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Prognostic value of the response to prednisone for children with acute lymphoblastic leukemia: a meta-analysis

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Abstract. – OBJECTIVE: To systematically review prednisone induced test results in the prognosis assessment of acute lymphoblastic leukemia in children.

MATERIALS AND METHODS: Based on the established inclusion and exclusion criteria, studies of prednisone induced test in evaluating the prognosis of childhood acute lymphoblastic leukemia were electronically searched from January 1990 to November 2016 using Pubmed, Embase, The Cochrane Library, Web of Science, WanFang, VIP, and CNKI database. Two independent researchers browsed literature, extracted data and assessed the risk of bias of studies. Meta-analysis was performed using RevMen 5.3 software. A total of 17 articles were included.

RESULTS: Meta-analysis showed that after complete prednisone induced test in children, 5y-EFS, 8y-EFS adverse reactions, persistent remission and relapse were statistically significant differences between the prednisone good response (PGR) and prednisone poor response (PPR). There were statistical significance in T cell immune typing and the initial WBC of the two groups. Prognosis of prednisone good response group is better than prednisone poor response group.

CONCLUSIONS: The prednisone induction test is an important factor in predicting the prognosis of children with ALL.

Key Words:
Prednisone, Lymphoblastic, Leukemia acute childhood, Prognosis.

Introduction

Acute lymphoblastic leukemia (ALL) is the most common malignant tumor in children. The cure rate of children with acute lymphoblastic leukemia is higher than 80%, which is closely related to the risk stratification and the progress of supportive therapy [1,2]. Glucocorticoids are essential drugs in all treatments because they induce apoptosis in leukemic cells [3,4]. The responsiveness of glucocorticoids affects the prognosis of patients. In the ALL-BFM83 trial, the BFM (the Berlin-Frankfurt-Münster) cooperative group began to find prednisone response can be used to evaluate the early prognosis of children with ALL. For all ALL diagnosed children, after orally taken prednisone for 7 days and methotrexate injection 1 once, the peripheral blood immature cell count was measured at the 8th day. If the number of immature cells in peripheral blood was < 1000/ul, then this indicated the good response to prednisone (PGR). If immature cells in peripheral blood were ≥ 1000/ul, this indicated adverse reactions to PGR[5]. This was used in BFM-86, BFM90 experiments. The prednisone response has been considered a prognostic factor for childhood acute lymphoblastic leukemia and is included in the criteria for risk stratification[6]. Currently, the prednisone induction test is the most commonly used test of hormone responsiveness. Multiple studies have shown that the long-term event free survival rate (EFS) of patients with prednisone adverse reactions is worse than that of positive reactions[7-20]. This study conducted a meta-analysis of the results of the prednisone induced test published online.

Materials and Methods

Materials Search

WE searched on PubMed, Embase, Cochrane Library, VIP (www.cqvip.com/), Wanfang (wanfangdata.com.cn), CNKI (www.cnki.net) according to the inclusion criteria. The reference literature was tracked, and the search time was set until November 2016. No language or national restrictions were limited.

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Inclusion and Exclusion Criteria

Inclusion criteria: (1) The subjects were patients who were first diagnosed with acute lymphoblastic leukemia and who had not received chemotherapy according to the international MIC standard; (2) The patients were younger than 18 years; (3) The study type was cohort study; (4) The interventions were oral prednisone for 7 days and intrathecal injection 1 time; (5) The primary outcome measures were event-free survival (EFS), relapse, and continuous complete remission rate (CCRR).

Exclusion criteria: (1) Repeated studies of the same population data; (2) Reference with limit data and information; (3) Reference with no conclusion; (4) Children with steroid hormone before the onset.

Reference Screening

All references were screened independently by 2 researchers. Firstly, case reports, reviews, systematic reviews, and repetitive literature were excluded, Secondly, the titles and abstracts were screened, and then the full text was also screened.

Materials Extraction

The extraction included: (1) Authors, titles, years and journals; (2) Designs sample sizes and case characteristics; (3) In each study, the two groups were evaluated for EFS rates. In case of disagreement, the third researcher had to assist in the settlement of the dispute.

