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Triple A Plus (AAA⁺) Survival Prediction Model for Essential Thrombocythemia: Analysis Involving 7308 Patients

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ABSTRACT

Survival prediction models in essential thrombocythemia (ET) include the International Prognostic Scoring System (IPSET) and the more recently introduced triple-A (AAA) prognostic score. The latter enlists age and absolute neutrophil (ANC) and lymphocyte (ALC) counts as risk variables. In the current study, a Mayo Clinic discovery cohort of 658 patients with ET was used to identify AAA-independent risk variables. Accordingly, multivariable analysis-derived HRs (95% CI) were 15.7 (8.4–29.5) for age > 70 years (8 points); 4.2 (2.3–7.5) for age 50 to 70 years (2 points); 1.8 (1.2–2.5) for ANC $\geq 8 \times 10^9/L$ (1 point); 1.4 (1.03–1.9) for ALC $< 1.7 \times 10^9/L$ (1 point); 1.8 (1.2–2.6) for absolute monocyte count (AMC) $\geq 0.5 \times 10^9/L$ (1 point); 1.8 (1.2–2.3) for male sex (1 point); 1.8 (1.3–2.4) for arterial hypertension (1 point); and 1.6 (1.2–2.3) for arterial thrombosis (1 point). HR-weighted scoring enabled a 4-tiered risk classification: ultra-low (0–1 points; $N = 94$; median survival 42.7 years), low (2–4 points; $N = 297$; 23 years), intermediate (5 points; $N = 66$; 17.3 years), and high (6–14 points; $N = 201$; 10.8 years). Time-dependent predictive performance at 20/25 years favored AAA⁺ (AUC 0.92/0.91) vs. AAA (0.86/0.86) vs. IPSET (0.81/0.84). The AAA⁺ risk model was subsequently validated by two external cohorts from Israel ($N = 5968$) and Italy ($N = 682$). In the cohort from Israel, disease-specific mortality was assessed by comparing observed survival to an age- and sex-matched reference population, which suggested near-normal life expectancy in ultra-low risk patients. The current study highlights host-related factors as the primary determinants of longevity in ET and provides a composite risk score (AAA⁺) that is based on complete blood count-derived parameters and host-related factors. Predictive performance of the new model was shown to be superior to that of IPSET and AAA.

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1 | Introduction

Essential thrombocythemia (ET) is one of three *JAK2* mutation-prevalent myeloproliferative neoplasms (JAK2-MPNs) and must be distinguished from the other two, polycythemia vera (PV) and primary myelofibrosis (PMF), in order to enable accurate prognostication and treatment [1]. A platelet count of $450 \times 10^9/L$ or more is a prerequisite for the formal diagnosis of ET, which also requires exclusion of other myeloid neoplasms and secondary thrombocytosis [2, 3]. Clinical presentation in ET is variable, with most patients being asymptomatic while a substantial minority might present with microvascular symptoms and, even less frequently, with thrombosis or hemorrhage [4]. The clinical course is characterized by relatively infrequent episodes of thrombosis or bleeding, while disease progression to acute myeloid leukemia (AML) or post-ET myelofibrosis (post-ET MF) occurs in <1% and <5% of patients, respectively, in the first 10 to 15 years of the disease [5, 6]. Fortunately, most patients with ET can expect normal life expectancy with median survival of >30 years in patients aged below 50 years [7–9].

Current drug therapy in ET is not disease-modifying and is primarily directed at preventing thrombosis in high-risk patients or alleviating disease-related symptoms. Contemporary risk models for thrombosis in ET include the original (IPSET-thrombosis) [10] and revised (R-IPSET-thrombosis) [11] International Prognostic Scoring Systems. The latter includes four risk categories: very low risk (age ≤ 60 years, no thrombosis history, *JAK2* wild-type), low risk (age ≤ 60 years, no thrombosis history, *JAK2* mutated), intermediate risk (age > 60 years, no thrombosis history, *JAK2* wild-type) and high risk (thrombosis history or age > 60 years with *JAK2* mutation) [11]. In very low-risk patients, annual rates of thrombosis ranged from 0.44% in the absence to 1.05% in the presence of cardiovascular (CV) risk factors; the corresponding rates in low-risk disease were 1.59% and 2.57%, in intermediate risk 1.44% and 1.64%, and in high risk 2.36% and 4.17% [11]. Aspirin therapy is recommended in the presence of CV risk factors and in low to high risk disease, while cytoreductive therapy is reserved for high-risk disease [5].

Unlike the case with R-IPSET-thrombosis [11], overall survival models in ET are not necessarily actionable and are used primarily to inform patients on their long-term outlook and assess the need for close monitoring. The IPSET, described in 2012 [12], is the first of three currently used prognostic models in ET. Risk variables used in the IPSET include age ≥ 60 years (2 points), leukocyte count $\geq 11 \times 10^9/L$ (1 point), and thrombosis history (1 point). The IPSET risk categories include low (0 points), intermediate (1–2 points), and high (3–4 points) with median survivals of “not reached”, 24.5 years, and 13.8 years, respectively [12]. The mutation-enhanced international prognostic system for ET (MIPSS-ET) was described in 2020 [13] and its risk variables include age > 60 years (4 points), adverse mutations such as *SF3B1*, *SRSF2*, *U2AF1*, and *TP53* (2 points), leukocyte count $\geq 11 \times 10^9/L$ (1 point), and male sex (1 point); risk categories in MIPSS-ET include low (0–1 points), intermediate (2–5 points), and high (6 points or more) with corresponding median survivals of 34.4, 14.1, and 7.9 years, respectively [12].

The most recently (2023) introduced risk model for survival in ET, the triple-A model (AAA), is also based on clinical variables

that include age > 70 years (4 points), age 50 to 70 years (2 points), absolute neutrophil count (ANC) $\geq 8 \times 10^9/L$ (1 point), and absolute lymphocyte count (ALC) $< 1.7 \times 10^9/L$ (1 point). AAA risk categories included low (0–1 points), intermediate-1 (2–3 points), intermediate-2 (4 points) and high (5–6 points), with corresponding median survivals of 47, 20.7, 13.5, and 8 years, respectively [14]. Of note, the aforementioned adverse mutations and abnormal karyotype displayed additional prognostic contribution in the context of the AAA model, without compromising the independent prognostic relevance of the clinical risk variables [14]. The current study was inspired by recurrent observations from previous work highlighting the prognostic relevance of additional host-related factors such as male gender [15, 16] and cardiovascular (CV) risk factors [17, 18] and disease-related factors such as thrombosis [6, 12, 16, 19–21]. The main objective of the current study was to upgrade the AAA model by incorporating host-related factors and also examine for the possibility of prognostic contribution from monocytosis, as has been previously noted in PV [22].

