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A practical tool for predicting outcomes in essential thrombocythemia: Triple A risk model and beyond

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Key Points

- Triple A is a reliable tool for predicting survival and thrombosis in ET, and incorporating monocytosis may further enhance its performance.
- NLR might serve both as independent risk marker and as a component of NLR-monocyte-age–based model for predicting survival.

The management of essential thrombocythemia (ET) relies on risk stratification; therefore, easily applicable risk scores with improved prognostic value are in demand. The Triple A risk score is a novel model incorporating age, absolute neutrophil, and absolute lymphocyte counts (AAA model). In this study, we aimed to evaluate the predictive performance of Triple A score in ET for survival and its complications in an independent cohort, in addition to refining the model by incorporating absolute monocyte count and neutrophil-to-lymphocyte ratio (NLR). Demographic, clinical, and laboratory data of 565 patients with ET were retrospectively collected. Based on Triple A score, 250 patients were classified as low risk, 228 as intermediate-1 risk, 37 as intermediate-2 risk, and 50 as high risk. Over a median follow-up of 6 years, 10.3% patients developed thrombosis, 4.4% experienced bleeding, 5.1% had post-ET myelofibrosis, and 10.9% died. There were significant differences in overall survival and thrombosis-free survival across risk groups. Monocytosis (>0.8 × 10^9/L) was associated with increased mortality and its prevalence increased progressively with higher Triple A scores. Elevated NLR was also linked to a higher risk of mortality, and moreover, NLR-monocyte-age–based risk score demonstrated significant differences in survival risk. Consequently, Triple A score is an easy-to-use and reliable tool for predicting survival and thrombosis in ET. Incorporating monocytosis into Triple A (AAA+A model) may further enhance its prognostic accuracy. NLR also demonstrated prognostic value both independently and as component of NLR-monocyte-age–based model, highlighting its potential as a robust tool for risk stratification.

Introduction

Essential thrombocythemia (ET) is a myeloproliferative neoplasm (MPN) characterized by thrombocytosis in the peripheral blood and megakaryocyte hyperplasia secondary to clonal stem cell proliferation.[1,2] The disease generally follows a relatively indolent course but can be complicated by

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All data generated or analyzed during this study are included in this article.

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The full-text version of this article contains a data supplement.

thrombosis, bleeding, fibrotic transformation, and leukemic progression.[3-5] Diagnosis may require exclusion of secondary causes and other MPNs, along with testing for driver mutations including *JAK2*, *CALR*, and *MPL*, and performing a bone marrow biopsy.[6]

In clinical practice, International Prognostic Score for ET (IPSET; age ≥60 years, leukocyte count of ≥11 × 10^9/L, previous thrombosis) is commonly used for the prediction of survival,[7] in addition to international prognostic score of thrombosis in ET (IPSET-T)[8] and revised IPSET-T,[9] which are used to predict thrombosis.

The currently available guidelines recommend treatment algorithms rely on risk scores.[10] Therefore, developing improved risk models to predict survival and ET complications particularly thrombosis is crucial. However, mutation-based risk scores such as the revised IPSET-T score,[9] which incorporates *JAK2* mutational status, might pose a high economic burden and may not be applicable in all regions.

Considering these limitations, along with the strong association between survival, thrombosis, and readily available parameters from the complete blood count (CBC), there is a growing need for new models with high prognostic accuracy. In 2023, Tefferi et al have developed a new risk model called the Triple A (AAA) score consist of age, absolute neutrophil count (ANC), and absolute lymphocyte count (ALC) (AAA model).[11] This scoring system has been validated for survival prediction in both Europe and United States. However, the global utility of this model is still on progress.

Lymphopenia is an independent risk factor on mortality in the general population,[12] as well as in patients with lymphoma and solid organ tumors.[13] Elevated neutrophil count has been also associated with increased mortality in aging population[14] and colorectal cancer.[15] Moreover, several studies have shown that lymphopenia or elevated neutrophil count correlates with worse prognosis and/or thrombosis in MPN.[16,17]

Inflammation has an important role in pathogenesis of ET and thrombosis.[18,19] Neutrophil-to-lymphocyte ratio (NLR) serves as a heightened inflammatory activity and has been associated with increased mortality even in the general population.[20] Similarly, elevated NLR has been linked to poorer overall survival (OS) and higher risk of thrombosis in ET.[21,22]

Furthermore, monocytes might contribute to hyperinflammation and oncoinflammation in MPN.[23,24] Monocytosis has been associated with disease progression and reduced survival in primary myelofibrosis (MF)[25] and, likewise, with decreased survival in polycythemia vera (PV).[26]

In this study, we aimed to evaluate the effectiveness and predictive performance of the Triple A score for survival, thrombosis, fibrotic transformation, and bleeding in our ET population in addition to further develop the model by incorporating monocytosis and NLR.

Methods

We retrospectively collected data of adult patients with ET, who were diagnosed according to World Health Organization criteria and who were followed up at 5 hematology centers in Turkey. We excluded patients without initial ANC and ALC results. Age, sex, comorbidities, CBC values (hemoglobin level, leukocyte and platelet counts, ANC, absolute monocyte count, and ALC), spleen size (either by physical examination or ultrasound measurement), driver mutations (*JAK2*, *CALR*, and *MPL*), history of thrombosis and/or bleeding, transformation to MF and/or acute leukemia, and the treatments were recorded from medical files and electronic health records of the hospital. We calculated the IPSET, revised IPSET-T, IPSET-T, and Triple A scores.

