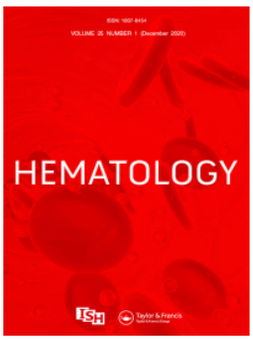

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ORIGINAL ARTICLE

Validation and reliability of current guidelines for the treatment of essential thrombocythemia under real-world clinical settings in Japan

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ABSTRACT

Objective: Current guidelines for essential thrombocythemia (ET) patients recommend different treatment approaches based on thrombosis risk stratification models. However, these recommendations may not be applicable to some patients under real clinical settings. Therefore, we carried out a retrospective real-world validation study.

Methods: Thrombosis-free survival (TFS) was compared between treatment naïve ET patients receiving different treatment approaches. ET patients were stratified by three representative risk models, the conventional, the International Prognostic Score for thrombosis in ET (IPSET-thrombosis), and revised IPSET-thrombosis. Treatment decisions were largely made by individual physicians, taking into account patient preferences and backgrounds.

Results: A total of 179 ET patients were included, and thrombotic events were observed in 26 patients. TFS was significantly longer in high-risk patients of all risk models receiving a combination of cytoreductive therapy (CRT) and antiplatelet therapy (APT) compared to CRT alone. Similar results were seen in intermediate-risk patients stratified by IPSET-thrombosis. In contrast, in very low- and low-risk patients of all risk models, TFS was not affected by addition of CRT, indicating that observation or APT alone is an appropriate treatment approach for these patients.

Conclusion: We demonstrate that current guidelines provide optimal treatment approaches for Japanese ET patients under real-world clinical settings.

KEYWORDS

Essential thrombocythemia; thrombosis; risk stratification model; cytoreductive therapy; antiplatelet therapy; guideline

Introduction

Essential thrombocythemia (ET) is classified as one of the Philadelphia-negative myeloproliferative neoplasms (MPNs), and is characterized by elevated platelet counts due to acquisition of driver mutations such as *JAK2*V617F, *CALR* exon 9, and *MPL* exon 10 in hematopoietic stem/progenitor cells [1–4]. Mortality and morbidity in ET patients largely depend on thrombohemorrhagic events, and thus prevention of these events is critical [5,6]. Various risk stratification models have been proposed for thrombotic events in ET patients: (1) a conventional risk stratification model that categorizes patients into low- and high-risk groups by age (≥60 years) and a history of thrombosis; (2) the International Prognostic Score for thrombosis in ET (IPSET-thrombosis), which categorizes patients into low-, intermediate-, and high-risk groups by age (>60 years), a history of thrombosis, the presence/absence of the *JAK2*V617F mutation, and cardiovascular (CV) risk factors; and (3) revised IPSET-thrombosis that was developed using the dataset excluding CV risk factors of the IPSET-thrombosis model that categorizes patients into very low-, low-, intermediate-, and high-risk groups [7–9]. These risk stratification models are used to select treatment approaches for ET patients in representative guidelines such as the IPSET-thrombosis model by European LeukemiaNet (ELN), the revised IPSET-thrombosis model by the National Comprehensive Cancer Network (NCCN), and the conventional model by the Japanese Society of Hematology (JSH) [10–12]. However, actual treatment is diverse under real-world clinical settings and not necessarily in line with these recommendations due to patient preferences and backgrounds. Limited information is currently available on the efficacy of the recommended treatments in reducing thrombotic events in ET patients. Therefore, we retrospectively investigated the impact of different treatment approaches on thrombotic events in treatment-naïve ET patients stratified by the above-described risk stratification models for thrombosis. This is also the first study to verify the precision of the current guideline in preventing thrombotic events.

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Materials and methods

Patients

ET patients newly diagnosed between February 1999 and March 2020 who were followed up at Juntendo University Hospital or one of its branch institutions (Urayasu Hospital, Shizuoka Hospital, and Nerima Hospital) were examined. The observation period of the present study was between February 1999 and August 2020. All patients were confirmed to fulfill the 2016 World Health Organization (WHO) criteria for ET [13]. A total of 179 newly diagnosed ET patients were included in the present study. Three patients with high Hb levels (>16.5 g/dL in males and >16.0 g/dL in females) were suspected of having polycythemia vera (PV); however, the results of bone marrow biopsy were not compatible with PV due to the absence of increased erythropoiesis and, thus, these patients were diagnosed with ET. Two patients with a PLT count below the diagnostic criterion (450×10^9/L) in the first visit were diagnosed with ET because of the persistence of a high PLT count on subsequent visits. There were two patients with Hb levels less than 10g/dL, one of which had a history of hemorrhagic gastric ulcers, and both patients were confirmed to have ET based on the results of driver gene mutations and bone marrow biopsies. Three patients presented with WBC above 20.0×10^9/L, and although one patient eventually transformed to myelofibrosis, all three patients were initially confirmed to have ET based on the results of driver gene mutations and bone marrow biopsies [14]. A driver mutation analysis of *JAK2*V617F, *CALR* exon 9, and *MPL* exon 10 was performed as previously reported [15–17]. CV risk factors were defined as hypertension, diabetes mellitus, hyperlipidemia, and smoking [8,18].