2 | Methods

Institutional review board approvals were obtained from the Mayo Clinic, USA (discovery cohort) and University of Florence, Italy (validation cohort-2), in order to conduct minimum risk research protocols that allowed retrospective collection and analysis of patient data. Analysis of validation cohort-1 from Israel was based on anonymized data obtained from electronic medical records of Maccabi Healthcare Services (MHS) members, after receiving approval number 045 to 2023 from the institution's ethical committee. Study patients were retrospectively accrued after central confirmation of diagnosis according to the 2016 World Health Organization (WHO) diagnostic criteria [23] and availability of information on ANC (Mayo Clinic reference range $1.56\text{--}6.45 \times 10^9/L$), ALC ($0.95\text{--}3.07 \times 10^9/L$), and absolute monocyte count (AMC; $0.26\text{--}0.81 \times 10^9/L$). Special attention was given to avoid inadvertent inclusion of patients with masked PV (in the presence of *JAK2* mutation associated with hemoglobin levels near or exceeding the thresholds for PV diagnosis) and prefibrotic PMF in the presence of anemia or special smear suggestions of leukoerythroblastosis. Data were collected retrospectively corresponding to the time of first referral, which, in the majority of cases, coincided within 1 year of initial diagnosis and always before initiation of cytoreductive therapy. All patients were followed until death or last follow-up, as assessed by medical records or through direct contact with patients or their physicians. Treatments received were according to the discretion of the treating physician and none are known to modify the natural history of the disease and thus unlikely to confound survival estimates. Conventional criteria were used for definitions of disease-associated complications, including leukemic or fibrotic transformation and major thrombotic or bleeding events [23, 24]. Driver mutation and cytogenetic analyses were performed according to institutional protocols for clinical use and reported in conformity with international guidelines [25].

Statistical analyses considered clinical and laboratory data collected at the time of initial diagnosis/referral. Receiver operating characteristic (ROC) curve analysis was utilized to determine the optimal cutoff points for age, ANC, ALC, and

AMC. Differences in the distribution of continuous variables between categories were compared using the Mann–Whitney or Kruskal–Wallis test. Categorical variables were compared using the χ^2 test. Cox regression analysis was applied in order to identify risk factors for overall (OS), leukemia-free (LFS), and myelofibrosis-free (MFFS) survival. The Kaplan–Meier method was used to construct time-to-event curves, which were compared by the log-rank test. The p -values of <0.05 were considered significant. Prognostic models were developed using hazard ratio (HR)-based risk point allocation. Prognostic models derived from the discovery cohort (Mayo Clinic, USA) were externally validated by their application to two separate external cohorts: validation cohort-1 (Ben-Gurion University, Israel) and validation cohort-2 (University of Florence, Italy).

To evaluate the discriminative ability of risk models at different time horizons, we calculated time-dependent area under the receiver operating characteristic curve (AUC) values using dynamic definitions of sensitivity and specificity. Time-specific AUC was computed at pre-defined landmark time points using the nonparametric estimator proposed by Blanche et al. [26] and implemented in R's *timeROC* library. The risk score derived from our model was used as the sole predictor input for AUC estimation, allowing evaluation of the model's discriminative ability at each time point. To account for right-censored data, inverse probability of censoring weighting (IPCW) was applied using the Kaplan–Meier estimator for the censoring distribution. This methodology allowed us to assess whether the predictive accuracy of our model remained sufficiently high across different follow-up periods, with AUC values closer to 1.0 indicating superior discriminative performance and values around 0.5 suggesting poor predictive ability. We then compared the time-dependent AUCs of different scoring models (AAA⁺, AAA, and IPSET) to evaluate whether the proposed AAA⁺ score outperforms existing scoring systems.

In addition to time-dependent AUC, we calculated the Akaike Information Criterion (AIC) and the concordance index (C-index) to evaluate the overall performance of the model. The AIC provides a measure of model fit while penalizing model complexity, thereby supporting model selection and comparison. Lower AIC values indicate a better trade-off between goodness-of-fit and parsimony. The C-index, a global measure of discrimination in survival analysis, quantifies the concordance between predicted risks and observed survival outcomes. It reflects the model's ability to correctly rank individuals by their risk of experiencing the event across all time points and not in specific time points (as in AUC). We used the package *compareC* in R to statistically compare the C-index of AAA⁺ to the C-indices of AAA and IPSET [27].

Because age and sex are major determinants of OS in the general population, we conducted an additional analysis to estimate the excess mortality risk attributable, specifically, to ET. To do this, we compared observed survival in our cohort to an age- and sex-matched reference population using data from the Human Mortality Database (www.mortality.org), which provides year-, age-, sex-, and country-specific mortality rates. For each patient, individualized expected survival

curves were constructed based on their age, sex, year of ET diagnosis, and their residence country, allowing us to isolate the disease-specific impact on mortality. Accessible statistical software with commercially verified licenses was used for all calculations, including some conducted using custom algorithms implemented in R version 4.5.0.