Quality Evaluation

Quality evaluation was carried out according to the Newcastle-Ottawa quality evaluation criteria, mainly from the selection of the queue, comparability and results measurement. The evaluation criteria included: (1) queue selection: a. representation of exposed cohort; b. selection of non-exposed queues; c. determination of exposure; d. at the start of the study, no disease was found. (2) Comparability between exposed and non-exposed cohorts (design and analysis sessions). (3) Results: (a) results determination method; (b) were the follow-up periods long enough for the studied disease? (c) follow-up integrity.

Outcome Index

The primary outcome measure was EFS, which means patients from the diagnosis, to the end of the follow-up, or the first event. Event included relapse, death, second tumors, and refractory ALL. Secondary outcome included relapse and sustained remission in the two groups. Other indicators were sex, initial leukocyte count, and T-cell markers.

Statistical Analysis

RevMan 5.3 statistical software was used for meta-analysis. The observed indexes were all measured data ± s. The mean difference was used as the effect index, and to each effect quantity was given a point estimation value and 95% confidence interval. The heterogeneity of the included results was analyzed by x^2-test and I^2 was used to quantify the size of the atypia. For no statistically significant differences between heterogeneous groups, a fixed effect model was used. For the presence of statistically significant heterogeneity between groups, after excluding the apparent clinical heterogeneity, a random effect model was used to incorporate effects. Subgroup analysis or sensitivity analysis was performed on clinically significant heterogeneity, and the meta-analysis was performed at $\alpha = 0.05$.

Results

Search Results

A total of 1839 articles were searched, and 16 articles were included according to the inclusion criteria (Figure 1). They were all cohort studies, including 14897 children with prednisone good reaction (13356 cases) and prednisone adverse reaction (1541 cases) (Figure 1).

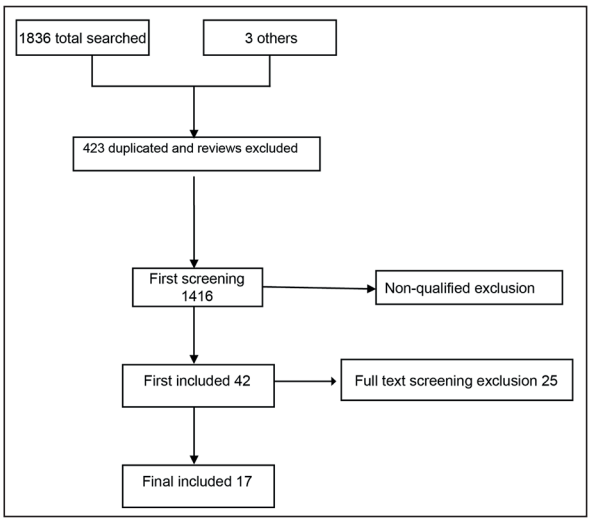

Figure 1. Reference search process.

Quality Evaluation

Quality evaluation was carried out according to the Newcastle-Ottawa quality evaluation criteria. Cohort selection: all two groups of patients enrolled in the literature actually represented the prognosis of the children with ALL. The two cohorts, from the same population, had reliable records of sources of exposure (prednisone induced trials), and no initial outcome was observed. The references[21,22] did not mention lost follow-up (* -); the references[21,23-25] indicated short duration of follow-up.

Results of Meta-analysis

EFS Rate

7 of these documents reported a comparison of the prednisone test results with a 5-year event-free survival rate (5y-EFS) in pediatric patients with acute lymphoblastic leukemia. Meta-analysis showed that the 5y-EFS of the children with ALL had a good response to prednisone and the other two groups with poor response to prednisone, and the differences were statistically significant (MD = 22.03, 95% CI (18.87,25.18), $p < 0.000001$, Heterogeneity test: $p = 0.0002$, I2 = 74%). 2 references reported 8-years of event-free survival rate (8y-EFS) in the two groups, and meta-analysis showed statistically significant differences between the two groups of 8y-EFS (MD = 27.9, 95% CI (20.94,34.85), $p < 0.00001$, Heterogeneity test: $p = 0.22$, I2 = 34%) (Figure 2). The heterogeneity of the two groups of 5y-EFS was higher. Subgroup analysis was performed according to the stratified standard of the child, and its heterogeneity decreased from the original I2 = 74% to I2 < 50%, which indicated that the difference was statistically significant (Figure 3).