Definition of thrombohemorrhagic events

Major thrombotic events were defined as stroke, myocardial infarction, pulmonary embolism, and peripheral arterial occlusive disease. Minor thrombotic events included erythromelalgia, angina pectoris, transient ischemic attack, and deep vein thrombosis. Hemorrhagic events included cerebral hemorrhage, gastrointestinal hemorrhage, hematuria, and mucosal hemorrhage. Major hemorrhagic events were defined as cerebral or retroperitoneal bleeding, overt hemorrhage accompanied by a decrease in hemoglobin (Hb) ≥2 g/dl, or overt hemorrhage requiring blood transfusions of two units or more. Minor hemorrhagic events were defined as other hemorrhagic events not fulfilling the criteria of major hemorrhagic events [19,20]. Erythromelalgia was diagnosed according to the clinical diagnostic criteria proposed previously [21].

Risk stratification and treatment evaluation

The conventional, IPSET-thrombosis, and revised IPSET-thrombosis models were used for risk stratification to predict thrombotic events [7–9]. When the risk group status of a patient changed during the observation period, the time until the status change was analyzed in accordance with the former risk group, and the time from the status change in accordance with the new risk group. Treatment approaches were selected based on the clinical judgement of the attending physicians. Cytoreductive therapy (CRT) was defined as treatment with hydroxyurea, anagrelide, or interferon. Antiplatelet therapy (APT) was defined by all medicines with antiplatelet components such as aspirin or clopidogrel, and anticoagulants were not included. Patients receiving any type of ET treatment for more than 1 day were added to the treatment group.

The type of CRT administered for each patient was defined as follows. The CRT used most recently at the end of follow-up or at the time of thrombotic event, and used for at least 3 months was selected [19]. If not, the agent used before the switch was selected. If CRTs were used concomitantly, the CRT added afterwards and used for at least 3 months was selected.

Statistical analysis

Fisher's exact test was used for categorical variables (sex, driver gene mutations, history of thrombohemorrhagic events, CV risk factors, thrombohemorrhagic events, and death) and the Kruskal–Wallis test for continuous variables [age, white blood cells (WBC), red blood cells (RBC), platelet (PLT) counts, and Hb]. Thrombosis-free survival (TFS) and overall survival (OS) were analyzed by the Kaplan-Meier method and comparisons were performed using the Log-rank test. The Holm method was employed for multiple comparison tests. EZR software was used for all statistical analyses, and *P-values* <0.05 was considered to be significant [22].

Results

Comparison of TFS and OS among different mutation groups

Thrombohemorrhagic events observed during the follow-up period (median 1,260 days, range 60–7,773 days) were examined (Table S1). Thrombotic events occurred in 26 patients (14.5%) and these were more frequent in patients harboring the *JAK2*V617F (20.0%) and *MPL* exon 10 mutations (25.0%) compared to those with the *CALR* exon 9 mutation (5.6%) and TN (3.2%) ($P < 0.05$, Table S1). Although no significant differences were observed in TFS among the

different mutation groups ($P = 0.055$), TFS tended to be shorter in patients with the *JAK2*V617F (65.2% at 10 years) and *MPL* exon 10 (69.3% at 10 years) mutations compared to the other groups (Figure S1(a)). The 10-year OS rate in the cohort was 95.7% and did not significantly differ among the different mutation groups ($P = 0.514$, Figure S1(b)).

Comparison of TFS among different treatment approaches according to representative risk models

The impact of different treatment approaches such as observation, APT alone, CRT alone, and combination of CRT and APT on thrombotic events were investigated in patients grouped by the three major stratification models for thrombosis. Since change of risk group in the same patient (becoming older than 60 years) occurred during the follow-up in 20 out of 179 patients, as a result, 199 risk group-based cases were studied. The patient characteristics of each treatment group at the time of risk assessment (hereinafter referred to as 'baseline') are shown in Table 1, and the details of thrombotic events occurring in different treatment groups are shown in Table 2. There were significant differences concerning some patient characteristics between different groups: patients in the CRT alone group and combination group were significantly older and had higher PLT counts compared to those in the observation and APT groups ($P < 0.001$ and $P < 0.001$, respectively, Table 1). The combination group had a significantly higher number of patients with a history of thrombosis ($P < 0.05$, Table 1). The incidence of thrombotic events was highest in the CRT alone group, and lowest in the combination group (30.2% and 3.9%, respectively, Table 2). Additionally, the frequencies of thrombotic events in each risk stratification group according to different treatment approaches are shown in Table 3. Lower frequency of thrombosis was seen in patients receiving combination therapy compared to CRT alone in all risk groups.

