TRES, a validated three-factor comorbidity score, is associated with survival in older patients with mantle cell lymphoma

Mantle cell lymphoma (MCL) is a rare and aggressive non-Hodgkin lymphoma.[1] MCL prognosis is impacted by clinical, pathologic and molecular features.[2-5] Age and comorbidities also impact survival in MCL.[6,7] In contrast to well-defined clinical prognostic tools such as the Mantle Cell Lymphoma International Prognostic Index (MIPI),[2] cellular proliferation rate measurements using Ki-67,[5] and molecular features such as *TP53* mutation/deletion and complex karyotype,[8,9] there is no standardized measure of comorbidity in MCL.

We previously developed and independently validated the chronic lymphocytic leukemia comorbidity index (CLL-CI), a three-category comorbidity scale which was associated with overall survival (OS) and event-free survival (EFS) in patients with CLL.[10,11] We subsequently evaluated the CLL-CI in older adults (>65 years) with non-Hodgkin lymphoma (NHL) using clinical information from the linked SEER-Medicare databases. As this study included patients with multiple NHL subtypes as well as CLL, we renamed it the three-factor risk estimate scale (TRES).[12] TRES is assigned in a manner identical to CLL-CI. The SEER-Medicare study included 40,486 patients with NHL with a median age of 77 years. TRES was independently associated with both OS and lymphoma-specific survival in multivariable models.

TRES has not been evaluated in an independent dataset of patients with MCL. Additionally, SEER-Medicare does not include patients younger than 65 years nor does it include the clinical and pathologic granularity needed to utilize currently available risk assessment tools. The aim of the current study was to evaluate the association of TRES score with survival in an independent real-world cohort of patients with MCL including younger patients and in the context of established prognostic models.

We conducted a multicenter retrospective study of patients with MCL from three US academic centers evaluated between 2007 and 2022. Patient demographic, diagnostic and therapeutic information were obtained from review of the electronic medical record. For the primary analysis cohort, we included all patients with newly diagnosed MCL who received frontline therapy and had at least 3 months of follow-up available from time of diagnosis. Comorbidity risk classification was retrospectively assigned using TRES at time of diagnosis. This was done by reviewing the patient's medical record including provider notes, medication lists and laboratory results.[10-12] TRES score is assessed by evaluating comorbidities in three categories: vascular, endocrine and upper gastrointestinal. If a comorbidity is present in each category one point is assigned, scores range from 0-3. A score of 0 is considered low-risk, 1 intermediate-risk, and 2-3 high-risk. We also stratified patients using the components of the MIPI score[2] and the Ki-67 proliferation index (≥30% was considered high risk).[5] OS was defined as time from diagnosis to death and EFS as time from treatment initiation to next line of therapy (excluding autologous stem cell transplant [ASCT] and rituximab maintenance), documented disease progression or death from any cause. Patient demographics were evaluated using descriptive statistics. Difference between groups was assessed by Fischer's exact test and χ^2. The Kaplan-Meier method was used to estimate OS and EFS with difference assessed by log-rank. Multivariable Cox regression models were utilized. Patients with missing data were removed from Cox models. A P value of <0.05 was considered significant for all. The study was approved by the City of Hope Institutional Review Board.

The primary analysis cohort included 361 patients with MCL who received frontline therapy (Table 1). Median age was 63 years (range, 49-86). The majority were male and had advanced stage disease. Bendamustine and rituximab (BR) was the most common induction regimen (31.9%); 43.5% received ASCT consolidation. A total of 102 patients had vascular comorbidities (28.2%), 79 (21.9%) upper gastrointestinal and 76 (21.1%) endocrine comorbidities. The most commonly combined comorbidity categories were vascular and endocrine in 23 patients (6.3%) and 2.8% had comorbidities in all three categories. TRES score was low in 50.1%, intermediate in 31.3% and high in 18.6% of patients. High TRES score was numerically more frequent in patients >65 years (23.0%) compared with patients ≤65 years (15.9%).