Arterial thrombosis includes coronary artery diseases, cerebrovascular disease, transient ischemic attack, carotid artery thrombosis, mesenteric or aortic thrombosis, and peripheral artery thrombosis; whereas venous thrombosis encompasses deep vein thrombosis, dural sinus thrombosis, pulmonary embolism, intra-abdominal thrombosis (portal vein thrombosis, Budd-Chiari, and/or mesenteric vein thrombosis), and central retinal vein thrombosis. We evaluated major organ bleeding according to International Society on Thrombosis and Haemostasis criteria,[27] including gastrointestinal, genitourinary, and intracranial bleeding in addition to skin-mucosal bleeding.

All patients were followed up until death or last recorded follow-up as assessed through medical records. Treatments administrated at any point during the disease course, at the discretion of treating physician, were also documented.

The study was approved by the local medical ethics committee (approval date and number: 1 January 2025, 1210317 Istanbul University Cerrahpaşa, clinical studies ethical committee) and conducted in accordance with the declaration of Helsinki.

Statistical analysis

Descriptive statistics were presented as mean ± standard deviation or median (interquartile range [IQR]) for continuous variables, and as frequency (percentage) for categorical variables. The normality of continuous variables was assessed using the Shapiro-Wilk test.

The 1-way analysis of variance test was applied to normally distributed continuous variables, whereas the Kruskal-Wallis test was used for nonnormally distributed ones, in the comparison of Triple A risk levels. The Wilcoxon signed-rank test was used for comparisons between 2 dependent groups. Categorical variables were compared using the χ^2 test or Fisher exact test, as appropriate. Correlation between variables was assessed using Spearman rho test.

OS was defined as the time from diagnosis to death. Thrombosis-free survival was defined as the time from diagnosis to the occurrence of the first thrombotic event. MF-free survival was calculated from the date of diagnosis to the development of post-ET MF. Bleeding-free survival was defined as the time from the occurrence of bleeding. Patients who did not experience the event of interest were censored at the date of last follow-up. Survival probabilities were estimated using the Kaplan-Meier method, and survival curves were compared using the log-rank test. First, a univariate Cox proportional hazards model was used to identify prognostic factors, and factors associated with survival were included in multivariable Cox model. The effects of risk factors on survival were reported as hazard ratio (HR) with 95% confidence intervals (CI) and *P* values. In groups for which the median survival time could not be reached, restricted mean survival time (RMST) was calculated to complement the survival analysis. RMST represents the expected average survival time up to a prespecified time

Table 1. Demographic and clinical data of patients at diagnosis and treatment details

Parameter	Result
Median age at diagnosis (IQR), y	53 (38-65)
Female, N (%)	359 (63.5)
Any comorbidity, N (%)	330 (58.4)
HT	223 (39.4)
DM	93 (16.4)
CAD	61 (10.7)
History of any thrombosis, N (%)	135 (23.8)
Arterial thrombosis	94 (69.6)
Venous thrombosis	32 (23.7)
Both venous and arterial thrombosis	9 (6.7)
History of bleeding, N (%)	60 (10)
*JAK2*V617F, n (%)	334 (59.1)
CALR (n = 424),* n (%)	75 (17.6)
MPL (n = 424),* n (%)	7 (1.6)
Splenomegaly, N (%)	110 (19.4)
Treatment(s), N (%)	
ASA	545 (96.4)
Cytoreductive treatment†‡	491 (87.1)
HU	460 (81.4)
Anagrelide	114 (20.1)
Interferon alfa	83 (14.6)

ASA, acetylsalicylic acid; CAD, coronary artery disease, DM, diabetes mellitus; HU, hydroxyurea; HT, hypertension.

*_CALR_ and _MPL_ mutations were analyzed in 424 patients.

†Some patients received ≥2 lines of cytoreductive treatment; therefore, total sum exceeds 100%.

‡One patient received busulfan.

point and provides a robust alternative in cases for which 50% event rates are not observed.

The predictive performance of the Triple A, IPSET, IPSET-T, and revised IPSET-T risk scores for survival and clinical outcomes such as thrombosis was comparatively evaluated. Model fit was assessed using the Akaike information criterion (AIC), with lower AIC values indicating better predictive performance. Logistic regression analysis was performed to assess the association between Triple A risk scores and elevated monocyte levels. A significance level of P value $< .05$ was considered statistically significant in all analyses. Statistical analyses were performed using R software (version 4.2.1).

Results

A total of 618 patients were screened initially, and 53 patients who did not fulfill the inclusion criteria were excluded. We included 565 patients for the final analysis. Median age at diagnosis was 53 years (IQR, 38-65), and 63.5% of the patients were female. At the time of diagnosis, 58.4% had at least 1 comorbidity, of which hypertension was the most common. Overall, 135 patients (23.8%) had either a history of thrombosis or had thrombosis at diagnosis. Among those patients, 32 (23.7%) had venous thrombosis, and 94 (69.6%) had arterial thrombosis. Furthermore, 9 patients (6.7%) had both arterial and venous thrombosis. Coronary artery disease and cerebrovascular disease were the most frequent arterial thrombosis. Intraabdominal thrombosis was the most common site for venous thrombosis. Sixty patients (10%) presented with a history of bleeding, and among these, 31 had a major organ bleeding. A total of 334 patients (59.1%) were positive for *JAK2*V617F mutation. *CALR* and *MPL* mutations were not tested in 141 patients, and the percentages of *CALR* and *MPL* mutations were in 17.6% (75/424) and 1.6% (7/424), respectively. Splenomegaly was present in 19.4% of patients (Table 1).