(1) **Conventional risk model**

The conventional risk model stratified patients into each risk group with significance. ($P < 0.05$, Figure S2 (a)). In low-risk patients, no significant differences were observed in TFS among different treatment groups ($P = 0.071$, Figure 1(a)). On the other hand, TFS significantly differed among high-risk patients grouped by treatment ($P < 0.001$, Figure 1(b)). Patients treated with a combination of CRT and APT (indicated as 'combination' in Figure 1(b)) had the lowest frequency of thrombosis (5.0%, Table 3), achieving significantly longer TFS than those with observation only or treated with CRT alone (*P-value* for combination vs observation or CRT alone: <0.001, Figure 1(b)), and no significant difference in TFS when compared to those treated with APT alone ($P = 0.076$, Figure 1(b)). High-risk patients treated with APT alone achieved a tendency of longer TFS compared to those with observation only or treated with CRT alone, but did not reach statistical significance. (*P-value* for APT alone vs observation or CRT alone: 0.84, Figure 1(b)).

These results showed the following for patients stratified by the conventional model: (1) treatment approaches had no impact on TFS in low-risk patients, (2) TFS in high-risk patients significantly differed depending on the treatments used, and (3) the combination of CRT and APT effectively prevented thrombosis in high-risk patients.

(2) **IPSET-thrombosis model**

TFS significantly differed among patients stratified into the low-, intermediate-, and high-risk groups by the IPSET-thrombosis model ($P < 0.05$, Figure S2(b)). In low-risk patients, a thrombotic event was observed in each treatment group (Table 3) and TFS did not significantly differ among those who received different treatments ($P = 1$, Figure 2(a)). In intermediate-risk patients, TFS significantly differed between patients grouped by treatment ($P < 0.05$, Figure 2(b)). TFS was

Table 1. Patient characteristics according to different treatment groups.

	All ($n = 199$, 100%)	Observation ($n = 40$, 20.1%)	APT[a] alone ($n = 39$, 19.6%)	CRT[b] alone ($n = 43$, 21.6%)	Combination ($n = 77$, 38.7%)	*P* value
Age, median (range), year	60 (8–87)	49 (18–81)	48 (25–81)	65 (8–87)	65 (15–86)	<0.001
Male, *n*	82 (41.2%)	17 (42.5%)	9 (23.1%)	21 (48.8%)	35 (45.5%)	0.068
Female, *n*	117 (58.8%)	23 (57.5%)	30 (76.9%)	22 (51.2%)	42 (54.5%)	–
WBC, median (range), $\times 10^9$/L	8.8 (3.2–29.5)	7.9 (4.1–13.8)	8.0 (3.2–15.4)	8.8 (4.3–19.3)	9.0 (4.0–29.5)	0.055
RBC median (range), $\times 10^4$/μL	464 (297–638)	459 (380–521)	456 (368–631)	467 (345–587)	470 (297–638)	0.170
Hb, median (range), ×g/dL	13.6 (9.1–16.9)	13.4 (10.4–15.7)	13.3 (10.8–16.1)	13.8 (9.6–16.9)	13.8 (9.1–16.7)	<0.05
PLT, median (range), $\times 10^9$/L	814 (370–4691)	742 (475–2337)	725 (418–1234)	903 (370–4691)	931 (439–1824)	<0.001
*JAK2*V617F, *n*	113 (56.8%)	17 (42.5%)	20 (51.3%)	24 (55.8%)	52 (67.5%)	0.058
CALR exon 9, *n*	41 (20.6%)	7 (17.5%)	9 (23.1%)	10 (23.3%)	15 (19.5%)	0.817
MPL exon 10, *n*	12 (6.0%)	3 (7.5%)	2 (5.1%)	4 (9.3%)	3 (3.9%)	0.333
Triple-negative, *n*	33 (16.6%)	13 (32.5%)	8 (20.5%)	5 (11.6%)	7 (9.1%)	<0.05
History of thrombosis, *n*	25 (12.6%)	0 (0.0%)	5 (12.8%)	4 (9.3%)	16 (20.8%)	<0.05
Cardiovascular risk factors, *n*	100 (50.3%)	16 (40.0%)	18 (46.2%)	26 (60.5%)	40 (51.9%)	0.276

Note: APT[a], antiplatelet therapy; CRT[b], cytoreductive therapy.

Table 2. Details of thrombotic events occurring in different treatment groups during the follow-up period.

