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# Commentary on "real world results of ibrutinib in patients with relapsed or refractory chronic lymphocytic leukemia: a meta-analysis of clinical studies"

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*Dear Editor*

Karimi et al., 2025, present a meta-analysis evaluating the real-world effectiveness of ibrutinib in patients with relapsed or refractory chronic lymphocytic leukemia (CLL) [1]. The study provides valuable insights into treatment outcomes beyond clinical trial settings, offering a broader perspective on efficacy and tolerability in diverse patient populations. However, several methodological and interpretative issues warrant further discussion.

## Heterogeneity in study selection and patient populations

A primary concern is the inherent heterogeneity among included studies, encompassing variations in patient demographics, prior treatments, and disease burden [2]. Differences in baseline characteristics, including genetic risk stratification (e.g., TP53 mutations, IGHV status), may significantly influence ibrutinib's efficacy and toxicity profile. Subgroup analyses addressing these critical factors are essential to refine the generalizability of the findings.

## Lack of uniform safety assessment

While the study reports on adverse events, the variability in toxicity definitions and reporting across the included studies may introduce bias. Ibrutinib's real-world discontinuation rates due to cardiovascular events, infections, and bleeding complications are clinically relevant but require standardized reporting criteria to enable a more precise assessment of tolerability [3]. Moreover, the study lacks a granular evaluation of dose modifications and their impact on treatment outcomes.

## Shortcomings in long-term efficacy evaluation

Although ibrutinib has transformed CLL treatment paradigms, long-term follow-up remains crucial. The meta-analysis does not adequately differentiate between early responses and sustained remissions. Given that resistance mechanisms, including BTK and PLCγ2 mutations, contribute to treatment failure, a detailed exploration of resistance evolution over time is necessary [4].

## Real-world vs. clinical trial discrepancies

Real-world data inherently differ from controlled trial settings due to variations in treatment adherence, access to supportive care, and monitoring strategies. The study does not account for potential confounders, such as socioeconomic factors and healthcare disparities, which may impact treatment accessibility and outcomes [5]. Addressing these real-world complexities would enhance the study's applicability to diverse clinical settings.

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## Potential implications for future research

To improve the translational impact of real-world studies on ibrutinib, future research should prioritize:

- Standardized data collection frameworks to minimize heterogeneity in safety and efficacy reporting.
- Prospective observational studies incorporating molecular and genomic profiling to refine patient selection for ibrutinib therapy.
- Comparative analyses evaluating next-generation BTK inhibitors in real-world settings to establish optimal sequencing strategies.

In summary, while Karimi et al. provide an informative synthesis of real-world data on ibrutinib in relapsed/refractory CLL, methodological inconsistencies and gaps in long-term outcome assessment necessitate cautious interpretation. Future studies addressing these limitations will be instrumental in optimizing therapeutic strategies and improving patient care.

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ABN: Writing and Editing the draft. MK: Study design, data collection, Writing and Editing the draft. All authors read and approved the final version of the manuscript.

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**Data availability**

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## Declarations

**Ethics and consent to participate**

Not applicable.

**Competing interests**

The authors declare no competing interests.

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**References**

1. Karimi MA, Noroozi seyedhosseini H, Khademi R, Ghajary A, Kargar H, Abdollahi SS, Belbasi M, Naziri M, Deravi N, Hajihosseini S, Mofidi S, et al. Real world results of ibrutinib in patients with relapsed or refractory chronic lymphocytic leukemia: a meta-analysis of clinical studies. BMC Pharmacol Toxicol. 2025;26(1):43.
2. Nugent BM, Madabushi R, Buch B, Peiris V, Crentsil V, Miller VM, Bull J, Jenkins R. Heterogeneity in treatment effects across diverse populations. Pharm Stat. 2021;20(5):929–38.
3. Moldovianu AM, Stoia R, Vasilica M, Ursuleac I, Badelita SN, Tomescu AA, Preda OD, Bardas A, Cirstea M, Coriu D, et al. Real-world clinical outcomes and adverse events in patients with chronic lymphocytic leukemia treated with ibrutinib: a single-center retrospective study. Medicina. 2023;59(2):324.
4. Maher N, Mouhssine S, Matti BF, Alwan AF, Gaidano G. Treatment refractoriness in chronic lymphocytic leukemia: old and new molecular biomarkers. Int J Mol Sci. 2023;24(12):10374.
5. Yared JA, Lee TY, Cooke CE, Johnson A, Summers A, Yang K, Liu S, Tang B, Onukwugha E, et al. Disparity in treatment patterns among medicare beneficiaries diagnosed with chronic lymphocytic leukemia: an analysis of patient and contextual factors. Leuk Lymphoma. 2024;65(5):598–608.

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