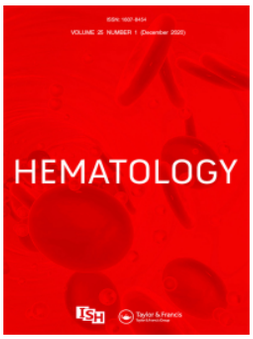

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The characteristics of *CALR* mutations in myeloproliferative neoplasms: a clinical experience from a tertiary care center in Qatar and a literature review

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ABSTRACT

Background: Myeloproliferative neoplasms (MPNs) are hematological disorders characterized by abnormal production of myeloid cells due to genetic mutations. Since 2013, researchers have identified somatic mutations in the Calreticulin (CALR) gene, primarily insertions or deletions, in two Philadelphia chromosome-negative MPNs; essential thrombocytosis (ET) and primary myelofibrosis (PMF), and occasionally in chronic myelomonocytic leukemia (CMML). This study aims to identify the various types of CALR mutations and their impact on CALR-positive MPN patients' clinical manifestations and outcomes.

Methods: A single-center retrospective study was conducted. The data was collected from pre-existing records. The study was carried out on Philadelphia-negative MPN patients who were being followed up on at the NCCCR (National Center for Cancer Care and Research) to assess the clinical manifestation and outcome of disease treatment. All patients included, were followed in our center between January 1, 2008, and November 20, 2021.

Results: A total of 50 patients with *CALR*-positive MPN were reviewed with a median follow-up of three years (1–11). This cohort included 31 (62%) patients with ET, 10 (20%) patients with PMF, and 9 (18%) patients with prefibrotic myelofibrosis (pre-MF). The study involved 38 (76%) male and 12 (24%) female patients. There were 16 (32%) patients diagnosed before the age of 40, 24 (48%) patients diagnosed between the ages of 40 and 60; and 10 (20%) patients diagnosed after the age of 60. Molecular analysis showed 24 (48%) patients with *CALR* type 1, 21 (42%) patients with *CALR* type 2, and 5 (10%) patients with none Type 1, none Type 2 *CALR* mutations. Two patients have double mutations; 1(2%) with none Type 1, none Type 2 *CALR* and *JAK2* mutations, and 1(2%) with *CALR* type 1 and *MPL* mutations. The thrombotic events were 3 (6%) venous thromboembolisms, 3 (6%) abdominal veins thromboses, 2 (4%) strokes, and 4 (8%) ischemic cardiac events. Only 4 (8%) patients progressed to Myelofibrosis and were carrying *CALR* 1 mutations, and 1 (2%) patient progressed to AML with *CALR* 2 mutation.

Conclusion: The data shows a significant rise in CALR-positive MPN diagnoses in younger people, emphasizing the need for a better assessment tool to improve disease management and reduce complications.

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Myeloproliferative neoplasms; CALR mutation; thrombosis; essential thrombocytosis; myelofibrosis

Introduction

The term myeloproliferative disorders, now known as myeloproliferative neoplasms (MPN), was first coined in 1951 to describe a group of overlapping hematological disorders that eventually lead to inappropriate production of mature myeloid cells [1]. In 1960, the Philadelphia chromosome was first identified in two chronic myeloid leukemia (CML) patients [2]. Later, in 1973, the reciprocal translocation between chromosomes 9 and 22 constituting the Philadelphia chromosome was discovered, subsequently known to harbor the *BCR-ABL* mutation [3]. Since then, the classic MPN has been divided broadly into Philadelphia chromosome-positive (Chronic Myeloid Leukemia – CML) and Philadelphia chromosome-negative (Polycythemia Vera – PV, Essential Thrombocythemia – ET, and Primary Myelofibrosis – PMF). Further research into the Philadelphia chromosome-negative MPN category has led to the discovery of *Janus Kinase 2* (*JAK2*) mutation in 2005 and *Myeloproliferative Leukemia virus oncogene* (*MPL*) mutation in 2006 [4, 5]. The latest breakthrough in this field was made in 2013 with the identification of *Calreticulin* (*CALR*) mutation in ET and PMF [6].