	All ($n = 199$)	Observation ($n = 40$)	APT[a] alone ($n = 39$)	CRT[b] alone ($n = 43$)	Combination ($n = 77$)
Total thrombotic events, *n*	26 (13.1%)	5 (12.5%)	5 (12.8%)	13 (30.2%)	3 (3.9%)
Major thrombosis, *n*	11 (5.5%)	2 (5.0%)	2 (5.1%)	6 (14.0%)	1 (1.3%)
Stroke, *n*	9 (4.5%)	1 (2.5%)	2 (5.1%)	5 (11.6%)	1 (1.3%)
Pulmonary embolism, *n*	1 (0.5%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Peripheral arterial thrombosis, *n*	1 (0.5%)	0 (0.0%)	0 (0.0%)	1 (2.3%)	0 (0.0%)
Minor thrombosis, *n*	15 (7.5%)	3 (7.5%)	3 (7.7%)	7 (16.3%)	2 (2.6%)
Erythromelalgia, *n*	7 (3.5%)	2 (5.0%)	1 (2.6%)	3 (7.0%)	1 (1.3%)
Angina pectoris, *n*	5 (2.5%)	1 (2.5%)	1 (2.6%)	3 (7.0%)	0 (0.0%)
Transient ischemic attack, *n*	3 (1.5%)	0 (0.0%)	1 (2.6%)	1 (2.3%)	1 (1.3%)

Please revise "combination (n=77)" as the others. (The two-level notation) Note: APT[a], antiplatelet therapy; CRT[b], cytoreductive therapy.

significantly shorter in patients treated with CRT alone than in those treated with the combination of CRT and APT ($P < 0.05$, Figure 2(b)), but TFS did not differ when CRT alone and observation only or APT alone were compared (*P-values* for CRT alone vs observation or APT alone: 0.444 and 0.824, respectively, Figure 2(b)). Although TFS did not significantly differ between patients treated with APT alone and those with other treatment approaches, 3 out of the 4 cases that developed thrombosis in the intermediate-risk group were treated with CRT alone (Table 3), which implies that the addition of APT might prevent thrombosis in these patients. In high-risk patients, TFS significantly differed between those grouped by different treatment approaches ($P < 0.001$, Figure 2(c)). Patients treated with a combination of CRT and APT had the lowest frequency of thrombosis (4.3%, Table 3) and exhibited significantly longer TFS than those with observation only or treated with CRT alone (*P-value* for combination vs observation or CRT alone: <0.001, Figure 2(c)), and no significant difference in TFS compared to APT alone ($P = 0.127$, Figure 2(c)). Patients treated with APT alone also showed no significant difference in TFS compared to those with observation only or treated with CRT alone (*P-value* for APT alone vs observation or CRT alone: 0.993, Figure 2(c)).

These results showed the following for patients stratified by the IPSET-thrombosis model: (1) treatment approaches had no impact on TFS in low-risk, but affected TFS in intermediate- and high-risk patients, (2) although CRT alone was not beneficial, the addition of APT appeared to prevent thrombosis in intermediate-risk patients, and (3) the combination of CRT and APT was the most beneficial approach for preventing thrombosis in high-risk patients.

(3) Revised IPSET-thrombosis model

TFS significantly differed in patients stratified into the very low-, low-, intermediate-, and high-risk groups by the revised IPSET-thrombosis model ($P < 0.05$, Figure S2(c)). Among very low-, low-, and intermediate-risk patients, no significant differences were observed in TFS when individual treatment groups were compared ($P = 0.742$, 0.076, and 0.447, respectively, Figure 3(a–c)), presumably due to a more detailed stratification than in other models, resulting in a lower number of patients in each treatment group. Similar to the results for the intermediate-risk group of IPSET-thrombosis, 5 out of the 7 cases experiencing thrombosis in low- and intermediate-risk patients of the revised IPSET-thrombosis received CRT alone and no APT (Table 3). High-risk patients treated with the combination of CRT and APT achieved longer TFS than those with other treatment approaches (Figure 3(d), *P-values* for combination vs observation, APT alone, or CRT alone: <0.001, <0.05, and <0.001, respectively) and had the lowest frequency of thrombotic events (4.3%, Table 3). Although TFS widely varied in the observation only, APT alone, and CRT alone groups, no significant differences were observed in TFS among these groups (Figure 3(d)).

Table 3. Frequency of thrombotic events in ET patients in different risk groups according to treatment approaches.

Risk stratification model	Risk category	All	Observation	APT[a] alone	CRT[b] alone	Combination
Unstratified	N/A[c]	26/199 (13.1%)	5/40 (12.5%)	5/39 (12.8%)	13/43 (30.2%)	3/77 (3.9%)
Conventional	Low	4/82 (4.9%)	0/27 (0%)	2/26 (7.7%)	2/12 (16.7%)	0/17 (0%)
	High	22/117 (18.8%)	5/13 (38.5%)	3/13 (23.1%)	11/31 (35.5%)	3/60 (5.0%)
IPSET-thrombosis	Low	4/60 (6.7%)	1/20 (5.0%)	1/15 (6.7%)	1/11 (9.1%)	1/14 (7.1%)
	Intermediate	4/46 (8.7%)	0/10 (0%)	1/10 (10.0%)	3/10 (30.0%)	0/16 (0%)
	High	18/93 (19.4%)	4/10 (40.0%)	3/14 (21.4%)	9/22 (40.9%)	2/47 (4.3%)
Revised IPSET-thrombosis	Very low	2/50 (4.0%)	1/20 (5.0%)	1/14 (7.1%)	0/7 (0%)	0/9 (0%)
	Low	3/34 (8.8%)	0/8 (0%)	1/13 (7.7%)	2/5 (40%)	0/8 (0%)
	Intermediate	4/33 (12.1%)	0/4 (0%)	0/3 (0%)	3/12 (25%)	1/14 (7.1%)
	High	17/82 (20.7%)	4/8 (50%)	3/9 (33.3%)	8/19 (42.1%)	2/46 (4.3%)

Note: APT[a], antiplatelet therapy; CRT[b], cytoreductive therapy; N/A[c], Not applicable.