After a median follow-up of 61.2 months, the estimated 5-year OS rate was 84.8%, 84.3% and 66.0% in low-, intermediate- and high-risk TRES groups, respectively (Figure 1A; P=0.002). Corresponding estimated 5-year EFS rates were 62.4%, 49.1% and 40.8% (Figure 1B; P=0.002). In multivariable Cox models including the components of the MIPI score (age, white blood cell count, lactate dehydrogenase [LDH, ratio of reported value to upper limit of normal], all considered as continuous variables, and Eastern Cooperative Oncology Group [ECOG] stratified 0-1 *vs*. 2-4) and Ki-67, a high TRES score, compared to low and intermediate, remained independently associated with OS (hazard ratio

Table 1. Patient demographics.

	All patients N (%)	TRES low N (%)	TRES int. N (%)	TRES high N (%)	*P*
Cohort	361 (100)	181 (50.1)	113 (31.3)	67 (18.6)	-
Age in years Median (range) >65 ≤65	 63 (49-86) 135 (37.4) 226 (62.6)	 62 (37-86) 59 (43.7) 122 (54.0)	 64 (41-86) 45 (33.3) 68 (30.1)	 65 (37-86) 31(23.0) 36 (15.9)	0.12
Sex Female Male	 91 (25.2) 270 (74.8)	 44 (24.3) 137 (75.7)	 32 (28.3) 81 (71.7)	 15 (22.4) 52 (77.6)	0.63
ECOG 0-1 2-4	 315 (87.5) 18 (12.5)	 159 (87.7) 11 (6.1)	 101 (89.4) 3 (2.7)	 55 (82.1) 4 (6.0)	0.40
Stage 1-2 3-4	 13 (3.6) 342 (94.7)	 5 (2.8) 174 (96.1)	 5 (4.4) 106 (93.8)	 3 (4.5) 62 (92.5)	0.69
B symptoms Yes No	 140 (38.8) 217 (60.1)	 79 (43.6) 100 (55.2)	 37 (32.7) 74 (65.5)	 24 (35.8) 43 (64.2)	0.15
Ki-67 >30% Yes No Unknown	 87 (24.1) 150 (41.6) 124 (34.3)	 51 (28.2) 71 (39.2) 59 (32.6)	 25 (22.1) 51 (45.1) 37 (32.7)	 11 (16.4) 28 (41.8) 28 (41.8)	0.29
Treatment regimen BR HyperCVAD/Nordic/DHAP RCHOP Other	 115 (31.9) 112 (31.0) 49 (13.6) 85 (23.5)	 57 (31.5) 69 (38.1) 27 (14.9) 28 (15.5)	 33 (29.2) 28 (24.8) 15 (13.2) 37 (32.7)	 25 (37.3) 15 (22.4) 7 (10.4) 20 (29.9)	0.007
Autologous stem cell transplant Yes No	 157 (43.5) 204 (56.5)	 85 (47.0) 96 (53.0)	 47 (41.6) 66 (58.4)	 25 (37.3) 42 (62.7)	0.35
Maintenance rituximab Yes No	 182 (50.4) 179 (49.6)	 98 (54.1) 83 (45.9)	 57 (50.4) 56 (49.6)	 27 (40.3) 40 (59.7)	0.15
Simplified MIPI score 0-3 (low risk) 4-5 (intermediate risk) 6+ (high risk) Missing data	 92 (25.5) 93 (25.5) 73 (20.2) 103 (28.5)	 54 (29.8) 50 (27.6) 31 (17.1) 46 (25.4)	 24 (21.1) 31 (27.4) 23 (20.4) 35 (31.0)	 14 (20.9) 12 (17.9) 19 (28.4) 22 (32.8)	0.17

BR: bendamustine and rituximab; TRES: three-factor risk estimate scale; int.: intermediate; ECOG: Eastern Cooperative Oncology Group; HyperCVAD: hyper-fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, cytarabine; Nordic: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, cytarabine; DHAP: dexamethasone, cytarabine, cisplatin; RCHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; MIPI: mantle cell lymphoma international prognostic index.