3 | Results

3.1 | Presenting Characteristics and Disease Course

The discovery cohort from the Mayo Clinic included 658 patients (median age 60 years, range 18–90; females 64%). IPSET risk categories were low (36%), intermediate (45%), and high (19%); AAA risk categories were low (29%), intermediate-1 (44%), intermediate-2 (11%) and high (16%). Table 1 illustrates clinical and laboratory characteristics at presentation and during the disease course. Driver mutation distributions included *JAK2* 63%, *CALR* 25%, *MPL* 4%, and triple-negative 8%. Median (range) values for leukocyte count were $8.4 \times 10^9/L$ (3.3–27.1), ANC $5.5 \times 10^9/L$ (1.5–23.3), ALC $1.8 \times 10^9/L$ (0.6–5.7), AMC $0.59 \times 10^9/L$ (0.1–2.5), platelet count $732 \times 10^9/L$ (450–3330), hemoglobin level 13.9 g/dL (10.2–17.2), absolute eosinophil count (AEC) $0.2 \times 10^9/L$ (0–1.4), absolute basophil count (ABC) $0.07 \times 10^9/L$ (0–0.79). Platelet count $\geq 1000 \times 10^9/L$ was seen in 132 (20%) patients and leukocytosis (leukocyte count $\geq 11 \times 10^9/L$) in 120 (18%). Microvascular symptoms were mentioned in 197 (31%) patients and 56 (9%) patients displayed palpable splenomegaly. Co-morbidities included any cardiovascular (CV) risk factor (55%), hypertension (39%), diabetes (10%), hyperlipidemia (53%), and tobacco use (21%).

Thrombohemorrhagic history at or prior to diagnosis included arterial thrombosis ($N=101$; 15%), venous thrombosis ($N=62$; 9%), and major hemorrhage ($N=54$; 8%). Thrombohemorrhagic history after diagnosis included arterial thrombosis ($N=71$; 11%), venous thrombosis ($N=44$; 7%), and major hemorrhage ($N=65$; 10%). Treatment strategies were at the discretion of the treating physician and included aspirin therapy in 570 (91%) patients, hydroxyurea in 475 (76%), anagrelide in 103 (16%), interferon-based in 49 (8%), and systemic anticoagulants in 110 (18%). At a median follow-up of 7.6 years (range 0.1–42.7) for living patients, 152 (23%) deaths, 23 (3.5%) leukemic transformations, and 59 (9%) fibrotic transformations were recorded. Among 79 (52% of deaths) patients in whom the cause of death was documented, 29 (37%) died of second cancers or other unrelated causes, 18 (23%) from progression into AML or post-ET MF, and 16 (10%) each from cardiovascular events or infections. Similar information on the two validation cohorts is outlined in Table 1.

3.2 | Clinical Risk Factors for Overall, Leukemia-Free, and Myelofibrosis-Free Survival

Multivariable analysis confirmed the prognostic relevance of previously established risk categories for age (>70 years and 50–70 years), ANC ($\geq 8 \times 10^9/L$), and ALC ($<1.7 \times 10^9/L$) [14]

TABLE 1 | Presenting clinical and laboratory features in 7326 patients with essential thrombocythemia (ET) stratified by assignment to discovery and validation cohorts.

	Discovery cohort	Validation cohort-1	Validation cohort-2
	Mayo clinic	Israel	Italy
	N = 658	N = 5968	N = 682
Median age in years (range)	60 (18–90)	61 (18–96)	59 (18–95)
Age < 50 years; n (%)	202 (31)	2333 (39)	225 (33)
Age 50–70 years; n (%)	298 (45)	1437 (24)	279 (41)
Age > 70 years; n (%)	158 (24)	2198 (37)	178 (26)
Female sex; n (%)	423 (64%)	3584 (60%)	448 (66)
IPSET risk categories ^a			
Low	236 (36)	1102 (19%)	249 (37)
Intermediate	298 (45)	3464 (58%)	315 (46)
High	124 (19)	1402 (24%)	118 (17)
AAA risk categories ^b			
Low	193 (29)	2188 (37%)	224 (33)
Intermediate-1	289 (44)	1409 (24%)	270 (40)
Intermediate-2	71 (11)	903 (15%)	93 (13)
High	105 (16)	1408 (25%)	95 (14)
Median leukocyte count $\times 10^9/L$ (range)	8.4 (3.3–27.1)	10 (2.8–35.6)	8.3 (2.7–23.4)
Median absolute neutrophil count $\times 10^9/L$ (range)	5.5 (1.5–23.3)	6.1 (1.1–26.8)	5.3 (1–19.1)
Absolute neutrophil count $\geq 8 \times 10^9/L$; n (%)	98 (15)	1899 (32%)	69 (10)
Median absolute lymphocyte count $\times 10^9/L$ (range)	1.8 (0.6–5.7)	2.1 (0.5–11.6)	2 (0.4–6)
Absolute lymphocyte count $< 1.7 \times 10^9/L$; n (%)	287 (44)	2082 (35%)	225 (33)
Median absolute monocyte count $\times 10^9/L$ (range)	0.59 (0.1–2.5)	0.58 (0.11–2.86)	0.52 (0.1–2.6)
Absolute monocyte count $\geq 0.5 \times 10^9/L$; n (%)	461 (70)	3764 (63%)	386 (57)
Median hemoglobin, g/dL (range)	13.9 (10.2–17.2)	12.1 (6.5–16.9)	14 (9.5–16)
Median platelet count $\times 10^9/L$ (range)	732 (450–3330)	544 (451–1518)	
Platelet count $\geq 1000 \times 10^9/L$	132 (20)	482 (8%)	695 (450–3125)
Palpable splenomegaly; n (%)	56 (9)	N/A	70 (10)
Microvascular symptoms	197 (31)	N/A	205 (30)
Cardiovascular risk factors; n (%)			
Hypertension; n (%)	255 (39)	2806 (47)	264 (39)
Diabetes; n (%) [evaluable N = 633]	62 (10)	1555 (26)	47 (7)
Hyperlipidemia; N (%) [evaluable N = 590]	314 (53%)	3408 (57)	152 (22)
Tobacco use; n (%) [evaluable N = 631]	135 (21)	1389 (23)	133 (19)
Abnormal karyotype; n (%) (evaluable N = 589)	39 (7%)	N/A	N evaluable = 248 21 (8)
Driver mutations; n (%)	N positive/N evaluated		

(Continues)

TABLE 1 | (Continued)

