Mediterranean Journal of Hematology and Infectious Diseases

Scientific Letters

Validation of a New Scoring System for Treatment Failure in CML Patients on Tyrosine Kinase Inhibitors in a Real-World Setting

Keywords: CML; Tyrosine Kinase Inhibitors; Real-World Setting.

Published: January 01, 2026 **Received: November 27, 2025** **Accepted: December 16, 2025**

Citation: Mattozzi A., Galli E., Autore F., Pansini I., Chiusolo P., Colangelo M., Sica S., Sorà F. validation of a new scoring system for treatment failure in CML patients on tyrosine kinase inhibitors in a real-world setting. Mediterr J Hematol Infect Dis 2026, 18(1): e2026013, DOI: http://dx.doi.org/10.4084/MJHID.2026.013

To the editor.

Tyrosine kinase inhibitor (TKI) therapy has significantly improved the survival of patients with chronic phase chronic myeloid leukemia (CML), with a 10-year survival rate of approximately 90%.[1] However, one-third of patients continue to experience treatment failure. Therapeutic failure occurs more frequently in patients at higher risk of disease progression and mortality during TKI therapy.[2]

According to the European LeukemiaNet (ELN) guidelines, a change in TKI therapy should be considered for patients who fail to achieve specific response milestones.[3]

Therefore, accurately predicting the likelihood of treatment failure in individuals with chronic phase CML is crucial to achieve precise response targets when selecting the initial TK.

The risk stratification of CML patients was based on scores predicting overall survival since the pre-imatinib era. The Sokal risk score was published in 1984, while the EURO score was established in 1998 using data from CML patients receiving interferon-α therapy.[4-5] After the introduction of imatinib, the EUTOS risk score was established in 2011 to predict the likelihood of achieving complete cytogenetic response (CCyR) at 18 months, serving as a proxy for survival.[6]

In 2022, Zhang et al.[7] proposed an imatinib therapy failure score (IMTF) for patients affected by chronic phase CML. The score was applied to 1364 patients to predict progression-free survival and overall survival (all p-values < 0.001). These data were also confirmed in a real-world experience.[8]

In 2024, Zhang et al. applied a new scoring system to predict the risk of first-line TKI[9] therapy in patients with CML treated in the chronic phase, as first-line therapy with imatinib or 2-generation TKI. The score is based on six prognostic factors: gender, age, hemoglobin level, blast percentage, spleen size, and the presence of additional cytogenetic abnormalities (ACAs), and was developed by analyzing data from 3,454 patients across 76 centers.

In our monocentric cohort, we retrospectively evaluated 135 patients to determine whether they experienced treatment failure during first-line therapy from 2000 to 2025, with a median follow-up of 8 years. Patients who switched TKI for toxicity reasons were excluded from the analysis. Chronic phase was defined according to World Health Organization (WHO) criteria.[10] Conventional cytogenetic analysis was performed on bone marrow samples using R-banding techniques, with at least 20 metaphases analyzed from both direct and short-term (24-hour) cultures.

Quantitative real-time polymerase chain reaction monitoring was performed at diagnosis and every 3 months thereafter until a major molecular response (MMR) was achieved, and every 3 to 6 months thereafter.[11] TKI-therapy failure was defined as meeting “failure” milestones in the 2020 ELN recommendations: loss of response, including CHR, CCyR, or MMR, or transformation to an advanced phase as defined by the ELN recommendations.[12]

The patients in our cohort were treated with imatinib (75%), dasatinib (12%), or nilotinib (13%). Regarding the Zhang score, the 135 patients

Table 1. Baseline characteristics of the study population and stratification according to score.

		Low Risk	Intermediate risk	High risk
N. Patients	135	48 (36%)	72 (53%)	15 (11%)
Sex M/F	64/ 71	13/ 35	31/ 41	10/ 5
Age	53 (17-87)	48 (17-67)	64 (18-87)	54 (39-81)
Elts High Risk	20 (6%)	0 (0%)	10 (13%)	10 (90%)
Eutos High Risk	20 (6%)	10 (21%)	10 (14%)	0 (0%)
Second Generation TKI	33 (24%)	13 (26%)	15 (20%)	10 (67%)