Based on the revised IPSET-T score, 27.8%, 28.3%, 9.4%, and 34.5% of the patients were classified as very low, low, intermediate, and high risk, respectively. Using the IPSET-T scoring system, 29% were in the low-risk group, 29.2% in the intermediate-risk group, and 41.8% in the high-risk group. For IPSET score, 36.5%, 40.3%, and 23.2% of the patients were categorized as low, intermediate, and high risk, respectively.

All patients received either acetylsalicylic acid or cytoreductive treatment during the course of their diseases and 73 patients received only acetylsalicylic acid. Among 492 patients with cytoreductive treatment, 81.4% had hydroxyurea, 20.1% had anagrelide, and 14.6% had interferon alfa (Table 1).

Forty-three patients had a secondary malignancy. The risk of thrombosis in patients with secondary malignancy was 1.8-times higher than those without, but this was not statistically significant (HR, 1.8; 95% CI, 0.85-3.82; $P = .123$). Six patients (1%) experienced AML transformation. At the time of data collection, after a median of 5.99 years (IQR, 2.66-10.19), 62 (10.9%) patients died and 138 (24.4%) were lost to follow-up.

Triple A score

According to the Triple A score, 250 (44.2%), 228 (40.4%), 37 (6.6%), and 50 patients (8.85%) were classified as low, intermediate-1, intermediate-2, and high risk, respectively. Patients classified as lower risk were significantly younger, had fewer comorbidities, and exhibited a lower prevalence of thrombosis ($P < .001$ for all; Table 2).

Survival according to Triple A score

OS was significantly shorter in the high-risk group ($P < .001$; Figure 1A). Median OS was not reached for the low- and intermediate-1–risk patients. RMST was calculated for patients in these risk groups for whom median survival could not be determined. RMST was 20.4 years (95% CI, 19.5-21.3) for the low-risk group and 17.5 years (95% CI, 15.84-19.18) for intermediate-1–risk group. Median OS for the intermediate-2– and high-risk groups were 10.5 and 8.7 years, respectively. For the low-risk patients, 5- and 10-year survival probabilities were both 99.5% (95% CI, 98.5-100), whereas the 20-year survival probability was 85.8% (95% CI, 74.6-98.9). The 5-year survival rate for the intermediate-1 group was 95.1% (95% CI, 92-98.3), whereas the 10- and 20-year survival rates were 86.5% (95% CI, 80.5-92.9) and 62.2% (95% CI, 43.8-88.4), respectively. For the intermediate-2–risk group, the 5-year survival rate was 64.4% (95% CI, 46.5-89.0), and the 10-year survival rate was 50.7% (95% CI, 31.8-80.7). The 5- and 10-year survival rates for high-risk patients were 69.9% (95% CI, 56.1-87.0), and 21.2% (95% CI, 6.9-65.4), respectively (Figure 1A).

Table 2. Demographic and clinical data according to Triple A score

Parameter	Low risk (n = 250)	Intermediate-1 risk (n = 228)	Intermediate-2 risk (n = 37)	High risk (n = 50)	*P* value
Median age at diagnosis (IQR), y	37 (29-44)	60 (55-65)	72 (68-76)	75 (73.3-79)	**<.001**
Comorbidity, N (%)					
Yes	75 (30)	177 (77.6)	32 (86.5)	46 (92)	**<.001**
No	175 (70)	51 (22.4)	5 (13.5)	4 (8)	
DM, N (%)					
Yes	17 (6.8)	57 (25)	9 (24.3)	10 (20)	**<.001**
No	233 (93.2)	171 (75)	28 (75.7)	40 (80)	
HT, N (%)					
Yes	31 (12.4)	120 (52.6)	29 (78.4)	43 (86)	**<.001**
No	219 (87.6)	108 (47.4)	8 (21.6)	7 (14)	
CAD, N (%)					
Yes	7 (2.8)	33 (14.5)	7 (18.9)	14 (28)	**<.001**
No	243 (97.2)	195 (85.5)	30 (81.1)	36 (72)	
History of thrombosis, N (%)					
Yes	36 (14.4)	62 (27.2)	12 (32.4)	25 (50)	**<.001**
No	214 (85.6)	166 (72.8)	25 (67.6)	25 (50)	
History of venous thrombosis, N (%)					
Yes	20 (8)	14 (6.1)	3 (8.1)	4 (8)	.834
No	230 (92)	214 (93.9)	34 (91.9)	46 (92)	
History of arterial thrombosis, N (%)					
Yes	18 (7.2)	52 (22.8)	10 (27)	23 (46)	**<.001**
No	232 (92.8)	176 (77.2)	27 (73)	27 (54)	
History of bleeding, N (%)					
Yes	29 (11.6)	26 (11.4)	2 (5.4)	3 (6)	.543
No	221 (88.4)	202 (88.6)	35 (94.6)	47 (94)	
Median Hgb level at diagnosis (IQR), g/dL	13.7 (12.4-14.78)	13.8 (12.6-14.7)	13.9 (13.3-15.7)	13.8 (12.03-14.68)	.163
Median leukocyte count at diagnosis (IQR), $\times 10^9$/L	9.6 (7.86-11.2)	9.7 (7.8-12.0)	10.2 (8.8-12.4)	11.5 (8.7-14.8)	**.009**
Median neutrophil count at diagnosis (IQR), $\times 10^9$/L	6.1 (4.9-7.6)	6.4 (4.7-8.3)	6.6 (5.3-8.7)	8.4 (6.0-10.6)	**.006**
Median lymphocyte count at diagnosis (IQR), $\times 10^9$/L	2.3 (1.9 -2.8)	2.1 (1.7-2.8)	1.9 (1.6-2.5)	1.6 (1.2-2.4)	**<.001**
Median monocyte count at diagnosis (IQR), $\times 10^9$/L	0.5 (0.4-0.7)	0.6 (0.5-0.8)	0.7 (0.5-0.9)	0.7 (0.6-1.1)	.824
Median platelet count at diagnosis (IQR), $\times 10^9$/L	844.5 (673-1048.5)	838 (670.5-1042.5)	867 (703-1000)	842.5 (690.5-1044)	.983
***JAK2*V617F mutation, N (%)**					
Yes	138 (55.2)	137 (60.1)	25 (67.6)	34 (68)	.228
No	112 (44.8)	91 (39.9)	12 (32.4)	16 (32)	
Splenomegaly, N (%)					
Yes	56 (22.4)	45 (19.7)	3 (8.2)	6 (12)	.103
No	194 (77.6)	183 (80.3)	34 (91.8)	44 (88)	

