Efficacy of Allogeneic Hematopoietic Stem Cell Transplantation in Relapse/Refractory B-ALL Patients After Chimeric Antigen Receptor T Cell Therapy: A Systematic Review and Meta-analysis

Linyan Tian
Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Tianjin's Clinical Research Center for Cancer
Jinhuan Wang
Second Hospital of Tianjin Medical University
Yixin Zhai
Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Tianjin's Clinical Research Center for Cancer
Su Liu
Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Tianjin's Clinical Research Center for Cancer
Yanan Jiang
Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Tianjin's Clinical Research Center for Cancer
Wenqi Wu
Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Tianjin's Clinical Research Center for Cancer
Yangyang Lv
Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Tianjin's Clinical Research Center for Cancer
Donghui Xing
Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Tianjin's Clinical Research Center for Cancer
Hong Xu
Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Tianjin's Clinical Research Center for Cancer
Huimeng Sun
Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Tianjin's Clinical Research Center for Cancer
Yafei Wang
Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Tianjin's Clinical Research Center for Cancer
Zhigang Zhao (zzhao01@tmu.edu.cn)
Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Tianjin's Clinical Research Center for Cancer

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Abstract

Background: Allogeneic hematopoietic stem cell transplantation(allo-HSCT) consolidation therapy after chimeric antigen receptor(CAR) T cell therapy has emerged as an alternative in patients with B-ALL in the past decade. However, the efficiency remains unclear. In this study, we aimed to systematically analysis the effect of allo-HSCT for Relapse/Refractory(R/R) B-ALL patients after CAR-T cell therapy on survival and relapse rate(RR).

Methods: We searched potential documents up to Jan.31st, 2021 in PUBMED, EMBASE, Cochrane Library and Springer and analyzed them by Cochrane Collaboration RevMan 5.3 software.

Results: Allo-HSCT was efficient in improving short(6-month) and long(1-year and 2-year) term overall survival(OS) and leukemia-free survival(LFS). Transplantation could also reduce RR of R/R B-ALL regardless of patients' characteristics and time of allo-HSCT. Besides, CAR-T cell products with 4-1BB domain bridging allo-HSCT were associated with a better survival. Subgroup analysis indicated allo-HSCT was more likely to exert a noticeable influence on survival of junior individuals(≤40) and Asian groups. A suitable period between allo-HSCT and CAR-T cell therapy(≤70 days) would make a difference. Interestingly, some features of patients, such as a HSCT history or BCR-ABL1 rearrangement (Philadelphia chromosome, Ph) may have an effect on the efficacy of allo-HSCT.

Conclusion: Allo-HSCT consolidation therapy after CAR-T cell therapy induced a promising short-and-long term survival of R/R B-ALL patients. Senior patients, prior HSCT history and BCR-ABL1 rearrangement (Ph) might be poor prognostic factors. Further studies are needed to explore the optimal time for allo-HSCT.

Background

Acute B-cell lymphoblastic leukemia (B-ALL), tending to disturb the young, is regarded as the most common cancer in pediatric patients[1, 2].Although different new agents come out, combination chemotherapy with vincristine, corticosteroids and anthracycline[3] serves as the backbone of treatment in B-ALL patients, however, around 15-20% adults eventually suffer from an inevitable relapse[4, 5].As for R/R B-ALL patients, consolidative allo-HSCT is more likely to be an option after high dose chemotherapy or a salvage regimen after relapse[6].

In recent years, the booming of CAR-T cell therapy has given hope to patients with R/R B-ALL with a complete remission(CR) of 70-90%[2, 7, 8]. CAR-T cell therapy induces high initial remission rates but no evidence indicates it can improve disease free survival(DFS) and 40-50% patients usually relapse within one year[9, 10]. Patients who achieve CR after CAR-T cell therapy often come across a dilemma when some of them are advised to undergo transplantation. In light of published clinical trials, allo-HSCT consolidation has been used in R/R B-ALL patients after CAR-T cell therapy and performed a favorable prognosis concerning efficiency and safety[11]. However, whether allo-HSCT consolidation is associated with a more durable remission and a better survival remains equivocal[12, 13].

As there is no solid evidence over merits of consolidative allo-HSCT, we summarized clinical data to identify the role of allo-HSCT after CAR-T cell therapy. This review intended to explore the impact of allo-HSCT on short and long term survival as well as RR for R/R B-ALL patients after CAR-T. Moreover, we will discuss some factors which may affect the efficacy of allo-HSCT post CAR-T cell therapy.

Methods

2.1. Literature Search

We carried out the study in compliance with the standards set by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement. Eligible studies with the latest update on Jan.30,2021 were searched in Pubmed, EMBASE, Cochrane Library and Springer. Only English and Chinese publications are included. We combined Medical Subject Heading (MeSH) terms and free-text terms concerning "CAR-T" and "B-ALL" to access potential studies. Meanwhile, relevant articles in the reference are also included.

2.2. Inclusion and exclusion criteria

The studies were included if they met the following criteria:(1)studies must have two arms of R/R B-ALL patients in which one arm used allo-HSCT whereas the other didn't use allo-HSCT after CAR-T;(2)studies must have reported at least one of the three outcomes in both arms: OS, LFS and RR;(3)patients with CR after CAR-T cell therapy were bridged to allo-HSCT or not.(4)sufficient data was provided in abstract although the full text was not available.

The exclusion criteria were (1) reviews, viewpoints, perspectives or correspondences; (2) lack of effective data of outcome as described above for two arms; (3) basic research or animal studies ;(4) duplicated publications.