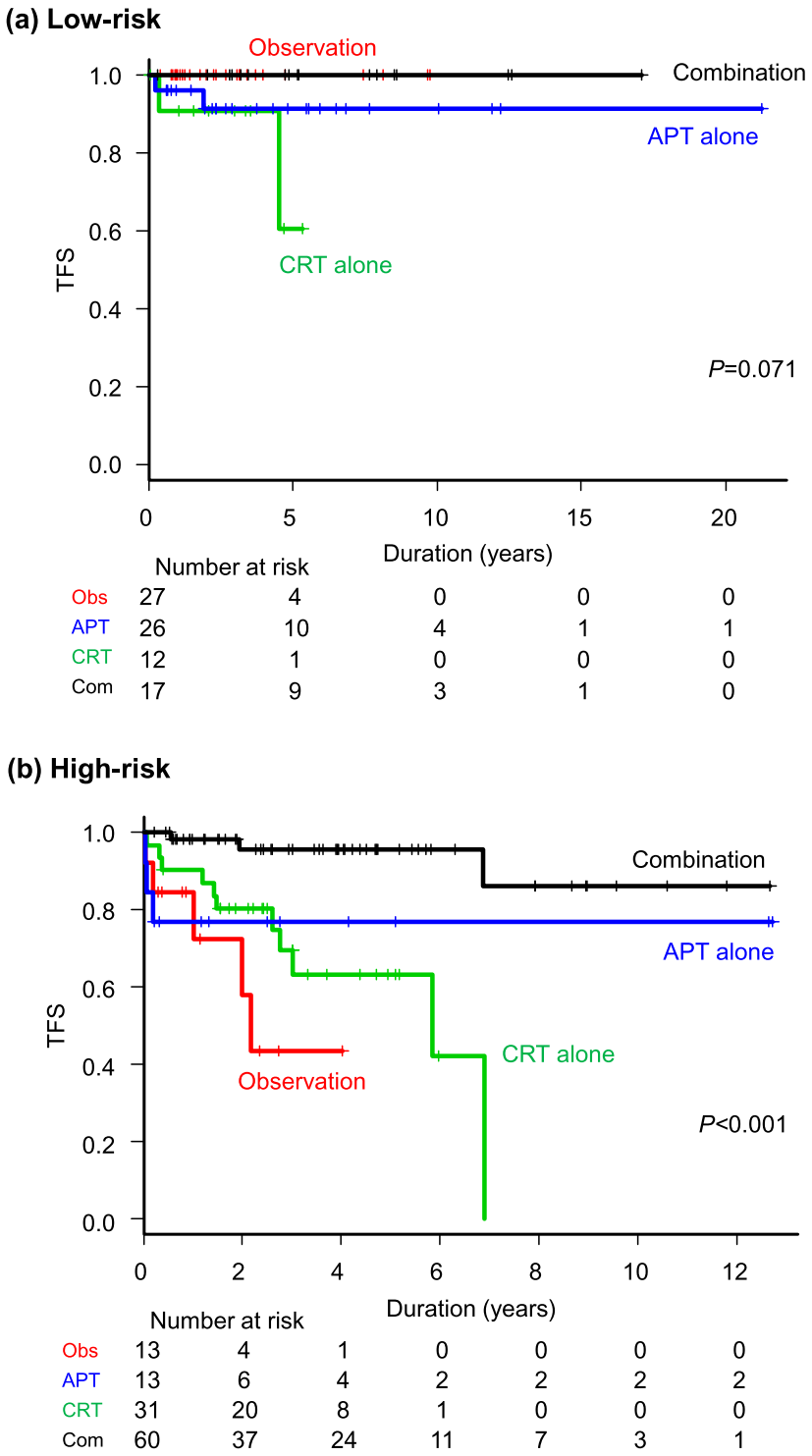

Figure 1. Impact of different treatment approaches on thrombosis-free survival (TFS) in patients stratified by the conventional risk model. Low- (a) and high-risk patients (b) are shown. Treatment groups consisted of observation (Obs), antiplatelet monotherapy (APT alone), cytoreductive monotherapy (CRT alone), and combination therapy (Com).

These results showed the following for patients stratified by the revised IPSET-thrombosis model: (1) in very low-, low-, and intermediate-risk patients, treatment approaches had no impact on TFS, (2) in low- and intermediate-risk patients, 5 out of the 7 cases with thrombosis received CRT alone, and (3) combination of CRT and APT was the most effective approach for preventing thrombosis in high-risk patients.

