Real-World Clinical Outcomes and Healthcare Resource Utilization in CLL/SLL Patients Using Covalent BTK Inhibitors (2020-2025): A Systematic Review

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Background

Chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL) is the most common adult leukaemia, primarily affecting an older, comorbid population with a median age at diagnosis of approximately 70 years.[1] It accounts for roughly one-third of all leukaemia cases in the United States and has an estimated incidence rate of 4.7 cases per 100,000 persons per year.[1,2] CLL/SLL is an indolent form of non-Hodgkin lymphoma characterized by the accumulation of mature but dysfunctional B-lymphocytes in the blood, bone marrow, and lymphoid tissues.[3] Risk increases with age and is about twice as high in males compared with females.[2] Over the past decade, the treatment landscape has evolved from chemotherapy-based regimens to targeted and immune-based therapies, including BCL-2 inhibitors, PI3K pathway inhibitors, CAR T-cell therapy, monoclonal antibodies, and Bruton tyrosine kinase inhibitors (BTKis).[3] Among these, covalent BTK inhibitors have become a foundational therapy in CLL/SLL, disrupting B-cell receptor signalling that drives cancer cell survival and proliferation.[3] The first-in-class covalent BTK inhibitor (BTKi) ibrutinib was approved in 2014, followed by second-generation agents acalabrutinib (2019) and zanubrutinib (2023).[4] Given these advances, understanding treatment patterns and outcomes in routine clinical practice has become increasingly important.[3]

Objectives

To systematically identify and synthesize real-world evidence (RWE) on clinical outcomes and healthcare resource utilization (HCRU) among patients with chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL) treated with covalent Bruton tyrosine kinase inhibitors (ibrutinib, acalabrutinib, zanubrutinib) in observational studies published between 2020 and 2025.

Methods

A systematic literature review was conducted in accordance with PRISMA guidelines[4], with inclusion and exclusion criteria defined using the PICO framework. Searches were performed in PubMed, Embase, and major conference proceedings (ASH, EHA, ASCO, AMCP, ISPOR) for observational studies published between 2020 and 2025 evaluating real-world clinical and healthcare resource utilization (HCRU) outcomes among patients treated with covalent BTK inhibitors (ibrutinib, acalabrutinib, zanubrutinib). Eligible studies included real-world analyses using claims, electronic health records, chart reviews, or registries that reported clinical (PFS, OS, ORR, TTNT, TTF) or economic (HCRU, costs) endpoints. Randomized trials, reviews, case reports, non-relevant populations, and studies outside the specified timeframe were excluded. Screening and deduplication were conducted in Rayyan, and data were systematically extracted in Microsoft Excel across standardized study variables.

Result

Inclusion criteria were met by 53 clinical studies and 10 HCRU studies (Figure 1).

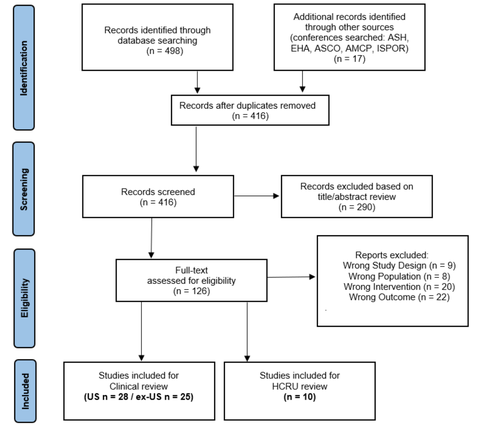
Review on Clinical Outcomes

Among clinical studies, 25 were conducted outside the U.S. and 28 within the U.S. Of the U.S.-based studies, 13 compared two or more cBTKi agents, while 6 evaluated ibrutinib vs. non-BTKi comparators, 4 examined dosing or treatment interruptions, and 5 reported subgroup analyses. Most records were conference abstracts or posters (n=16) and retrospective cohort designs (n=26). Among U.S. comparative studies, Ermann (2025) showed acalabrutinib was associated with lower rates of new or worsening hypertension and longer time to treatment failure versus ibrutinib in Medicare-eligible patients. In contrast, Fitzgerald (2024) reported similar overall survival across BTKi cohorts in the Veterans Health Administration, with adjusted analyses showing slightly higher mortality for acalabrutinib versus ibrutinib, likely reflecting shorter follow-up for newer agents. Huntington (2025) found premature discontinuation rates of 36% for ibrutinib and 29% for acalabrutinib, while Jacobs (2024) demonstrated longer time to next treatment with ibrutinib compared with acalabrutinib (adjusted HR 1.89). Shadman (2024) found that patients who underwent ibrutinib dose reduction maintained comparable or longer treatment duration than standard-dose acalabrutinib. Yang (2025) reported median time-to-discontinuation of 18.9 mo (zanubrutinib), 17.8 mo (acalabrutinib), and 14.5 mo (ibrutinib), and Zhou Hou (2025) observed higher treatment persistence with zanubrutinib versus acalabrutinib.

