A Structured Literature Review on Treatment Patterns, Unmet Need, Clinical Complications, Disease Transformation, and Survival Among Patients with Essential Thrombocythemia

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Background

- Essential thrombocythemia (ET) is an acquired Philadelphia chromosome–negative myeloproliferative neoplasm characterized by clonal blood cell proliferation and excessive platelet production[1]
- Patients with ET are associated with an increased risk of vascular complications (thrombotic and hemorrhagic events) and potential disease transformation to myelofibrosis or acute myeloid leukemia (AML).[1] Vascular complications and disease transformation are among the major causes of morbidity and mortality among patients with ET[2-4]
- Current treatment options for ET include oral medications like hydroxyurea or hydroxycarbamide, anagrelide, and ruxolitinib, as well as interferon-α, peginterferon-α and ropeginterferon-α[1,5]
- An up-to-date summary of the currently available evidence describing clinical complications, disease transformation, survival, treatment patterns, and unmet need among patients with ET is currently lacking

Objectives

- This review aims to identify and summarize the available peer-reviewed literature to better understand the complications, disease progression, survival, treatment patterns, and unmet needs associated with ET

Methods

- Two targeted literature reviews were conducted to identify available evidence for disease management and epidemiological outcomes. Searches were conducted in MEDLINE® and Embase® databases (January 1, 2011, to October 5, 2023). Relevant conferences were also searched to retrieve the latest studies that have not yet been published in journals as full-text articles or to supplement the results of previously published studies (2020 to 2023)
- The studies were screened based on predefined criteria for population, intervention, comparator, outcomes, time, study design (PICOTS) (**Table 1**). Complications, disease transformation, survival, and treatment patterns were prioritized for inclusion in this poster
- The first-stage screening (based upon titles and abstracts) was undertaken by a single reviewer, followed by a sample (20%) check of excluded studies by another independent reviewer. Full texts of relevant studies were then examined to determine a final list of included studies, using the same approach. Data extraction was conducted by a single reviewer and validated by an independent reviewer

Table 1. PICOTS criteria

Parameter	Inclusion criteria	
Population(s)	• Disease: ET • No restriction on age, gender, or race	
Intervention	No restriction	
Comparator	No restriction	
Outcomes	**Disease management review:** • Treatment guidelines and recommendations[a] • Treatment patterns and practices • Treatment adherence and discontinuation • Disease management and diagnosis[a] • Standard of care and critical pathways[a]	**Epidemiological review:** • Incidence and prevalence[a] • Mortality,[a] survival rates, risk factors,[a] and comorbidities[a] • Complication rates (frequency of thrombotic events, hemorrhagic incidents, and splenomegaly) • Sociodemographic factors
Time	Studies published from January 1, 2011, to October 5, 2023	
Study designs	**Disease management review:** • Published treatment guidelines or management algorithms • Long-term observational studies in a real-world setting • Case-control/cross-sectional studies • Literature reviews/systematic reviews/relevant general reviews for bibliographic searching	**Epidemiological review:** • Cohort studies (retrospective observational) • Cohort studies (prospective observational) • Database/registries-based studies • Case-control/cross-sectional studies • Literature reviews/systematic reviews/relevant general reviews for bibliographic searching
Other	Regions: Global (no restriction) Languages: Studies with full texts published in the English language	

[a]Included in the scope of the overall literature search but results not presented in the current poster.

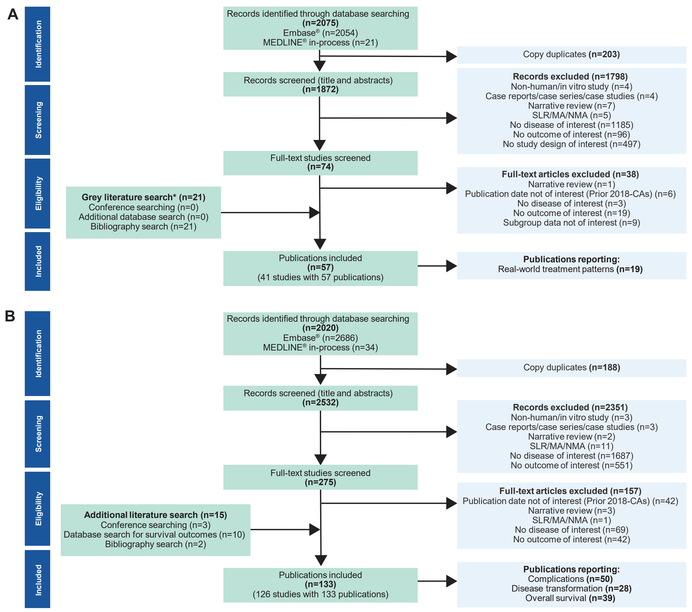
ET, essential thrombocythemia.