CCRR

6 references reported a CCRR of two groups of children, and the meta-analysis showed statistically significant difference (OR = 4.82, 95% CI (2.81, 8.29), $p < 0.00001$) (Figure 4).

Relapse

7 references reported relapse in the two groups, and meta-analysis showed statistically significant difference (OR = 0.26, 95% CI (0.11, 0.59), $p = 0.001$) (Figure 5).

T Cell Immunophenotyping

5 references reported two groups of T cell immune expression, and meta-analysis showed that the difference between the two groups of T expression was statistically significant (RR=0.30, 95% CI (0.20, 0.44), $p < 0.00001$) (Figure 6).

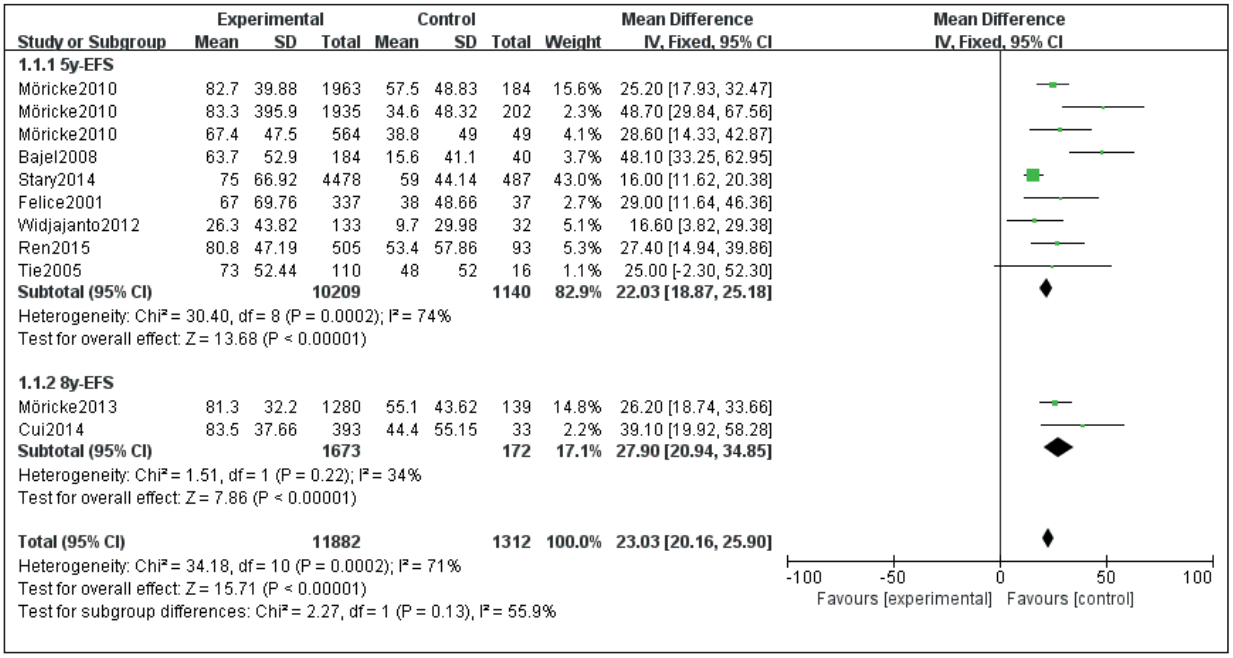

Figure 2. The prednisone group responded well to the prednisone response group, and the results of 5y-EFS and 8y-EFS were compared.