2.3. Study Qualitative Assessment

We adopt the Methodological Index for Non-randomized Studies(MINORS) to assess the quality of the inclusive studies[14]. As all studies involved are non-randomized studies, MINORS is a scoring tool for evaluation of both internal and external validity.

2.4. Data Extraction

Two authors independently collected and extracted the following information: first author, publication year, number of patients in different groups, details of treatments (costimulatory domain, days between CAR-T cell therapy and allo-HSCT, dose of CAR-T cells), patient characteristics (age, ethnicity, rate of prior-

HSCT patients, patients with BCR-ABL1 rearrangement (Ph), patients with complex karyotype) and survival outcomes (OS, LFS and RR). Disputes were settled by a third reviewer or through discussion.

2.5. Statistical analysis

We use the Cochrane Collaboration RevMan 5.3 software (The Cochrane Collaboration, London, United Kingdom) to analysis therapeutic efficacy. In addition, the I^2 statistic was used to test for heterogeneity. A fixed-effect model was applied to calculate pooled effects when I^2≤50%. Otherwise, we use the random-effect model. In order to explore the source of heterogeneity, we performed subgroup analysis by middle time interval between CAR-T cell therapy and allo-HSCT(≤70 days vs ＞70 days), the proportion of patients with a HSCT history(≤20% vs ＞20%) and the rate of BCR-ABL1 rearrangement(Ph) patients(≤30% vs ＞30%).*P* values ＜0.05 were considered statistically significant. Sensitivity analysis was conducted to estimate the effect with removal of the largest sample size among all studies.

Results

3.1. Literature Search Results and Study characteristics

The flowchart shown in Fig 1 illustrated our search process. 774 results were accessible in different databases, of which 393 duplicates were excluded. Meanwhile, another 8 records available in the reference were regarded as relevant reports. In terms of the exclusion criteria above, 16 studies, involving 690 patients, were included ultimately[15-30]. Three studies which had sufficient data in abstract despite no available full text were also included.

Table 1 depicts the characteristics of the inclusive studies. All studies were two-arm clinical trials on 690 R/R B-ALL patients in total published from 2015 to 2021.The sample sizes ranged from 9 to 122.The patients' age varied across studies. The CAR-T dose ranged from 0.1×10^6 to 500×10^6（Table S1）and the median days between CAR-T cell therapy and allo-HSCT were 44-104 days. The costimulatory domain was either CD28 or 4-1BB. In respect of obtainable data, the proportion of patients with prior HSCT, BCR-ABL1 rearrangement (Ph) and complex karyotype was 0-40%, 2.1-100% and 4.9-50%,respectively. More details were shown in Table S1.

Data for OS were available in 12 studies with 558 patients[15-19, 21-24, 28-30], 8 studies of which with 446 patients in total provided data of LFS or EFS[15-17, 19, 22, 24, 29, 30]. Event was defined as no treatment failure, relapse or death. Fortunately, all objectives in the five studies reporting EFS achieved CR or CR with incomplete hematologic recovery(CRi) after CAR-T cell therapy[16, 19, 22, 29, 30]. Due to the fact that no "relapse" event occurred, the data of EFS and LFS could be merged and analyzed as LFS. With regard to the other two studies, DFS data were available rather than LFS or EFS[18, 21]. As difference existed between the definition of DFS and LFS, it was not proper to merge them all.

3.2.Study Quality

The quality of each study was assessed by the Methodological Index for Non-randomized Studies (MINORS). The detailed scores are listed in Table S2. Generally, the overall quality was adequate.

3.3.Association of allo-HSCT after CAR-T cell therapy with short or long term OS

10 studies with 512 patients reported 6-month OS[15-19, 22-24, 28, 29]. 10 studies with 485 patients reported 1-year OS[15-19, 21-24, 29]. 6 studies with 324 patients reported 2-year OS[15, 19, 22, 24, 29, 30]. As demonstrated in Fig 2, those who chose HSCT regimen after CAR-T cell therapy got a significantly better OS of both short and long term(6-month OS: odds ratio(OR)= 0.34; 95% confidence interval (CI) = 0.19–0.61; P =0.0003; 1-year OS: OR =0.24; 95% CI = 0.15–0.38; P < 0.00001; 2-year OS: OR= 0.26; 95% CI = 0.16–0.43; P < 0.00001). Since there was low heterogeneity between these studies, a fixed-effect model was applied.

Subgroup analysis（Fig 3） based on general characteristics acquired of patients such as median age, ethnicity and costimulatory domain illustrated allo-HSCT exerted a noticeable influence on survival of junior individuals(≤40) (P < 0.00001) and Asian groups(P < 0.00001).Little promotion of survival was caught in senior individuals(＞40) (P=0.1) and Caucasian groups(P=0.11). Moreover, CAR-T with 4-1BB rather than CD28 bridging allo-HSCT brought about a better survival.

Intensive study was carried out as follows in Fig 4. Subgroup analysis of 1-year OS by period between CAR-T cell therapy and allo-HSCT showed HSCT was observed to exert a marked influence on patients who received HSCT less than 70 days(P < 0.00001) whereas no obvious effect on those who received HSCT more than 70 days (P=0.31). Furthermore, allo-HSCT brought an improvement in OS in subgroups with the proportion of prior HSCT≤20%(P < 0.00001).However, no apparent improvement was observed in the other group(P=0.07). Regarding the rate of BCR-ABL1 rearrangement (Ph) patients (≤30% and ＞30%), allo-HSCT after CAR-T cell therapy did not seem to be beneficial for survival in the subgroup with more high-risk subtype patients(P=0.28). But allo-HSCT were observed to be efficacious in "≤30% "group(P < 0.00001).