	Discovery cohort	Validation cohort-1	Validation cohort-2
	Mayo clinic	Israel	Italy
	N = 658	N = 5968	N = 682
<i>JAK2</i>	415 (63)	1263/2132 (59%)	443 (65)
<i>CALR</i>	163 (24.8)	100/388 (26%)	132 (19)
<i>MPL</i>	24 (3.7)	1/44 (2%)	37 (5)
<i>Triple-negative</i>	56 (8.5)	9/43 (21%)	70 (10)
Arterial thrombosis at/prior diagnosis; <i>n</i> (%)	101 (15)	73 (1%)	96 (14)
Venous thrombosis at/prior diagnosis; <i>n</i> (%)	62 (9)	168 (3%)	41 (6)
Major hemorrhage at/prior diagnosis; <i>n</i> (%)	54 (8)	N/A	24 (4)
Arterial thrombosis post-diagnosis; <i>n</i> (%)	71 (11)	41 (0.7%)	85 (12)
Venous thrombosis post-diagnosis; <i>n</i> (%)	44 (7)	132 (2%)	55 (8)
Major hemorrhage post-diagnosis; <i>n</i> (%)	65 (10)	N/A	49 (7)
Treatments documented; evaluable <i>N</i> = 626			
Aspirin; <i>n</i> (%)	570 (91)	5216 (87%)	609 (89)
Hydroxyurea; <i>n</i> (%)	475 (76)	1985 (33%)	482 (71)
Anagrelide; <i>n</i> (%)	103 (16)	425 (7%)	61 (9)
Interferon-based; <i>n</i> (%)	49 (8)	111 (2%)	31 (4)
Systemic anticoagulants; <i>n</i> (%)	110 (18)	1585 (27%)	94 (14)
Median follow-up for living patients, years (range)	7.6 (0.1–42.7)	6.1 (0.1–22.1)	9.2 (0.1–40.2)
AML transformations; <i>n</i> (%)	23 (3.5)	85 (1.4%)	16 (2)
Post-ET MF transformations; <i>n</i> (%)	59 (9)	207 (3.4%)	47 (7)
Deaths; <i>n</i> (%)	152 (23)	1688 (28.2)	153 (22)
Evaluable for causes of death; <i>n</i> (%)	79 (52)	0	69 (45)
AML/post-ET MF transformations; <i>n</i> (%)	18 (23)	N/A	20 (29)
Cardiovascular; <i>n</i> (%)	16 (10)	N/A	12 (17)
Infections; <i>n</i> (%)	16 (20)	N/A	9 (13)
Second cancers/other unrelated	29 (37)	N/A	28 (41)

^aIPSET = International prognostic scoring system for essential thrombocythemia: age 60 years (2 points); leukocyte count $\geq 11 \times 10^9/L$ (1 point); and any arterial or venous thrombosis history (1 point). IPSET low risk = 0 points; IPSET intermediate = 1–2 points; IPSET high = 3–4 points.

^bAAA: Age > 70 years (4 points); Age 50 to 70 years (2 points); Absolute neutrophil count $\geq 8 \times 10^9/L$ (1 point); and Absolute lymphocyte count $< 1.7 \times 10^9/L$ (1 point); AAA low risk = 0 to 1 points; AAA intermediate-1 = 2 to 3 points; AAA intermediate-2 = 4 points; and AAA high = 5 to 6 points.

and also disclosed an additional impact from AMC ($p < 0.01$). The optimal cutoff level for the latter (i.e., AMC) was calculated by ROC analysis to be at $0.49 \times 10^9/L$ at 30 years, $0.40 \times 10^9/L$ at 25 years, and $0.65 \times 10^9/L$ at 20 years. In order to be consistent with the current ICC [23] and WHO-HAEM5 [28] threshold used for CMML diagnosis [23], we used the 0.5 cutoff level for further analysis. In an all-inclusive multivariable analysis (Table 2), predictors of inferior OS included age > 70 years (HR 15.7, 95% CI 8.4–29.5), age 50 to 70 years (4.2, 2.3–7.5), ANC $\geq 8 \times 10^9/L$ (1.8, 1.2–2.5), AMC $\geq 0.5 \times 10^9/L$ (1.8, 1.2–2.6), ALC $< 1.7 \times 10^9/L$ (1.4, 1.03–1.9), male sex (1.8, 1.2–2.3), arterial hypertension (1.8, 1.3–2.4), and arterial thrombosis history at or prior to diagnosis 1.6

(1.2–2.3). In addition, borderline significance was appreciated for platelets $> 1000 \times 10^9/L$ ($p = 0.05$). Not significant were venous thrombosis history at or prior to diagnosis ($p = 0.6$), hyperlipidemia ($p = 0.7$), diabetes ($p = 0.15$), smoking history ($p = 0.16$), platelet count ($p = 0.17$), hemoglobin level ($p = 0.98$), hemorrhage at or prior to diagnosis ($p = 0.9$), palpable splenomegaly ($p = 0.8$), microvascular symptoms ($p = 0.14$), driver mutation status ($p = 0.16$; age-adjusted 0.9), and abnormal karyotype ($p = 0.12$). Driver mutation status was known for all 658 study patients; in univariate analysis of OS, the only significant difference noted was between *JAK2* and *CALR* mutated cases (HR 1.6 (1.07–2.3)) and significance was lost ($p = 0.5$) when age was added to the multivariable model. Among the

TABLE 2 | Analysis of risk factors for overall survival among 7326 patients with essential thrombocythemia.