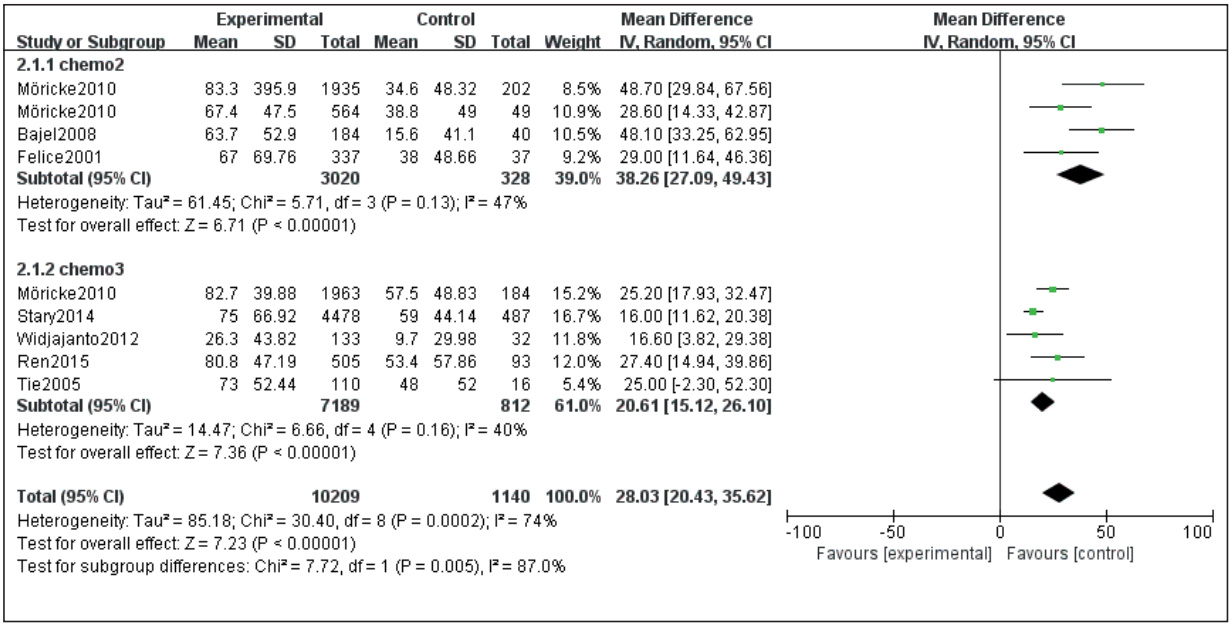

Figure 3. Different subgroups analysis on PGR and PPR 5y-EFS according to stratified chemotherapy.

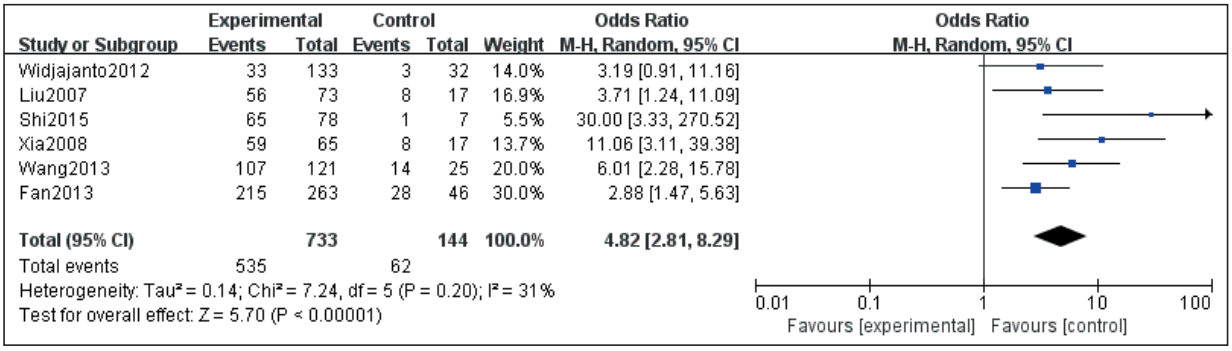

Figure 4. Comparison of continuous complete remission between PGR and PPR.

