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TRES Comorbidity Score Predicts Survival Outcomes in an International Cohort of Patients with Waldenstrom's Macroglobulinemia

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Abstract:

Background. Waldenstrom's macroglobulinemia (WM) is an indolent B-cell lymphoma primarily affecting the elderly, with a median age of diagnosis of 70 years. Although outcomes are influenced by disease-specific factors, mortality from unrelated causes including comorbidities, exceeds mortality related to WM in older adults. Despite this, there are currently no standardized measures of comorbidity in WM available to predict outcomes. Gordon et al, previously developed and validated the three-factor risk comorbidity scale, named the TRES score, and demonstrated its association with survival in several lymphoma subtypes. In the present study we evaluated the association of high-risk comorbidity burden utilizing the TRES score with survival in an independent real-world international cohort of patients with WM from the United States and Asia.
Methods. We conducted a multicenter retrospective study of patients with WM from two large academic centers (City of Hope/USA and Singapore General Hospital). Patients diagnosed between 1998 and 2020 were included if they had at least 6 months of follow up. TRES score was calculated at time of diagnosis as previously described. A score of 0 is considered low-risk, 1 intermediate risk, and 2-3 high-risk. Patient demographics were evaluated using descriptive statistics. Difference between groups was assessed by Fischer's exact test and chi-squared test. The Kaplan-Meier method was used to estimate OS (date of diagnosis until death) and EFS (date of diagnosis until death, progression of disease, or start of next treatment) with difference assessed by log-rank. Multivariable Cox regression models were utilized, incorporating variables with a p-value of <0.1 in the univariable analysis. The study was approved by the participating Institutional Review Boards.
Results. A total of 140 patients with WM were included, 81 at COH and 57 at SGH (Table 1). The median follow-up for the entire cohort was 59 months (range 6-242 months). The COH cohort was more enriched for IPSS-WM high-risk patients (n=60; 79%) compared to the SGH cohort (n=13; 22%). The estimated 5-year OS rate was not different between TRES risk groups being 93.2% (95%CI:80.30%-97.78%), 90.0% (95%CI:47.3%-98.53%), and 84.0% (95%CI:71.13%-91.51%) in low, intermediate and high-risk TRES groups respectively, p=0.981. Corresponding estimated 5-year EFS rates were 80.45% (95%CI:64.51%-89.77%), 74.24% (95%CI:38.24%-91.19%) and 53.05% (95%CI:39.79%-64.66%) (p=0.056; Figure 1). On univariate analysis, either the presence of severe impairment in ≥1TRES system (HR:2.31, p=0.002), or TRES score 2 vs. 0 (HR:2.01, p=0.033) were associated with shortened EFS from diagnosis, but not with OS. On multivariable analysis, after adjusting for age, center, and presence of complications, a high-comorbidity TRES score was associated with inferior EFS from diagnosis (HR:2.22, p=0.013), but not OS (HR:1.87, p=0.286).
Discussion. Here we present data from a large international cohort of WM patients from the US and Asia and identify the TRES comorbidity score as a predictor of inferior EFS. Meanwhile, TRES score was not predictive of OS possibly due to the small number of OS events which occurred over a relatively short follow-up period in this cohort. Additional study is needed to elucidate the underlying relationship between comorbidities and disease relapse.