Results

Summary of included studies

- Overall, 2,075 studies were identified by the disease management literature review, and 2,720 studies were identified by the epidemiological review. Following the screening process, a total of 57 and 126 studies were included (all outcomes) in the disease management and epidemiological reviews, respectively (**Figure 1**)
- Among those, the following outcomes were prioritized for inclusion in this poster:
  - Epidemiology review: Complications (n=50), disease transformation (n=28), and overall survival (n=39)
  - Disease management review: Real-world treatment patterns, including adherence/discontinuation/switch (n=19)
  - Notably, some studies reported evidence for multiple outcomes

Figure 1. PRISMA flow diagrams for disease management (A) and epidemiological (B) reviews



First-line treatment patterns

- Hydroxyurea (HU) was the most commonly reported first-line treatment among patients with ET (53.8% to 93.3%), followed by anagrelide (3.7% to 25.0%) (**Figure 2**)[6-10]
- One study conducted across 13 European countries found that first-line therapies for patients with ET varied substantially by age at diagnosis (**Table 2**)[10]
  - The majority of older patients received HU as their initial therapy, whereas treatment patterns varied amongst younger patients, with higher usage of anagrelide and interferon in addition to HU observed[10]

Table 2. Proportion of patients with ET receiving treatments by age group[10]

	<40	40 to <60	60 to <80	>80
Treatment	**n=48**	**n=148**	**n=433**	**n=62**
HU	35.4	57.4	88.5	93.5
Anagrelide	45.8	37.2	10.4	4.8
Interferon	18.8	4.7	0.2	0
Other monotherapy	0	0.7	0.9	1.6

HU, hydroxyurea.

Treatment discontinuations/switching and unmet need with HU

- Estimated discontinuation rates of HU ranged from 10.9% to 26.0%, with physician-reported reasons for discontinuation including intolerance (35.4%), resistance (23.8%), toxicity (27%), and lack of efficacy (13%)[7,11]
- An estimated 65.9% of patients who discontinued HU did not receive subsequent treatment, while 14.6% received anagrelide and another 14.6% received ruxolitinib[7]
- Furthermore, 19.4% of patients were estimated to switch from HU. Of those, 27.9% were due to intolerance and 12.1% due to lack of efficacy[12]
- Among patients who continued HU, 35.5% did not achieve desired platelet counts, 25% had persistent symptoms, and 1.2% experienced thrombotic events[7]

Thrombotic events

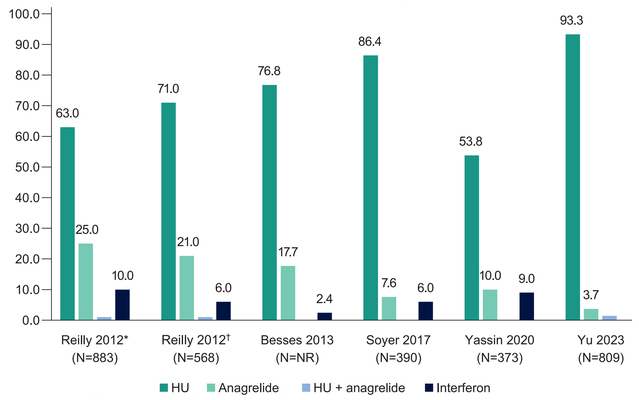
- Importantly, patients with ET can experience thrombotic events before confirmed diagnosis, with estimates ranging from 4.3% to 37.2% (**Table 3**).[9,13-21] Variations in the reported range were likely influenced by differences in study population and sample size
- Rates of all thrombotic events reported post-diagnosis ranged from 2.8% to 55.5%, with ranges varying due to differences in level of follow-up, as well as differences in study population and sample size of patients observed[13, 14, 17,19, 20-39]
  - The cumulative incidences of thrombotic events following diagnosis generally increased over time (**Figure 3**).[17,28,30,35,40-42] Median follow-up differed across the studies (ranging from approximately 4-7 years, with variable definitions), limiting comparisons across studies
  - Median time from diagnosis to first event was 4.2 to 4.6 years[17,28]