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The *CALR* gene is located in chromosome 19p13.2 and encodes for the Calcium-binding protein Calreticulin [6]. *CALR* plays a vital role in protein folding and calcium homeostasis when located in the endoplasmic reticulum (ER). While it is mainly found in the ER, it has become evident that it is also present in the cytosol, cell membrane, and extracellular matrix, with a wide range of biological effects that are not fully revealed yet [7]. Since its discovery, several studies have identified multiple frameshift mutations in *CALR* that eventually lead to *JAK/STAT* signaling activation in ET and PMF patients with non-mutated *JAK2* or *MPL* [8]. These *CALR* mutations have produced disease phenotypes that are clinically distinct from the well-known manifestations of MPN [9]. In our study, we aim to identify the clinical characteristics of *CALR* mutations in Qatar and provide a summary of the significant articles addressing this topic up to this date.

Materials and methods

This retrospective study was conducted on Philadelphia-negative MPN patients under follow-up at the National Center for Cancer Care and Research (NCCCR). The primary aim was to evaluate the disease's clinical manifestation and treatment outcomes. All participants were previously followed at our center between January 1, 2008, and November 20, 2021.

Study population

We reviewed the records of about 100 patients from the NCCCR in Qatar, from which 50 patients met our inclusion criteria and were included in the study.

Inclusion criteria

Adult patients aged 18 years or older diagnosed with Philadelphia-negative MPN (ET, PV, MF, and prefibrotic myelofibrosis – Pre-MF) based on the 2008 and 2016 WHO criteria, and tested positive for any of the *CALR* mutations at the NCCCR between 2008 and 2021.

Exclusion criteria

MPN patients with Philadelphia-positive or other genetic mutations.

Sequencing analysis

DNA sampling have undergone molecular analysis for mutations within exon 9 of the *CALR* gene using fragment analysis and DNA sequencing. We observed 36 different types of *CALR* mutations, all of which were somatic insertions or deletions in exon 9. The sensitivity of fragment analysis for detection of type 1 and type 2 mutations is approximately 5%. Sensitivity of detection for other mutation types may vary up to approximately 10%. Genbank accession number is NM004343.3. Mutation nomenclature is according to HGVS guidelines.

Statistical analysis

We used descriptive statistics to present the demographic data of the study cohort. We classified *CALR* mutations as type 1, 2, or other (none Type 1, none Type 2). Continuous variables were summarized as mean (SD) and median (IQR), while categorical variables were summarized as percentages. We compared continuous parametric variables using unpaired t-tests and ANOVA. Man-Whitney U and Kruskal – Wallis tests compared non-parametric continuous data. We used the Chi-square test to compare categorical variables.

Results

We reviewed 50 patients with *CALR*-positive MPN who presented to our tertiary care center in Qatar. The median follow-up duration was three years. The baseline characteristics of the study population is summarized in Table 1 and subcategorized further according to the *CALR* mutations in Table 2. Most of the patients were diagnosed with ET (31, 62%). The rest were having PMF (10, 20%) and pre-MF (9, 18%). Our population was predominantly males (38, 76%), Arabs (27, 54%), and relatively young (40, 80% below the age of 60). Most *CALR* mutations were type 1 (24, 48%). Type 2 mutations were (21, 42%) and the none Type 1, none Type 2 *CALR* mutations were (5, 10%). The patients were treated with hydroxyurea (22, 44%), *JAK2* inhibitor (6, 12%), anagrelide (1, 2%), and antiplatelet (36, 72%). The complication rates were relatively low with ischemic cardiac events being the highest (4, 8%), followed by venous thromboembolisms (3, 6%), abdominal veins thromboses (3, 6%), strokes (2, 4%). It is also noted that the cardiac events were preferentially occurring the most in the none Type 1 none Type 2 *CALR* mutation with statistical significance. The progression of *CALR*-positive MPNs to Myelofibrosis and acute myeloid leukemia (AML) was rare (4, 8% and 1, 2% respectively). We reported one mortality case, and that happened in the *CALR* type 2 group. One patient with *CALR* type 1 mutation had a concurrent *MPL* mutation, and one patient with non-type 1, non-type 2 *CALR* mutation had a concurrent *JAK2* mutation. We saw a trend towards lower levels of hemoglobin, White cell counts, and platelets in *CALR* type 1 compared to other mutations. We also noted the development of secondary malignancies happened only in the *CALR* type 1 mutation group.