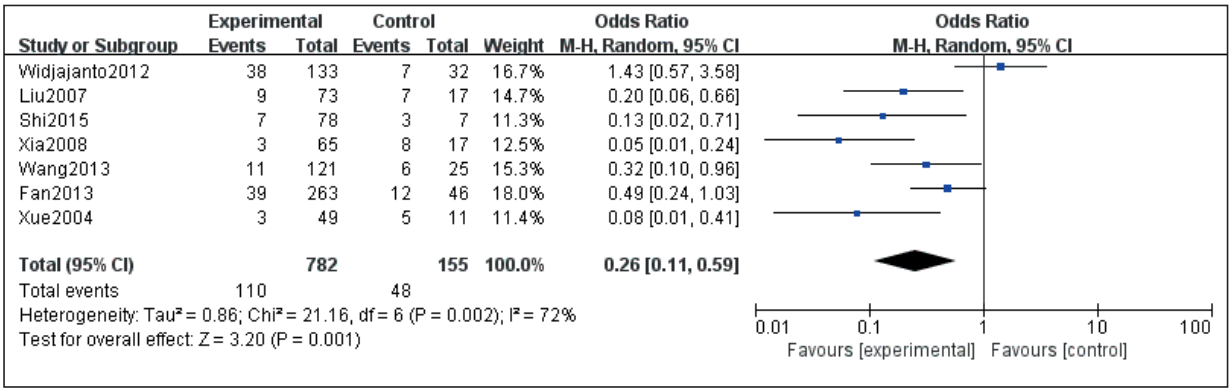

Figure 5. Comparison of relapse between PGR and PPR.

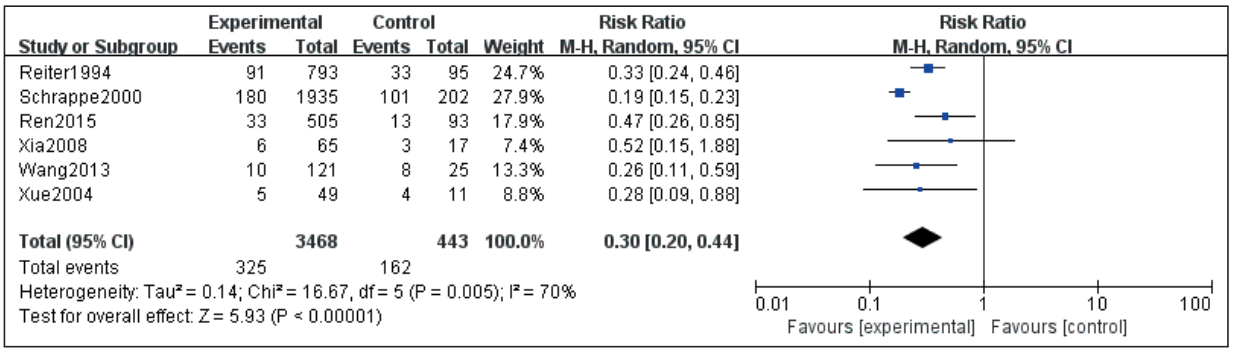

Figure 6. Comparison of T cell-mediated immunity in PGR and PPR.

Initial Peripheral Blood White Blood Count

5 references reported the clinical characteristics of two groups of initial peripheral blood leukocyte count. The meta-analysis showed that the difference was statistically significant (OR = 0.11, 95% CI (0.08, 0.16), $p < 0.00001$) (Figure 7).

Sex

3 references reported the clinical characteristics of the two groups of children, and the meta-analysis showed no statistically significant difference between the two groups (OR = 0.89, 95% CI (0.62, 1.28), $p = 0.53$; Heterogeneity test: $p = 0.23$, I2 = 32%) (Figure 8).

