RESEARCH ARTICLE

Association of minimal residual disease with clinical outcomes in Philadelphia chromosome positive acute lymphoblastic leukemia in the tyrosine kinase inhibitor era: A systemic literature review and meta-analysis

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Abstract

Minimal residual disease (MRD) appeared to be a potent prognostic indicator in patients with Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL), with potential value in informing individualized treatment decisions. Hence, we performed herein a systemic literature review and meta-analysis to comprehensively address the prognostic value of MRD in Ph+ ALL. Systematic literature review was conducted in PubMed, Embase, and Cochrane databases with the data access date up to September 23, 2020. Pooled hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated with fixed-effects or random-effects models. Furthermore, subgroup analyses were performed to assess the robustness of the associations. 27 studies with a total number of 3289 patients were eligible for this meta-analysis. Combined HRs suggested that MRD positivity was associated with inferior event-free survival (EFS) (HR = 2.00, 95% CI 1.77–2.26) and overall survival (OS) (HR = 2.34, 95% CI 1.86–2.95). The associations remained statistically significant in subgroup analyses including age group, MRD timing, disease status at MRD, MRD cutoff level, et al. Our findings suggested MRD as a potent clinical tool for assessing the prognosis of Ph + ALL. Further studies using MRD-based risk stratification might help optimize individualized treatment strategies for Ph+ ALL patients.

Introduction

Philadelphia (Ph) chromosome is the der(22) product of the reciprocal translocation between 9q34 and 22q11.2, which generates the BCR-ABL1 fusion gene [1]. It can be detected in 25–40% of adult patients with acute lymphoblastic leukemia (ALL) [2, 3]. Historically, Philadelphia chromosome was associated with a dismal prognosis, with long-term survival rates of less than 20%, and the only curative possibility was based on intensive chemotherapy followed by allogeneic hematopoietic stem cell transplantation (allo-HSCT) [4–6]. The addition of tyrosine

kinase inhibitors (TKIs) has remarkably improved the treatment response and long-term survival of Ph+ ALL patients [7–12]. However, a substantial proportion of patients still die as a result of disease progression. Thus, prediction and intervention before hematological relapse are important in reducing the incidence of relapse and improving clinical outcomes.

Minimal residual disease (MRD) refers to the persistence of residual leukemic cells that cannot be detected by conventional morphological methods [13]. It is a powerful prognostic factor in ALL and is used for patient stratification and treatment decisions, but its precise role in Ph+ ALL is less clear. In the TKI era, a plenty of studies have investigated the prognostic significance of MRD in Ph+ ALL patients. However, timing of MRD analysis, cutoff levels and treatment strategies varied across different studies, and consensus is still yet to be reached. Furthermore, Ph+ ALL differs from Ph- ALL not just in prognosis, but also in treatment regimens and method of MRD assessment. Hence, we performed herein a systemic literature review and meta-analysis to comprehensively explore the impact of MRD status in Ph+ ALL patients.

Methods

Literature search and study selection

This meta-analysis was performed and reported according to the PRISMA statement [14]. A PRISMA checklist (S1 Checklist) was used to ensure standardized reporting. The review protocol has been registered in the PROSPERO international prospective register of systematic reviews (registration number: CRD42021233397).

PubMed, Embase and Cochrane databases were searched for studies with the data access date up to September 23, 2020 with free-style words and Medical Subjects Headings (MeSH): (("Philadelphia Chromosome"[Mesh] OR BCR-ABL1) AND "Precursor Cell Lymphoblastic Leukemia-Lymphoma"[Mesh]) OR Ph positive acute lymphoblastic leukemia OR BCR-ABL1 positive acute lymphoblastic leukemia. The search strategy for Pubmed was provided in S1 File. References of included studies in this meta-analysis and relevant reviews were also screened for potentially eligible studies.

Two reviewers independently evaluated the eligibility of studies according to the predefined inclusion criteria: (1) randomized controlled trials (RCT) or cohort studies that investigated the association between MRD and prognosis in Ph+ ALL patients treated with regimens containing TKIs; (2) the study outcomes were time-dependent endpoints, such as disease-free survival (DFS)/relapse-free survival (RFS)/leukemia-free survival (LFS)/progression-free survival (PFS)/event-free survival (EFS) and overall survival (OS); (3) hazard ratios (HRs) with 95% confidence intervals (CIs) were reported or could be calculated from sufficient data presented. Studies were excluded if they: (1) included patients not treated with TKIs; (2) included less than 50 patients; (3) without sufficient data to calculate HRs and 95% CIs. For overlapped cohorts, only the latest and most intact report was included.

Data extraction and quality assessment

Two reviewers independently extracted data from eligible studies using a standardized data collection sheet including the following items: first author, year of publication, study region, recruitment time, study design, treatment protocol, TKI used, transplant status, sample size, age range, ethnicity, sex distribution, follow-up time, MRD sample, MRD timing, disease status at MRD, pre-MRD treatment, post-MRD treatment, MRD test location, MRD detection method, MRD cutoff level, number of cases with positive MRD, outcomes, statistical methods, and HRs with 95% CIs.

The Quality in Prognosis Studies (QUIPS) tool [15] was used to assess the risk of bias of included studies in six domains: study participation, study attrition, prognostic factor

measurement, outcome measurement, study confounding, statistical analysis and reporting. The risk of bias for each domain was indicated as low, moderate or high according to the rating criteria. The overall risk of bias for individual studies was marked as high if one or more domains were rated as high risk of bias, or moderate if one or more domains were rated as moderate risk of bias, or low if all domains were rated as low risk of bias.

Two reviewers independently performed the study screening, data extraction and quality assessment procedure. Any disagreements were resolved by consulting with a third reviewer.

Statistical analyses

The primary endpoints were EFS and OS. DFS, RFS, LFS and PFS were interpreted as synonymous with EFS. HRs and 95% CIs for EFS and OS were pooled to assess the prognostic value of MRD. If both univariate and multivariate analyses results were presented, we used the latter. If HRs with 95% CIs were not reported, we estimated the data from Kaplan-Meier survival curves using the methods described by Tierney et al [16].