Discussion and conclusion

CALR mutations have been identified in two of the three classic Philadelphia chromosome-negative

Table 1. Baseline characteristics of patients with CALR mutation in myeloproliferative neoplasm

Characteristic	*CALR* Mutated MPN Patients (N = 50), n (%)
Male Gender	38 (76%)
Age At Diagnosis	
<40 years	16 (32%)
40–60 years	24 (48%)
>60 years	10 (20%)
Weight (kg, mean)	77.5
Height (cm, mean)	169.9
Ethnicity	
Asian	15 (30%)
Black/African	6 (12%)
White	2 (4%)
Arabs	27 (54%)
Comorbid Medical Conditions	
Diabetes mellitus	9 (18%)
Hypertension	18 (36%)
Obesity	11 (22%)
Cigarette Smoking	5 (10%)
Baseline Blood Works Results	
Hemoglobin (Median, IQR)	13.05 (11.7-14.28)
WBCs (Median, IQR)	8.20 (5.98-10.30)
Platelets (Median, IQR)	850.00 (525.25-1120.25)
LDH (Median, IQR)	214.00 (177.00-317.00)
Molecular Tests	
CALR type 1	24 (48%)
CALR type 2	21 (42%)
Other *CALR*	5 (10%)
JAK2 (with other *CALR*)	1 (2%)
MPL (with *CALR* type 1)	1 (2%)
Diagnosis	
preMF	9 (18%)
ET	31 (62%)
PMF	10 (20%)
Treatment	
Hydroxyurea	22 (44%)
JAK2 inhibitors	6 (12%)
Anagrelide	1 (2%)
Antiplatelet (Aspirin or Clopidogrel)	36 (72%)
Progression	
MF (carrying *CALR* 1 mutations)	4 (8%)
AML (carrying *CALR* 2 mutations)	1 (2%)
ALL	0
CML	0
Complications	
VTE	3 (6%)
Stroke	2 (4%)
Cardiac ischemic events	4 (8%)
Abdominal veins thrombosis	3 (6%)
Hemorrhage	1 (2%)
Secondary malignancy (carrying *CALR* type 1 mutations)	3 (6%)
Mortality (carrying *CALR* type 2 mutation)	1 (2%)

***CALR*:** Calreticulin; **MPN:** Myeloproliferative Neoplasm; **kg:** Kilogram; **cm:** Centimeter; **IQR:** Interquartile Range; **WBC:** White Blood Cell; **LDH:** Lactate Dehydrogenase; ***JAK2*:** Janus kinase 2; ***MPL*:** Myeloproliferative Leukemia virus oncogene; **pre-MF:** Prefibrotic Myelofibrosis; **ET:** Essential Thrombocytopenia; **P/MF:** Primary/Myelofibrosis; **AML:** Acute Myeloid Leukemia; **ALL:** Acute Lymphocytic Leukemia; **CML:** Chronic Myeloid Leukemia; **VTE:** Venous Thromboembolism

(*BCR-ABL*-negative) MPN, namely ET and PMF [6]. Several mutations were detected in the *CALR* gene, but more than 80% of them are attributed to two mutations: 52-bp deletion (known as type 1) and 5-bp insertion (known as type 2) [9]. The clinical implications of these *CALR* mutations are yet to be explored, and it is an emerging field that can have therapeutic implications in the future. In a recent animal-based study, *CARL* was investigated as being a novel target of monoclonal antibody (4D7) used to treat PMF [10].

The research and knowledge of the *CALR* gene and its mutations is rapidly growing. Since 2013, several published articles addressed *CALR* mutations and their impact on the course of *BCR-ABL*-negative MPNs. It is evident from the current literature that *CALR*-mutated patients tend to be younger and have male predominance compared to *JAK2*-mutated counterparts [11–18]. It is well-established that *CALR* mutations are associated with higher platelet and lower hemoglobin and white cell counts in ET than *JAK2* mutations [6, 11–17, 19]. Despite the increase in platelet production, *CALR*-mutated patients have a lower risk of thrombosis and at least equal, or even better, overall survival than any other molecular subtypes [6, 11–17, 19–21]. On the other hand, most studies reported an increased risk of myelofibrotic transformation in *CALR*-mutated ET patients. In contrast, others showed them to have an equivalent risk to *JAK2* mutations [6, 11–17, 19–22]. We summarized the key elements of the main studies that looked into the *CALR*-mutated MPNs in Table 3.