3.4.Association of allo-HSCT after CAR-T cell therapy with short or long term LFS

6 studies with 307 patients reported 6-month LFS[15, 17, 19, 22, 24, 29]. 7 studies with 409 patients reported 1-year LFS[15-17, 19, 22, 24, 29]. 6 studies with 324 patients reported 2-year LFS[15, 19, 22, 24, 29, 30]. As demonstrated in Fig 5, those who chose allo-HSCT regimen after CAR-T cell therapy got a significantly better short-and-long-term LFS. (6-month LFS: OR = 0.13; 95% CI = 0.05–0.29; P < 0.00001; 1-year LFS: OR =0.19; 95% CI = 0.09–0.41; P < 0.0001; 2-year LFS: OR= 0.26; 95% CI = 0.16–0.43; P < 0.00001). A fixed-effect model was applied to analysis data of 6-month LFS and 2-year LFS while a random-effect one was applied to analysis data of 1-year LFS as I^2=55%.

After the removal of one article[16], I^2 got down to 18%. And the removal of other articles respectively didn't lead to a decrease of I^2. So the study of Zhang et al. was considered to be the source of heterogeneity. As indicated in Table S1, the proportion of patients with a complex karyotype(47.4%) was dominantly larger than that in other studies with available data. So we conjectured chromosome abnormalities might affect the efficiency of post-HSCT therapy.

Subgroup analysis(Fig 6) similar to that of 1-year OS presented that there were associations between allo-HSCT and 1-year LFS in younger groups(age ≤40，P < 0.00001) instead of older ones(age ＞40，P=0.34) and Asian（P < 0.00001）rather than Caucasian(p=0.15).As the lack of accurate data in studies concerning 1-year LFS, we conducted subgroup analysis about the relationship between costimulatory domain and 2-year LFS. CAR-T with 4-1BB (P < 0.00001) rather than CD28(P =0.15) bridging allo-HSCT improved the long-term prognosis.

In a deep analysis(Fig 7), HSCT played a significant role in improving 1-year LFS in subgroups of "period between CAR-T cell therapy and allo-HSCT no more than 70 days"(P < 0.00001), "the proportion of prior HSCT≤20%"(P < 0.00001) and "the proportion of BCR-ABL1 rearrangement (Ph)≤30%"(P < 0.00001) , yet in the other subgroups, no remarkable difference was observed.

Of note, there was an obvious inter-group difference of prior-HSCT between CART and CART+HSCT groups (P < 0.001), so it was omitted in the second subgroup analysis[15]. As shown in Fig 7 , a moderate heterogeneity existed in one of the second subgroups with the probable reason that only two studies were included with the proportion of patients with BCR-ABL1 rearrangement(Ph) was 100% for one study and 10% for the other[22, 24]. Subsequently, we removed the study of Bin Gu in the subgroup analysis as no object in this study had a prior-HSCT regimen therapy, which was more likely considered as an interference.

3.5.Relapse rate

We analyzed the potential influence of allo-HSCT in reducing RR. The outcomes were shown in Fig 8, allo-HSCT was promising in reduction of RR(I^2=32%,P < 0.00001).Subgroup analysis above illustrated allo-HSCT after CAR-T cell therapy worked in reducing RR which were not restricted by time of HSCT, a prior-HSCT history and BCR-ABL1 rearrangement (Ph).

3.6. Sensitive analysis and publication bias

In the sensitivity analysis, after removal of the largest sample size of all the studies included, the pooled OS, LFS and RR didn't change prominently.

Despite few studies involved for assessing publication bias, there was no evident publication bias as visual inspection of the funnel plot (Fig 9). The sources of potential bias were primarily a lack of blind evaluation of endpoints and a calculation of 95% CI in several studies.

Discussion

Recently, a subset of R/R B-ALL patients who underwent a CAR-T cell therapy gained molecular remissions and later achieved CR in related studies[31]. It is still under discussion if a sequent allo-HSCT should be conducted for a better prognosis. As no randomized controlled trials(RCT) was published, our meta-analysis examined 16 studies involving 690 patients and demonstrated consolidative allo-HSCT could improve both short(6 month) and long(1 year,2 year) term survival and decrease RR of R/R B-ALL patients, which supported the conclusion of the only meta-analysis published before[32]. However, it seemed not all R/R B-ALL patients could gain benefit from allo-HSCT after CAR-T cell therapy in our study.

Previous researches made multivariable analysis and represented that age was considered as a factor to impact survival after allo-HSCT therapy[15, 24]. In our study, we set the cut-off value as 40 years old(median age) for a subgroup analysis where allo-HSCT was not observed to work significantly on survival in the senior groups. Besides, they are more susceptible for adverse effect, such as graft-versus-host disease(GVHD) and severe infection[33, 34]. Hence, the senior might be precluded from allo-HSCT consolidation given an inconspicuous improvement on survival, a torturing adverse event and a high cost.

Furthermore, patients with a transplantation history were inclined to have little response to another allo-HSCT and suffer from a high risk of treatment-related mortalities even though they were fortunate enough to achieve CR after CAR-T cell therapy[22, 23, 35]. It was revealed that patients didn't show a good response to a second infusion of HSCT from the same donor[36]. In an analysis on behalf of the acute leukemia working Party of European Group for Blood and Marrow Transplantation (EBMT), 93 patients with a HSCT history underwent a second transplantation[37]. Only 6 of them kept alive at last. As for our study, patients with a HSCT history didn't show a considerable improvement on survival after allo-HSCT. So, we inferred those patients were probably suitable for a targeted therapy or other regimen rather than another transplantation as consolidation.