The heterogeneity between included studies was evaluated using chi-square based Q-test and I^2 test. Random-effects model was applied to pool the HRs and 95% CIs if significant heterogeneity existed ($P < 0.10$ or $I^2 > 50\%$). Otherwise, fixed-effects model was used. Subgroup analyses were further performed to investigate the source of heterogeneity and to assess the potential effect modification of factors including study design, age group, study region, ethnicity, type of TKI used, transplant status, MRD timing, disease status at MRD, MRD cutoff level, and statistical method.

Publication bias was evaluated using Begg's funnel plot and Egger's test, with significance defined as $P < 0.05$. A trim-and-fill analysis was performed if publication bias was suggested. Sensitivity analyses were performed to evaluate single study's influence on pooled HRs by sequentially omitting one study at a time. All of the analyses were performed with Stata version 16.0 software (Stata Corporation, College Station, TX, USA).

Results

Study selection and characteristics

Initial literature searches in PubMed, Embase and Cochrane databases identified 5467 records published up to September 23, 2020. After screening the title and abstract of each record, 236 records were included in the full text screen. 209 records were discarded for the following reasons: not investigating the correlation between MRD and outcomes (n = 166), including non-TKIs treated patients (n = 7), less than 50 patients (n = 15), insufficient data to attain HRs and 95% CIs (n = 10), overlapped cohorts (n = 11). Finally, 27 records were included in the qualitative analysis [7, 9, 11, 17–40]. The study selection process is summarized as a flow chart in Fig 1.

The characteristics of included studies are summarized in S1 Table. The raw data is supplied in S2 File. Most studies were published from 2012 onwards, except for an RCT in Germany and two prospective cohort studies in Japan and Korea, spanning a time period from 2000 to 2019. Studies were mainly conducted in East Asia or Europe. The sample size ranged from 51 to 441, with a total number of 3289 patients. The age of patients was above 14 years in most studies. Only two studies included patients solely in the second complete remission (CR2) or later, and 22 studies were in patients in the first complete remission (CR1). Treatment protocols were typically multi-agent chemotherapy plus TKIs, followed by allo-HSCT, in most studies. Two studies applied CD19-targeted chimeric antigen receptor T cell (CAR-T) therapy for relapse/refractory patients. In ten studies patients all received HSCT, and five studies enrolled exclusively non-transplant patients, and the rest studies comprised both transplant and non-transplant individuals.
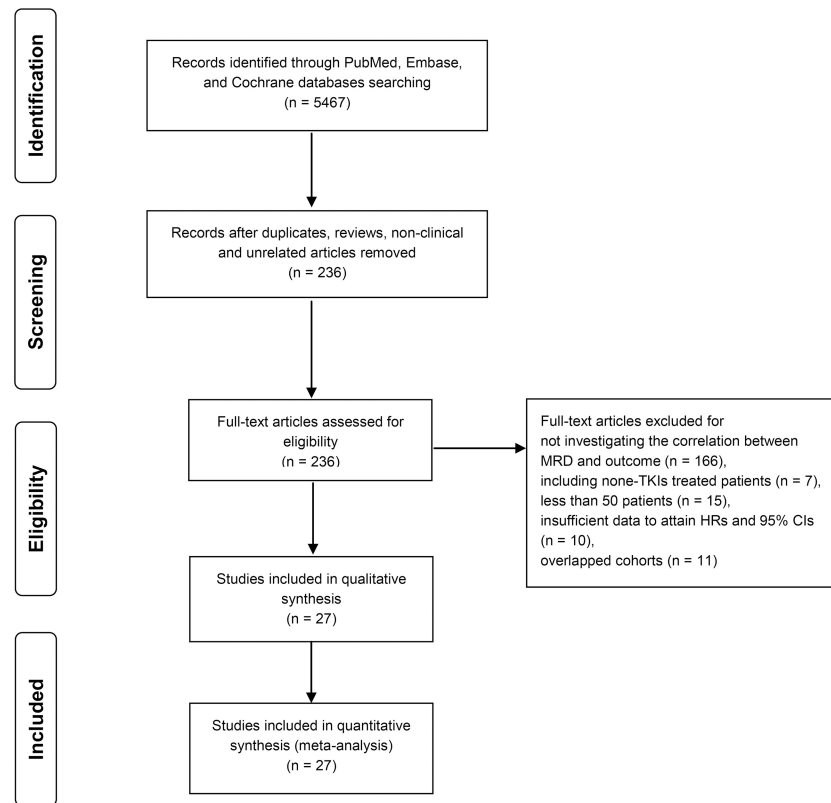
Fig 1. PRISMA flow diagram for study review and inclusion.

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Almost all studies used BCR-ABL1 transcript level as a marker of MRD and used real-time quantitative polymerase chain reaction (RT-qPCR) to quantify the BCR-ABL1 transcript level, mostly based on bone marrow samples. The cutoff levels were set at 10^{-5}, 10^{-4} or 10^{-3}, or 4-log, 3-log or 1-log reduction from baseline. The measurements of MRD were generally taken within three months from induction treatment (n = 12) or before HSCT (n = 8).

According to the QUIPS tool, 15 studies were ranked as low risk of bias, and the rest were moderate risk of bias. The details are listed in S2 Table.

Association between MRD status and EFS

Fig 2A shows the meta-analysis result for EFS including 25 studies. Overall, MRD positivity was associated with worse EFS (HR = 2.00, 95% CI 1.77–2.26). The effect was consistent across all studies, with the confidence intervals crossing the null value in seven studies. No significant heterogeneity existed between the studies (I^2 = 26.0%) and fixed-effects model was employed to pool the HRs.