Table 3. Proportion of patients experiencing thromboses

Study	Sample size, n	Thromboses, % Any	Median follow-up, years (unless otherwise specified)
Pre-diagnosis			
Alvarez-Larrán 2023[13]	1,366	14.0	–
Hashimoto 2022[14]	1,135	18.2	–
Fu 2023[15]	903	13.7-37.2	–
Zhang 2020[16]	468	29.0	–
Soyer 2016[9]	390	15.1	–
Sobas 2022*[17]	318	8.5	–
Song 2021[18]	139	15.8	–
Horvat 2019[19]	134	10.4	–
Aswad 2021[20]	119	19.3	–
Navarro 2016[21]	46	4.3	–
Post-diagnosis			
Pemmaraju 2022#[22]	124,569	24.5	2.1
Podoltsev 2023[23]	2,201	55.6	3.8
Stuckey 2023[24]	1,381	10.8	5.6
Alvarez-Larrán 2023[13]	1,366	7.7	7.1
Andriani 2016[25]	1,297	8.6-15.7	5.7
Hashimoto 2022[14]	1,152	6.5	3.6
Szuber 2019[26]	1,074	21.0	9.9
Pérez 2021[27]	983	15.6	7.6
Fu 2014[28]	970	11.4	4.1
Elala 2016[29]	495	18.0	15.1
Zhang 2020[16]	468	20.0	7.0
Lussana 2014[30]	375	10.0	7.25
Sobas 2022*[17]	318	10.1	9.7
Randi 2014†[31]	158	15.8	2.8
Chou 2013[32]	146	19.2	3
Chiaranairungrot 2022[33]	144	2.8	NR
Horvat 2019[19]	134	26.9	4.8
Kaifie 2016[34]	132	25.0	–
Aswad 2021[20]	119	23.5	NR
Kim 2021[35]	108	15.7	4.5
Duangnapasatit 2015[36]	83	3.6	NR
Lim 2015[37]	69	24.6	4.5
Porto-Soares 2020[38]	50	24	4.1
Navarro 2016[21]	46	13.0	NR
Sefer 2022[39]	27	11.1	275 patient-years

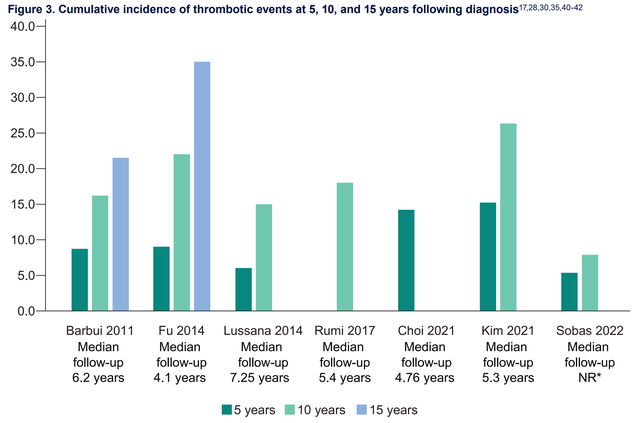
*Included only patients aged < 25 years; #Included ET patients more than 65 years of age only; †Female patients only; NR: Not reported.

Figure 2. Proportion of patients with ET receiving treatments in 1L setting[6-10]



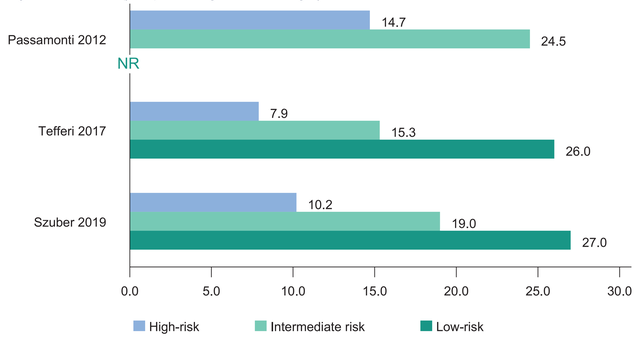
*Wave 1: Sept-Oct 2009, †Wave 3: Apr-May 2010. HU, hydroxyurea; NR, not reported.

Figure 3. Cumulative incidence of thrombotic events at 5, 10, and 15 years following diagnosis[17,28,30,35,40-42]



*Sobas 2022 included only patients aged from 2 to 25 years

Figure 4. Median OS (years) according to ET risk category [26,51,53]



NR, not reached.