Discussion

In the present study, we took advantage of treatment diversity under real-world clinical settings and retrospectively compared the impact of different treatment approaches on TFS in ET patients stratified by thrombosis risk models. Patients who received treatment in accordance with the Hematopoietic Tumor Guidelines of the Japanese Society of Hematology were 56.8%

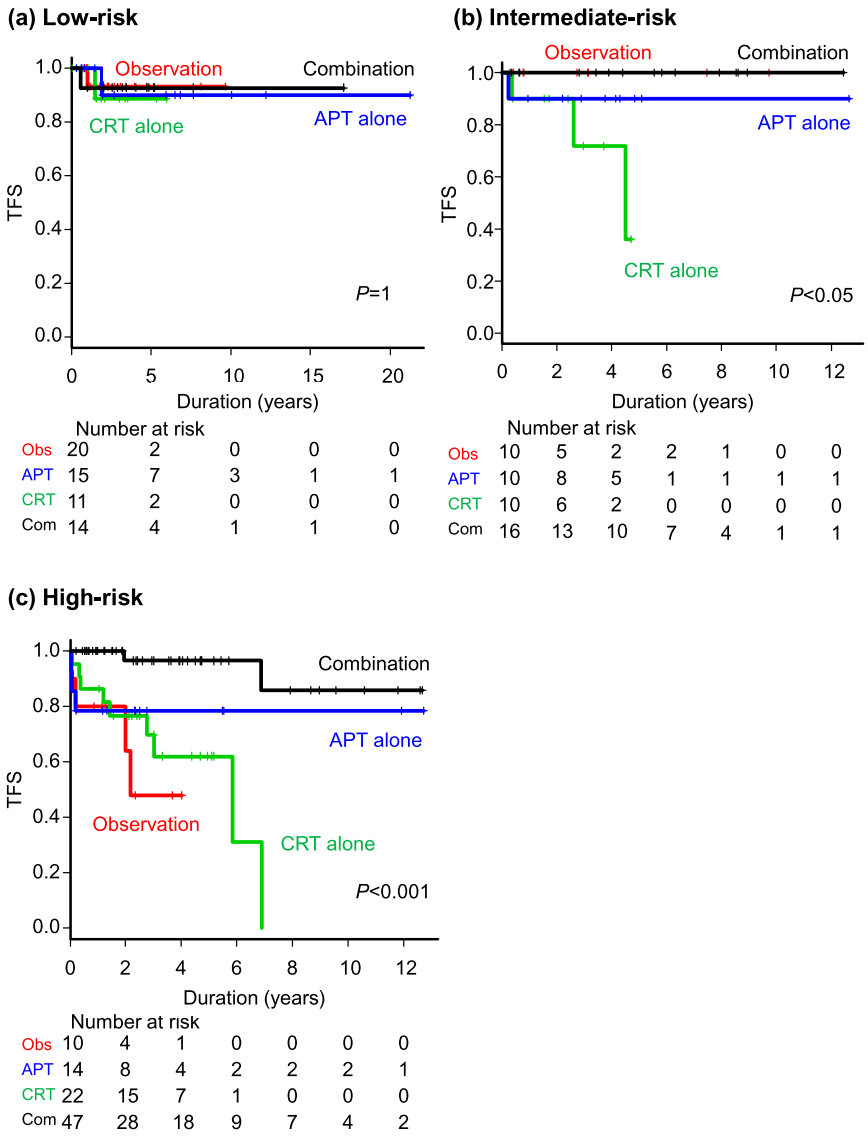

Figure 2. Impact of different treatment approaches on thrombosis-free survival (TFS) in patients stratified by the IPSET-thrombosis risk model. Low- (a), intermediate- (b), and high-risk patients (c) are shown. Treatment groups consisted of observation (Obs), antiplatelet monotherapy (APT alone), cytoreductive monotherapy (CRT alone), and combination therapy (Com).

(113/199) of cases in the conventional model, 51.3% (102/199) in the IPSET-thrombosis model proposed by the European LeukemiaNet (ELN), and 54.3% (108/199) in the revised IPSET-thrombosis model proposed by the National Comprehensive Cancer Network (NCCN). The following results were obtained in all risk stratification models: (1) TFS in very low- and low-risk patients was not significantly affected by different treatment approaches, (2) in intermediate-risk patients stratified by the IPSET-thrombosis model, APT prolonged TFS. Although similar results were not observed in low- and intermediate-risk patients stratified by the revised IPSET-thrombosis model, the majority of patients experiencing thrombosis received CRT alone, and (3) treatment approaches had a significant impact on TFS in high-risk patients, and the combination of CRT and APT contributed to prolongation of TFS. Overall, the present results, which were obtained under real-world clinical settings in Japanese ET patients, support the ELN, NCCN, and JSH guideline recommendations [10–12].