In subgroup analysis, positive MRD was associated with inferior EFS in almost all subgroups (median age of 0–14, 15–39 or above 40 years; first- or second-generation TKIs treated patients; transplant or non-transplant cohort; MRD tested before or after three months from induction, before or after HSCT; different cutoff levels of 10^{-5}, 10^{-4} or 10^{-3}, or 4-log, 3-log or 1-log reduction from baseline; et al.), with non-significant confidence intervals in few subgroups (S3 Table). The prognostic value of MRD appeared to be stronger in the median age of 0–14 years (HR = 3.80, 95% CI 0.97–14.82) than in the 15–39 years (HR = 2.35, 95% CI 1.93–2.86) or ≥ 40 years subgroup (HR = 1.77, 95% CI 1.51–2.08). But it should be noted that the 0–14 years subgroup was
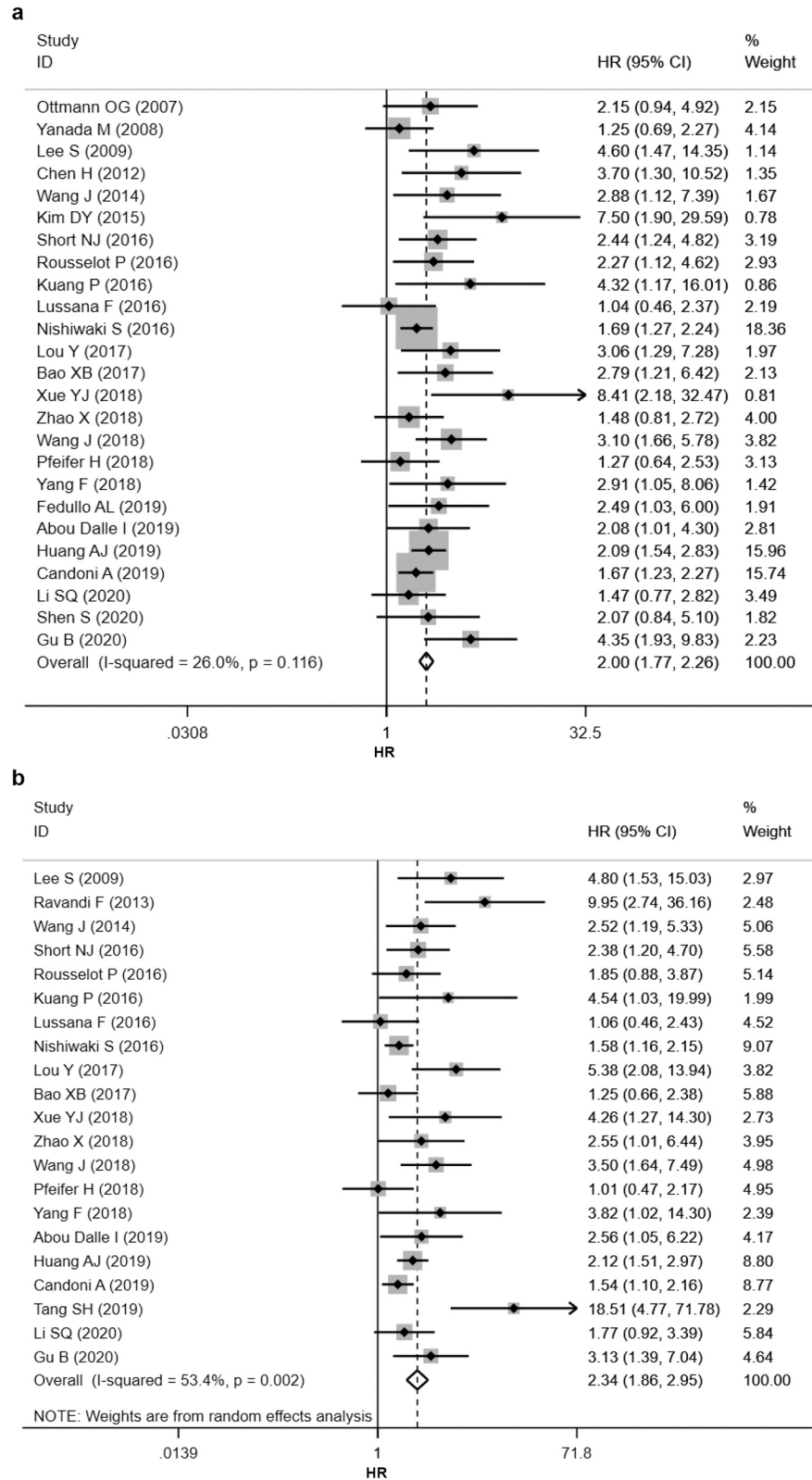
Fig 2. Forest plots for the impact of MRD status on the clinical outcomes of Ph+ ALL patients. (a) Forest plot for event-free survival (EFS). (b) Forest plot for overall survival (OS).

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only based on two studies and the confidence interval was very wide. The subgroup that received second-generation TKIs had a hazard ratio of 3.55 (95% CI 1.14–11.03), bigger than that of the first-generation TKI subgroup (HR = 2.03, 95% CI 1.65–2.50). Again it should be noted that the result of the second-generation TKIs subgroup was based on two studies, and their confidence intervals overlapped. The prognostic value of MRD also seemed to be stronger in $\geq$ CR2 patient cohorts (HR = 4.35, 95% CI 1.93–9.83), but this was only based on one study.

Association between MRD status and OS

21 studies were included in the OS analysis. The overall result suggested inferior OS for patients with positive MRD (HR = 2.34, 95% CI 1.86–2.95) (Fig 2B), and the results were consistent across all studies. Moderate heterogeneity exited among the studies (I^2 = 53.4%) and random-effects model was applied.

In subgroup analysis, MRD positivity remained a negative marker for OS. As for EFS, the prognostic value of MRD seemed to be stronger in the median age of 0–14 years subgroup (HR = 4.26, 95% CI 1.27–14.30) than in the 15–39 years (HR = 2.28, 95% CI 1.84–2.83) or $\geq$ 40 years subgroup (HR = 1.94, 95% CI 1.40–2.68). Similar to EFS, the 0–14 years subgroup was only based on one study and the confidence interval was very wide. The inferior effect was less notable in European patients (HR = 1.44, 95% CI 1.10–1.89) than in East Asian (HR = 2.68, 95% CI 2.00–3.59) or USA patients (HR = 3.01, 95% CI 1.83–4.96). In non-transplant cohorts, the prognostic value of MRD seemed to be greater (HR = 3.41, 95% CI 1.95–5.95) than in transplant cohorts (HR = 1.58, 95% CI 1.32–1.90).