P values set in bold indicate statistical significance.

Thrombosis-free survival

During follow-up, 58 patients (10.3%) developed any kind of thrombosis. Among them, 18 (31%) had venous, 38 (65.5%) arterial, and 2 (3.5%) had both arterial and venous thrombosis. Thrombosis-free survival shortened as the risk group increased ($P = .0003$). RMST for the low-, intermediate-1–, intermediate-2–, and high-risk patients were 17.5 years (95% CI, 16.65-18.4), 17.88 years (95% CI, 16.91-18.86), 11.25 years (95% CI, 8.57-13.95), and 8.87 years (95% CI, 7.48-10.25), respectively. For the low-risk group, 5-, 10-, and 20-year survival probabilities were 92.7% (95% CI, 89-96.5), 86.1% (95% CI, 80.3-92.3), and 70.8% (95% CI, 53.5-93.7), respectively. In the intermediate-1 group, 5- and 10-year survival probability rates were 93.2% (95% CI, 89.6-96.9) and 88.9% (95% CI, 83.5-94.6),

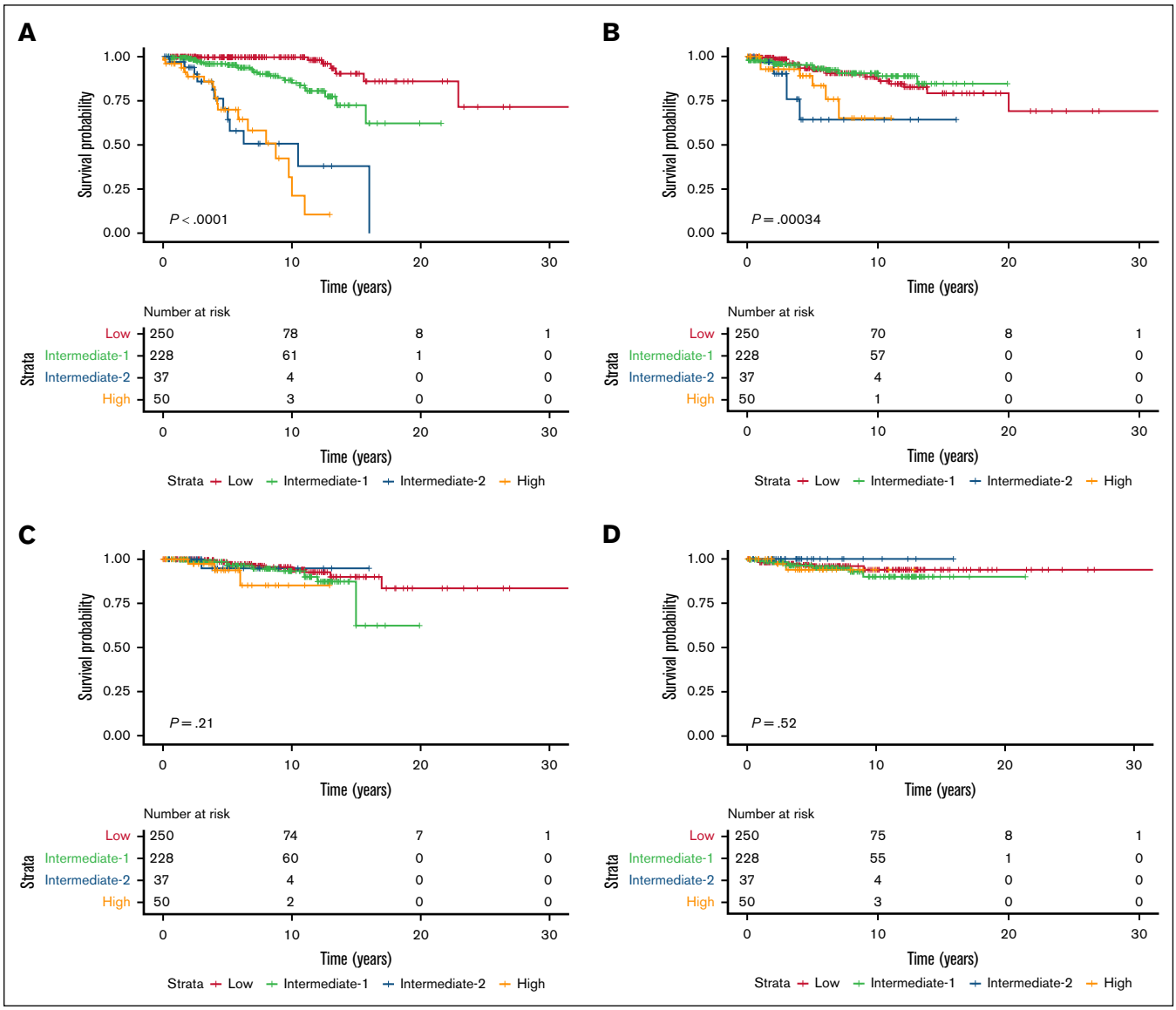


Figure 1. Kaplan-Meier analysis depicting survival stratified by Triple A score. Overall (A), thrombosis-free (B), MF-free (C), and bleeding-free (D) survival curves according to Triple A risk groups.