In this retrospective study, we evaluated 50 patients diagnosed with MPN who tested positive for *CALR* mutations with a median follow-up period of three years. Whether *CALR* mutations are more common in ET or PMF is a question that is not fully answered yet, as shown in Table 3. More than half of our study population were ET patients; the rest were either PMF or Pre-MF (62%, 20%, and 18%, respectively). *CALR* type 1 mutation was more common than type 2 (48% vs. 42%), which is consistent with most of the available literature [6, 11, 12, 15–18]. The incidence of thrombotic events recorded in our study is quite low, which supports the known overall low risk of thrombosis in *CALR*-mutated MPNs. We did not find statistically significant differences in myelofibrotic transformation between the different *CALR* mutations. However, the number of events leaned towards a higher risk with *CALR* type 1 rather than the others. This important finding can be examined in detail with more extensive studies in the future.

In our study, we had five patients (10%) who carried *CALR* mutations that were none Type 1 or Type 2. Such mutations are scarce, and little is known about their clinical significance. It is worth mentioning that despite the few patients who carry such a mutation type in our sample, we had a statistically significant increase in cardiac events. This raises concerns about their potential higher cardiac thrombotic risk and fatal outcomes. An initial presentation of myocardial infarction has been reported in the literature in this particular population [23]. It is interesting to note that one of those five patients had a concurrent *JAK2* mutation, and diagnosed with pre-MF. The patient was a young female who developed portal vein thrombosis. Based on our review, we could not find a similar reported case of pre-MF in the literature. Given the

Table 2. Association between Different CALR Mutations and Baseline Characteristics of Patients.

Characteristics	*CALR* Mutations			*P* Value
	Type 1 (n = 24), n (%)	Type 2 (n = 21), n (%)	Other (n = 5), n (%)	
Male Gender	19 (79.2)	14 (66.7)	4 (80.0)	0.602
Age Group				
Below 40	5 (20.8)	9 (42.8)	2 (40.0)	0.396
40–60	10 (41.6)	12 (50.0)	2 (40.0)	0.884
Above 60	7 (29.2)	2 (9.5)	1 (20.0)	0.259
Arab Ethnicity	12 (50.0)	14 (66.7)	1 (20.0)	0.082
Comorbid Medical Conditions				
Diabetes mellitus	3 (12.5)	5 (23.8)	1 (20.0)	0.611
Hypertension	11 (45.8)	7 (33.3)	0 (0)	0.143
Obesity	2 (8.3)	7 (33.3)	2 (40.0)	0.077
Cigarette Smoking	4 (16.7)	1 (4.8)	0 (0)	0.304
Baseline Blood Works Results				
Hemoglobin (Median, IQR)	11.8 (2.7)	13.4 (3.2)	13.95 (1.6)	0.323
WBCs (Median, IQR)	6.45 (2.8)	8.3 (5.2)	7.0 (3.6)	0.557
Platelets (Median, IQR)	713.0 (363.0)	874.0 (673.0)	1062.5 (738)	0.673
LDH (Median, IQR)	207.5 (281.0)	221.0 (80.0)	180.5 (232.0)	0.464
Molecular Tests				
JAK2	0 (0)	0 (0)	1 (20.0)	0.010
MPL	1 (4.2)	0 (0)	0 (0)	0.575
Diagnosis				
preMF	3 (12.5)	4 (19.1)	2 (40.0)	0.501
ET	16 (66.7)	12 (57.1)	3 (60.0)	0.928
PMF	5 (20.8)	5 (23.8)	0 (0)	0.484
Treatment				
Hydroxyurea	8 (33.3)	11 (52.4)	3 (60.0)	0.329
JAK2 inhibitors	3 (12.5)	3 (14.3)	0 (0)	0.673
Anagrelide	1 (4.2)	0 (0)	0 (0)	0.575
Aspirin	14 (58.3)	15 (71.4)	3 (60.0)	0.844
Clopidogrel	2 (8.3)	0 (0)	2 (40.0)	0.012
Progression				
MF	4 (16.7)	0 (0)	0 (0)	0.095
AML	0 (0)	1 (4.8)	0 (0)	0.494
ALL	-	-	-	N/A
CML	-	-	-	N/A
Complications				
VTE	1 (4.2)	2 (9.5)	0 (0)	0.630
Stroke	0 (0)	2 (9.5)	0 (0)	0.237
Cardiac ischemic events	1 (4.2)	1 (4.8)	2 (40.0)	0.021
Abdominal veins thrombosis	2 (8.4)	0 (0)	1 (20.0)	0.078
Hemorrhage	1 (4.2)	0 (0)	0 (0)	0.575
Secondary malignancy	3 (12.5)	0 (0)	0 (0)	0.750
Mortality	0 (0)	1 (4.8)	0 (0)	0.494

