THE EUTOS LONG-TERM SURVIVAL SCORE (ELTS) ACCURATELY PREDICTS THE RISK OF DEATH IN CHRONIC MYELOID LEUKAEMIA PATIENTS TREATED OUTSIDE OF CLINICAL TRIALS

Running title: Validation of ELTS score in CML patients

Matteo Molica, Martina Canichella, Danilo Alunni Fegatelli, Gioia Colafigli, Fulvio Massaro, Roberto Latagliata, Robin Foà, Massimo Breccia

Hematology, Department of Cellular Biotechnologies and Hematology, Policlinico Umberto 1, Sapienza University, Rome, Italy

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Corresponding author:
Matteo Molica, MD
Hematology, Department of Cellular Biotechnologies and Hematology
Policlinico Umberto 1
Sapienza University
Via Benevento 6, 00161 Rome, Italy
Tel. 003906857951
Fax 00390644241984
e-mail: molica@bce.uniroma1.it

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The Eutos long-term survival score (ELTS) which stratifies chronic myeloid leukaemia (CML) patients according to age, percentage of peripheral blasts, spleen size and platelet count in order to establish the risk of disease-related death has been recently validated in independent series, demonstrating its impact compared to previous prognostic systems (Pfirrmann *et al*, 2016). The ELTS score, calculated through a specific formula (Castagnetti *et al*, 2016), stratifies patients in low- , intermediate- and high-risk group. To date, a comparative performance analysis between ELTS and other prognostic scores in cohorts of patients treated outside clinical trials has not yet been carried out. The aim of present study was to assess the capability of ELTS, in a large cohort of chronic phase CML (CP-CML) patients treated with all available frontline tyrosine kinase inhibitors (TKIs), to predict the risk of disease-related death compared to the other specific prognostic scores, Eutos, Sokal and Hasford. The study focused on 417 CP-CML patients diagnosed at the Sapienza University of Rome. Both the ELTS and other prognostic scores were applicable to 339 patients treated with imatinib and 78 patients treated with a second generation TKI. Statistical analysis has been performed according to the receiver operating characteristic (ROC) analysis, indicating the specificity of each prognostic score in predicting the risk of dying of CML and the Kaplan Meyer analysis showing the cumulative incidence of CML-related death at 8 years for the imatinib group and at 2 years for the nilotinib/dasatinib group, and its significance in terms of p-value between the prognostic risk categories considering each score. Among the 417 CML patients enrolled, 339 patients received imatinib (253 as frontline and 86 following interferon failure) and 78 patients received a second generation TKI (25 dasatinib and 53 nilotinib). After a median follow-up of 119 months (range 2-343), 75 deaths were observed among the 339 patients who received imatinib [25 CML-related (33.3%) and 50 CML-unrelated (66.7%)]. According to the ELTS score, 241 (71.1%) patients were stratified as a low risk, while 77 (22.7%) and 21 (6.2%) were categorized as intermediate risk and high risk, respectively. The cumulative 10-year incidence (CI) of CML-related death was 2%, 15% and 40%, respectively, for patients belonging to the low, intermediate and high risk ELTS score ($p<0.001$). We observed a significant difference not only between the low- and high-risk groups, but also between the intermediate- and low-risk groups ($p<0.001$). In our series of patients, the Sokal score retained its predictive value for the risk of death ($P=0.007$), but only between the low- and high-risk groups. We failed to find a statistical significance for the Hasford ($p=0.221$) and Eutos scores ($p=0.840$) (Figure 1). The ROC analysis clearly underlined that ELTS (AUC 0.737) better predicted the risk of CML-related deaths than the

