Comparison of targeted therapy in adult Philadelphia chromosome-positive B-cell acute lymphoblastic leukemia (Ph+ B-ALL)

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Background

- Acute Lymphocytic Leukemia (ALL) is a cancer caused by the overproduction of abnormal lymphoblasts in the bone marrow. It is classified into B-cell and T-cell types. B-cell ALL includes Philadelphia chromosome-positive (Ph+), which accounts for 20-30% of cases, and Philadelphia chromosome-negative (Ph-).
- Compared to Ph- patients, those with Ph+ have poorer outcomes in terms of disease-free survival (DFS), event-free survival (EFS), and overall survival (OS) with traditional treatments.
- When tyrosine kinase inhibitors (TKIs) are incorporated into chemotherapy regimens, Ph+ B-ALL patients achieve higher rates of complete remission (CR) and DFS, EFS and the feasibility of subsequent hematopoietic stem cell transplantation (HSCT) increases.
- **This study aims to conduct a systematic review and pooled survival analysis to evaluate the impact of TKI plus chemotherapy regimens on the survival rates of Ph+ B-ALL patients among various treatment regimens.**

Methods

The systematic review and pooled survival analysis were performed following the guidelines outlined in the 2020 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).

- **Eligibility criteria** (i) patients: adults with Philadelphia chromosome-positive ALL, (ii) intervention: treatment with TKIs plus chemotherapy regimens, and (iii) outcomes: data on CR rate, OS, EFS, and DFS.
- **Search strategy and databases** Search filters were adapted to capture potentially relevant studies from OVID-Medline and PubMed until March 1, 2024.
- **Quality assessment** Clinical trials and randomized controlled trials were assessed using the Downs and Black checklist.
- **Pooled survival analysis** We used software to reconstruct individual patient data and analyzed the reconstructed data to calculate the variance, mean, and standard deviation for each treatment regimen, while also performing subgroup analyses. Therefore, effectiveness outcomes were summarized according to each treatment regimens.

Objectives

To evaluate CR, OS, DFS, and EFS outcomes in newly diagnosed adult Ph+ B-ALL patients treated with TKI plus chemotherapy, combining survival analysis to predict survival curves across treatment regimens, compare treatment efficacy, and propose the optimal therapy.

Results

- **Study selection** Overall, 17 studies were included in the review (Figure 1). There are 15 clinical trials and 2 randomized controlled trials (RCTs) among the studies (Table 1).

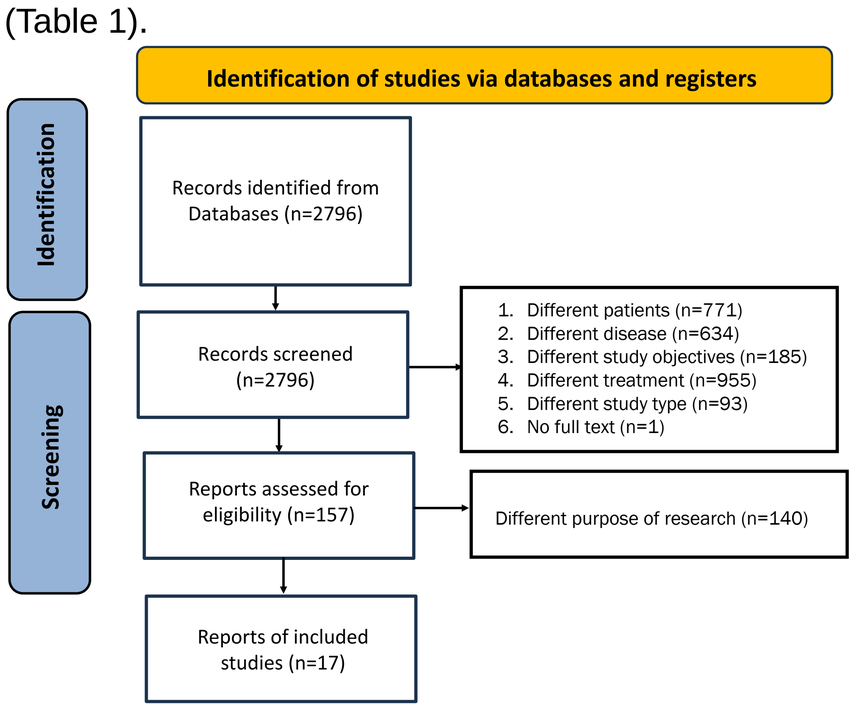

Figure 1. *PRISMA flow diagram*

Table 1. *Treatment regimens and the number of included studies*

Clinical trials:15	
Treatment regimens (TKI + chemotherapy)	Number of studies
Imatinib + chemotherapy	6
Dasatinib + chemotherapy	3
Nilotinib + chemotherapy	2
Ponatinib + chemotherapy	4
Randomized controlled trials: 2	
Dasatinib + chemotherapy vs. imatinib + chemotherapy	
Ponatinib + chemotherapy vs. imatinib + chemotherapy	

- **Quality assessment :**

The overall quality, based on the 26 items of the Downs and Black quality checklist, ranged from fair to good (Figure 2).