Chi-square analysis and Kruskal-Wallis test were applied at alpha = 0.05. ***CALR*:** Calreticulin; **IQR:** Interquartile Range; **WBC:** White Blood Cell; **LDH:** Lactate Dehydrogenase; ***JAK2*:** Janus kinase 2; ***MPL*:** Myeloproliferative Leukemia virus oncogene; **pre-MF:** Prefibrotic Myelofibrosis; **ET:** Essential Thrombocytopenia; ***P*/MF:** Primary/Myelofibrosis; **AML:** Acute Myeloid Leukemia; **ALL:** Acute Lymphocytic Leukemia; **CML:** Chronic Myeloid Leukemia; **VTE:** Venous Thromboembolism

rarity of *CALR* mutations other than Type 1 and Type 2, this area remains a topic with many unmet needs including its co-existence with other mutations.

To date, we do not have a treatment that targets *CALR* mutations. MPNs are treated the same, whether they carry *CALR* mutations or not, with cytoreductive agents [24–26]. This is also true in our study, as both groups were treated with Hydroxyurea, *JAK2* inhibitor, and antiplatelet agents, regardless of the mutation status. While such interventions might provide some clinical response, developing a targeted therapy is obviously the standard of care and will be an active field for research in the coming years.

It is unknown whether *CALR* mutations have malignant transformation roles. *CALR* is a chaperon protein that is largely present in the endoplasmic reticulum (ER). ER activity is increased in proliferating malignant cells leading to tumor progression and preventing cell death signaling. This process involves the utilization of ER chaperon proteins to promote the protein folding capacity and maintain ER homeostasis [27]. In our study population, secondary malignancy was diagnosed in three patients carrying *CALR* type 1 mutation, which can open the door for more research to investigate this finding further.

Our study is unique since it has the largest sample size for research conducted in this geographic region, showing a descriptive analysis of *CALR* mutation. In addition, It involves a relatively young population (80% below the age of 60), and more than half of them are Arab (54%). Furthermore, the differential occurrence of MF transformation and secondary malignancy raises questions about the possible involvement of *CALR* type 1 mutations in these processes. We believe that the small sample size is the major limitation of our study, as it is reflected in the statistical significance of most of our results. Conducting prospective or randomized-controlled trials can help to provide answers regarding some of the interesting points raised in our paper. In addition, this

Table 3. Summary of Major CALR Studies.