Table 1. Baseline characteristics

Parameter	**COH (N=81)**	**SGH (N=59)**	**All (N=140)**	**P**
Age at treatment, mean, stdev	65.5, 10.7	65.2, 12.4	65.4, 11.4	0.884
Sex, Male, n (%)	48 (59.3)	41 (69.5)	89 (63.6)	0.214
MYD88 mutation, n (%)				0.207
Mutated	36 (85.7)	26 (74.3)	62 (80.5)	
Unmutated	6 (14.3)	9 (25.7)	15 (19.5)	
Not done	39	24	63	
IPSS-WM score, n (%)				0.368
Low	8 (21.1)	10 (23.3)	18 (22.2)	
Intermediate	18 (47.4)	14 (32.6)	32 (39.5)	
High	12 (31.6)	19 (44.2)	31 (38.3)	
Missing	43	16	59	
Complication of WM	20 (24.7)	10 (17.0)10	30 (21.4)	0,270
Vascular	62 (82)	11 (19)	73 (55)	<0.001
	14 (18)	47 (81)	61 (45)	
Endocrine	58 (76)	7 (12)	65 (49)	<0.001
	18 (24)	51 (88)	69 (52)	
Upper GI	62 (82)	20 (34)	82 (61)	<0.001
	14 (18)	38 (66)	52 (39)	
TRES				<0.001
Low	10 (13)	35 (60)	45 (34)	
Intermediate	6 (8)	10 (17)	16 (12)	
High	60 (79)	13 (22)	73 (54)	
Missing	5	0	5	
TRES Score				<0.001
No	19 (25)	51 (88)	70 (48)	
Yes	51 (57)	7 (12)	64 (52)	
Treatment, n (%)				<0.001
Watchful waiting	10 (12)	11 (18)	21 (15)	
Rituximab alone	26 (32)	0 (0)	26 (19)	
BR	13 (32)	17 (29)	30 (21)	
BTKi	11 (14)	9 (15)	20 (14)	
DRC	0 (0)	7 (12)	7 (5)	
BDR	3 (3.7)	4 (7)	7 (5)	
Others	18 (22.2)	11 (19)	29 (21)	
Second line Treatment in 57 patients				0.851
BR	9 (20)	2 (17)	11 (19)	
BTKi	8 (18)	3 (25)	11 (29)	
BDR	16 (36)	5 (42)	21 (37)	
Others	12 (27)	2 (27)	14 (25)	

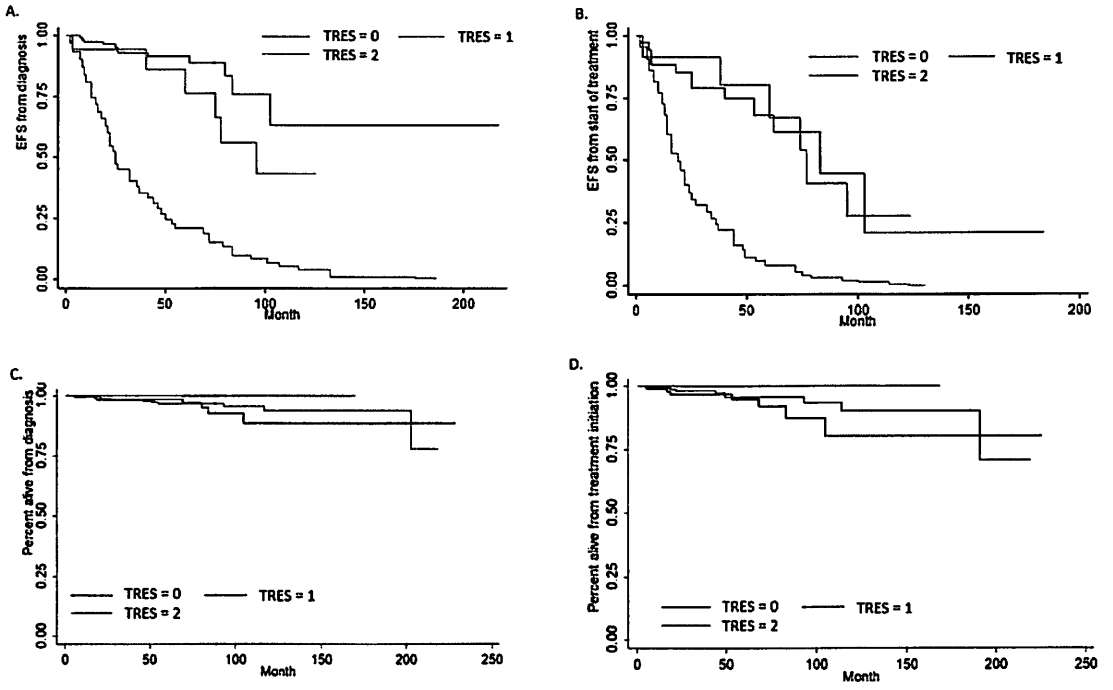

Figure 1: Survival and treatment outcomes, adjusted by center (A) EFS from diagnosis by TRES (B) EFS from start of treatment by TRES (C) OS from diagnosis by TRES (D) OS from start of treatment by TRES