Publication bias and sensitivity analyses

Begg's and Egger's test suggested potential risks of publication bias for EFS and OS. By trim-and-fill analyses, eight and seven hypothesized studies were imputed for EFS and OS, respectively. Meta-analyses incorporating these studies did not significantly change the results (for EFS: HR = 1.83, 95% CI 1.54–2.19; for OS: HR = 1.87, 95% CI 1.45–2.40), which suggested the stability of the results (Fig 3). Sensitivity analyses revealed that no single study significantly altered the results (Fig 4).

Discussion

In this meta-analysis, we demonstrated that positive MRD was associated with worse clinical outcomes in Ph+ ALL patients. The effect was consistent and robust in all subgroups that we were able to address, including studies that recruited patients of different age groups or disease status, used different therapies, cutoff levels and time points. In some subgroups, there were some preliminary indications that the effect of MRD status on EFS might be stronger than in others. These results should be interpreted with caution, since no significant differential subgroup effects were seen, and most of the confidence intervals overlapped. For OS, the prognostic value of MRD seemed to be greater in East Asian and USA patients than in European patients, and also greater in non-transplant cohorts than in transplant cohorts.

Recently there have been two meta-analyses that comprehensively analyzed the association of MRD and clinical outcomes in ALL patients [41, 42], which regarded Ph+ ALL patients as a subgroup in their analyses. Although their results uniformly indicated that MRD positivity was a negative marker in the Ph+ ALL subgroup, the number of studies included was very limited, which might influence the power of the results. In the meta-analysis of Berry et al [41], only five studies enrolling Ph+ ALL patients were included, with one study also included in our analysis. The other four studies were excluded because of including patients not treated with TKIs or less than 50 patients. The analysis of Bassan et al [42] included eleven studies in
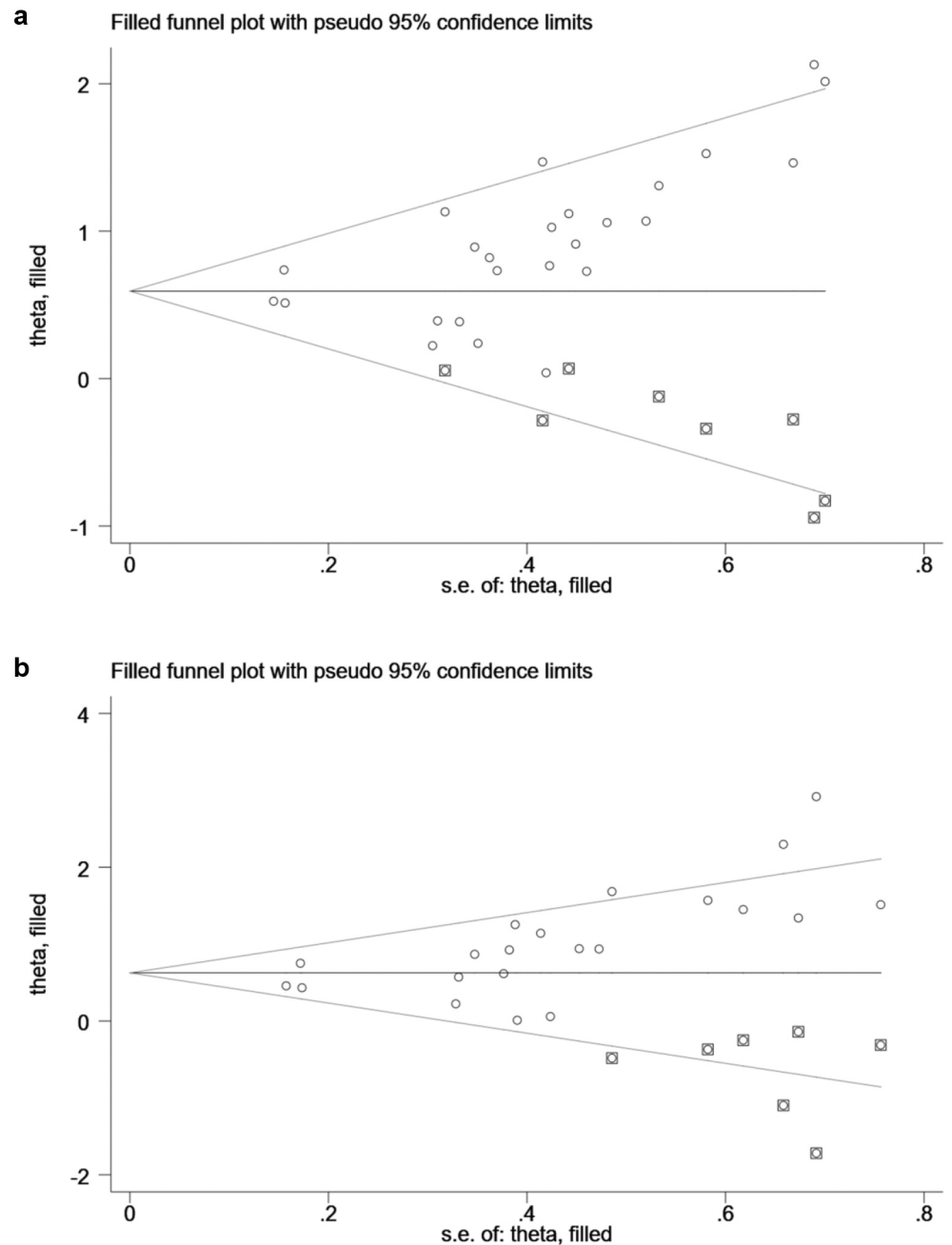
Fig 3. Begg's funnel plot with trim-and-fill analysis for publication bias. (a) event-free survival (EFS) and (b) overall survival (OS). The circles in squares indicated the hypothesized studies, which were also incorporated to generate symmetrical funnel plots.