respectively. For the patients in the intermediate-2–risk group, 5- and 10-year survival probabilities were both 63.3% (95% CI, 45.4-88.3). In the high-risk group, 5- and 10-year survival probability were 83.5% (95% CI, 70.4-99.2) and 65.1% (95% CI, 43.9-96.6), respectively (Figure 1B).

MF-free survival

MF transformation was observed in 29 patients (5.1%). MF-free survival was similar between risk groups ($P = .21$). RMST for the low-, intermediate-1–, intermediate-2–, and high-risk groups were 18.6 years (95% CI, 17.84-19.36), 17.2 years (95% CI, 15.61-18.81), 15.32 years (95% CI, 14.01-16.62), and 11.71 years (95% CI, 10.35-13.06), respectively. The 5-year survival probability was calculated as 97% (95% CI, 94.5-99.6), and the 10- and 20-year survival probabilities were 93.9% (95% CI, 89.7-98.3) and 83.5% (95% CI, 70.8-98.4), respectively, for the low-risk group. In the intermediate-1–risk group, the 5- and 10- year survival probabilities were 96.3% (95% CI, 93.5-99.3) and 93.2% (95% CI, 88.7-97.8), respectively. For patients in the intermediate-2–risk group, the 5- and 10-year survival probabilities were both 94.7% (95% CI, 85.2-100); and the 5- and 10-year survival probabilities were both 85% (95% CI, 69-100) for the high-risk group (Figure 1C).

Bleeding-free survival

Bleeding was observed in 25 patients (4.4%), with 15 experiencing major organ bleeding. Bleeding-free survival was comparable across risk groups ($P = .52$). RMST was estimated at 20.56 years (95% CI, 19.39-21.19) for the low-risk group, 19.99 years (95% CI, 19.15-20.85) for the intermediate-1 group, 16 years for the intermediate-2 group, and 12.3 years (95% CI, 11.47-13.14) for the high-risk group. In the low-risk group, 5-year survival

Table 3. Cox regression model evaluating the association of monocytosis and Triple A score with mortality

Variable	No. of patients	HR	95% CI	*P* value
Monocyte count (>0.8 × 10^9/L)	114	1.79	1.05-3.05	**.033**
Triple A score				
Intermediate-1	223	4.46	1.81-10.96	**.001**
Intermediate-2	37	21.46	7.91-58.24	**<.001**
High	49	28.98	10.97-76.56	**<.001**

P values set in bold indicate statistical significance.

probability was 96% (95% CI, 93.3-98.8) and the 10- and 20-year survival probabilities were both calculated as 94% (95% CI, 90.2-97.9). In the intermediate-1–risk group, the 5-year survival probability was 95.2% (95% CI, 92.1-98.3), whereas the 10- and 20-year survival probabilities were both 90.2% (95% CI, 84.7-96). Because no events occurred in the intermediate-2–risk patients, the 5-, 10-, and 20-year survival probabilities could not be calculated. In the high-risk group, 5- and 10-year survival probabilities were both 94% (95% CI, 86.3-100; Figure 1D).

Comparison of risk models

We used AIC to compare the predictive performance of various prognostic models in estimating mortality. Triple A has the lowest AIC values (AIC = 583.369), which suggests better prediction performance than the IPSET score (AIC = 609.328) for survival. Both risk scores have significant difference between risk groups compared with low risk ($P < .001$; supplemental Table 1).

We also evaluated the ability of the Triple A, IPSET-T, and revised IPSET-T scores to predict thrombosis. Because the Triple A model (AIC = 652.975) had the lowest AIC value, it was found to provide a statistically better fit than the other models. However, the IPSET-T (AIC = 663.396) and revised IPSET-T (AIC = 665.256) models demonstrated weaker thrombotic risk prediction performance in terms of AIC.

Monocytosis and Triple A

According to the Cox regression analysis, a baseline monocyte count of >0.8 × 10^9/L was significantly associated with an increased risk of mortality compared with those with baseline monocyte count of ≤0.8 ×10^9/L (HR, 1.79; 95% CI, 1.05-3.05; $P = .033$). The strong association between the Triple A risk score and mortality risk was also preserved in this model. Compared with the low-risk group, significantly increased mortality risks were observed in the intermediate-1 (HR, 4.46; 95% CI, 1.81-10.96), intermediate-2 (HR, 21.46; 95% CI, 7.91-58.24), and high-risk (HR, 28.98; 95% CI, 10.97-76.56) groups (all $P < .001$; Table 3). The AIC value of the AAA+A model (inclusion of monocyte count to the Triple A model) was found to be 573.694.