[HR] =1.95; 95% confidence interval [CI]: 1.07-3.57). Models of EFS showed a similar trend with high TRES score compared to low and intermediate (HR=1.34; 95% CI: 0.85-2.12). Because TRES had previously been studied only in older adults with MCL, we evaluated the association of TRES score with survival separately in older patients (>65 years) and younger patients (≤65 years). A total of 135 patients (37.4% of our cohort) were >65 years old, in whom BR was the most common induction regimen (41.4%). The estimated 5-year OS rate in older adults was 74.3%, 84.0% and 40.1% in low-, intermediate- and high-risk TRES groups, respectively (Figure 1C; *P*=0.007). Corresponding to 5-year EFS rates of 55.4%, 55.0% and 26.5%, respectively (Figure 1D; *P*=0.051). In patients ≤65 years old, 66.8% received a cytarabine-containing induction regimen and 32.7% BR. OS was favorable independent of the TRES score with estimated 5-year rates of 90.2%, 84.7% and 86.4% in low, intermediate and high TRES, respectively (*P*=0.056).

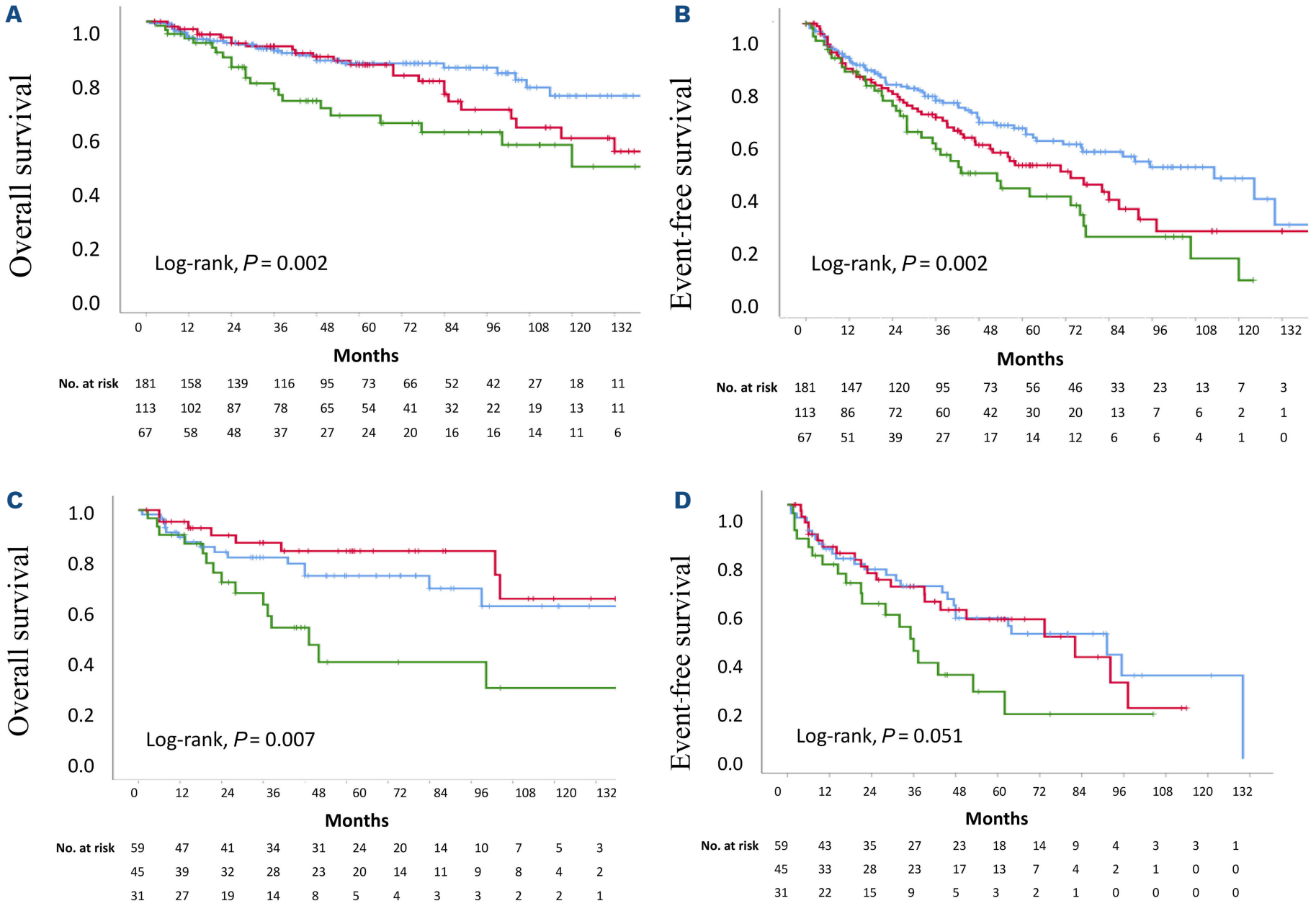

Figure 1. Survival by three-factor risk estimate scale comorbidity score risk group. Overall and event-free survival by three-factor risk estimate scale (TRES) score in all patients (A, B) and in those >65 years old (C, D). Low TRES score in blue, intermediate score in red and high score in green.

However, TRES remained significantly associated with EFS in younger patients with estimated 5-year rates of 66.1%, 45.3% and 52.2%, respectively (*P*=0.038). Notably, in multivariable models of the full study cohort which included TRES, age as a continuous variable and induction regimen (BR *vs.* cytarabine containing *vs.* rituximab, cyclophosphamide, doxorubicin, vincristine and oral prednisolone [RCHOP] *vs.* other), high TRES compared to low or intermediate TRES remained independently associated with OS (HR=2.18; 95% CI: 1.32-3.59) and EFS (HR=1.67; 95% CI: 1.15-2.43).

In our previous work, we used propensity-matched models to demonstrate that TRES score was associated with OS in the MCL cohort derived from the SEER-Medicare database.[12] In this report we validate the association of the TRES comorbidity score with survival in patients >65 years old using an independent cohort of patients with MCL treated at academic medical centers.[12] A high TRES score, which was present in nearly one in five patients with MCL, was associated with significantly shorter OS and EFS. When adjusted for MIPI a high TRES score remained independently associated with OS and was associated with nearly a two-fold increased risk of death. High-risk comorbidities were more common in patients >65 years old and were associated with a 5-year OS of only 40% in that population. In contrast to previous studies, we did not find a significant difference in survival between low- and intermediate-TRES risk patients.