Bleeding events

- Rates of all bleeding events reported pre-diagnosis ranged from 2.1% to 6.0%, while those of major bleeding events reported pre-diagnosis were 1.1% to 4.3% (**Table 4**)[15,17,18,32]
- Rates of all bleeding events and major bleeding events reported post-diagnosis ranged from 2.1% to 33.7% and 1.1% to 14%, respectively (**Table 4**)[14,15,17,18,27,28,31-34,43-50]
- Variations in the reported ranges in bleeding events post-diagnosis were likely influenced by differences in study population, sample size, and level of follow-up

Table 4. Proportion of patients experiencing bleeding events

Study	Sample size, n	Any bleeding event (%)	Major bleeding event (%)	Median follow-up, years (unless otherwise specified)
Pre-diagnosis				
Fu 2023[15]	903	–	1.1-4.3	–
Sobas 2022*[17]	318	6.0	–	–
Chou 2013[32]	146	2.1	–	–
Song 2021[18]	139	2.9	–	–
Post-diagnosis				
Wu 2022#[43]	7,630	12.7	–	NR
Hashimoto 2022[14]	1,152	5.2	–	3.6
Pérez 2021[27]	983	–	2.0	7.6
Fu 2014[28]	970	–	4.4	4.1
Ahlstrand 2020[44]	922	2.4	–	2
Fu 2023[15]	903	–	1.1-3.6	4.9
Sobas 2022*[17]	318	8.5	–	NR
Wille 2022[45]	266	18.0	6.0	5.5
Lee 2012[46]	239	5.0	–	4.3
Seguro 2020[47]	159	–	4.4	NR
Randi 2014†[31]	158	14.5	–	2.8
Chou 2013[32]	146	18.5	14.4	3.0
Chiaranairungrot 2022[33]	144	11.1	–	NR
Kander 2015[48]	144	10.4	–	NR
Kaifie 2016[34]	140	3.8	–	NR
Song 2021[18]	139	6.5	–	3.8
Kamiunten 2018[49]	117	–	1.1	3.9
Barbui 2021[50]	48	2.1	–	50.5 days

*Included only patients aged < 25 years; †Female patients only; #ET patients with myocardial infarction; NR: Not reported.

Disease transformation

- Among 1,076 patients with ET (median follow-up of 9.9 years), 13% of patients experienced fibrotic transformation and 4% of patients experienced leukemic transformation[26]
- The reported rates of cumulative incidence for transformation to myelofibrosis and AML increased over time:
  - Myelofibrosis transformation rate at 5 years was 0.2% to 1.9%[14,17,40], at 10 years was 0.8% to 13.7% [14,17,18,40] and at 15 years was 9.3% to 48.4%[18,40]
  - AML transformation rate at 5 years was 0.2%[40], at 10 years was 0.7% to 7.9% [18,26,40,41] and at 15 years was 2.1% to 16.9%[18,40]
  - Variations in the reported range were likely influenced by differences in study population and sample size

Overall survival

- Overall median OS for ET patients ranged from 12.0 (median-follow-up: 4.1 years) to 19.8 years (median-follow-up: 17.3 years)[51,52]
  - Median OS was lowest among patients with high-risk ET (7.9 to 10.2 years) compared to intermediate risk (15.3 to 24.5 years) and low-risk (26.0 to NR years) (**Figure 4**)[26,51,53]
  - Duration of median OS was reported to be significantly lower in patients with ET (enrolled in the US Medicare system) vs. non-ET controls (68 months vs. 101 months, respectively; $P<0.05$)[54]
  - Duration of follow-up varied considerably across studies, with heterogeneous statistical definitions for data cut-off. Some studies specified duration of follow-up, while others followed patients until death

Limitations

- The included studies showed variations in sample sizes, study populations and follow-up times, that limit the ability to compare findings across these studies

Conclusions

- Current real-world treatment patterns indicated that patients are heavily reliant on HU in the first-line setting, with up to a quarter of patients reported to have discontinued or switched treatment
- Almost two thirds of patients were reported not to receive subsequent treatment, and treatment options in subsequent lines of therapy were limited, with most patients re-initiating HU +/- anagrelide, and a minority of patients receiving ruxolitinib or interferon
- Thrombotic and bleeding events were frequently reported among patients with ET and increased over time, with some patients experiencing these events before diagnosis, suggesting delays in the diagnosis and treatment of ET
- Overall, patients with ET may have survival expectations comparable to those observed in the general population, although one study suggested lower survival in US Medicare patients with ET relative to similarly matched individuals without ET. In addition, outcomes vary due to variable clinical course, with impaired survival particularly reported among patients who experience vascular complications, or among high-risk subgroups
- The current literature describes substantial clinical burden in ET, including considerable clinical complications and treatment challenges, with rates of transformation to myelofibrosis or AML increasing with time from diagnosis. Novel approaches to the management of patients with ET are required to help improve patient outcomes and reduce disease burden

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