D19 Days Bone Marrow Response

2 references reported the bone marrow reaction of two groups with chemotherapy at d 19, in which the expression of bone marrow response at d 19 between two groups was M1, and the difference of M2 was statistically significant. Meta-analysis showed that two groups of M1 comparison results were (OR = 8.35, 95% CI (2.85, 25.52), $p = 0.0001$; Heterogeneity test: $p = 0.97$, I2 = 0%). M2 comparison results were (OR = 0.12, 95% CI (0.03, 0.39), $p = 0.0005$; Heterogeneity test: $p = 0.56$, I2 = 0%). Meta-analysis showed that the expression of M3 in the two groups was not statistically significant (OR = 0.24, 95% CI (0.04, 1.44), $p = 0.12$; Heterogeneity test: $p = 0.34$, I2 = 0%) (Figure 9).

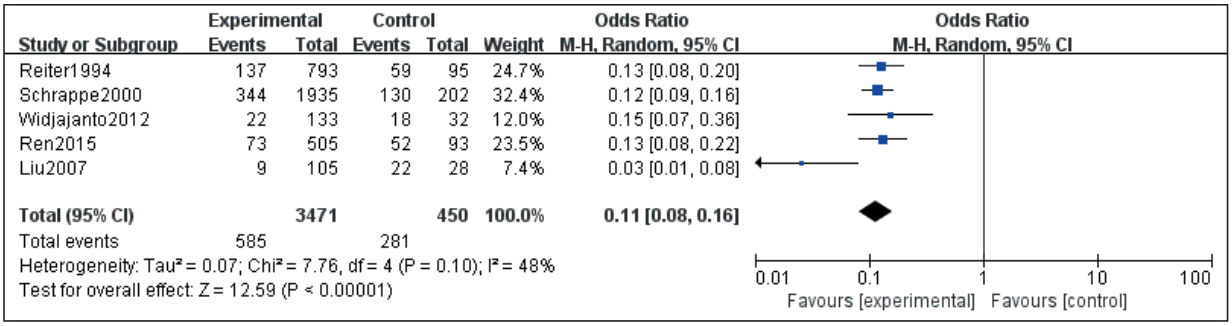

Figure 7. Comparison of initial peripheral blood leukocyte count > 50×10^9 between PGR and PPR.

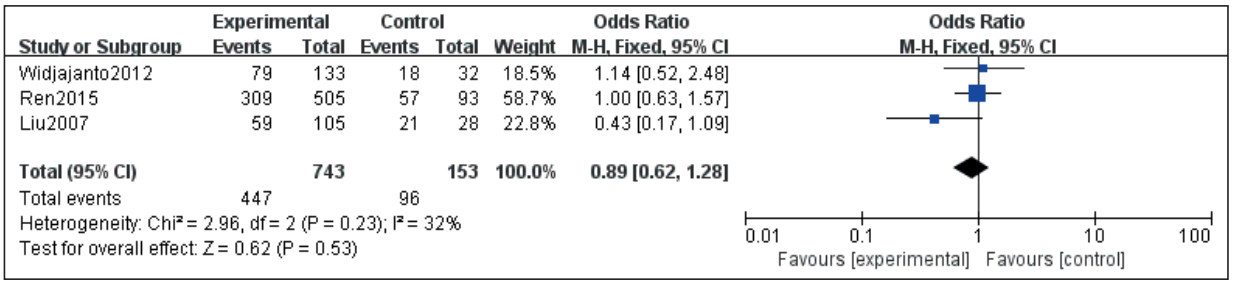

Figure 8. Sex comparison between PGR and PPR.