TRES was not significantly associated with OS in patients ≤65 years old, although it should be noted that OS events were rare in this population. TRES did remain associated with EFS in the younger patient cohort. Similar to prior reports,[10,13] the impact of comorbidity appears greatest in older adults receiving frontline therapy. Whether the negative impact of comorbidity can be overcome by more effective, and/or better tolerated, treatments is an important area of future investigation.

There are important limitations to studies which retrospectively assess comorbidity burden as only those conditions which are documented in the medical record or for

which patients are receiving active therapy can be identified. There are also inherent selection biases in treatment selection which may confound the stratification of patients based on treatment type and intensity. Additionally, information regarding *TP53* mutation or deletion, complex karyotype and blastoid or pleomorphic histology were missing in a significant proportion of patients and, therefore, were excluded from all analyses. Bruton tyrosine kinase (BTK) inhibitors are increasingly used to treatment MCL and rare use of BTK inhibitors in this study cohort represents another potential limitation. We have previously shown that CLL-CI/TRES is predictive of outcomes among patients with CLL treated with ibrutinib.[10] BTK inhibitors have demonstrated promising activity in MCL,[14,15] whether they can improve outcomes for patients with comorbidities is an area for future investigation.

TRES is a simple comorbidity score associated with survival in older patients with MCL. In addition to clinical and genetic prognostication, TRES could be a useful tool for designing prospective trials, including non-pharmaceutical interventions, targeting high-risk populations.

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Contributions

MJG, DAB, AVD designed the research. NA, AS, SH, VN, GS and JBC collected the data. MJG and AVD analyzed the data. MJG, DAB, ASK, GS, JBC, TP and AVD wrote and edited the manuscript. All authors reviewed the manuscript and agree with presented format.

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Data-sharing statement

Data will not be available.

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