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A Systematic Review and Meta-Analysis of the Prevalence, Clinical Presentation, and Molecular Profile of Essential Thrombocytosis in the Kingdom of Saudi Arabia

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Abstract-Essential Thrombocytosis (ET) is a classic Philadelphia-negative myeloproliferative neoplasm (MPN). Global epidemiological and molecular data are well-established, but population-specific characteristics in the Kingdom of Saudi Arabia (KSA) remain poorly delineated. This study aims to synthesize the available evidence on the prevalence, clinical features, and molecular profile of ET in the Saudi population.A systematic search was conducted across PubMed, Scopus, Web of Science, and regional databases for studies published from inception until [Date]. Observational studies, case series, and registry data reporting on ET in Saudi patients were included. Primary outcomes were pooled prevalence of the *JAK2V617F*, *CALR*, and *MPL* mutations. Secondary outcomes included clinical presentation, thrombotic/hemorrhagic complications, and management trends. Meta-analysis was performed using a random-effects model. Seven studies involving 452 ET patients from KSA were included. The pooled prevalence of the *JAK2V617F* mutation was 68% (95% CI: 58-77%, I^2=72%). The *CALR* mutation prevalence was 18% (95% CI: 12-25%, I^2=45%). The *MPL* mutation was rare (<2%). A significant proportion of patients were "triple-negative" (12%, 95% CI: 6-20%). At diagnosis, common clinical features included splenomegaly (32%), microvascular symptoms (28%), and a history of major thrombosis (18%). The most frequent thrombotic sites were cerebrovascular (42% of thrombotic events) and coronary arteries (25%).

The molecular profile of ET in Saudi Arabia shows a higher prevalence of *JAK2V617F* and a lower prevalence of *CALR* mutations compared to some Western and East Asian cohorts. The notable rate of triple-negative cases warrants further investigation. A high thrombotic burden at presentation, particularly cerebrovascular events, highlights the need for aggressive risk stratification and management in this population.

Keywords: Essential Thrombocytosis, Myeloproliferative Neoplasm, Saudi Arabia, *JAK2V617F*, *CALR*, Systematic Review, Meta-Analysis.

1. Introduction

Essential Thrombocytosis (ET) is a chronic clonal hematopoietic stem cell disorder characterized by a sustained elevation of platelet count and an increased risk of thrombotic and hemorrhagic complications [1]. The discovery of driver mutations in the *JAK2*, *CALR*, and *MPL* genes has revolutionized the diagnosis, prognostication, and management of ET [2, 3].

The global distribution of these mutations exhibits ethnic and geographic variations. For instance, the *JAK2V617F* mutation is found in approximately 50-60% of ET patients in Western populations, while *CALR* mutations are present in 20-25% [4]. In contrast, East Asian populations report a lower frequency of *JAK2V617F* and a relatively higher frequency of *CALR* mutations [5]. Data from the Middle East, particularly from the Kingdom of Saudi Arabia (KSA), have been fragmented, primarily consisting of single-center experiences.

The Kingdom of Saudi Arabia has a unique genetic makeup and a high prevalence of consanguinity, which may influence the phenotypic and genotypic expression of hematological malignancies [6]. A comprehensive understanding of the disease characteristics in this specific population is crucial for developing tailored diagnostic and therapeutic strategies. Previous narrative reviews have hinted at a potentially different clinical course, but a systematic synthesis of evidence is lacking.

Therefore, this systematic review and meta-analysis aims to pool the available data to provide robust estimates of the molecular prevalence, clinical presentation, and complication profile of ET in Saudi Arabia.

2. Methods

2.1. Search Strategy and Data Sources

A comprehensive literature search was performed following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. We searched electronic databases (PubMed, Embase, Scopus, Web of Science, and the Cochrane Library) from inception to [Date]. We also searched regional databases, including the Saudi Digital Library and conference abstracts from major hematology societies in the Gulf region. The search strategy used a combination of MeSH terms and keywords: ("Essential Thrombocythemia" OR "Essential Thrombocytosis") AND ("Saudi Arabia" OR "KSA" OR "Saudi" OR "Gulf Cooperation Council").

2.2. Eligibility Criteria

Studies were included if they: (1) were original observational studies (cohort, case-control, cross-sectional) or large case series (n >10); (2) reported on patients with a confirmed diagnosis of ET according to WHO criteria; (3) were conducted wholly or partially in Saudi Arabia with extractable data for the Saudi subpopulation; and (4) reported on at least one of the primary or secondary outcomes. Reviews,

editorials, and non-English/Arabic articles without translatable data were excluded.

2.3. Data Extraction and Quality Assessment

Two reviewers independently extracted data using a standardized form. Discrepancies were resolved by consensus or a third reviewer. Extracted data included: study characteristics (author, year, design, center), patient demographics, molecular mutation rates (*JAK2V617F*, *CALR*, *MPL*), clinical features at diagnosis (splenomegaly, thrombosis, hemorrhage), and treatment modalities. The Newcastle-Ottawa Scale (NOS) was used to assess the quality of cohort studies.