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the Ph+ ALL subgroup. However, only four studies were also included in our analysis. The rest were excluded because of congress abstract, less than 50 patients or including patients not treated with TKIs. With our broad search strategy, we were able to include studies that investigated the prognostic value of MRD as many as possible, and restricted studies to TKIs treated cohorts. These ensured the reliability of the results, and allowed sufficient studies to be included for more detailed subgroup analyses.
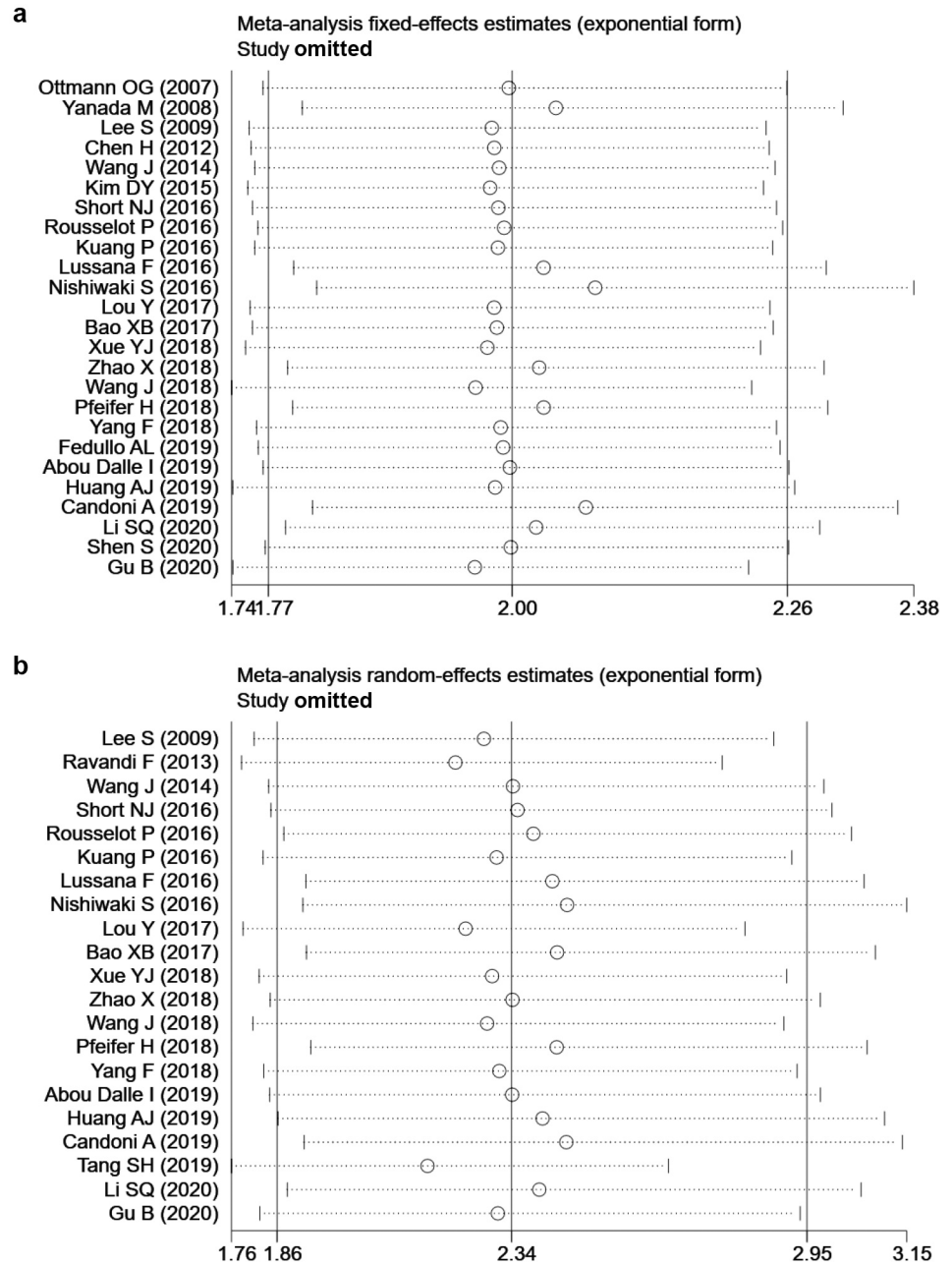
Fig 4. Sensitivity analysis for (a) event-free survival (EFS) and (b) overall survival (OS).

We divided the timing of MRD measurement into four categories: before three months from induction, after three months from induction, pre-HSCT and post-HSCT. Studies that measured MRD before three months from induction mainly conducted the procedure at the end of induction or during early phase consolidation therapy. These fall into the first scenario raised by Bassan et al [42] that MRD measurement was to evaluate the quality of treatment response. Almost all studies that investigated the prognostic value of MRD taken after three months from induction conducted the measurement within six months from induction. These along with post-HSCT fall into the second scenario raised by Bassan et al [42] that MRD

monitoring was used as a predictor for pending relapse. MRD negativity in the four categories all endowed benefit on EFS and OS. Although a larger effect was seen in the subgroup of after three months from induction, their confidence intervals overlapped.

With increasingly diverse approaches available for treating Ph+ ALL, there is particular interest in considering for whom allo-HSCT could be avoided. In a study of investigating the effects of nilotinib plus multi-agent chemotherapy in newly diagnosed Ph+ ALL [11], patients achieving complete molecular response (CMR) showed similar RFS between non-recipients and recipients of allo-HSCT. In another study by Wang et al [29], although there was benefit for allo-HSCT in the whole cohort, the effect was no longer evident for patients with low presenting white blood cell counts and 3-log reduction of BCR-ABL1 levels from baseline after two consolidation cycles. In a pediatric analysis [28], no significant difference existed between the transplant and non-transplant arms for OS and EFS in the standard-risk group defined as achieving CR at the induction end and major molecular response (MMR) at three months. These preliminary evidences suggested that MRD might play a role in sparing some low-risk Ph+ ALL patients for whom the toxic procedure of allo-HSCT might be dispensable.

Quantification of BCR-ABL1 transcript by RT-qPCR was used as the method to detect MRD by almost all the studies included in our meta-analysis. Various cutoff levels were used in different studies. The adverse impact of positive MRD was consistent in all cutoff level subgroups, although it should be noted that for the subgroup of $\geq$ 4-log reduction from baseline there was only one study, which contributed to non-significant confidence interval. The RT-qPCR assay is a convenient and straightforward approach for the detection of MRD in Ph + ALL. However, BCR-ABL1 quantification in Ph+ ALL has yet been standardized like that in chronic myeloid leukemia (CML). Different approaches are used by individual physicians and national study groups. This contributed to the diverse rates and degrees of molecular response in clinical trials. Recently, the EURO-MRD consortium proposed guidelines for the work-flow and reporting of e1a2 BCR-ABL1 transcript levels in Ph+ ALL [43]. Their detailed laboratory recommendations provided a robust framework for the precise and reproducible RT-qPCR based analysis of e1a2 BCR-ABL1 transcript and will facilitate valid comparison of MRD results between clinical trials for Ph+ ALL.