As one of the high-risk cytogenetic features according to AIEOP-BFM ALL 2017 protocol, BCR-ABL1 fusion gene, which results from Ph chromosome translocation reminds a poor prognosis[38].Those patients are inclined to relapse and hardly response to conventional treatments[39]. In our study, consolidative allo-HSCT barely exerted an influence on survival of patients with BCR-ABL1 rearrangement(Ph). However, in study of Gu et al., HSCT seemed beneficial for survival in patients with BCR-ABL1 rearrangement(Ph), which seems to be contradictory to our results[24]. It is in suspension which factor, "no transplantation history" or "patients with BCR-ABL1 rearrangement(Ph)", was associated to a better survival after HSCT consolidation in their research. Before more solid evidence was found, we reckoned patients with BCR-ABL1 rearrangement (Ph) should prudently choose consolidative allo-HSCT on a case-by-case basis.

Additionally, time to allo-HSCT was more likely related to survival. Present studies illustrated that shorter time from CAR-T therapy to allo-HCT was associated with a lower risk for death and a better overall survival[40, 41]. Here, we made a subgroup analysis aiming to select a suitable therapeutic window. We set the window at 60 or 65 days and no difference between subgroups was found. In our study, allo-HSCT exerted a positive effect on survival as the median time interval shorter than 70 days while no influence was observed in the other subgroup. Therefore we speculated an optional period between the two treatments

would be around 70 days for a rewarding consolidative therapy. As for other thresholds, however, we failed to make a subgroup analysis due to the limitation of data. More experimental data are warranted to settle a deadline for allo-HSCT after CAR-T cell therapy.

In conclusion, CAR-T-cell bridging allo-HSCT is capable of enhancing short and long term survival and reducing RR in suitable patients with R/R B-ALL. However, no RCT in this field is available up to now. Anyway, we hope this review could arouse more attention of professors in this field to set a standard about authoritative instructions for allo-HSCT in R/R B-ALL patients with CAR-T cell therapy. A rating scale to appraise the necessity of allo-HSCT is supposed to be performed and more details are eager to be refined as more relevant studies emerge.

Declarations

Ethics approval and consent to participate As this study was based on published data, no ethics approval was sought for the study.

Consent for publication Not applicable.

Availability of data and material All data generated or analysed during this study are included in this published article [and its supplementary information files].

Competing interests The authors declare that they have no conflict of interest.

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Authors Contributions Z.Z.G and W.Y.F designed the study. T.L.Y, W.J.H, and Z.Y.X made the statistical plan. T.L.Y and W.J.H performed the key analyses. L.S,J.Y.N, W.W.Q and X.D.H collected the data. X.H and S.H.M assisted in data interpretation and quality assessment. T.L.Y wrote the manuscript. W.J.H revised the manuscript. All authors have read and approved the manuscript.

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Tables

Table 1 Characteristics of included studies

Study	Year	No.of Patients(HSCT/non-HSCT)	Mean age(years)	Ethnicity	Costimulatory domain	Mid days between CART and HSCT	Prior HSCT(%*)	BCR-ABL1/ph+ (%*)	Outcome	MINOR
Bin Gu[24]	2020	51(30/21)	34	Asian	4-1BB	46d	0	100%	OS,LFS	24
Jia Wang[17]	2020	20(5/15)	42	Asian	4-1BB	NR	21.70%	35%	OS LFS RR	23
Houli Zhao[15]	2020	122(55/67)	27	Asian	4-1BB	66.9d	inter-group difference	18%	OS,LFS	24
YONGYONG MA[21]	2020	9(5/4)	34	Asian	4-1BB	104d	NR	22.20%	OS	21
Xian Zhang[16]	2020	102(75/27)	12	Asian	4-1BB+CD28	63d	14.50%	13.70%	OS,LFS,RR	22
Noelle V. Frey[29]	2019	24(9/15)	35	Caucasian	4-1BB	78d	NR	9%	OS,LFS	21
Huiwen Jiang, Ph.D[22]	2019	47□21/26□	30	Asian	NR	44d	5.20%	10.34%	OS,LFS	22
Kevin A. Hay[23]	2019	45(18/27)	45	Caucasian	4-1BB	70d	40%	20%	OS	21
Tu[18]	2019	22(8/14)	36	Asian	CD28	45d	24%	36%	OS,RR	22
Zuo[30]	2019	37(25/12)	8	Asian	CD28	NR	6.25%	2.10%	OS,LFS,RR	23
Jae H. Park, M.D[19]	2018	43(17/26)	44	Caucasian	CD28	74d	36.00%	30.20%	OS,LFS,RR	23
Zhimin Zhai[27]	2018	25(4/21)	NR	Asian	4-1BB	NR	NR	NR	RR	21
Olivia C. Finney[25]	2018	38(13/25)	NR	Caucasian	4-1BB	NR	NR	NR	RR	23
J Pan[20]	2017	41(23/18)	11	Asian	4-1BB	84d	38.20%	NR	RR	23
DW Lee III[26]	2016	28(21/7)	54	Caucasian	CD28	54d	NR	9.40%	RR	19
Jae H Park[28]	2015	36(12/24)	45	Caucasian	CD28	NR	39%	32%	OS	21

Abbreviations: OS: overall survival, LFS:leukemia-free survival, RR: relapse rate, NR: not reported