	Clinical variables <i>p</i> values (95% CI)					
	Mayo Clinic Discovery cohort		Israel Validation cohort-1		Italy validation cohort-2	
	<i>N</i> = 658		<i>N</i> = 5968		<i>N</i> = 682	
	Univariate	Multivariate	Univariate	Multivariate	Univariate	Multivariate
Age > 70 years	<0.01 (25.6, 14.0–46.6)	<0.01 (15.7, 8.4–29.5)	<0.01 (41.4, 29.8–56.6)	<0.01 (26.7, 18.8–37.9)	<0.01 (49.1; 25.2–95.7)	<0.01 (42.9; 21.1–87.3)
Age 50–70 years	<0.01 (5.2, 2.9–9.2)	<0.01 (4.2, 2.3–7.5)	<0.01 (10, 7.1–14)	<0.01 (7.9, 5.6–11.4)	<0.01 (6.7; 3.6–12.3)	<0.01 (6.1; 3.2–11.5)
ANC $\geq 8 \times 10^9/L$	<0.01 (2.4, 1.7–3.3)	<0.01 (1.7, 1.2–2.5)	<0.01 (1.8, 1.5–2)	<0.01 (1.7, 1.4–1.9)	<0.01 (1.9; 1.3–2.9)	<0.01 (1.9; 1.2–2.9)
ALC < $1.7 \times 10^9/L$	0.02 (HR 1.4, 1.1–1.9)	0.03 (HR 1.4, 1.03–1.9)	<0.01 (3.1, 2.7–3.5)	<0.01 (1.3, 1.1–1.5)	<0.01 (1.7; 1.2–2.4)	0.3 (1.2; 0.8–1.7)
AMC $\geq 0.5 \times 10^9/L$	<0.01 (2.3, 1.6–3.3)	<0.01 (1.8, 1.2–2.6)	0.03 (1.8, 1.1–2.5)	0.19 (1.1, 0.97–1.3)	<0.01 (1.3–2.7)	0.4 (1.1; 0.8–1.7)
Male sex	<0.01 (1.7, 1.2–2.3)	<0.01 (1.7, 1.3–2.4)	0.04 (1.4, 1.2–1.7)	<0.01 (1.2, 1.03–1.32)	<0.01 (1.7; 1.2–2.3)	<0.01 (1.6; 1.2–2.3)
Arterial thrombosis	<0.01 (2.4, 1.7–3.4)	<0.01 (1.6, 1.2–2.3)	<0.01 (2, 1.2–3.3)	0.04 (1.4, 1.2–1.7)	0.01 (1.7; 1.1–2.6)	0.4 (1.2; 0.8–1.9)
Hypertension	<0.01 (3.2, 2.4–4.3)	<0.01 (1.8, 1.3–2.4)	<0.01 (7.2, 6.1–8.4)	<0.01 (1.7, 1.5–2.1)	<0.01 (2.4; 1.7–3.3)	0.2 (1.2; 0.9–1.8)

AAA⁺ risk variables, only male sex predicted leukemic (HR 3.2, 1.4–7.5) or fibrotic (HR 2.3, 1.4–3.8) transformation.

3.3 | Development of the Triple A Plus Survival Prediction Model and Its Validation

Using the Mayo clinic discovery cohort (*N* = 658), HR-weighted adverse point assignment allocated 8 points for age > 70 years, 2 points for age 50 to 70 years, and one point each for ANC $\geq 8 \times 10^9/L$, AMC $\geq 0.5 \times 10^9/L$, ALC < $1.7 \times 10^9/L$, male sex, arterial hypertension, and arterial thrombosis. Subsequent scoring resulted in a 4-tiered risk classification (AAA⁺ model; Figure 1) that included ultra-low (0–1 points; *N* = 94; median survival 42.7 years with 95% CI of 26.3–42.7), low (2–4 points; *N* = 297; 23 years with 95% CI of 21.1–26.7), intermediate (5 points; *N* = 66; 17.3 years with 95% CI of 15.3–21.6), and high (6–14 points; *N* = 201; 10.8 years with 95% CI of 10–11.8). OS data was significantly different between the four strata with HR (95% CI) of 117.5 (27.9–495) for high risk, 31 (7.1–134.7) for intermediate risk, and 11.1 (2.7–46.2) for low risk, all with ultra-low risk as reference. The corresponding 10/20/30-year survival rates were 57%/5%/0%, 89%/35%/0%, 96%/71%/26%, and 98%/98%/86%. Predictive performance at 20/25 years favored AAA⁺ (AUC 0.92/0.91) versus AAA (0.86/0.86) versus IPSET (0.81/0.84).

The AAA⁺ model was externally validated by two independent cohorts from Israel (validation cohort-1; *N* = 5968) and Italy (validation cohort-2; *N* = 682). The 4-tiered risk classification applied to the validation cohort-1 (Figure 2) included ultra-low (0–1 points; *N* = 1006; median survival not reached), low (2–4 points; *N* = 2230; median survival not reached), intermediate (5 points; *N* = 334; 14.4 years with 95% CI of 12.1–NA), and high (6–14 points; *N* = 2398; 5.7 years with 95% CI of 5.4–6.1). OS data was significantly different between the four strata with HR (95% CI) of 51.3 (32.6–80.7) for high risk, 18.3 (11.2–29.8) for intermediate risk, and 4.8 (3–7.7) for low risk, all with ultra-low risk as the reference. The corresponding 10/20-year survival rates were 28%/6%, 66%/47%, 95%/74%, and 98%/97%. The 4-tiered risk classification applied to the validation cohort-2 from Italy (Figure 3) included ultra-low (0–1 points; *N* = 153; median survival 39 years with 95% CI of 31–NA), low (2–4 points; *N* = 263; 28.2 years with 95% CI of 26.3–NA), intermediate (5 points; *N* = 66; 19.1 years with 95% CI of 14.2–NA), and high (6–14 points; *N* = 200; 12.1 years with 95% CI of 11.2–13.8). OS data was significantly different between the four strata with HR (95% CI) of 38 (17.4–83.1) for high risk, 10 (4.4–22.9) for intermediate risk, and 3.5 (1.6–7.7) for low risk, all with ultra-low risk as the reference. The corresponding 10/20/30-year survival rates were 64%/3%/0%, 80%/49%/24%, 95%/74%/49%, and 99%/94%/74%.

3.4 | Comparison of Observed Versus Model-Expected Versus Matched Population-Expected Survival Data

In each of the four AAA⁺ risk groups, we compared model-based expected survival with observed survival of the ET patient cohort from Israel (*N* = 5968) and their age- and sex-matched