Several limitations of the present meta-analysis should be mentioned. Firstly, emerging immunotherapy approaches such as CAR-T, blinatumomab and inotuzumab ozogamicin, and the potent third-generation TKI ponatinib have shown impressive efficacy in relapse/refractory or de novo Ph+ ALL. However, due to the limited data available, we were unable to address the role of MRD in these regimens treated cohorts. Secondly, some of the HRs were extracted from Kaplan-Meier curves, which might be less reliable than the original data or multivariate analysis results.

In conclusion, this meta-analysis indicated that MRD was a promising prognostic marker in the management of patients with Ph+ ALL. Overall, and in all subgroups analyzed, MRD positivity was associated with higher risk of relapse and mortality. The adverse impact appeared to be unaffected by variation in the timing or cutoff level of the MRD assay applied. Prospective trials using MRD-based risk stratification for patients with Ph+ ALL might elucidate the optimal post-remission management of these patients.

Supporting information

S1 Checklist. PRISMA 2009 checklist.
(DOC)

S1 File. Search strategy for Pubmed.
(DOCX)

S2 File. Raw data of this meta-analysis.
(XLSX)

S1 Table. Characteristics of the studies included in this meta-analysis.
(DOCX)

S2 Table. Quality assessment of the included studies using the QUIPS tool.
(DOCX)

S3 Table. Subgroup analyses of the impact of MRD status on the prognoses of Ph+ ALL.
(DOCX)

Author Contributions

Conceptualization: Wanhua Zhang.

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Formal analysis: Wanhua Zhang.

Methodology: Wanhua Zhang.

Project administration: Wanhua Zhang.

Supervision: Wanhua Zhang.

Validation: Erguai Jang.

Writing – original draft: Wanhua Zhang, Erguai Jang.

Writing – review & editing: Wanhua Zhang, Erguai Jang.

References

1. Bernt KM, Hunger SP. Current concepts in pediatric Philadelphia chromosome-positive acute lympho-blastic leukemia. Front Oncol. 2014; 4: 54. https://doi.org/10.3389/fonc.2014.00054 PMID: 24724051

2. Burmeister T, Schwartz S, Bartram CR, Gökbuget N, Hoelzer D, Thiel E. Patients' age and BCR-ABL frequency in adult B-precursor ALL: a retrospective analysis from the GMALL study group. Blood. 2008; 112(3): 918–919. https://doi.org/10.1182/blood-2008-04-149286 PMID: 18650471

3. Moorman AV, Chilton L, Wilkinson J, Ensor HM, Bown N, Proctor SJ. A population-based cytogenetic study of adults with acute lymphoblastic leukemia. Blood. 2010; 115(2): 206–214. https://doi.org/10.1182/blood-2009-07-232124 PMID: 19897583

4. Dombret H, Gabert J, Boiron JM, Rigal-Huguet F, Blaise D, Thomas X, et al. Outcome of treatment in adults with Philadelphia chromosome-positive acute lymphoblastic leukemia—results of the prospective multicenter LALA-94 trial. Blood. 2002; 100(7): 2357–2366. https://doi.org/10.1182/blood-2002-03-0704 PMID: 12239143

5. Gleissner B, Gökbuget N, Bartram CR, Janssen B, Rieder H, Janssen JW, et al. Leading prognostic rel-evance of the BCR-ABL translocation in adult acute B-lineage lymphoblastic leukemia: a prospective study of the German Multicenter Trial Group and confirmed polymerase chain reaction analysis. Blood. 2002; 99(5): 1536–1543. https://doi.org/10.1182/blood.v99.5.1536 PMID: 11861265

6. Fielding AK, Rowe JM, Richards SM, Buck G, Moorman AV, Durrant IJ, et al. Prospective outcome data on 267 unselected adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia confirms superiority of allogeneic transplantation over chemotherapy in the pre-imatinib era: results from the International ALL Trial MRC UKALLXII/ECOG2993. Blood. 2009; 113(19): 4489–4496. https://doi.org/10.1182/blood-2009-01-199380 PMID: 19244158

7. Lou Y, Ma Y, Li C, Suo S, Tong H, Qian W, et al. Efficacy and prognostic factors of imatinib plus CALLG2008 protocol in adult patients with newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia. Front Med. 2017; 11(2): 229–238. https://doi.org/10.1007/s11684-017-0506-y PMID: 28349299

8. Hatta Y, Mizuta S, Matsuo K, Ohtake S, Iwanaga M, Sugiura I, et al. Final analysis of the JALSG Ph +ALL202 study: tyrosine kinase inhibitor-combined chemotherapy for Ph+ALL. Ann Hematol. 2018; 97 (9): 1535–1545. https://doi.org/10.1007/s00277-018-3323-8 PMID: 29694642

9. Rousselot P, Coudé MM, Gokbuget N, Gambacorti Passerini C, Hayette S, Cayuela JM, et al. Dasatinib and low-intensity chemotherapy in elderly patients with Philadelphia chromosome-positive ALL. Blood. 2016; 128(6): 774–782. https://doi.org/10.1182/blood-2016-02-700153 PMID: 27121472

10. Yoon JH, Yhim HY, Kwak JY, Ahn JS, Yang DH, Lee JJ, et al. Minimal residual disease-based effect and long-term outcome of first-line dasatinib combined with chemotherapy for adult Philadelphia chromosome-positive acute lymphoblastic leukemia. Ann Oncol. 2016; 27(6): 1081–1088. https://doi.org/10.1093/annonc/mdw123 PMID: 26951627

11. Kim DY, Joo YD, Lim SN, Kim SD, Lee JH, Lee JH, et al. Nilotinib combined with multiagent chemotherapy for newly diagnosed Philadelphia-positive acute lymphoblastic leukemia. Blood. 2015; 126(6): 746–756. https://doi.org/10.1182/blood-2015-03-636548 PMID: 26065651