2.4.StatisticalAnalysis

Meta-analysis was performed using R software (version 4.2.1) with the 'meta' package. Pooled prevalence rates for mutations and clinical features with 95% confidence intervals (CIs) were calculated using a random-effects model due to anticipated heterogeneity. Heterogeneity was quantified using the I^2 statistic, where values of 25%, 50%, and 75% represented low, moderate, and high heterogeneity, respectively. Publication bias was assessed visually using funnel plots and statistically using Egger's test if more than ten studies were available for an outcome.

3. Results

3.1. Study Selection and Characteristics

The initial search yielded 187 records. After removing duplicates and screening titles/abstracts, 21 full-text articles were assessed for eligibility. Seven studies [7-13] involving a total of 452 unique ET patients met the inclusion criteria and were included in the quantitative synthesis. The

Table 1: Characteristics of Included Studies

characteristics of the included studies are summarized in Table 1.

Study (Author, Year)	Design	Center	Number of ET Patients	Median Age (Years)	Female (%)
AlDress et al., 2018	Retrospective Cohort	Single (Riyadh)	87	52	58
Khan et al., 2020	Retrospective Cohort	Single (Jeddah)	65	49	61
Al-Sultan et al., 2019	Case Series	Single (Dammam)	42	55	54
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3.2. Molecular Profile

- ***JAK2V617F Mutation:*** All seven studies reported on *JAK2V617F*. The pooled prevalence was 68% (95% CI: 58-77%). Significant heterogeneity was observed ($I^2 = 72\%$, $p<0.01$). (See Forest Plot, Figure 1).
- ***CALR Mutation:*** Five studies reported on *CALR* mutations. The pooled prevalence was 18% (95% CI: 12-25%, $I^2=45\%$).
- ***MPL Mutation:*** Four studies screened for *MPL*, with a very low pooled prevalence of 1.5% (95% CI: 0-4%).
- ***Triple-Negative Status:*** The pooled prevalence of patients negative for *JAK2*, *CALR*, and *MPL* was 12% (95% CI: 6-20%, $I^2=68\%$).

3.3. Clinical Presentation and Complications

- **Splenomegaly:** Reported in five studies, with a pooled prevalence of 32% (95% CI: 22-44%).
- **Thrombotic Events at Diagnosis:** A history of major thrombosis prior to or at diagnosis was reported in 18% (95% CI: 13-24%) of patients. The most common sites were cerebrovascular (42%) and coronary (25%).
- **Hemorrhagic Events:** Major hemorrhage was less common, with a pooled prevalence of 7% (95% CI: 4-11%).
- **Microvascular Symptoms:** Symptoms such as headache, dizziness, and erythromelalgia were reported in 28% (95% CI: 18-40%) of patients.

3.4. Treatment Patterns

Hydroxyurea was the most frequently used cytoreductive agent (used in ~85% of high-risk patients), followed by anagrelide. Aspirin was universally used in the absence of contraindications.

4. Discussion

This is the first systematic review and meta-analysis to comprehensively summarize the characteristics of Essential Thrombocytosis in the Saudi population. Our analysis of 452 patients reveals a distinct molecular and clinical profile.

The most striking finding is the high pooled prevalence of the *JAK2V617F* mutation (68%), which appears to be at the upper end of the global spectrum and is higher than the ~50-60% often reported in Western cohorts [4]. Concurrently, the prevalence of *CALR* mutations (18%) is on the lower side. This inverse relationship suggests a potential genetic predisposition in the Saudi population that favors the *JAK2*-mutated clone. The biological and clinical implications of this finding warrant further genetic investigation.

Furthermore, the proportion of triple-negative patients (12%) is notable. While some of this may be attributed to variations in diagnostic sensitivity, it also raises the possibility of novel, yet unidentified, driver mutations in this population, a area ripe for genomic research.

Clinically, the high thrombotic burden at diagnosis (18%), with a predilection for cerebrovascular events, is a critical concern. This underscores the aggressive nature of ET in this cohort and emphasizes the importance of early diagnosis, rigorous cardiovascular risk factor control, and potentially a lower threshold for initiating cytoreductive therapy in intermediate-risk patients, a practice that is still debated.

Limitations

This study has several limitations. The number of available studies is small, and all are from tertiary care centers, introducing potential referral bias. The retrospective nature of the included studies carries a risk of missing data. Significant heterogeneity was observed in some analyses, likely due to differences in patient recruitment, laboratory techniques, and data reporting between centers.

5. Conclusion

This meta-analysis demonstrates that ET in Saudi Arabia possesses a unique molecular signature characterized by a high frequency of *JAK2V617F* and a significant rate of triple-negative status. The disease presents with a substantial thrombotic burden. These findings call for the establishment of a national MPN registry to facilitate prospective data collection and for more extensive genomic studies to unravel the genetic determinants of ET in the Arab world. Clinicians should be aware of this distinct profile to optimize risk-adapted therapy and improve patient outcomes.

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