 (9.8-66.4)	32.64 ± 10.10 (16.3-57.7)	0.134
MCV Fl	75.6 ± 13.1 (28-96.1)	80.4 ± 13.0 (54.8-125.1)	0.117
MCH Pg	29.45 ± 12.03 (14.8-75.7)	29.98 ± 7.98 (18.6-49)	0.827
MCHC g/l	36.13 ± 9.56 (26.5-79.5)	37.28 ± 8.41 (29.5-63.8)	0.587
RDW %	18.45 ± 4.58 (11.8-35.1)	20.23 ± 7.07 (10.9-42)	0.191
Platelets count (×103)/µl	354.0 ± 245.3 (15.4-921)	461.2 ± 320.9 (59-1184)	0.106

*Significant difference between two independent means using Student-t-test at 0.05 level. RBC: Red blood cells, WBC: White blood cells.

Table 3: Hematologic phenotypes according to the analysis of blood film

Blood film	No
CML	13
Dicytopenia	7
Dicytopenia with neutrophilia	1
Dicytosis	4
Hypochromic microcytic anemia with leukocytosis	1
Hypochromic normocytic RBCS	1
Hypochromic RBCs with erythrocytosis	1
Leukocytosis with left shift	12
Mild normochromic anemia with relative neutrophilia	1
Moderate normochromic anemia	1
Moderate normochromic anemia, relative neutrophilia	1
MPN	4
MPN mostly CML	14
MPN mostly ET	1
Normochromic anemia	2
Pancytopenia	3
Pancytosis	5
Thrombocytosis	2
Thrombocytosis and leukocytosis	1

RBC: Red blood cells.

The analysis of bone marrow aspirate, as shown in Table 4, reveals that the prevalent hematologic phenotype is CML (21 cases) as the most common.

Table 4: Hematologic phenotypes according to the analysis of bone marrow aspirate

BM aspirate	No
CML	27
Dry tap	21
MPN	14
MPN (CML)	4
MPN mostly ET	5
MPN mostly PV	3
Normo cellular marrow	1

The analysis of bone marrow aspirate, as shown in Table 5, reveals the hematologic phenotypes with MPN, mostly CML, as the most prevalent (24 cases). There are two types of ET: one with fibrosis and the other is without. This means that there is a

fibroblastic reaction in BM of these patients which could be alarming findings of progression or transformation of ET to mycosis fungoides (MFs) disease.

Table 5: Hematologic phenotypes according to the analysis of bone marrow biopsy

BM biopsy	No
CML	30
MPN	3
MPN (CML)	2
MPN (myelofibrosis)	1
MPN mostly ET	6
MPN mostly ET with fibrosis	2
MPN mostly MF	1
MPN mostly PV	9
Myelofibrosis	21

MF: Mycosis fungoides

Then, final diagnosis of patient samples with frequency and percentages of total is shown in Table 6.

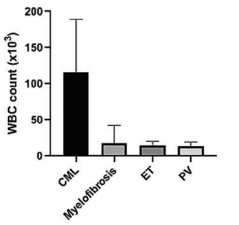
Table 6: The subtype of MPN of patient samples showing the types frequency and percentage from total

Final diagnosis	No	%
CML	35	46.7
Myelofibrosis	22	29.3
ET	9	12.0
PV	9	12.0

By analyzing the samples according to blood parameters, we got the analysis first for WBC count, as shown in Table 7. CML has the highest WBC count

Table 7: WBC count in different types of myeloproliferative disorders in terms of mean ± SD and range. Data are illustrated in a relevant figure

Final diagnosis	No	WBC count (x10^3)/µl	
		Mean ± SD	Range
CML	35	115.8 ± 73.0	10.35–243.96
Myelofibrosis	22	17.1 ± 25.2	2.06–117.82
ET	9	14.1 ± 6.1	3.84–20.94
PV	9	13.3 ± 6.1	5.31–25.06
p-value		0.0001*	

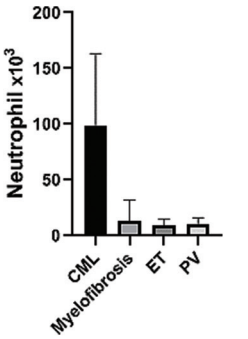


WBC: White blood cells.

Then, looking at the neutrophil count, we got Table 8 which shows CML with the highest neutrophil count as compared with other myeloproliferative disorders.