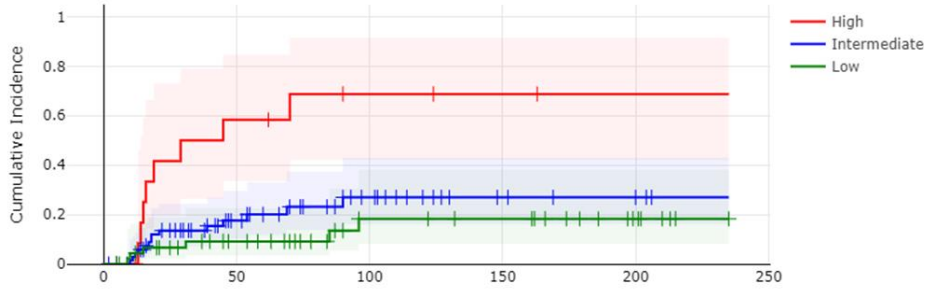

Figure 1. Cumulative incidences of the TKI-therapy failure (p <0.001).

Commentato [S1]: di solito si mettono 3 decimali, e la p non è puntata. Quindi p<0.001

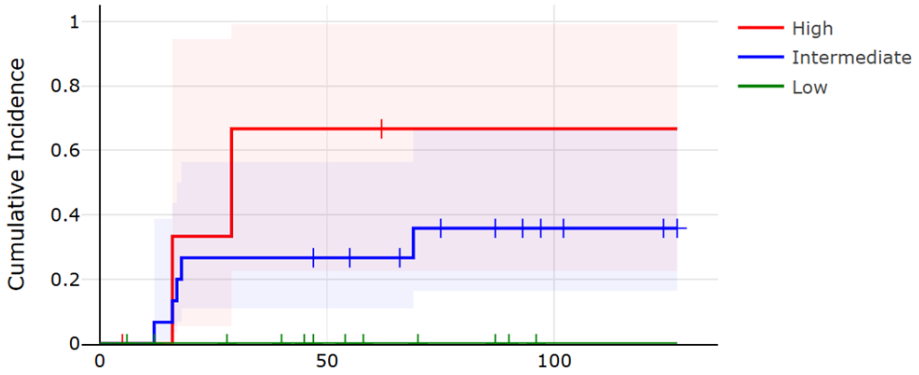

Figure 2. Cumulative incidences of treatment failure for patients treated with a second-generation TKI-therapy in first line according to the score classification (p=0.037).

were divided into three risk categories: low-risk (48 patients, 36%), intermediate-risk (76 patients, 56%), and high-risk (11 patients, 8%) (**Table 1**).

In the original validation cohort, 8-year cumulative incidences of treatment failure were 10%, 34%, and 69% for the low-, intermediate-, and high-risk groups, respectively (p < .001).

In our cohort, the 8-year cumulative incidence of treatment failure was 18% in the low-risk group, 27% in the intermediate-risk group, and 68% in the high-risk group (p. 0.0002; **Figure 1**).

Using the low-risk group as the reference, in univariate analysis, the hazard ratios (HRs) for treatment failure were 1.79 (95% CI, 0.72–4.40; p = .21) for the intermediate-risk group and 7.50 (95% CI, 1.8–17.5; p = .002) for the high-risk group. These findings were compared to the original cohort, which reported HRs of 3.8 (95% CI, 2.9–5.0; p < .001) and 10.4 (95% CI, 7.7–14.0; p < .001) for the intermediate- and high-risk groups, respectively.

In the cohort of patients treated with second-

generation TKIs, the model demonstrated good capacity to stratify risk of treatment failure (p = 0.037; **Figure 2**). At 8 years, the cumulative incidence of failure was 66% in the high-risk group and 35% in the intermediate-risk group, while no treatment failure occurred among low-risk patients.

Despite the limited size and single-center nature of our cohort, our results support the predictive validity of this novel scoring system in a demographically distinct population. Overall, the Zhang score demonstrated good discriminative and predictive accuracy, which could help physicians optimize the selection of initial TKI therapy in clinical practice.

Andrea Mattozzi[1], Eugenio Galli[2], Francesco Autore[2], Ilaria Pansini[1,2], Patrizia Chiusolo[1,2,] Maria Colangelo[3], Simona Sica[1,2] and Federica Sorà[1,2].

[1] Sezione di Ematologia, Dipartimento di Scienze Radiologiche ed Ematologiche, Università Cattolica del Sacro Cuore, Roma, Italy.
[2] UOC Ematologia e Trapianto di Cellule Staminali Emopoietiche, Dipartimento di Scienze di Laboratorio ed Ematologiche, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy.
[3] UOC di Genetica Medica, Dipartimento di Scienze di Laboratorio ed Ematologiche, Roma, Italy.