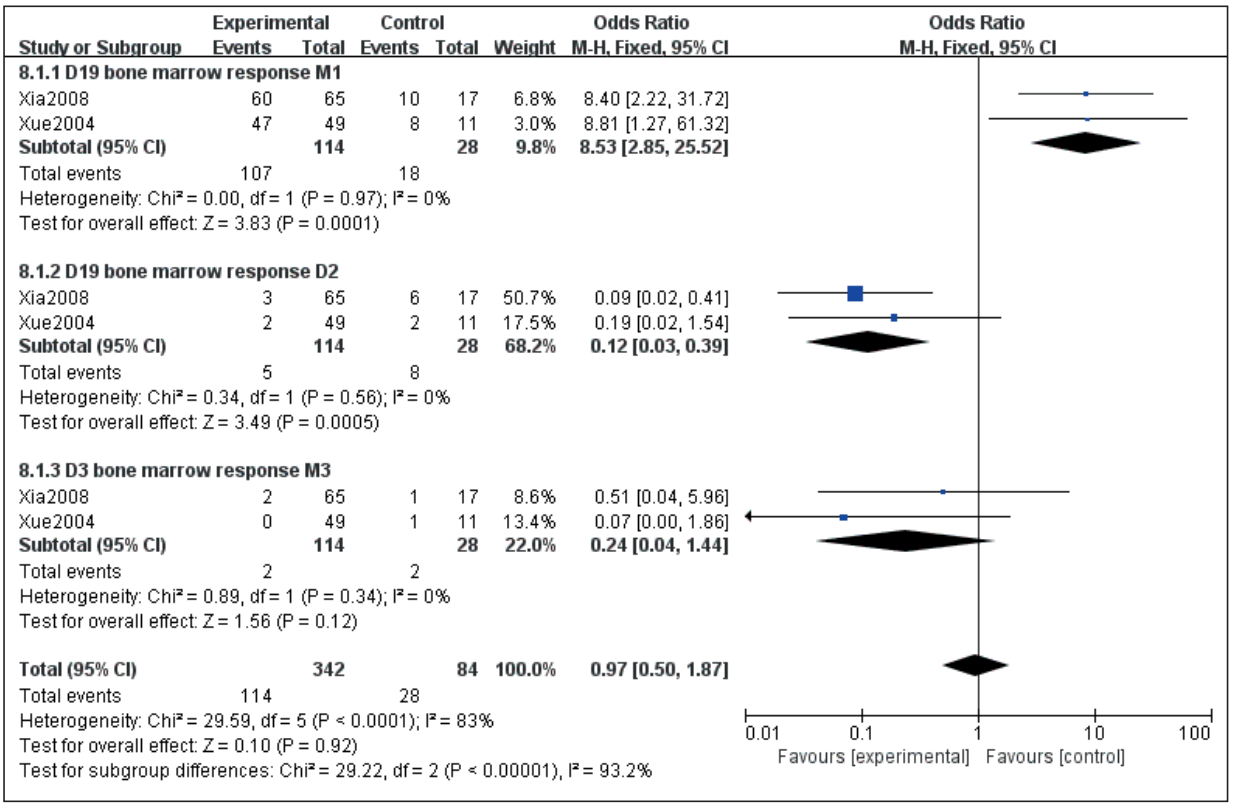

Figure 9. Comparison of d 19 bone marrow responses in PGR and PPR.

Discussion

Acute lymphoblastic leukemia accounts for about 70%-85% of leukemia in children, and its occurrence rate is far higher than that of adults[26,27]. There were a lot of researches about prognostic factors for ALL children in the world, the main factors affecting the prognosis including initial white blood cell count, gender, immunophenotype, cytogenetics, early response to therapy

Table I. General data.

Authors	Year	PGR/PPR	Type	Conclusion
Möricke et al[9]	2013	1280/139	Cohort study	EFS
Felice et al[10]	2001	337/37	Cohort study	EFS
Widjajanto et al[11]	2012	133/32	Cohort study	EFS, CCR, Relapse
Möricke et al[12]	2010	2527/233	Cohort study	EFS
Reiter et al[13]	1994	793/95	Cohort study	EFS
Bajel et al[14]	2008	184/40	Cohort study	EFS
Stary et al[15]	2014	4478/487	Cohort study	EFS
Schrappe et al[16]	2000	1935/202	Cohort study	EFS
Cui et al[17]	2014	393/33	Cohort study	EFS
Tie et al[18]	2005	110/16	Cohort study	EFS
Ren et al[19]	2015	505//93	Cohort study	EFS
Xue et al[20]	2004	49/11	Cohort study	Relapse
Fan et al[21]	2013	263/46	Cohort study	CCR, Relapse
Liu et al[22]	2007	105/25	Cohort study	EFS, CCR, Relapse
Wang et al[23]	2013	121/25	Cohort study	CCR, Relapse
Xia et al[24]	2008	65/17	Cohort study	CCR, Relapse
Shi et al[25]	2015	78/7	Cohort study	CCR, Relapse