*: the proportion of enrolled patients with a HSCT history or BCR-ABL/ph+

Figures

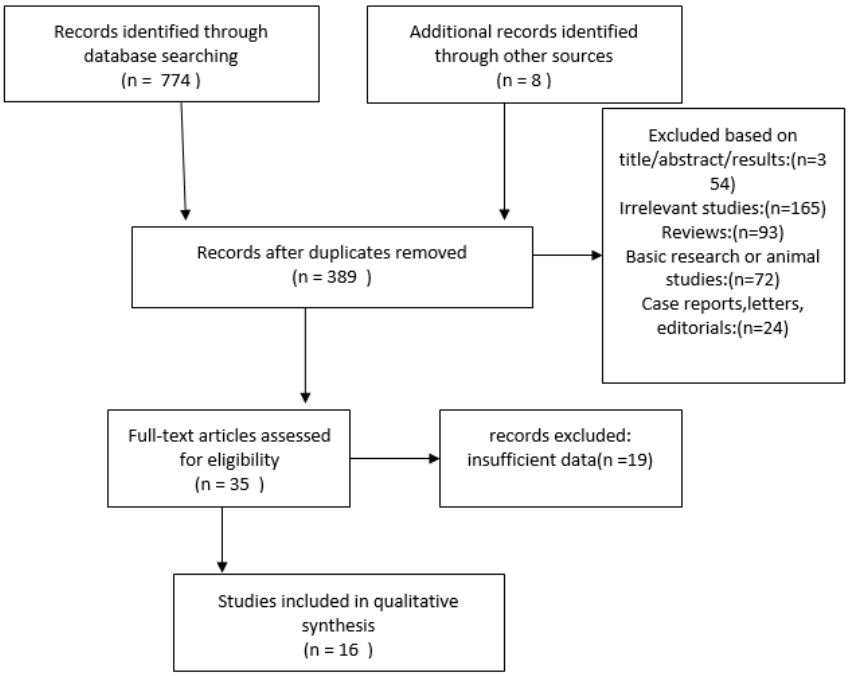
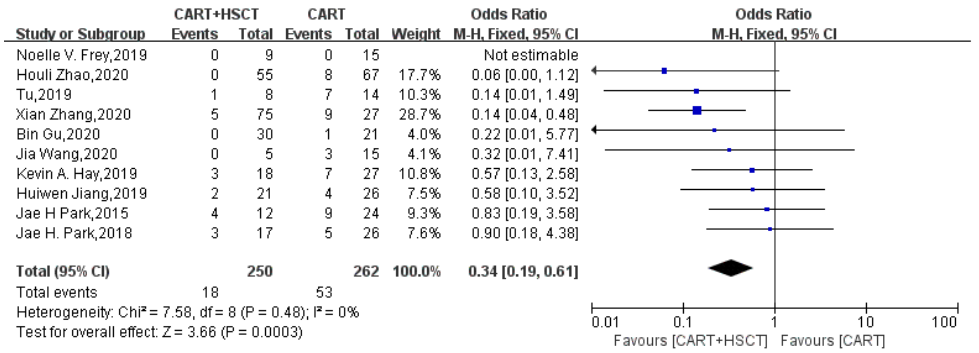
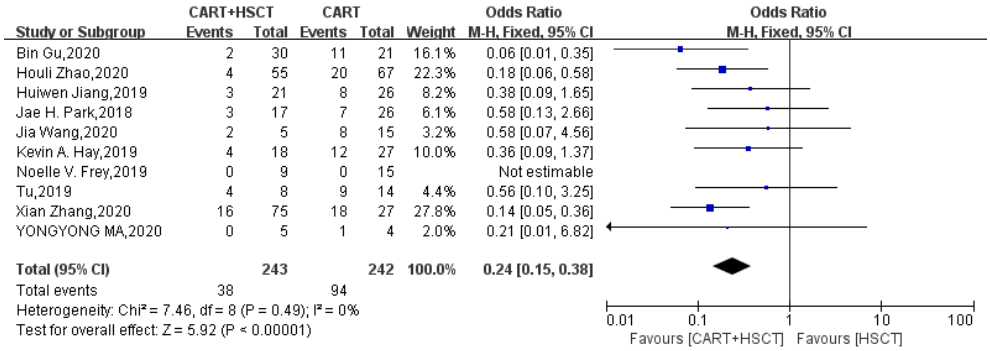


Figure 1

Flow diagram of selecting eligible studies





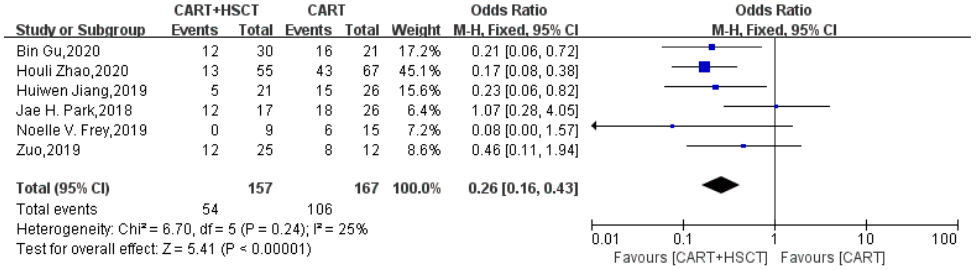
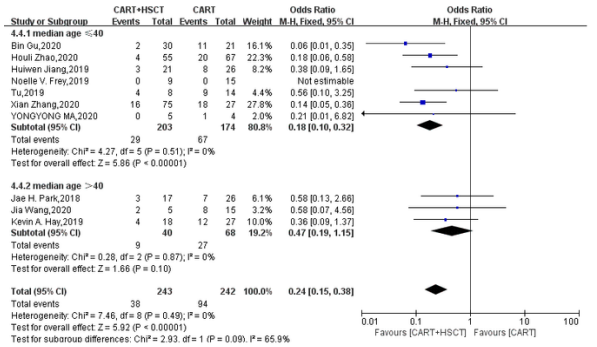
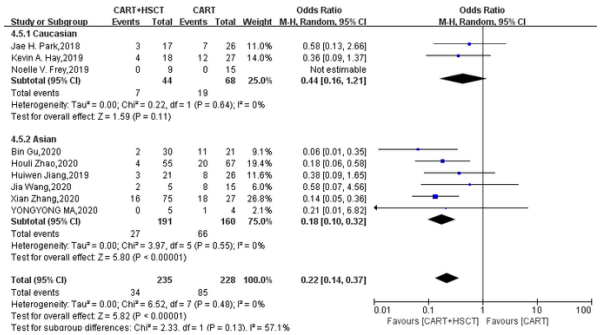