Some patients in the very low- and low-risk groups in our cohort received CRT. Although the reasons why they received CRT are unknown, the CRT alone and combination therapy groups had significantly higher PLT counts than the observation and APT alone groups ($P < 0.05$, Table S2b). This may have influenced the decision of treatment. However, the addition of CRT did not always have a positive impact on TFS (Figures 1(a), 2(a), 3(a), and 3(b)). These results suggest that CRT showed little benefit for longer TFS in very low- and low-risk patients, even if prominent thrombocytosis was present (except for patients with hemorrhagic symptoms mostly due to acquired von Willebrand syndrome). No significant differences in TFS between CRT and no CRT in low-risk patients stratified by the conventional model with extreme thrombocytosis ($>1{,}000 \times 10^9$/L) was reported [23], and

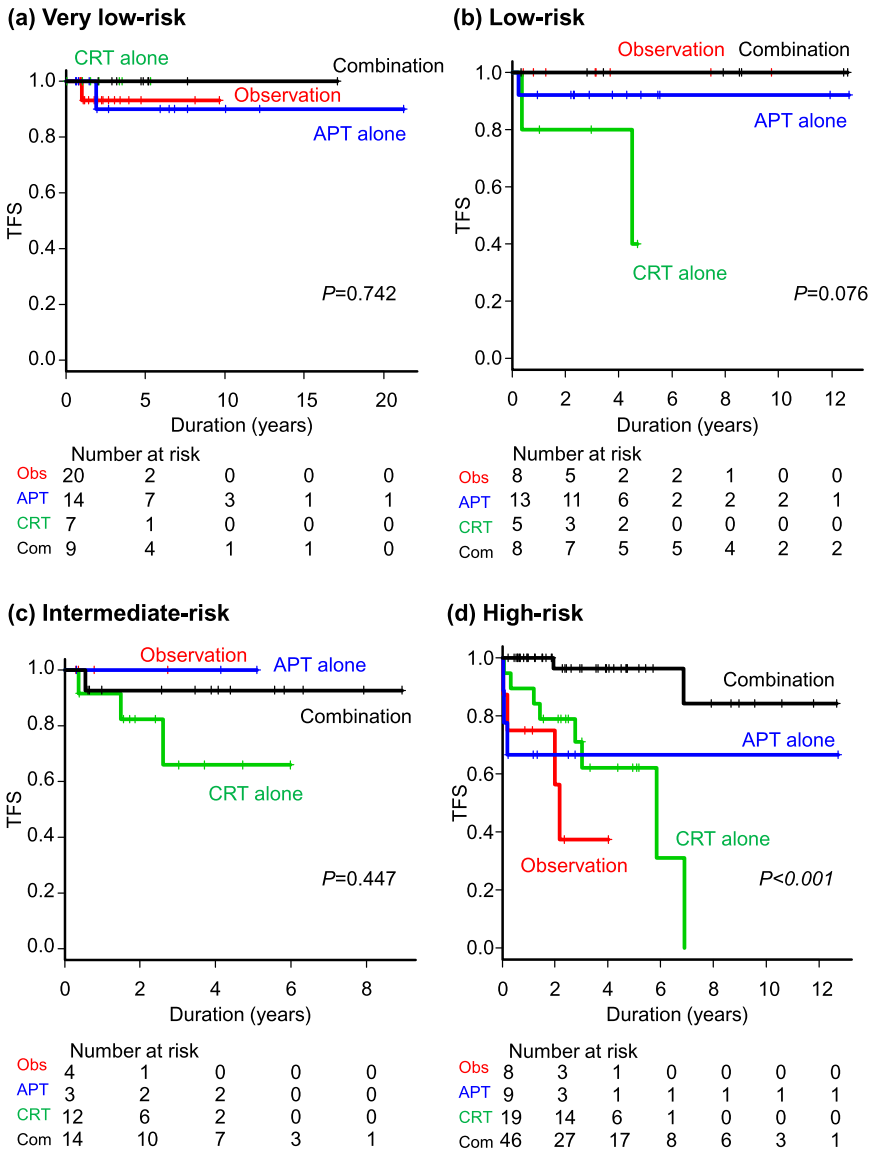

Figure 3. Impact of different treatment approaches on thrombosis-free survival (TFS) in patients stratified by the revised IPSET-thrombosis risk model. Very low- (a), low- (b), intermediate- (c), and high-risk patients (d) are shown. Treatment groups consisted of observation (Obs), antiplatelet monotherapy (APT alone), cytoreductive monotherapy (CRT alone), and combination therapy (Com).

together with our observations, it can be concluded that observation only or APT as recommended by the aforementioned guidelines are reasonable treatment approaches for very low- and low-risk patients.

In our cohort, some high-risk patients were followed up without any treatment (observation group). Since treatment decisions were largely made by each physician, the actual reasons for choosing observation in these patients are unknown. Compared to patients receiving CRT alone or a combination of CRT and APT, patients in the observation group were younger, had lower PLT count, and had no history of thrombosis at baseline (Table S2(a)), and these differences in patient background may have influenced treatment decisions of attending physicians. Patient preferences may have also affected treatment choices. However, the present results strongly suggest that high-risk patients stratified by all three stratification models need to receive combination therapy aligned with the guideline regardless of their background [10–12].