According to the logistic regression analysis, the likelihood of having a monocyte count of >0.8 × 10^9/L significantly increases as Triple A risk scores increase. When the low-risk group was used as reference, individuals in the intermediate-1–risk group were 3.28 times more likely to have monocyte counts of >0.8 × 10^9/L compared with those in the low-risk group (odds ratio [OR], 3.28; 95% CI, 1.95-5.68; $P < .001$). Similarly, this likelihood increased by 6.66 times in the intermediate-2–risk group (OR, 6.66; 95% CI, 3.01-14.72; $P < .001$) and by 7.33 times in the high-risk group (OR, 7.33; 95% CI, 3.59-15.12; $P < .001$; Figure 2).

In the multivariable Cox regression analysis evaluating the effect of baseline monocyte level on thrombotic risk, patients with a monocyte count of >0.8 × 10^9/L had a significantly increased risk of thrombosis compared with those with monocyte count of ≤0.8 × 10^9/L (HR, 1.99; 95% CI, 1.08-3.66; $P = .03$). Compared with the low-risk group of the Triple A risk score, only the intermediate-2 group was significantly associated with an increased thrombotic risk (HR, 2.99; 95% CI, 1.29-6.93; $P = .01$), whereas no significant difference was observed in the intermediate-1 and high-risk groups ($P = .25$ and $P = .13$, respectively; supplemental Table 2).

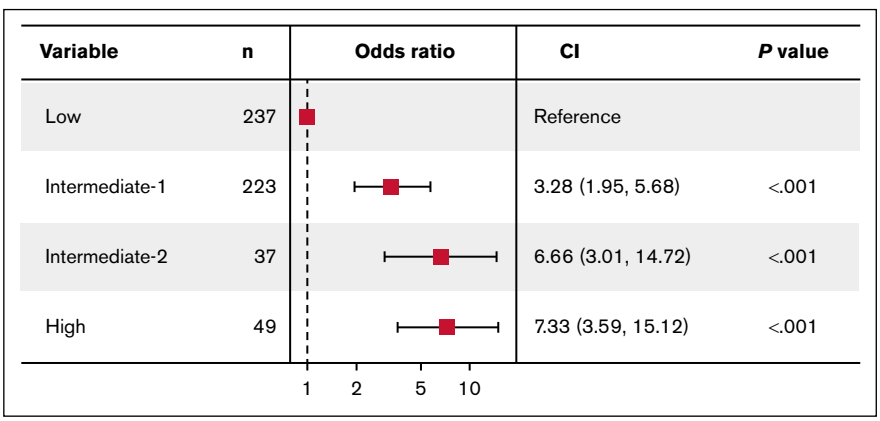


Figure 2. Logistic regression analysis of Triple A risk scores and monocyte count. Logistic regression analysis was conducted to evaluate the association between Triple A risk score and monocyte count, in which monocytosis (monocyte count of >0.8 × 10^9/L) was used as the dependent variable.

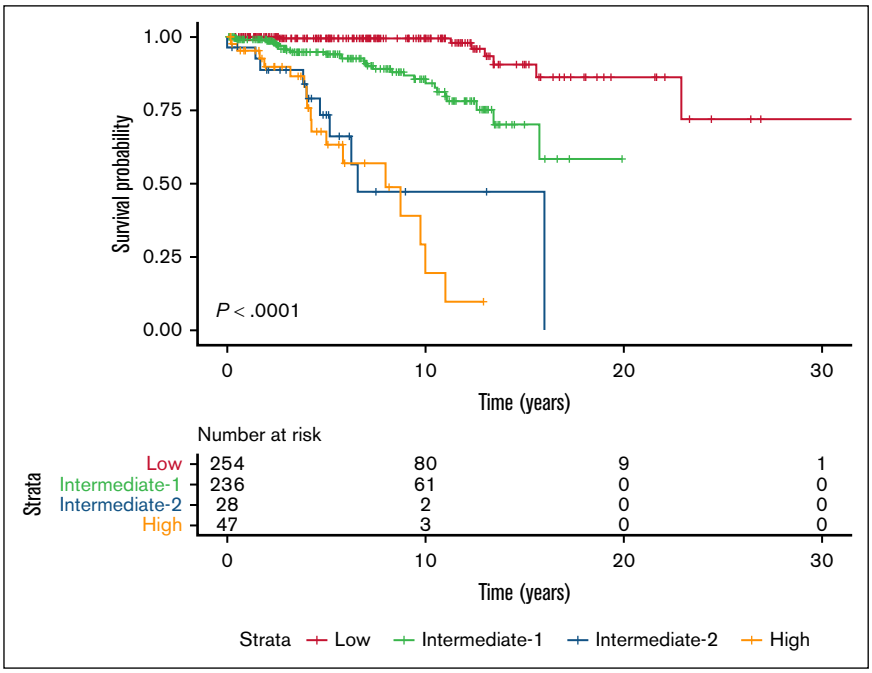


Figure 3. Kaplan-Meier curves depicting survival stratified by NLR-age–based model.

NLR

An increase in the NLR at the time of diagnosis was associated with a higher risk of mortality (HR, 2.18; 95% CI, 1.52-3.13; $P <$ .001). The ROC curve analysis identified a threshold value of 3.21, and patients with an NLR of >3.21 had significantly reduced survival (HR, 2.04; 95% CI, 1.22-3.3; $P = .006$). When examining the relationship between NLR values and the Triple A risk score, a moderate, positive, and significant correlation was found ($r = 0.441$; $P < .001$; supplemental Figure 1).

Additionally, we examined the potential role of NLR in predicting thrombosis. NLR was not associated with thrombosis risk (HR, 1.01; 95% CI, 0.96-1.06; $P = .6$), and Kaplan-Meier analysis demonstrated no significant difference in thrombosis-free survival when patients were stratified according to an NLR cutoff of 3.21 ($P = .33$).