Competing interests: The authors declare no conflict of Interest.

Correspondence to: Simona Sica. UOC Ematologia e Trapianto di Cellule Staminali Emopoietiche, Dipartimento di Scienze di Laboratorio ed Ematologiche, Fondazione Policlinico Universitario A. Gemelli IRCCS, Largo Gemelli 8, 00184, Rome, Italy. E-mail: Simona.sica@unicatt.it

References:

1. Hehlmann R, Lauseker M, Saußele S, et al. Assessment of imatinib as first-line treatment of chronic myeloid leukemia: 10-year survival results of the randomized CML study IV and impact of non-CML determinants. Leukemia. 2017;31(11):2398-2406. https://doi.org/10.1038/leu.2017.253 PMid:28804124 PMCid:PMC5668495
2. Lau A, Seiter K. Second-line therapy for patients with chronic myeloid leukemia resistant to first-line imatinib. Clin Lymphoma Myeloma Leuk. 2014 Jun;14(3):186-96. doi: 10.1016/j.clml.2013.11.002. Epub 2013 Nov 14. https://doi.org/10.1016/j.clml.2013.11.002 PMid:24456839
3. Hochhaus A, Baccarani M, Silver RT, et al. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. Leukemia. 2020;34(4):966-984. https://doi.org/10.1038/s41375-020-0776-2 PMid:32127639 PMCid:PMC7214240
4. Sokal JE, Cox EB, Baccarani M, Tura S, Gomez GA, Robertson JE, et al. Prognostic discrimination in "good-risk" chronic granulocytic leukemia. Blood. 1984;63:789-99. https://doi.org/10.1182/blood.V63.4.789.789 PMid:6584184
5. Hasford J, Pfirrmann M, Hehlmann R, Allan NC, Baccarani M, Kluin-Nelemans JC, et al. A new prognostic score for survival of patients with chronic myeloid leukemia treated with interferon alfa. Writing Committee for the Collaborative CML Prognostic Factors Project Group. J Natl Cancer Inst. 1998;90:850-8. https://doi.org/10.1093/jnci/90.11.850 PMid:9625174
6. Hasford J, Baccarani M, Hoffmann V, Guilhot J, Saussele S, Rosti G, et al. Predicting complete cytogenetic response and subsequent progression-free survival in 2060 patients with CML on imatinib treatment: the EUTOS score. Blood. 2011;118:686-92. https://doi.org/10.1182/blood-2010-12-319038 PMid:21536864
7. Zhang, XS., Gale, R.P., Zhang, MJ.et al.A predictive scoring system for therapy-failure in persons with chronic myeloid leukemia receiving initial imatinib therapy. Leukemia 36, 1336-1342 (2022). https://doi.org/10.1038/s41375-022-01527-y PMid:35194158
8. Ielo, C., Scalzulli, E., Carmosino, I., et al. (2023). Validation of imatinib therapy failure score (IMTF) in chronic phase chronic myeloid leukemia in real-life practice. Leukemia & Lymphoma,64(14), 2324-2326. https://doi.org/10.1080/10428194.2023.2255804 PMid:37689986
9. Zhang X, Liu B, Huang J, et al. A predictive model for therapy failure in patients with chronic myeloid leukemia receiving tyrosine kinase inhibitor therapy. Blood. 2024;144(18):1951-1961. https://doi.org/10.1182/blood.2024024761 PMid:39046786 PMCid:PMC11551847
10. Khoury JD,Solary E,Abla O, et al.The 5th edition of the World Health Organization classification of haematolymphoid tumours: myeloid and histiocytic/dendritic neoplasms. Leukemia 2022;36(7):1703-1719. https://doi.org/10.1038/s41375-022-01613-1 PMid:35732831 PMCid:PMC9252913
11. Hughes T, Deininger M, Hochhaus A,et al Monitoring CML patients responding to treatment with tyrosine kinase inhibitors: review and recommendations for harmonizing current methodology for detecting BCR-ABL transcripts and kinase domain mutations and for expressing results. Blood. 2006;108:28-37. https://doi.org/10.1182/blood-2006-01-0092 PMid:16522812 PMCid:PMC1895821
12. Hochhaus A. A further milestone towards comprehensive standardization of quantitative RT-PCR protocols for leukemic fusion gene transcripts has been reached. Leukemia. 2003;17:2383. https://doi.org/10.1038/sj.leu.2403137 PMid:14562123