Table 8: Neutrophil absolute count in different types of myeloproliferative disorders in terms of mean±SD and range. Data are illustrated in a relevant figure

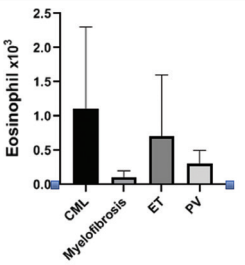
Neutrophil count (×10^3)/µl			
Final diagnosis	No	Mean ± SD	Range
CML	35	98.5 ± 64.7	8.02–218.10
Myelofibrosis	22	13.1 ± 18.9	0.66–86.01
ET	9	9.9 ± 5.2	2.34–16.75
PV	9	10.1 ± 6.1	2.60–23.65
P value		0.0001*	



The eosinophil count was highly variable, but it is the highest with CML (Table 9).

Table 9: Eosinophil count in different types of myeloproliferative disorders in terms of mean±SD and range. Data are illustrated in a relevant figure

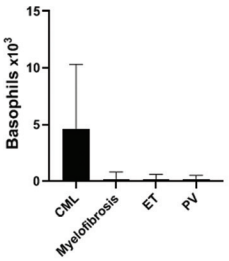
Eosinophil count (×103)/µl			
Final diagnosis	No	Mean ± SD	Range
CML	35	1.1 ± 1.2	0.04–4.47
Myelofibrosis	22	0.1 ± 0.1	0–0.40
ET	9	0.7 ± 0.9	0.06–3.00
PV	9	0.3 ± 0.2	0.02–0.45
p-value			



Similarly, the basophil count is the highest with CML (Table 10).

Table 10: Basophil count in different types of myeloproliferative disorders in terms of mean±SD and range. Data are illustrated in a relevant figure

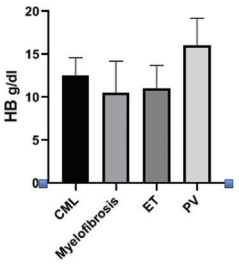
Basophil count (×103)/µl			
Final diagnosis	No	Mean ± SD	Range
CML	35	4.6 ± 5.7	0.07–20.94
Myelofibrosis	22	0.2 ± 0.6	0–2.59
ET	9	0.2 ± 0.4	0–1.20
PV	9	0.2 ± 0.3	0–0.74
p-value			



In terms of hemoglobin level, the highest level is with polycythemia, and the lowest is with meylofibrosis (Table 11).

Table 11: Hemoglobin level in different types of myeloproliferative disorders in terms of mean±SD and range. Data are illustrated in a relevant figure

Hb g/l			
Final diagnosis	No	Mean ± SD	Range
CML	35	12.5 ± 2.1	9.5–17.4
Myelofibrosis	22	10.5 ± 3.7	3.7–22.5
ET	9	11.0 ± 2.7	5.3–14.1
PV	9	16.0 ± 3.2	8.9–19.3
p-value		0.0001*	



Finally, platelets count is the highest with ET and the lowest with meylofibrosis (Table 12).

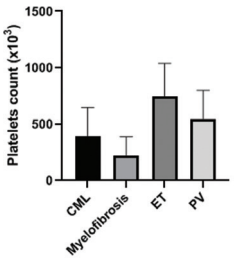
Discussion

Up to our knowledge, this is the first epidemiological study about MPNs in Iraq. The diversity

of the various types of MPN has made full characterization of their symptom profiles challenging. PV, ET, and MF may concurrently shorten survival and impair quality of life. For decades, gender differences in MPN have been observed and documented but remained of low investigational priority given the paucity of exploratory tools.

Table 12: Platelets count in different types of myeloproliferative disorders in terms of mean±SD and range. Data are illustrated in a relevant figure

Final diagnosis	No	Platelets count (×10^3)/μl	
		Mean ± SD	Range
CML	35	393.0 ± 254.9	59–1173
Myelofibrosis	22	218.9 ± 170.4	15.4–716
ET	9	748.5 ± 290.6	100.8–1184
PV	9	543.3 ± 256.1	156–1043.7
p-value		0.0001*	



Hematological indices, in terms of RBCs, they show a broad spectrum from anemia to erythrocytosis. The other related indices (Hg, MCV, MCH, MCHC, and RDW) follow a similar pattern from very low to very high levels.

Similarly, the platelet count varies from very low to very high counts.

Regarding WBCs, MPNs show signs of hypercellularity, in the form of a high number of WBCs, notably in CML. Other MPNs also have shown high WBCs count but much less than CML. This is also evident with neutrophil counts that are very high count with CML but much less with other MPNs.

In terms of eosinophils count, the CML and ET show elevated counts, while PV and myelofibrosis show counts within normal limits.