Sokal (AUC 0.61), Eutos (AUC 0.505) and Hasford scores (AUC 0.557) (Figure 2). Among the 78 patients who received a second-generation TKI frontline, we observed only 2 deaths for CML progression and 2 deaths related to other causes after a median follow-up of 39 months (range 4-76). In this subset of patients, according to ELTS score 61 (78.2%) were stratified as low risk, 14 (17.9%) as intermediate risk and 3 (3.9%) as high risk. At 2 years, the CI of CML-related death was 36% for high-risk patients, while the CI was 15% and 0% for patients stratified as intermediate and low risk, respectively ($p<0.001$). We did not observe any statistical significance considering the Eutos ($p=0.051$), Sokal ($p=0.247$) and Hasford scores ($p=0.34$) in these subsets of patients, probably due to the low number of patients analysed. TKIs have dramatically improved the prognosis for CML patients (Deninger *et al*, 2009) and a direct consequence of the improved survival is the increased probability of dying of causes other than CML (Etienne *at al*, 2014). This radical change in the scenario of CML management has led to the definition of a new prognostic score that more accurately could predict the CML-related risk of death. The ELTS score, based on the analysis of a cohort of 2290 CML patients treated frontline with imatinib, has been recently validated in registry cohorts showing a better accuracy in predicting the risk of death in CML compared to others prognostic scores (Pfirrmann *et al*, 2016). In this study, the ELTS score identified a further 20% of low-risk patients compared to the Sokal (Sokal *et al*, 1994) and Hasford (Hasford *et al*, 1998) scores, and this improved stratification justified its impact on predicting global OS of the entire cohort of patients (8-year OS probability of 89%). Furthermore, neither the Sokal nor the Hasford scores showed any difference between low- and intermediate-risk groups in terms of CML-related risk of death. Conversely, ELTS identified a significant difference between these latter two groups; the intermediate-risk patients had an increased risk of dying of CML compared to the low-risk group ($p = .035$). In our study the percentage of patients categorized as low risk according to the ELTS score was significantly higher compared to the Sokal and Hasford scores both in patients receiving imatinib and in patients receiving a second-generation TKI (71.1% vs 50.4% vs 62.2%; 78.2% vs 55.1% vs 58.9%). In the cohort of patients receiving imatinib, the ELTS score significantly predicts the risk of CML-related death not only between high and low risk patients, but also between low and intermediate risk categories ($p<0.001$) and it appears the best prognostic score according to the ROC analysis (AUC 0.737). The validity of the ELTS score was also assessed in a smaller cohort of patients with a shorter follow-up who received frontline nilotinib or dasatinib. In

this group, the ELTS score was the only one that retained its predictive value for the CML risk of death ($p<0.001$).

Our results indicate that in the real-life and outside of clinical trials the ELTS score allows a more precise stratification of the risk of death at diagnosis of CML patient regardless of the type of TKI used compared to the other scores. Its use in the clinic practice should be recommended.

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Conflict of interest

All authors declare no conflict of interest.

Authors' contribution

MB designed the study and wrote the manuscript; MM collected data and wrote the manuscript; DAF analyzed data; MC, GC and FM followed patients; RF critically revised the paper and approved the final version.

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Figure 1. Cumulative incidence probabilities of dying because of CML at 8 years in 339 patients treated frontline with imatinib and stratified for the risk groups according to the ELTS, Sokal,Hasford and Eutos scores.

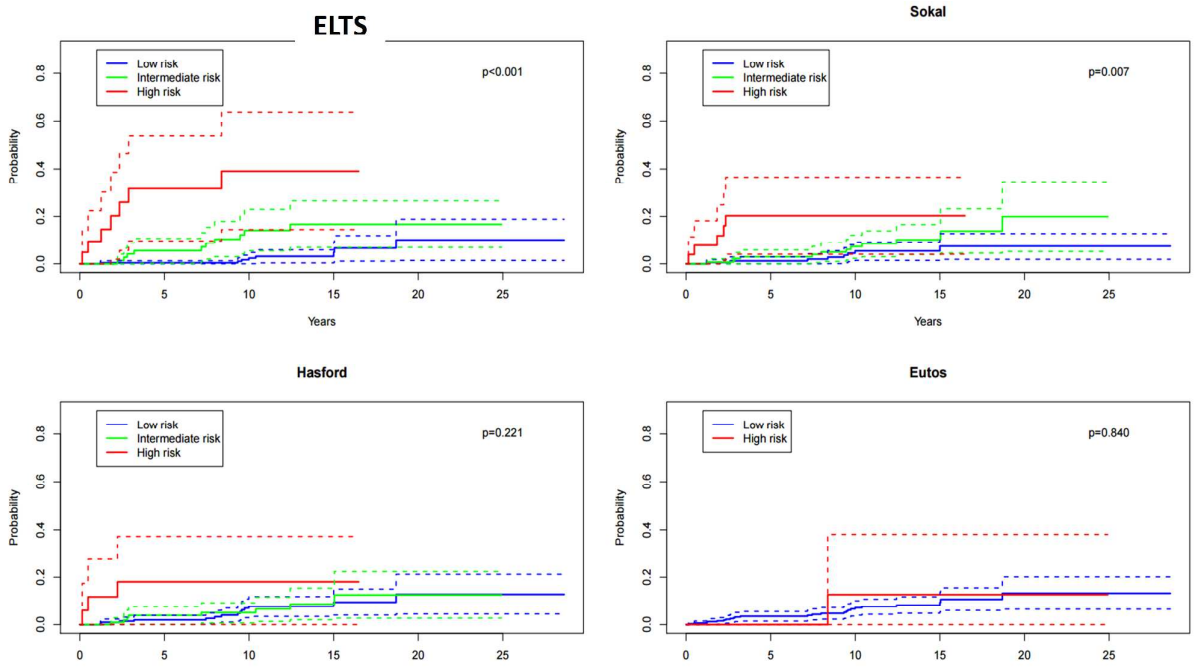

Figure 2. ROC analysis of the risk of dying of CML applied to the Eutos, Hasford, Sokal and ELTS scores