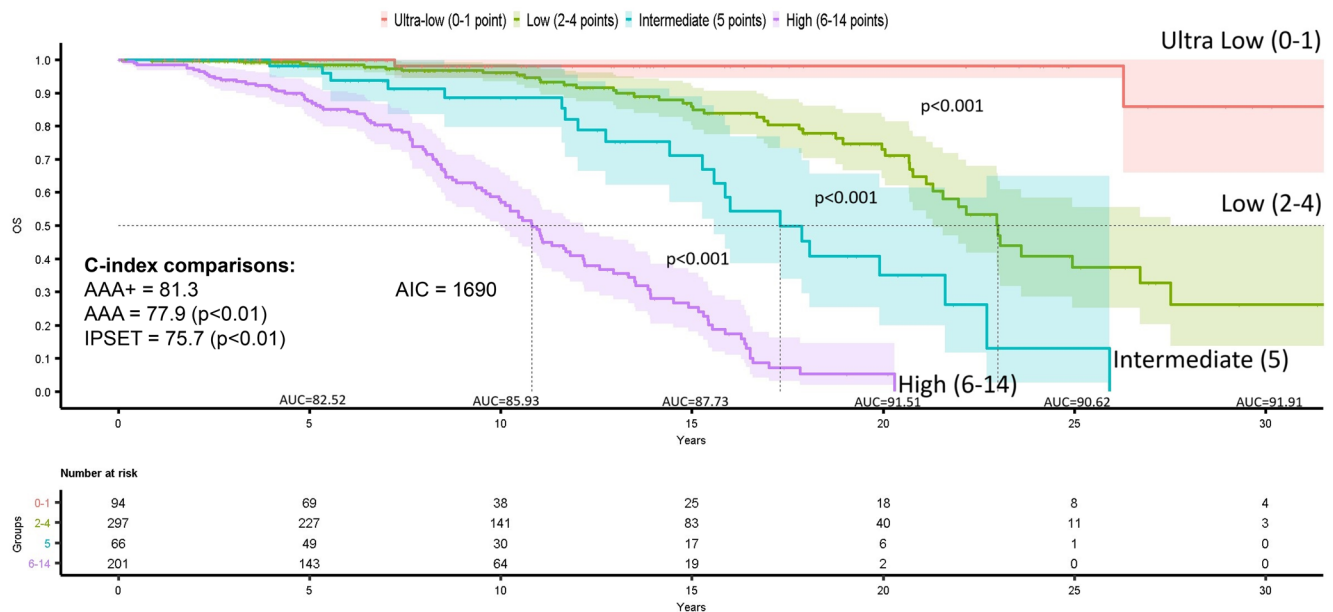


FIGURE 1 | Overall survival data of 658 Mayo Clinic patients with essential thrombocythemia stratified by the AAA+ risk model (age > 70 years = 8 points; age 50–70 years = 2 points; and 1 point each for male sex, hypertension, arterial thrombosis, ANC $\geq 8 \times 10^9/L$, AMC $\geq 0.5 \times 10^9/L$, and ALC $< 1.7 \times 10^9/L$). [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com)]

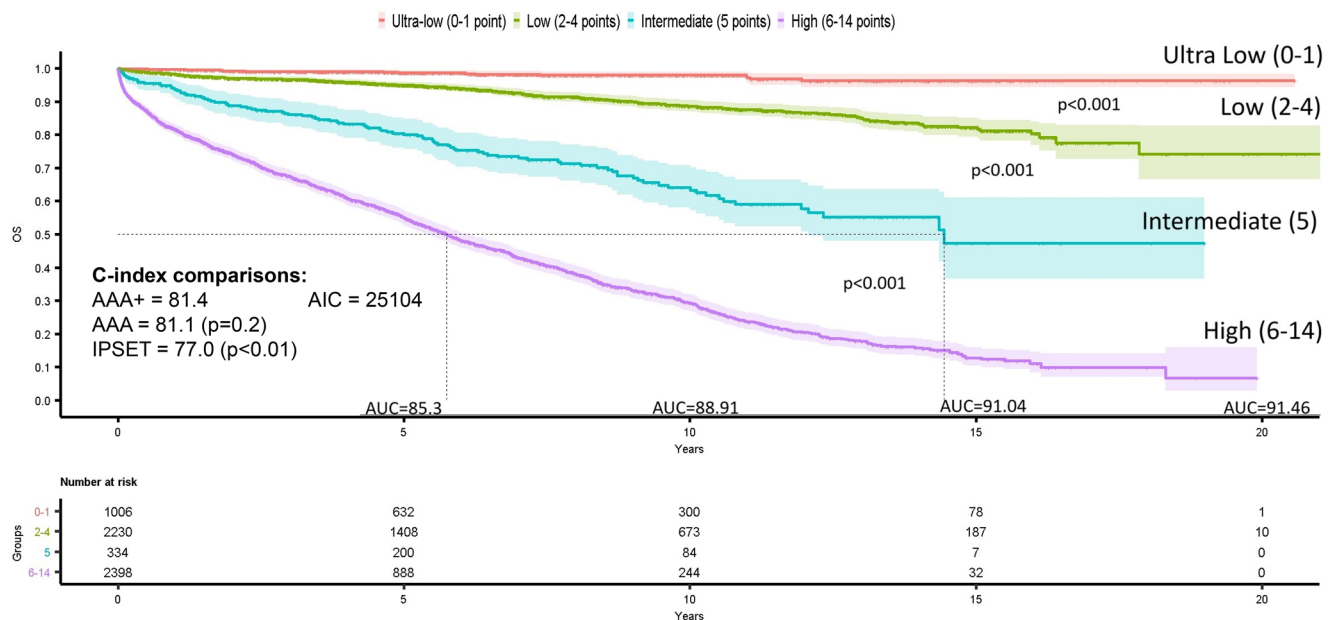


FIGURE 2 | Overall survival data of 5968 Israeli patients with essential thrombocythemia stratified by the AAA+ risk model (age > 70 years = 8 points; age 50–70 years = 2 points; and 1 point each for male sex, hypertension, arterial thrombosis, ANC $\geq 8 \times 10^9/L$, AMC $\geq 0.5 \times 10^9/L$, and ALC $< 1.7 \times 10^9/L$). [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com)]

counterparts from the general population (Figure 4). Across all four risk groups, the observed survival of ET patients was consistently lower than the expected survival of the general population, reflecting the presence of disease-related excess mortality. Notably, in the ultra-low risk group, the observed survival approached that of the general population, suggesting limited disease-related excess mortality in the particular risk group. In contrast, higher-risk groups demonstrated more pronounced divergence from general population survival, indicating a greater impact of disease-related mortality. However,

these observations are confounded by the fact that the age- and sex-matched general population reference was not stratified for hypertension and arterial thrombosis history.