12. Jabbour E, Short NJ, Ravandi F, Huang X, Daver N, DiNardo CD, et al. Combination of hyper-CVAD with ponatinib as first-line therapy for patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia: long-term follow-up of a single-centre, phase 2 study. Lancet Haematol. 2018; 5(12): e618–e627. https://doi.org/10.1016/S2352-3026(18)30176-5 PMID: 30501869

13. Shen Z, Gu X, Mao W, Yin L, Yang L, Zhang Z, et al. Influence of pre-transplant minimal residual disease on prognosis after Allo-SCT for patients with acute lymphoblastic leukemia: systematic review and meta-analysis. BMC Cancer. 2018; 18(1): 755. https://doi.org/10.1186/s12885-018-4670-5 PMID: 30037340

14. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol. 2009; 62(10): 1006–1012. https://doi.org/10.1016/j.jclinepi.2009.06.005 PMID: 19631508

15. Hayden JA, van der Windt DA, Cartwright JL, Côté P, Bombardier C. Assessing bias in studies of prognostic factors. Ann Intern Med. 2013; 158(4): 280–286. https://doi.org/10.7326/0003-4819-158-4-201302190-00009 PMID: 23420236

16. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials. 2007; 8: 16. https://doi.org/10.1186/1745-6215-8-16 PMID: 17555582

17. Ottmann OG, Wassmann B, Pfeifer H, Giagounidis A, Stelljes M, Dührsen U, et al. Imatinib compared with chemotherapy as front-line treatment of elderly patients with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ALL). Cancer. 2007; 109(10): 2068–2076. https://doi.org/10.1002/cncr.22631 PMID: 17429836

18. Yanada M, Sugiura I, Takeuchi J, Akiyama H, Maruta A, Ueda Y, et al. Prospective monitoring of BCR-ABL1 transcript levels in patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia undergoing imatinib-combined chemotherapy. Br J Haematol. 2008; 143(4): 503–510. https://doi.org/10.1111/j.1365-2141.2008.07377.x PMID: 18986386

19. Lee S, Kim YJ, Chung NG, Lim J, Lee DG, Kim HJ, et al. The extent of minimal residual disease reduction after the first 4-week imatinib therapy determines outcome of allogeneic stem cell transplantation in adults with Philadelphia chromosome-positive acute lymphoblastic leukemia. Cancer. 2009; 115(3): 561–570. https://doi.org/10.1002/cncr.24026 PMID: 19117346

20. Chen H, Liu KY, Xu LP, Liu DH, Chen YH, Zhao XY, et al. Administration of imatinib after allogeneic hematopoietic stem cell transplantation may improve disease-free survival for patients with Philadelphia chromosome-positive acute lymphobla stic leukemia. J Hematol Oncol. 2012; 5: 29. https://doi.org/10.1186/1756-8722-5-29 PMID: 22682059

21. Ravandi F, Jorgensen JL, Thomas DA, O'Brien S, Garris R, Faderl S, et al. Detection of MRD may predict the outcome of patients with Philadelphia chromosome-positive ALL treated with tyrosine kinase inhibitors plus chemotherapy. Blood. 2013; 122(7): 1214–1221. https://doi.org/10.1182/blood-2012-11-466482 PMID: 23836561

22. Wang J, Huang X, Jiang B, Qin Y, Bao L, Jiang H, et al. [Molecular response and prognostic factors of patients with Philadelphia chromosome/BCR-ABL-positive acute lymphoblastic leukemia treated by imatinib with chemotherapy]. Zhonghua Xue Ye Xue Za Zhi. 2014; 35(2): 120–125. https://doi.org/10.3760/cma.j.issn.0253-2727.2014.02.013 PMID: 24606652

23. Lussana F, Intermesoli T, Gianni F, Boschini C, Masciulli A, Spinelli O, et al. Achieving Molecular Remission before Allogeneic Stem Cell Transplantation in Adult Patients with Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia: Impact on Relapse and Long-Term Outcome. Biol Blood Marrow Transplant. 2016; 22(11): 1983–1987. https://doi.org/10.1016/j.bbmt.2016.07.021 PMID: 27492792

24. Short NJ, Jabbour E, Sasaki K, Patel K, O'Brien SM, Cortes JE, et al. Impact of complete molecular response on survival in patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. Blood. 2016; 128(4): 504–507. https://doi.org/10.1182/blood-2016-03-707562 PMID: 27235138

25. Nishiwaki S, Imai K, Mizuta S, Kanamori H, Ohashi K, Fukuda T, et al. Impact of MRD and TKI on allogeneic hematopoietic cell transplantation for Ph+ALL: a study from the adult ALL WG of the JSHCT. Bone Marrow Transplant. 2016; 51(1): 43–50. https://doi.org/10.1038/bmt.2015.217 PMID: 26389833

26. Kuang P, Liu T, Pan L, Zhu H, Wu Y, Ye Y, et al. Sustaining integrating imatinib and interferon-α into maintenance therapy improves survival of patients with Philadelphia positive acute lymphoblastic leukemia ineligible for allogeneic stem cell transplantation. Leuk Lymphoma. 2016; 57(10): 2321–2329. https://doi.org/10.3109/10428194.2016.1144882 PMID: 26879808

27. Bao XB, Cai WZ, He XF, Chen SN, Qiu HY, Sun AN, et al. [Risk Factors of Leukemia-free Survival in Ph (+) ALL Patients with Allogeneic Hematopoietic Stem Cell Transplantation]. Zhongguo Shi Yan Xue Ye Xue Za Zhi. 2017; 25(6): 1787–1792. https://doi.org/10.7534/j.issn.1009-2137.2017.06.038 PMID: 29262917

28. Xue YJ, Cheng YF, Lu AD, Wang Y, Zuo YX, Yan CH, et al. Allogeneic Hematopoietic Stem Cell Transplantation, Especially Haploidentical, May Improve Long-Term Survival for High-Risk Pediatric Patients with Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia in the Tyrosine Kinase Inhibitor Era. Biol Blood Marrow Transplant. 2019; 25(8): 1611–1620. https://doi.org/10.1016/j.bbmt.2018.12.007 PMID: 30537550