When we replaced the ANCs and ALCs with NLR in the Triple A score, the NLR-age–based model had an AIC value of 585.592. In addition, this NLR-age–based model showed significant difference in survival across risk groups (Figure 3). Furthermore, we also explored a potential novel model, by substituting ANCs and ALCs with NLR and incorporating monocyte count, while maintaining the same age variable and scoring framework. We termed this as the NLR-monocyte-age–based model. This model had an AIC value of 578.293 and the survival probability had significantly differed between risk groups ($P < .001$; Figure 4).

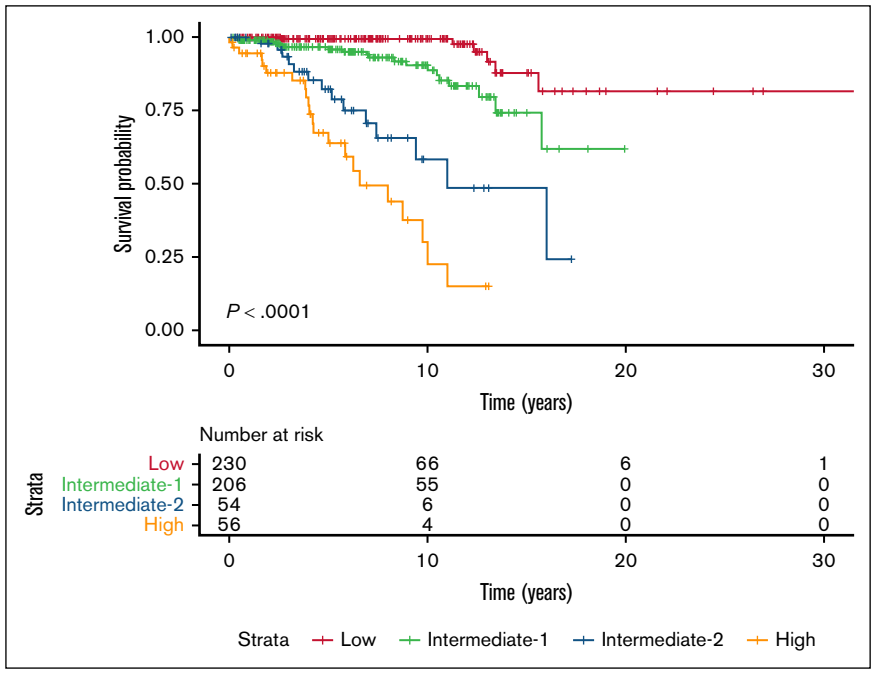
Discussion

This study demonstrated the prognostic utility of the Triple A model in predicting survival outcomes within our ET population and highlighted a significant stratification of survival across the risk groups. According to the Triple A score, patients classified as high-risk exhibited markedly shorter survival compared with those in the low-risk group, with a median survival of 8.7 years in our high-risk patients. These findings are consistent with those reported by Tefferi et al in a study conducted at the Mayo Clinic,[11] which included 598 patients across the discovery cohort and documented a median survival of 8 years among those in the high-risk group. Similarly, a study from Italy including 314 patients, reported a median survival of 13.2 years in the high-risk group.[28] Despite the differences in survivals, all studies, including ours, consistently demonstrated significant survival differences across Triple A risk groups. Notably, all 3 cohorts demonstrated a female predominance. Our cohort had the lowest median age (53 years), whereas the Italian cohort had the highest (63 years), and the median age of the Mayo Clinic cohort was 59 years. In terms of follow-up durations,[11] the longest median follow-up was reported by Tefferi et al[11] (8.4 years), whereas we (6 years) and Tosoni et al[28] (6.1 years) reported similar follow-up durations. In all 3 cohorts, most patients were classified as the low- and intermediate-1–risk groups. Although no formal statistical comparison was conducted, the survival outcomes of the high-risk patients in our cohort closely aligned with those observed in the Mayo Clinic cohort, whereas the Italian study reported a longer survival. Importantly, when compared with the IPSET score, according to AIC, the Triple A model demonstrated superior performance in predicting survival in line with the findings of Tefferi et al.[11]

In our cohort, high-risk patients had a shorter thrombosis-free survival, which was consistent with previous findings in the literature.[11,28] Moreover, we also showed that the predictive power of the Triple A model for thrombosis outperformed both the revised IPSET-T and the IPSET-T models, which, to the best of our knowledge, has been demonstrated for the first time.

Our study demonstrated that the Triple A score was superior to other scoring systems in predicting both thrombosis and OS. However, current treatment guidelines, including those following

Figure 4. Kaplan-Meier curves depicting survival stratified by NLR-monocyte-age–based model.



the National Comprehensive Cancer Network therapeutic algorithm, continue to base treatment planning primarily on the revised IPSET-T score. Based on our findings, together with previous reports,[11,28] it may be time to consider updating treatment guidelines to incorporate the Triple A score and develop corresponding therapeutic algorithms.

In contrast to the findings reported by Tosoni et al,[28] we did not detect any significant difference regarding bleeding incidences across risk groups. This discrepancy may be attributable to differences in outcome definitions, because our study included all bleeding events, whereas the Italian study focused exclusively on major bleeding episodes.