3.5 | Age-Stratified Analysis of Risk Factors

Considering the outsized impact of age on survival, additional multivariable analyses of OS were conducted within each of the three age categories. For patients age > 70 years, only male

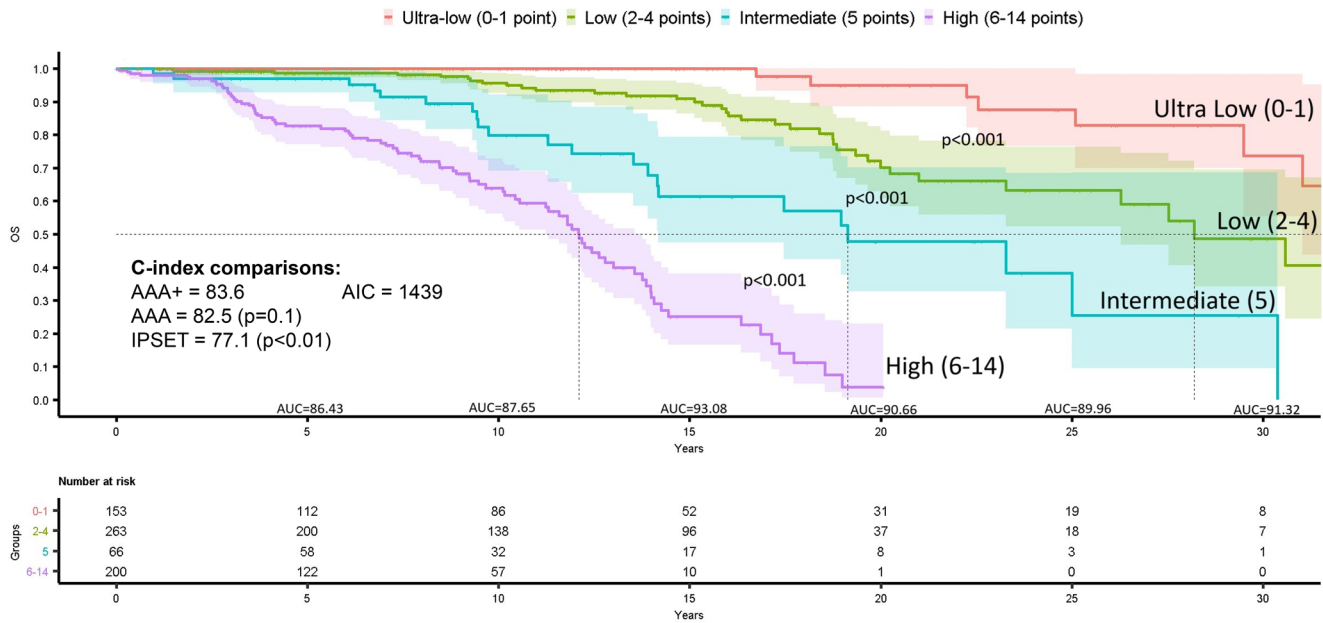


FIGURE 3 | Overall survival data of 682 Mayo Clinic patients with essential thrombocythemia stratified by the AAA⁺ risk model (age > 70 years = 8 points; age 50–70 years = 2 points; and 1 point each for male sex, hypertension, arterial thrombosis, ANC $\geq 8 \times 10^9/L$, AMC $\geq 0.5 \times 10^9/L$, and ALC $< 1.7 \times 10^9/L$). [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com)]

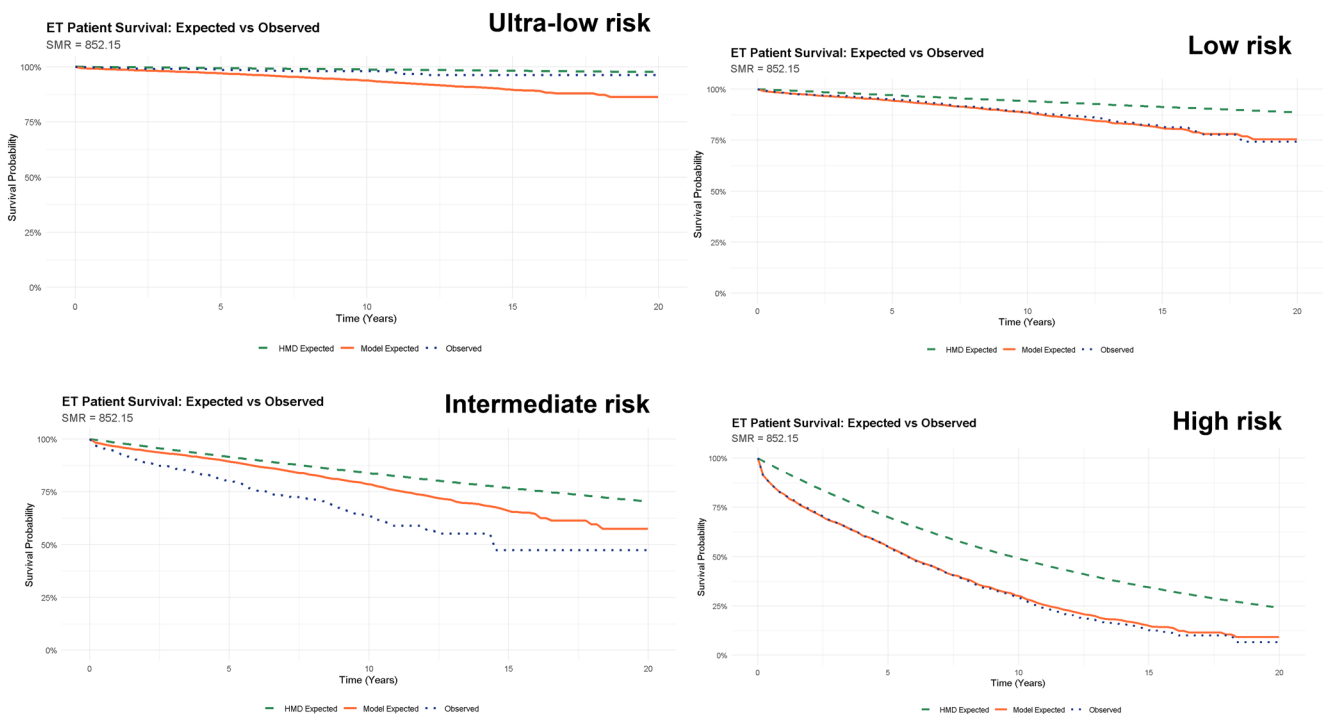


FIGURE 4 | Expected versus observed survival data among 5968 Israeli patients with essential thrombocythemia. HMD expected = age- and sex-matched general population expected. [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com)]

sex retained significance (HR 2.3, 95% CI 1.5–3.6; $p < 0.01$). In patients age < 50 years, multivariable analysis identified arterial thrombosis to be significantly associated with inferior OS (HR 4.3, 95% CI 1.3–14.2; $p = 0.01$) while AMC $\geq 0.5 \times 10^9/L$ became borderline significant ($p = 0.07$). In patients age 50 to 70 years, significance was sustained for all AAA⁺ risk variables including male sex (HR 1.7; $p = 0.03$), arterial thrombosis (HR 2.1; $p < 0.01$), arterial hypertension (HR 2.0; $p < 0.01$), ANC