Study	Population Size	*CALR* Patients Demographics	*CALR* Prevalence	Clinical Phenotype	Thrombotic Complications	Hematologic Transformation	Survival and Follow-up Duration
Klampfl et al, 2013 [6]	311 ET & 203 MF	-	25% of ET and 35% of MF had *CALR* mutation. Among *CALR* mutations, type 1 and type 2 percentages were 53% and 31.7%, respectively.	ET with *CALR* mutation had ↓ Hgb, ↓ WBC, &↑ Plt at diagnosis than mutated *JAK2*. MF with *CALR* mutation had ↓ WBC, &↑ Plt then mutated *JAK2*.	ET with *CALR* mutation had a lower risk of thrombosis than mutated *JAK2*.	-	*CALR* mutation had a more prolonged overall survival than mutated *JAK2*.
Nangalia et al, 2013 [19]	151 ET & MF	-	*CALR* mutations were found in 70-84% of MPNs.	MPN with *CALR* mutation had ↑ Plt & ↓ Hgb than mutated *JAK2*.	-	ET with *CALR* mutation had a significantly higher incidence of transformation to MF than mutated *JAK2*.	There were no significant differences in rates of survival.
Rumi et al, 2013 [11]	717 ET	ET with *CALR* mutation patients were significantly younger and had more males compared to those with *JAK2*-mutated ET. *CALR*-1 patients were younger than *CALR*-2.	24.5% of ET had *CALR* mutation. Among *CALR* mutations, type 1, type2, and others percentages were 46%, 38%, and 16%, respectively.	ET with *CALR* mutation had ↓ Hgb, ↓ WBC, ↑ Plt, &↑ serum EPO, then mutated *JAK2*. *CALR*-1, compared to *CALR*-2, had ↓ Hgb, ↓ WBC, ↓ frequency of splenomegaly, & ↓ LDH, ↑Plt, ↑ serum EPO, & ↑ CD34 count.	ET with *CALR* mutation had a lower risk of thrombosis at diagnosis than mutated *JAK2*.	No significant difference in myelofibrotic transformation was noted, and no polycythemic transformation was observed in *CALR*-mutated. Patients.	*CALR*-mutated PMF, but not ET, had better overall survival than *JAK2*. The median follow-up period was 5.2 years (range 0–32 years)
Andrikovics et al, 2014 [9]	289 ET & 99 PMF	*CALR*-mutated patients were younger compared to those with *JAK2*-mutation	50% and 32% of MPN carried type 1 and type 2 *CALR*, respectively. 33% of ET and 25% of MF had *CALR* mutation.	*CALR* mutation had ↑ Plt than mutated *JAK2*.	ET with *CALR* mutation had a lower risk of venous thrombosis than mutated *JAK2*.	ET with *CALR* mutation had a higher risk of progression than mutated *JAK2*.	*CALR*-mutated PMF, but not ET, had better overall survival than *JAK2*.
Li et al., 2014 [13]	357 Chinese patients with PMF	*CALR*-mutated patients were younger compared to those with *JAK2*-mutation	21% of PMF had *CALR* mutation. 32% and 64% of *CALR* mutations were type-1 and type-2, respectively.	PMF with *CALR* type 2 mutation had ↓ Hgb, ↓ WBC, abnormal platelet levels (<100 × 109/L, or >450 x 109/L), & no splenomegaly compared to mutated *JAK2*.	-	-	Type 2 *CALR*-mutated, but not type 1, PMF had significantly shorter survival compared with *JAK2* mutations. The median follow-up period was 28 months (range 1-385).
Rotunno et al, 2014 [14]	576 ET	*CALR*-mutated patients were preferentially males compared with *JAK2* mutation.	15.5% of ET had *CALR* mutation	ET with *CALR* mutation had ↓ Hgb, ↓ WBC, & ↑ Plt than mutated *JAK2*.	ET with *CALR* mutation had a lower risk of thrombosis than mutated *JAK2*.	*CALR* mutation had no impact on transformation to post-ET Myelofibrosis	*CALR* mutation had no impact on survival. Median follow-up was 71.9 months (range, 2–257 months)
Gisslinger et al, 2014 [20]	115 ET & 85 pre-MF	-	18% of ET and 39% of pre-MF had *CALR* mutations	-	-	-	*CALR*-mutated pre-MF, but not ET, had better overall survival than *JAK2*. Such a striking difference was not seen at the time of transformation into overt Myelofibrosis.
Chen et al, 2014 [15]	147 ET	*CALR*-mutated patients were	22.5% of ET had *CALR*	ET with *CALR* mutation had ↓	ET with *CALR* mutation had	*CALR*-mutated patients had	*CALR*-mutated ET had a favorable

(*Continued*)

Table 3. Continued.