Figure 2

Forest plot of association between allo-HSCT after CAR-T cell therapy and OS (a)6 month OS (b)1 year OS (c)2 year OS





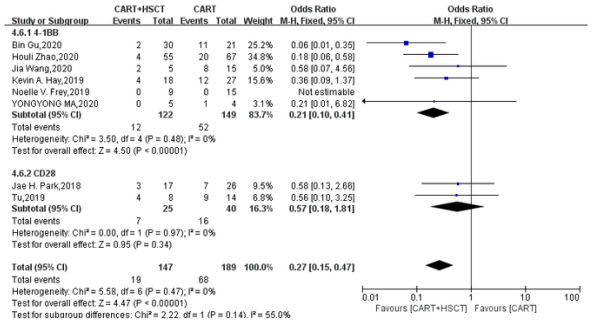


Figure 3

Subgroup analyses of the relationship between allo-HSCT after CAR-T cell therapy and 1 year OS (a) classified by age (b) classified by ethnicity (c) classified by costimulatory domain

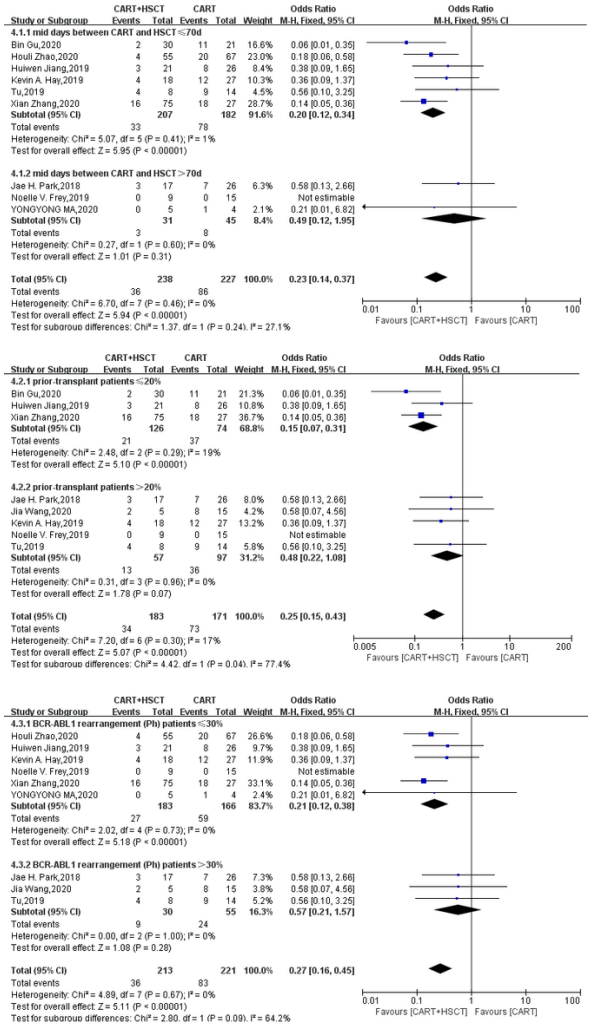


Figure 4

Intensive subgroup analyses of the relationship between allo-HSCT after CAR-T cell therapy and 1 year OS (a) classified by period between CAR-T cell therapy and allo-HSCT (b) classified by proportion of patients with a HSCT history (c) classified by proportion of BCR-ABL1 rearrangement (Ph) patients