In our study, hydroxyurea and anagrelide were mainly selected as CRT. No significant difference in TFS was observed between patients administered hydroxyurea and anagrelide ($P = 0.090$, Figure S3(a)). Importantly, both agents showed significant TFS prolongation by combination with APT ($P < 0.001$, Figure S3(b)). A previous study reported that the frequency of hemorrhagic events was significantly higher in patients who received combination therapy than in those who received CRT alone [24]. In the present study, the incidence of hemorrhagic events were 18.6% (8/43 cases) in the CRT alone group, and 15.6% (12/77cases) in the combination group, suggesting that combination therapy may prevent thrombotic events without increasing the risk of hemorrhagic events. TFS was shorter in the CRT

alone group of intermediate- and high-risk patients stratified by IPSET-thrombosis. In contrast, a previous study reported that CRT alone reduced the frequency of thrombotic events in these patients [25]. This discrepancy may be due to erythromelalgia not being defined as a thrombotic event in the previous study. However, even when erythromelalgia was not considered as a thrombotic event in our cohort, the present results showing shorter TFS in the CRT alone group did not change, and the incidence of thrombotic event was highest in CRT alone group (Table 2). In our cohort, the CRT alone group presented with significantly older age and higher PLT counts at baseline compared with observation and APT groups (Table 1). It cannot be denied that these differences may have influenced the incidence of thrombotic events. On the other hand, the combination group showed no significant difference in patients characteristics compared with the CRT alone group, but at the same time showed significantly longer TFS (Table 1, Figures 1(b), 2(c), and 3(d)). Our results are consistent with previous findings showing that the combination of CRT and APT more effectively prevents thrombotic events than CRT alone in patients older than 60 years and that sole control of thrombocytosis by CRT did not reduce thrombotic events [24,26].

Some have reported that high WBC count is a risk factor for thrombotic events. Therefore, we studied the effects of baseline WBC counts on incidence of thrombotic events using the thresholds suggested by previous studies, 8.4×10^9/L and 15.0×10^9/L [27]. As a result, no significant difference was observed between patients with different baseline WBC counts ($P = 0.835$ and $P = 0.401$, respectively). Additionally, in our cohort, intermediate- and high-risk patients stratified by IPSET-thrombosis who received CRT alone had well controlled median PLT and WBC counts of 540×10^9/L and 7.4×10^9/L, respectively, at the end of follow-up. Despite this, TFS was significantly shorter in the CRT alone group. In other words, these results suggest that reductions in PLT or WBC counts by CRT alone were not sufficient in preventing thrombotic events. Since the majority of patients in the combination group were treated with aspirin and TFS was significantly longer in intermediate-risk patients stratified by IPSET-thrombosis and in high-risk patients stratified by all three risk stratification models in this group, decreases in thromboxane levels by aspirin may have contributed to the prevention of thrombotic events in these patients [28].

Although the design of the present study allowed us to compare the preventative effects of different treatment approaches on thrombosis in each risk group, several limitations need to be considered. This study was retrospective in nature, and thus there may have been a bias in the selection of treatment approaches by attending physicians.

In conclusion, a combination of APT and CRT can effectively prevent thrombotic events in high-risk and possibly intermediate-risk ET patients. On the other hand, observation only or APT alone is an appropriate treatment approach for very low- and low-risk patients. To sum it up, adherence to the representative ET guidelines based on the three major thrombotic risk stratification models results in reduction of thrombotic events, and is the optimal treatment approach for the patient with ET.

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Author contributions

TB contributed to the study design, acquisition and analysis of research data, and preparation of the manuscript. YH, HY, MA and NK contributed through the analysis of research data and writing of the manuscript. YE, SM, TO, SS, JA, and NK contributed through the acquisition of research data.

Availability of data and material

The datasets are available from the corresponding author upon request.

Conflicts of interest

Author TB has received a salary from company Shire/Takeda where she is an employee and author NK has received a salary from company PharmaEssentia Japan where he is a board member. Author YH and NK have received a speaker honorarium from company Shire/Takeda. Author YH, MA, YE, SM, TO, SS, and NK have received research grants from company Meiji Seika Pharma and PharmaEssentia. SS has received a speaker honorarium from company Novartis, Nippon Shinyaku, and Astellas. NK has received a speaker honorarium from company Novartis, PharmaEssentia, Abbvie, Celgene, Japan Tobacco, and Otsuka, and grants from company Shire/Takeda,

Novartis, FUJIFILM Wako Pure Chemical Corporation, Fuso Pharmaceutical, Pfizer, Perseus Proteomics, Otsuka, Chugai, Kyowa Kirin, Sumitomo Dainippon Pharma, and Bristol-Myers Squibb. All other authors have no relevant financial or non-financial interests to disclose.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Consent for publication

Patients signed informed consent regarding publishing their data.

Ethics approval

Approval was obtained from the ethics committee of Juntendo University Hospital (IRB #20-024). The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

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