In terms of basophils, all MPNs show elevated counts.

These changes in blood indices reflect the dominant pathology affecting the bone marrow, whether it is hypercellularity or fibrotic in nature.

MPNs are well known for being more common in males than females. Our study shows male-to-female ratio to be 1.2, which is compatible with a Norwegian study male-to-female ratio is 1.2 for all MPNs [8]. Another Swedish study has shown male-to-female ration as 1.07 [9].

CML occurs more commonly in males across all age groups [8]. Norwegian registry constantly reported a male-to-female ratio 1.2–1.7 [10]. In our study, the ratio is 0.94. This can be explained by the low number of cases included in our study.

Regarding myelofibrosis, in our study, the male-to-female ratio is 2.14. Although it is more prevalent in males, the ratio is higher than that of the Swedish study, in which the ratio is 1.48 [9]. A study that was conducted in the USA has shown that the ratio is 1.83 [11]. Obviously, the prevalence in males is higher and this could be explained by the high exposure to benzene and toluene which are well known to be causative agents for myelofibrosis [12], [13], [14]. Toluene and benzene are natural ingredients of crude oil and gasoline [15]. Iraq is known to be highly polluted with these compounds as these compounds come from motor engines fuel combustion [16]. Iraq has an electricity shortage; thus, diesel generators are in every street emitting a lot of toxic fumes that would contain the carcinogenic compounds in addition to those emitted from cars.

Regarding ET, our study shows a male-to-female ratio of 0.5. This is compatible with the US study that shows the ratio to be 0.77 [11], while the Swedish study shows the ratio to be 0.81 [9].

Regarding PV, our study shows male-to-female ratio to be 2. This is compatible with the US study that shows a ratio of 1.83 [11], while the Swedish study reported a ratio of 1.48 [9].

Gender variations in MPN are not specific to hematological malignancies. Many diseases, such as acute lymphoblastic leukemia, chronic lymphocystic leukemia, and multiple myeloma, have shown similar discordance in sexual prevalence [17].

Although the etiological cause of this discord is obscure, the complement of the sex chromosome/aberrations/aneuploidy, influence of sex hormones, all contribute to immune competence, and gene expression [18], [19].

Research into these factors would be beyond the scope of this study, but in future studies, it would be worth exploring. The previous studies have shown that thrombotic risk typically differs among subtypes of MPN by sex [20].

The platelet count is much higher in CML and PV females, 415.9 ± 291.2 × 10^3 plt/μL and 763.7 ± 243.14 × 10^3 plt/μL, respectively, as compared with CML and PV males 368.6 ± 216.13 × 10^3 plt/μL and 433.11 ± 193.84 × 10^3 plt/μL, respectively, with a statistical significance $p < 0.0001$ as calculated by ANOVA test.

This finding explains the higher risk of developing thrombotic complications as mentioned by ECLAP study; female PV patients were more likely than males to suffer thrombotic complications (11% vs. 8%), particularly within the splanchnic system [21].

Gender also appears to influence the location of vascular events. A recent investigation identified that women were more likely to experience macro thrombosis within the abdominal venous system (hepatic, portal, mesenteric, or splenic veins), whereas males were more likely to experience events in the deep venous system, including limb thrombosis and pulmonary emboli [22]. While gender influence on thrombosis remains unclear, increasing evidence suggests that in the thrombotic

cascade, the type and ratio of circulating sex hormones play a significant role [17].

Limitations of the study were the low number of patients and the unavailability of advanced techniques (mentioned in the introduction) like the genetic study to confirm the diagnosis.

One obstacle that we have faced is the high number of dry tap which affected 21/74 (28.3%) of bone marrow aspirates. Basically, the dry tap is relatively common finding with bone marrow aspirates. A study conducted in Pakistan reported the prevalence of 9.5% of all bone marrow aspirates, while another study conducted in the USA showed a ratio of 3.9% [23]. Dry tap occurs when there is a fibrotic reaction that is primary like in myelofibrosis, or secondary reaction to hypercellularity which is a common finding in MPNs [24].

Conclusions

MPN male-to-female ratio in Iraq, which is 1.2. CML, is the most common subtype. Regarding myelofibrosis, in our study, the male-to-female ratio is 2.14, which is much higher in other countries. This could be attributed to high exposure to benzene and toluene which are well known to be causative agents for myelofibrosis. Regarding ET or PV, the male-to-female ratios were compatible with other countries. The platelet count is much higher in CML and PV females than males. This explains the higher risk of thrombotic complications in such patients.

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