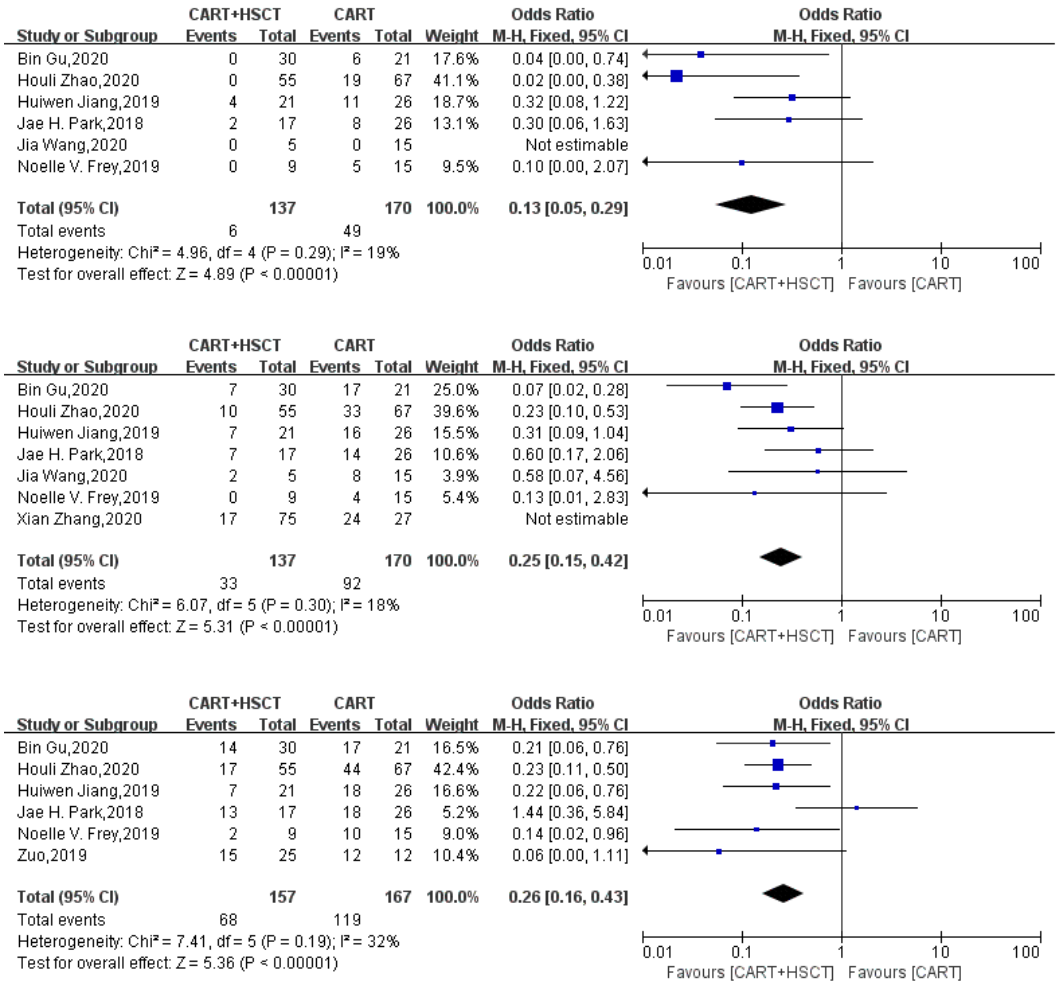


Figure 5

Forest plot of association between HSCT after CAR-T cell therapy and LFS (a)6 month LFS (b)1 year LFS (c)2 year LFS

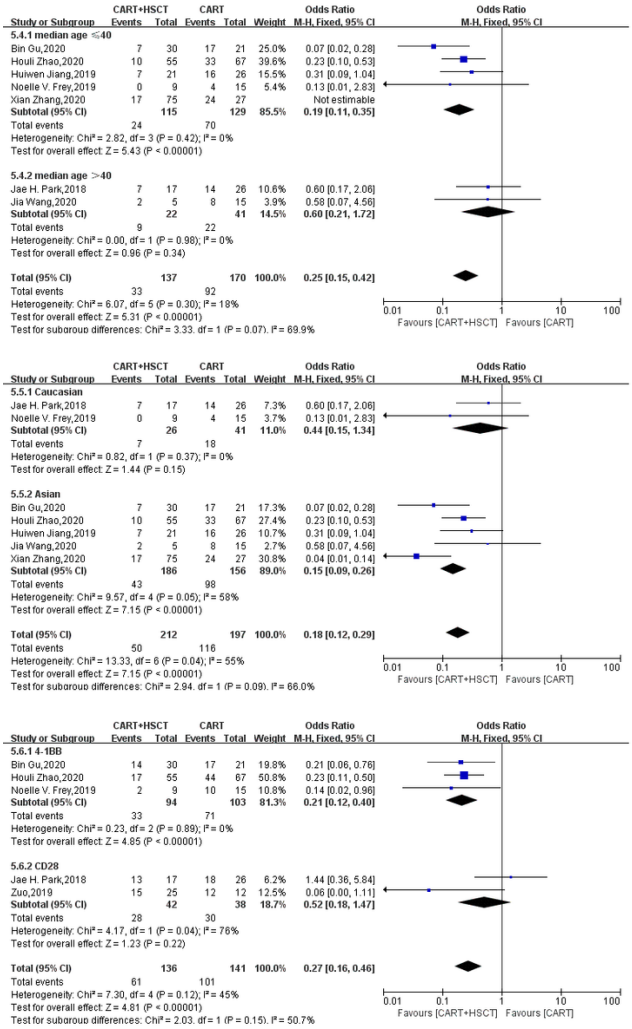


Figure 6

Subgroup analyses of the relationship between HSCT after CAR-T cell therapy and 1 year LFS (a) classified by age (b) classified by ethnicity (c) classified by costimulatory domain(2 year LFS)