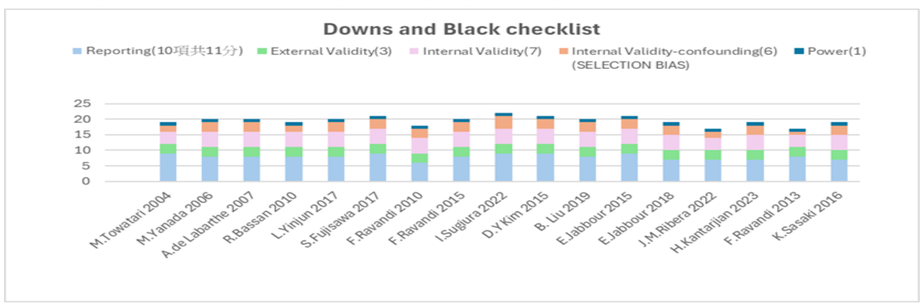

Figure 2. *Quality assessment of included studies by using Downs and Black quality checklist.*

- **Pooled survival analyses for all patients**
  - In 3 years, the ponatinib + chemotherapy treatment regimen demonstrated the best survival rates in terms of OS and EFS, with rates of 76.0% [95%CI: 70.7%–81.6%] and 71.2% [95%CI: 65.6%–77.6%], respectively. The nilotinib + chemotherapy regimen showed superior DFS compared to other regimens: 66.2% [95%CI: 57.7%–75.9%].
  - The survival rates for the imatinib + chemotherapy regimen were lower in both OS and DFS: 54.4% [95%CI: 49.4%–59.8%] and 41.6% [95%CI: 32.2%–53.9%] (Figure 3).

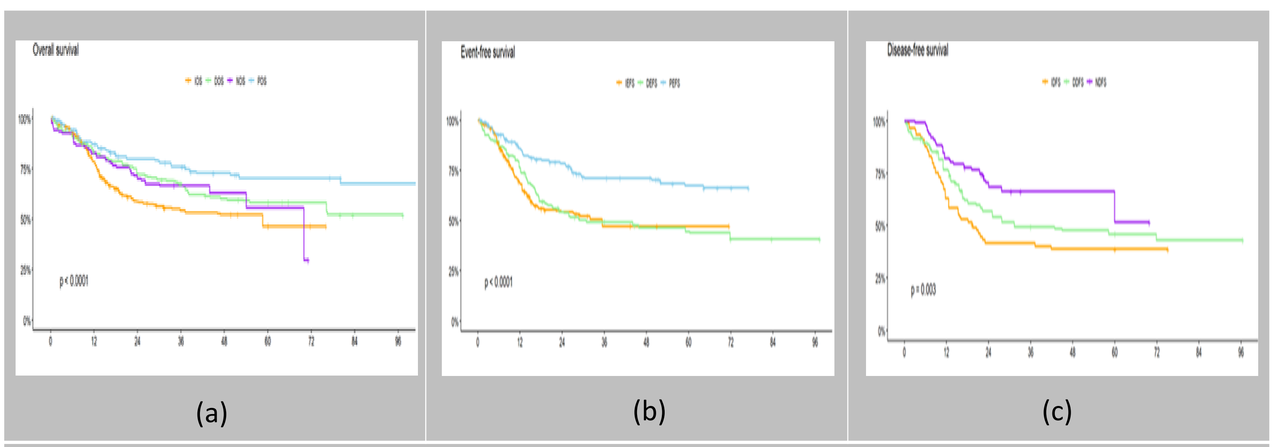

Figure 3. *Pooled survival analyses of overall. Comparison of (a) OS (b) EFS (c) DFS between groups for all patients.*

- **Subgroup analyses - HSCT**
  - Of the 17 studies, 9 reported results divided into subgroups with and without transplantation. Only OS has complete data (Figure 4), while EFS data were incomplete for the non-HSCT group, and DFS includes data only for nilotinib + chemotherapy.
  - In the HSCT group, the 3-years survival rate for nilotinib + chemotherapy is 77.8% [95%CI: 68.7%–88.0%]. In the non-HSCT group, the 3-years survival rate for ponatinib + chemotherapy is 90.6% [95%CI: 68.7%–88.0%], significantly higher than that of other treatment regimens, while imatinib + chemotherapy rate is 31.0% [95%CI: 23.9%–40.3%], far lower than others.

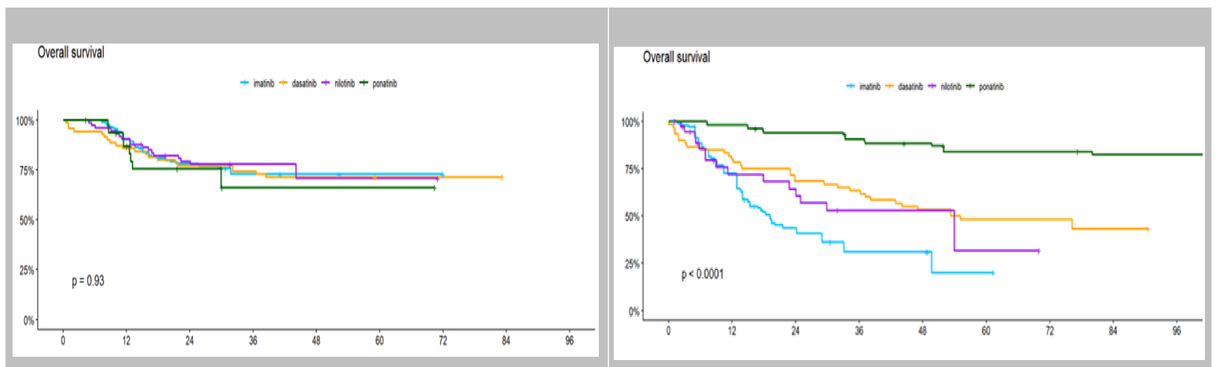

Figure 4*. Pooled survival analyses of overall. Within-group comparison between the (a) HSCT (b) non-HSCT groups.*

Conclusions

For all patients, OS and EFS were highest with ponatinib + chemotherapy, while DFS survival rate was better with nilotinib + chemotherapy compared to other treatment regimens. In the transplantation group, the survival rates for the four TKIs in combination with chemotherapy were similar. For non-transplantation patients, ponatinib + chemotherapy had the best survival rate.

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