29. Wang J, Jiang Q, Xu LP, Zhang XH, Chen H, Qin YZ, et al. Allogeneic Stem Cell Transplantation versus Tyrosine Kinase Inhibitors Combined with Chemotherapy in Patients with Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia. Biol Blood Marrow Transplant. 2018; 24(4): 741–750. https://doi.org/10.1016/j.bbmt.2017.12.777 PMID: 29247779

30. Zhao X, Zhao X, Chen H, Qin Y, Xu L, Zhang X, et al. Comparative Analysis of Flow Cytometry and RQ-PCR for the Detection of Minimal Residual Disease in Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia after Hematopoietic Stem Cell Transplantation. Biol Blood Marrow Transplant. 2018; 24(9): 1936–1943. https://doi.org/10.1016/j.bbmt.2018.03.015 PMID: 29572111

31. Pfeifer H, Raum K, Markovic S, Nowak V, Fey S, Obländer J, et al. Genomic CDKN2A/2B deletions in adult Ph(+) ALL are adverse despite allogeneic stem cell transplantation. Blood. 2018; 131(13): 1464–1475. https://doi.org/10.1182/blood-2017-07-796862 PMID: 29348129

32. Yang F, Cai WZ, Huang XW, Xue SL, Fu CC, Tang XW, et al. [Comparison of efficacy of first-line administration of generic dasatinib or imatinib in patients with Philadelphia chromosome positive acute lymphoblastic leukemia treated by hematopoietic stem cell transplantation]. Zhonghua Xue Ye Xue Za Zhi. 2018; 39(8): 661–667. https://doi.org/10.3760/cma.j.issn.0253-2727.2018.08.010 PMID: 30180468

33. Huang AJ, Wang LB, Du J, Tang GS, Cheng H, Gong SL, et al. [Efficacy of Hyper-CVAD/MA and CHALL-01 regimens in the treatment of Philadelphia chromosome-positive adult acute lymphoblastic leukemia patients under 60 years old]. Zhonghua Xue Ye Xue Za Zhi. 2019; 40(8): 625–632. https://doi.org/10.3760/cma.j.issn.0253-2727.2019.08.001 PMID: 31495127

34. Candoni A, Rambaldi A, Fanin R, Velardi A, Arcese W, Ciceri F, et al. Outcome of Allogeneic Hematopoietic Stem Cell Transplantation in Adult Patients with Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia in the Era of Tyrosine Kinase Inhibitors: A Registry-Based Study of the Italian Blood and Marrow Transplantation Society (GITMO). Biol Blood Marrow Transplant. 2019; 25(12): 2388–2397. https://doi.org/10.1016/j.bbmt.2019.07.037 PMID: 31400502

35. Tang SH, Lu Y, Zhang PS, Liu XH, Du XH, Chen D, et al. [Ikaros family zinc finger 1 mutation is a poor prognostic factor for adult Philadelphia chromosome positive acute lymphoblastic leukemia]. Zhonghua Nei Ke Za Zhi. 2019; 58(4): 301–306. https://doi.org/10.3760/cma.j.issn.0578-1426.2019.04.012 PMID: 30917424

36. Abou Dalle I, Kantarjian HM. Philadelphia chromosome-positive acute lymphoblastic leukemia at first relapse in the era of tyrosine kinase inhibitors. Am J Hematol. 2019; 94(12): 1388–1395. https://doi.org/10.1002/ajh.25648 PMID: 31595534

37. Fedullo AL, Messina M, Elia L, Piciocchi A, Gianfelici V, Lauretti A, et al. Prognostic implications of additional genomic lesions in adult Philadelphia chromosome-positive acute lymphoblastic leukemia. Haematologica. 2019; 104(2): 312–318. https://doi.org/10.3324/haematol.2018.196055 PMID: 30190342

38. Shen S, Chen X, Cai J, Yu J, Gao J, Hu S, et al. Effect of Dasatinib vs Imatinib in the Treatment of Pediatric Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia: A Randomized Clinical Trial. JAMA Oncol. 2020; 6(3): 358–366. https://doi.org/10.1001/jamaoncol.2019.5868 PMID: 31944221

39. Gu B, Shi BY, Zhang X, Zhou SY, Chu JH, Wu XJ, et al. Allogeneic haematopoietic stem cell transplantation improves outcome of adults with relapsed/refractory Philadelphia chromosome-positive acute lymphoblastic leukemia entering remission following CD19 chimeric antigen receptor T cells. Bone Marrow Transplant. 2020; https://doi.org/10.1038/s41409-020-0982-6 PMID: 32581286

40. Li SQ, Fan QZ, Xu LP, Wang Y, Zhang XH, Chen H, et al. Different Effects of Pre-transplantation Measurable Residual Disease on Outcomes According to Transplant Modality in Patients With Philadelphia Chromosome Positive ALL. Front Oncol. 2020; 10: 320. https://doi.org/10.3389/fonc.2020.00320 PMID: 32257948

41. Berry DA, Zhou S, Higley H, Mukundan L, Fu S, Reaman GH, et al. Association of Minimal Residual Disease With Clinical Outcome in Pediatric and Adult Acute Lymphoblastic Leukemia: A Meta-analysis. JAMA Oncol. 2017; 3(7): e170580. https://doi.org/10.1001/jamaoncol.2017.0580 PMID: 28494052

42. Bassan R, Brüggemann M, Radcliffe HS, Hartfield E, Kreuzbauer G, Wetten S. A systematic literature review and meta-analysis of minimal residual disease as a prognostic indicator in adult B-cell acute lymphoblastic leukemia. Haematologica. 2019; 104(10): 2028–2039. https://doi.org/10.3324/haematol. 2018.201053 PMID: 30890593

43. Pfeifer H, Cazzaniga G, van der Velden VHJ, Cayuela JM, Schäfer B, Spinelli O. Standardisation and consensus guidelines for minimal residual disease assessment in Philadelphia-positive acute lymphoblastic leukemia (Ph + ALL) by real-time quantitative reverse transcriptase PCR of e1a2 BCR-ABL1. Leukemia. 2019; 33(8): 1910–1922. https://doi.org/10.1038/s41375-019-0413-0 PMID: 30858550