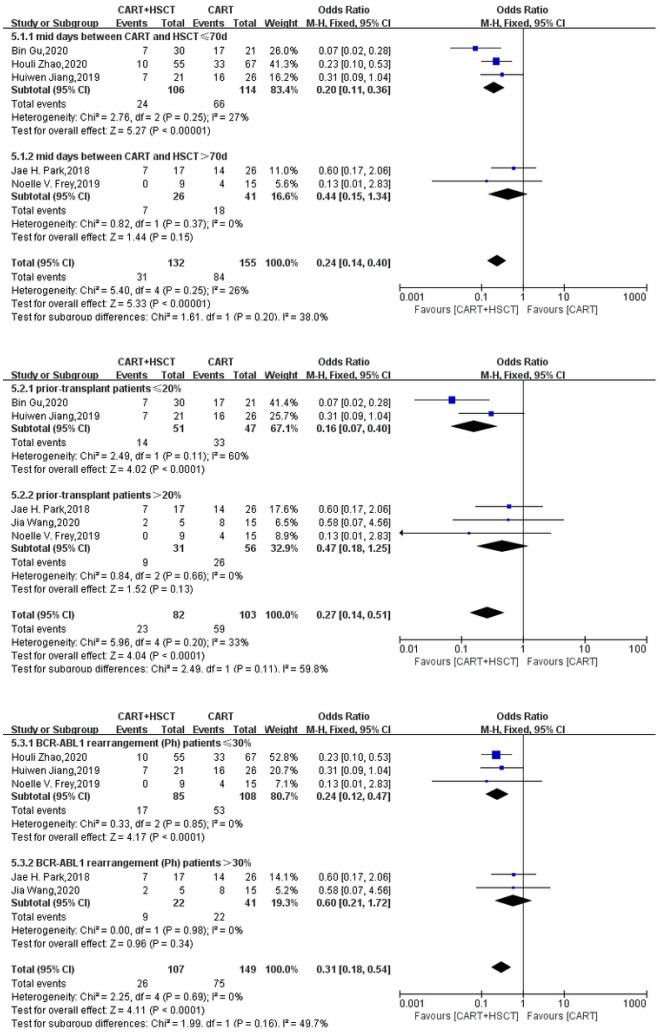


Figure 7

Intensive subgroup analyses of the relationship between HSCT after CAR-T cell therapy and 1 year LFS (a) classified by period between CAR-T cell therapy and allo-HSCT (b) classified by proportion of patients with a HSCT history (c) classified by proportion of BCR-ABL1 rearrangement (Ph) patients

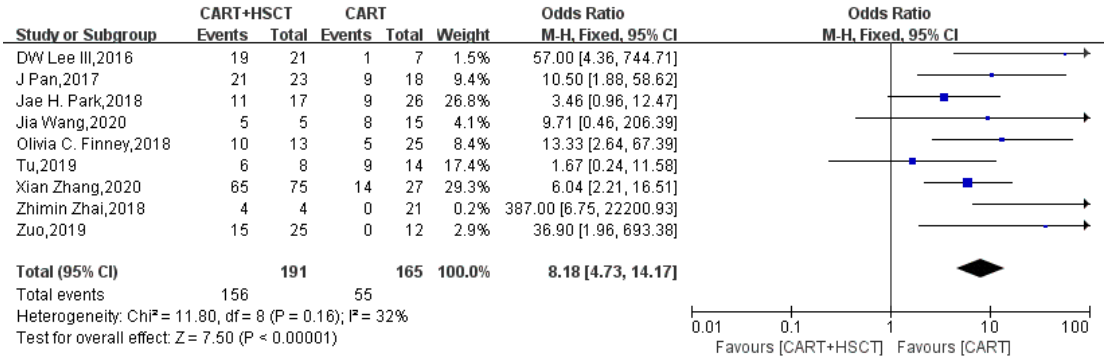


Figure 8

Forest plot of association between allo-HSCT after CAR-T cell therapy and RR

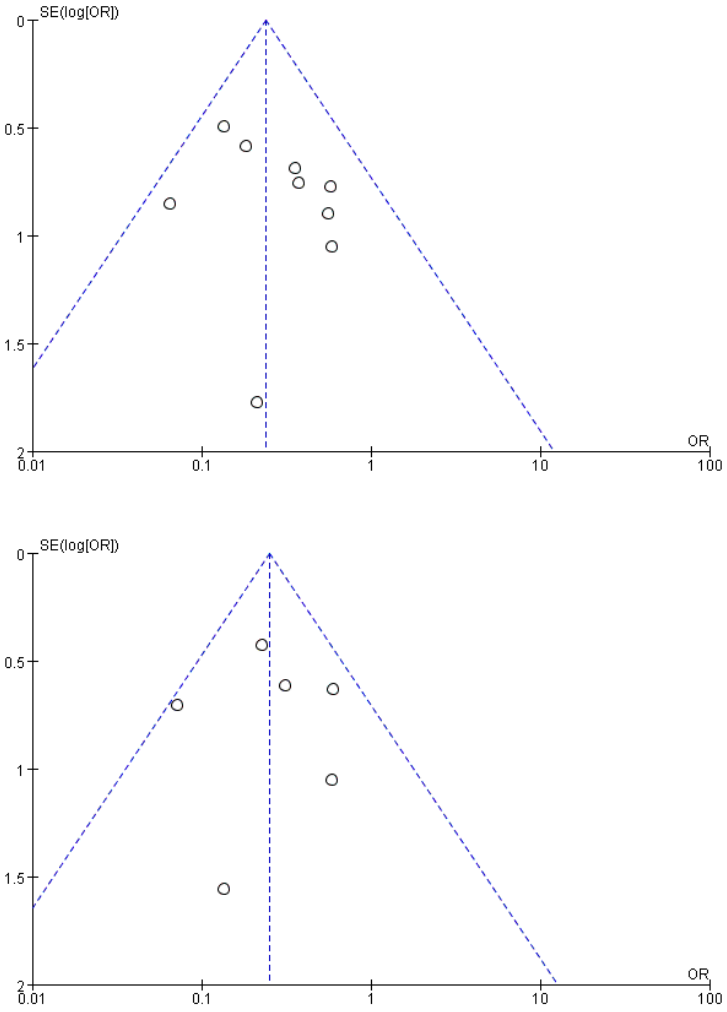


Figure 9

Funnel plot of OS and LFS (a) OS (b)LFS

Supplementary Files

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- tableS1.docx
- tableS2.docx