(prednisone d 19, d 33 test, bone marrow response, MRD), etc.[23,28]. The prednisone-induced test was distinguished by the number of peripheral blood cells at d 8 after oral prednisone, resulting in prednisone good-response (PGR) and prednisone poor-response (PPR)[29]. In this research, we enrolled the patients with an initial onset of peripheral blood immature cell number less than 1000/ul into a prednisone responsive group. No subgroup analysis was performed. It has been showed[10] that in PGR group, regardless of the number of initial peripheral blood immature cells, the prognosis between the two subgroups was not statistically different. In some researches[30], the results were divided into 3 groups according to the prednisone induction test (highly sensitive 0/ul, sensitive 1-999/ul, poor ≥ 1000/ul). It was believed that the EFS rate in highly sensitive 0/ul group was significantly higher than the other patients; the difference was statistically significant. Moreover, Manabe et al[30] suggested no statistical difference of EFS rate between B and T ALL children in highly sensitive group. The prednisone-induced test can be an independent predictor of poor prognosis. The groups of peripheral blood blast count ≥ 1000/ul and < 1000 ul had no further analysis. This standard classification is different from this study, therefore not included in this work. Glucocorticoid is an important chemotherapeutic agent in the treatment of ALL children [31]. Glucocorticoid plays the role mainly through glucocorticoid receptor (GR), after entering the cell cytoplasm and the receptor (GR) binding induced receptor activation, combined by reaction with specific glucocorticoid components, so that the target gene is transcriptional activated or inhibited, induced cell cycle arrest or apoptosis[1,32,33]. For children with acute lymphoblastic leukemia, the glucocorticoid response is poor and is a negative prognostic indicator [32]. In the clinical practice, the individual sensitivity of children to glucocorticoids is significantly different. Even in new cases, approximately 20% of ALL children are resistant to glucocorticoids, which is related to the quantity and quality of GR. In children with ALL chemotherapy, the use of hormones is also evolving. In the references involved in this study, there were specific implementation methods of prednisone induced test, such as oral prednisone, some oral dexamethasone, but all regarding to the peripheral blood cell numbers at d 8 to show the sensitivity. However, it is not obvious to the final result whether there are statistical differences. This study included a total of 17 references. The results showed prednisone good response in children with 5y-EFS, 8y-EFS is better than prednisone poor response. The continuous remission rate in the PGR group was higher than that in the PPR group, and the relapse rate was low. The difference was statistically significant. For the PPR group, the high-risk stratified markers were greater than those in the PGR group. This study analyzed the T cell markers, the initial peripheral blood leukocyte count, and the sex characteristics. The immunophenotype of T cells and the initial peripheral blood leucocytes in PPR group were significantly higher than those in PGR group, and the difference was statistically significant. However, there were no statistically significant differences in gender (male) characteristics between the two groups. For the two groups of d 19 bone marrow reactions, the two groups showed statistical difference between M1 and M2, and no statistical difference between the two groups of expressions of M3. The heterogeneity of the literature included in this study may be inconsistent with the subject race, the risk stratification of the disease, and the specific implementation of the chemotherapy protocols. Moreover, since the included studies are cohort studies with low levels of evidence, there may be selection bias.

Conclusions

In children with ALL, prednisone induced test can response to hormone sensitivity; prednisone poor response was unfavorable factor in ALL prognosis, which had important clinical significance in childhood ALL by hierarchical chemotherapy.

Acknowledgements

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Conflict of Interest

The Authors declare that they have no conflict of interests.

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