We observed no significant difference in the development of post-ET MF across the risk groups, in line with the findings of Tefferi et al.[11] Due to the limited number of patients who developed AML in our study, we were unable to assess the predictive power of the Triple A risk score for AML transformation. This parameter was not specifically evaluated in previously published study,[28] most probably due to the relatively low risk of AML progression and need for a longer follow-up. However, we believe that this aspect warrants further investigation in future multicenter studies with larger patient populations and a longer follow-up to evaluate its potential role in predicting progression to AML.

We found that monocytosis at diagnosis was associated with increased risk of mortality. Prominently, the strong association between the Triple A score and mortality risk remained significant even after the incorporation of monocytosis to the model. This suggests that the AAA+A model could further enhance its predictive power. We also demonstrated that the AAA+A model might have a better predictive performance. Additionally, according to our analysis, as Triple A risk scores increase, the probability of having elevated monocyte counts also rises significantly. Consistent with our findings, monocytosis has previously been identified as an independent risk factor for survival and proposed as a potential addition to the Triple A model.[29] Furthermore, recently, the predictive value of AAA+A model was validated in 472 patients with ET.[30]

We also examined the relationship between monocytosis and thrombosis and explored the potential impact of integrating monocytosis into the Triple A model. Our findings indicate that the monocyte count at diagnosis may serve as independent risk factor for thrombosis. However, the predictive power of the score for thrombosis varied across different risk categories. In the aforementioned study by Tefferi et al[29] exploring the AAA+A model, monocytosis was not associated with thrombosis, even in multivariate analysis, despite showing significance in univariate analysis. These finding underscore the complexity of the relationship between monocytosis and thrombotic risk. The AAA+A model warrants further investigation in future studies, with a broader extending beyond survival and thrombosis to include outcomes such as myelofibrotic transformation and bleeding.

We believe the main strength of the Triple A model lies in its simplicity and objectivity, relying only on age and CBC parameters. More recently, Tefferi et al[31] introduced the AAA^{+} model, which incorporates arterial thrombosis, hypertension, sex, and monocyte count in addition to previously established ANC, ALC, and age, based on their large cohort of 7308 patients with ET. This expanded model integrates both CBC-derived and host-related clinical factors. This approach is both innovative and promising, further highlighting the Triple A model as a solid foundation with potential for future refinement.

In our study, elevated NLR was found to be associated with increased risk of mortality. Patients with an NLR of >3.21 at diagnosis had inferior survival outcomes. However, incorporating

the NLR into the Triple A risk model did not result in significant improvement in mortality risk prediction. A previous study involving 835 430 individuals from the Danish General Suburban Population Study investigated the association of NLR in both the general population and patients with MPN.[22] In patients with ET an NLR of ≥2 was associated with more than a twofold increase in all-cause mortality. Furthermore, the study demonstrated an alignment between NLR and the Triple A risk score, indicating that individuals with higher Triple A scores also exhibited higher NLR values and this association was most pronounced in the high-risk group. Consistently, Barbui et al[32] recently demonstrated that NLR may help guide early treatment decisions in patients with low-risk PV, further highlighting the prognostic value of inflammatory markers in MPNs. They also showed that NLR functions as a dynamic marker of treatment response with reductions in NLR being associated with improved event-free survival.[33]

In this study, we evaluated 2 potential NLR-based survival models. Although the NLR-age model did not demonstrate superior predictive performance compared with the established Triple A model, the inclusion of monocyte count (resulting in NLR-monocyte-age–based model) improved predictive accuracy beyond the that of the Triple A model. Our findings suggest that monocyte count may provide incremental prognostic information, either as an extension the NLR-monocyte-age–based model or as an enhancement to the original Triple A model. Moreover, NLR-based risk scores represent a promising avenue for future model development, offering potential to refine prognostic assessment and guide clinical decision-making.

In our cohort, elevated NLR values appeared to be associated with an increased risk of thrombosis, although this did not reach statistical significance. In contrast, a previous study has shown that an NLR value of ≥4 at the time of diagnosis was also predictive of thrombotic events,[21] and similarly, an NLR value of ≥5 was also found to be associated with venous thrombosis in patients with PV.[34] This discrepancy may stem from our relatively small sample size; given that NLR reflects systemic inflammation, an increased thrombosis risk was expected. Furthermore, there is considerable variability in the reported NLR cutoff values, reflecting lack of consensus on a standardized threshold. This heterogeneity may be attributed to differences in study population and methodologies. Despite this, the consistent association between elevated NLR and adverse outcome across studies supports its potential utility as an independent, practical, and readily accessible marker for broader implementation in clinical practice. In addition, very recently, lymphocyte-to-monocyte ratio was identified as a potential predictor of OS among patients with ET.[30]

The main limitation of this study is its retrospective data collection. Although this study is among one of the largest outside Europe and United States focusing specifically on patients with ET, we believe that examining the Triple A model in a larger patient population would be beneficial. Consequently, Triple A risk score could be involved to routine practice as a user-friendly tool for prediction of survival and thrombosis. Addition of monocytosis seems to enhance to performance of this score, possibly making it the so called AAA+A or "quadruple A" risk model. NLR should be engaged into clinical practice as either an independent risk factor or it could be incorporated into the NLR-monocyte-age–based risk score for predicting survival in patients with ET.

Authorship

Contribution: Ö.S., E.O., İ.Y.H., F.H., M.S., A.K., Z.A., T.S., and A.E.E. contributed to study conception or design, or analysis and interpretation of data, or both; Ö.S. and A.E.E. drafted and reviewed the manuscript, and provided intellectual content of critical importance to the work described; and Ö.S., E.O., İ.Y.H., F.H., M.S., A.K., Z.A., T.S., and A.E.E. approved the final version of the manuscript for publication.

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