Study	Population Size	*CALR* Patients Demographics	*CALR* Prevalence	Clinical Phenotype	Thrombotic Complications	Hematologic Transformation	Survival and Follow-up Duration
		younger compared to those with *JAK2*-mutation	mutations. 54.5%, 27.3%, and 6.1% of *CALR* mutations were type-1, type-2, and type-3, respectively.	WBC, & ↑ Plt then mutated *JAK2*.	a lower risk of thrombosis than mutated *JAK2*.	3.3% post-ET MF Transformation.	impact on thrombosis-free survival (TFS) than *JAK2*.
Al Assaf et al, 2015 [16]	160 ET	*CALR*-mutated patients were younger compared to those with *JAK2*-mutation. *CALR* type 1 is strongly associated with male gender compared to the *JAK2*.	63.7% of double-negative and 56% of *JAK*-negative ET were *CALR* positive. 60.3% and 31% of double-negative ET *CALR* were type 1 and type 2, respectively. 34%, 17%, and 5% of *JAK2*-negative ET *CALR* were type-1, type-2, and other types, respectively.	ET with *CALR* mutation had ↓ Hgb, ↓ WBC, & ↑ Plt than mutated *JAK2*.	*CALR* mutation had no impact on thrombotic complications.	ET with *CALR* mutation had a higher risk of progression to MF than mutated *JAK2*.	*CALR*-mutated ET had better overall survival than *JAK2*, in particular patients of age 60 years or younger.
Pietra et al, 2016 [17]	908 ET & 374 PMF	*CALR*-mutated ET was younger compared to those with *JAK2*-mutation.	24% of ET and 26% of PMF had *CALR* mutation. 65%, 32%, and 3% of *CALR* mutations were type-1 like, type-2 like, and others, respectively.	*CALR* type 1-like mutations were mainly associated with a Myelofibrosis phenotype, while *CALR* type 2 was preferentially associated with the ET phenotype.	Despite higher platelet count, *CALR* type 2 mutation in ET had a lower risk of thrombosis than mutated *JAK2* or type 1-like *CALR* mutation.	ET with type 1-like *CALR* mutations were mainly associated with a significantly higher risk of myelofibrotic transformation but no impact on leukemic transformation.	Type 1-like *CALR*-mutated PMF, but not ET, had better overall survival than *JAK2*. The median follow-up period was 4.7 years (range 0–31 years).
Kong et al, 2016 [22]	3,141 ET and 1,605 PMF (Meta-analysis)	-	19% of ET and 22% of PMF had *CALR* mutation.	-	-	ET with *CALR* mutations had a slight trend toward fibrotic transformation but no impact on leukemic transformation.	-
Tefferi et al, 2017 [18]	709 PMF	*CALR* type 1 is associated with male gender. Type 2 is associated with younger age.	16% and 3.4% of PMF carried *CALR* type 1-like and *CALR* type 2-like mutations, respectively.	PMF with *CALR* type 2-like mutation had ↓ Hgb, ↑ WBC, ↑ Plt, & ↑ circulating blasts than mutated *JAK2*.	-	*CALR* mutation did not impact the progression rate to Myelofibrosis or the risk of leukemic transformation. *CALR* mutations had the lowest red cell transfusion need.	*CALR*-mutated PMF, but not ET, had better overall survival than *JAK2*. The median follow-up period was 3.5 years.
Kim et al, 2022 [21]	510 ET & MF	-	6.2% of ET and 3.3% of PMF had *CALR* mutation. 49% and 51% of *CALR* mutations were type 1-like and type 2-like, respectively.	*CALR* type 1-like mutations were associated with a Myelofibrosis phenotype (↓ Hgb & ↓ Plt), while *CALR* type 2-like was associated with ET phenotype (↑ Plt & ↑ ANC).	Despite higher platelet counts, *CALR* type 2 mutation in ET had no thrombotic events.	-	-

***CALR*:** Calreticulin; **MPN:** Myeloproliferative Neoplasm; **ET:** Essential Thrombocytopenia; ***P*/MF:** Primary Myelofibrosis; **Hgb:** Hemoglobin; **WBC:** White Blood Cell; **Plt:** Platelet; ***JAK2*:** Janus kinase 2; **EPO:** erythropoietin; **pre-MF:** Prefibrotic Myelofibrosis; **ANC:** Absolute Neutrophilic Count

study did not investigate the response to the treatment modalities used in managing *CALR*-mutated patients.

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Data availability statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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Statement of ethics

The study was approved by Hamad Medical Corporation Medical Research center.

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