$\geq 8 \times 10^9/L$ (HR 1.8; $p = 0.04$), ALC $< 1.7 \times 10^9/L$ ($p = 0.04$), and AMC $\geq 0.5 \times 10^9/L$ (HR 2.1; $p < 0.01$).

4 | Discussion

ET is prognostically the most favorable among the MPNs in terms of both overall and progression-free survival [29]. The

disease affects the young disproportionately, with 20% of patients presenting at age 40 years old or younger, compared to 12% with PV and 5% with PMF [9]. Median survival in the particular age group exceeds three decades [29] and it is, therefore, reasonable to query the impact of host-related factors on longevity in ET. In the general population, the latter include non-actionable (e.g., age, gender) [30] and actionable (e.g., hypertension [31, 32], diabetes [33], tobacco use [34], and hyperlipidemia [35]) risk factors. Considering the pro-thrombotic nature of the underlying disease in ET, it is important to decipher the prognostic contribution of cardiovascular risk factors to long-term survival [36]. In this regard, previous studies in MPN have underlined the prognostic impact of thrombosis history and hypertension, in terms of both overall and thrombosis-free survival [37–40]. The findings in the current study are consistent with these earlier observations and highlight the predominant impact of host-related factors, especially age and sex, but also the history of hypertension and arterial thrombosis, on long-term survival in ET. These observations suggest that lifestyle modification and optimal management of medical co-morbidities, as opposed to treatment of blood counts, are more likely to positively impact long-term survival in ET.

The currently proposed AAA⁺ risk model employs readily accessible disease-related factors derived from a simple CBC (ANC, AMC, ALC) and well-recognized host-related factors (age, sex, cardiovascular risk factors) in order to estimate long-term survival in ET. Approximately 17% of the 5968 patients in the Israeli cohort belonged to the ultra-low risk category with median survival that was not reached and appeared to be similar to the age- and sex- and race-matched general population (Figure 4). The particular observation was also replicated in the other two cohorts with ultra-low risk representation of 14.3% (Mayo cohort) and 22% (Italian cohort) and represents an important piece of information that should be gracefully communicated to patients and also considered when selecting patients for participation in clinical trials. In addition to identifying long-lived ultra-low risk patients, the AAA⁺ model was also effective in partitioning risk groups among middle-aged patients (age 50–70 years), mostly determined by co-morbidities including hypertension and arterial thrombosis history. In this regard, the model-based survival closely matched observed survival in patients belonging to low and high risk categories, indicating good model calibration, and suggesting that the model accurately captures the survival dynamics in these subgroups (Figure 4). These findings reinforce the prognostic relevance of the model and highlight the varying degrees of disease impact across risk categories.

The observations made in developing the AAA⁺ risk model in ET carry significant practical and clinical research implications. The predominant role of host-related factors in determining longevity in ET should be clearly communicated to patients along with advice on lifestyle modification and optimal management of cardiovascular disease risk factors. The AAA⁺ model also helps identify the 14% to 23% of ET patients who belong to the ultra-low risk category with near-normal life expectancy and exceedingly low risk of leukemic transformation; in the Mayo Clinic discovery cohort, median OS for ultra-low risk patients ($N=94$) was in excess of 40 years and none of the patients had experienced leukemic transformation. Accordingly, it is difficult to demonstrate an overall or progression-free

survival benefit of investigational or conventional drug therapy in such patients.

According to the current AAA⁺ risk model, age > 70 years qualifies as high risk disease with little additional prognostic contribution from the other six risk variables. As such, the value of the AAA⁺ model was most apparent in (i) patients age 50 to 70 years where, in the Mayo discovery cohort, 64% belonged to the low, 22% intermediate, and 14% high risk disease category and (ii) patients younger than age 50 years where 47% belonged in the ultra-low and 53% in the low risk disease category. We are currently in the process of accruing mutation information in order to examine AAA⁺ risk-stratified additional prognostic value. Finally, we acknowledge limitations of the current study that are inherent in its retrospective design. These include missing data, including causes of death. Whether or not emerging novel therapies would favorably influence long-term survival in ET remains to be seen.

Author Contributions

All authors reviewed the final manuscript draft and approved its content. A.T., G.G.L., T.T., G.M., H.A., A.P., K.H.B., M.P., N.S., P.G., N.G., and A.M.V. provided patient care. A.T., G.G.L., L.R., T.T., P.F., G.M., H.A., M.A., R.M.A., M.Y., M.N., P.G., N.G., and A.M.V. participated in patient data collection. A.T., G.G.L., L.R., A.C., T.B., P.G., N.G., and A.M.V. participated in data analysis and interpretation. K.K.R. and R.H. provided hematopathology expertise. L.R. provided statistical and bioinformatics expertise. A.T. and L.R. wrote the paper.

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Conflicts of Interest

M.M.P.: received research funding from Kura Oncology, Stemline therapeutics, Epigenetix, Solutheraapeutics, Polaris and has served on the advisory board for AstraZeneca and SOBI pharmaceuticals; T.B.: Speaker honoraria from AOP Orphan, advisory role from IONIS, Institutional Research funding from AOP and GSK; P.G.: Speakers bureau-ABBVIE, GSK, Novartis; Advisory board-GSK, Incyte, Novartis; N.G.: Advisory board to DISC Medicine and Agios; A.M.V.: Advisory board and speakers bureau from Novartis, GSK, Incyte, Sobi. The other authors declare no conflicts of interest.

Data Availability Statement

By email request to the corresponding author.

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