Review on HCRU/Cost Outcomes

Among all studies assessing real-world HCRU or cost endpoints (n=10), six included at least two covalent BTK inhibitors, with only one study incorporating zanubrutinib. Most analyses came from diverse data sources such as Optum Clinformatics®, Medicare claims, Acentrus EMR, and ConcertAI. Ermann (2025) in R/R disease reported lower rates of medical events of interest and related HCRU with acalabrutinib than ibrutinib, whereas Fitzgerald (2025, VA) found numerically lower first-year total and CLL-related costs with 1L ibrutinib versus acalabrutinib (–$2,422 and –$3,804; NS). In commercial claims, Muluneh (2023) observed fewer CLL-related office/outpatient visits and lower CLL-related PPPM costs with ibrutinib than acalabrutinib, and Rogers (2025) showed longer 1L duration and fewer CLL-related outpatient visits with ibrutinib, alongside lower all-cause monthly costs in Acentrus (–$1,355; significant) and numerically lower in IQVIA. Kusi (2024) showed that incident cardiovascular AEs regardless of agent inflated inpatient use and total costs, with similar overall medical-service days between ibrutinib and acalabrutinib. Huang (2020) in both VHA and Medicare/MA cohorts found ibrutinib reduced medical utilization and offset pharmacy spend versus chemo-immunotherapy. Finally, within ibrutinib users experiencing AEs, Shadman (2025) found dose reduction, compared with no reduction, was associated with longer TTNT, fewer inpatient/ED encounters, and lower medical and total costs.

Figure 1. PRISMA Flow Diagram of Study Selection



Discussion

Across U.S. real-world studies, several signals support ibrutinib's continued relevance: longer time to next treatment in a specialty-pharmacy cohort, maintenance of treatment duration and lower utilization with dose-reduction strategies after adverse events, and lower or numerically lower costs and clinic/outpatient use versus acalabrutinib in multiple datasets (with similar overall survival in the VA). However, other analyses reported more favourable tolerability profiles for acalabrutinib in older or R/R populations and longer persistence with zanubrutinib, underscoring that observed differences may reflect population mix, follow-up length, and analytic choices rather than a definitive better agent. Overall, the evidence supports individualized selection and proactive toxicity management (including dose modification) to sustain therapy and mitigate resource use. Further research should include prospective, head-to-head or target-trial-emulated comparisons with harmonized endpoint definitions (TTD, TTNT, rwPFS/OS), balanced follow-up across agents, and consistent rules for add-on therapies. Linking EHR and claims with genomic risk (TP53/IGHV), frailty, and patient-reported outcomes, and conducting U.S. cost-effectiveness analyses that incorporate cardiovascular toxicity and dose-adjustment strategies-especially for zanubrutinib-would help reconcile heterogeneous findings. This SLR is limited by the predominance of retrospective cohorts, potential confounding by indication and immortal-time bias, heterogeneous outcome definitions across data sources (Flatiron, Acentrus, Optum, Medicare, VA), shorter observation for newer agents, and a high proportion of conference abstracts. Therefore, this body evidence should be considered descriptive in nature, as no meta-analytic comparisons were performed.

Conclusion

Real-world U.S. data show mixed clinical and economic outcomes across covalent BTK inhibitors, with several analyses supporting ibrutinib (e.g., maintained duration and lower utilization with dose-reduction), but also some studies favour acalabrutinib for tolerability and zanubrutinib for persistence. Rigorous, standardized head-to-head or target-trial-emulated studies with balanced follow-up are needed to clarify comparative value.

References

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Records included in the systematic literature review

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