# Double vs. single autologous stem cell transplantation in patients with multiple myeloma and high-risk factors: A systematic review and meta-analysis

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**Abstract.** Multiple myeloma (MM) remains a challenging hematological malignancy despite therapeutic advances. The present systematic review and meta-analysis aimed to evaluate the comparative efficacy of double vs. single high-dose therapy (HDT) followed by autologous stem cell transplantation (ASCT) for MM, with a specific interest in its application for individuals presenting with high-risk disease factors. A comprehensive search of the literature available in the PubMed, Cochrane and Embase databases was performed from inception to April 12, 2023. The analysis incorporated randomized controlled trials (RCTs) that directly compared single HDT followed by ASCT (HDT/ASCT; administered with or without consolidation therapy) against double transplantation. A total of 8 RCTs were included in the final meta-analysis. The aggregated data demonstrated a hazard ratio of 0.58 [95% confidence interval (CI), 0.43-0.80; P=0.001] for PFS and 0.70 (95% CI, 0.54-0.90; P=0.006) for overall survival (OS). These results imply that the double HDT/ASCT strategy may confer significant improvements in both PFS and OS for patients with at least one unfavorable prognostic marker. Findings from the network meta-analysis revealed no statistically significant disparities in PFS or OS outcomes when comparing double HDT/ASCT with single HDT/ASCT supplemented with consolidation therapy. Nevertheless, the double transplantation approach was associated with a markedly higher incidence of achieving at least a very good partial response relative to single HDT/ASCT (relative risk, 1.17; 95% CI, 1.03-1.33; P=0.02). Moreover, the risk of treatment-related mortality (TRM) was comparable between the double and single HDT/ASCT cohorts. In conclusion, the results of the present meta-analysis indicate that double HDT/ASCT was associated with a significantly higher rate of achieving at least a very good partial response without elevating TRM in the general MM population, indicating an improved treatment response. Notably, it offers superior PFS and OS advantages for high-risk patients. Therefore, double HDT/ASCT may be regarded as a viable and beneficial therapeutic option for this high-risk subgroup.

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*Abbreviations:* ASCT, autologous stem cell transplantation; CCT, conventional chemotherapy; CI, confidence interval; CR, complete response; EFS, event-free survival; HDT, high-dose therapy; HR, hazard ratio; IFN-α, interferon-α; ISS, international staging system; MM, multiple myeloma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RCTs, randomized controlled trials; RoB 2, risk of bias tool version 2; RR, risk ratio; TRM, treatment-related mortality; VAD, vincristine, doxorubicin, dexamethasone; VGPR, very good partial response

*Key words:* multiple myeloma, autologous stem cell transplantation, double transplantation, high-risk, meta-analysis, systematic review, progression-free survival, overall survival

## Introduction

Multiple myeloma (MM), recognized as the second most prevalent hematological malignancy globally, is responsible for ~1% of all cancer diagnoses and ~14% of hematological cancers worldwide, with annual new cases estimated at ~188,000 (1). Even with progress in treatment modalities, MM is still considered an incurable disease for most patients, exhibiting a 5-year relative survival rate of ~60% in developed nations. The global incidence of MM shows geographical variation, with higher rates observed in North America, Europe and Australia compared with Asia (1).

The relapsing-remitting nature of MM and the necessity for ongoing treatment interventions place a substantial burden on healthcare systems. Although novel agents such as immunomodulatory drugs and proteasome inhibitors have

been introduced, high-dose therapy (HDT) with melphalan followed by autologous stem cell transplantation (ASCT) continues to be a cornerstone treatment for eligible patients, as per established guidelines (2-4). Notably, regional variations in treatment protocols exist; for example, recommendations from the European Myeloma Network (3), the American Society for Blood and Marrow Transplantation (2) and Chinese (Chinese Hematology Association, Chinese Society of Hematology and Chinese Myeloma Committee-Chinese Hematology Association) guidelines (4) differ concerning the use of consolidation therapy and the specific role of double ASCT, reflecting differences in clinical practice and resource allocation.

The landmark study by Attal *et al* (5) in 1996 first provided a comparative analysis of response rates, event-free survival (EFS) and overall survival (OS) between HDT followed by ASCT (HDT/ASCT) and conventional chemotherapy (CCT). This was followed by several randomized controlled trials (RCTs) that corroborated the finding that single HDT/ASCT led to an improved complete response (CR) rate compared with CCT (6-9). Double HDT/ASCT is defined as the administration of a second HDT/ASCT procedure within a 6-month window following the initial transplantation (10). A 2003 report by Attal *et al* (11) indicated superior EFS and 7-year survival rates with double HDT/ASCT compared with the single transplantation approach.

Nonetheless, the clinical benefit of double transplantation remains a point of contention, as evidenced by the mixed results from subsequent clinical trials (12-17). In 2009, Kumar *et al* (18) published a meta-analysis assessing the effectiveness and safety profile of single vs. double HDT/ASCT. However, the retraction of one study included in the analysis has cast doubt on the robustness of its conclusions. To address these uncertainties in a comprehensive manner, the present study performed an updated systematic review and meta-analysis to re-assess the efficacy and safety of single vs. double HDT/ASCT. Moreover, a network meta-analysis was performed to draw comparisons between double HDT/ASCT and single HDT/ASCT, the latter with or without consolidation therapy.

## Materials and methods

*Study registration*. The present study was performed and reported in adherence to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (19). The protocol for the present systematic review is registered with the International Prospective Register of Systematic Reviews (registration no. CRD42022300207).

*Data sources*. A systematic search of the literature was performed across the following electronic databases: PubMed (https://pubmed.ncbi.nlm.nih.gov/), the Cochrane Library (https://www.cochranelibrary.com/) and Embase (https://www.embase.com/), covering all entries from database inception to April 12, 2023. The search strategy employed a combination of key words and Medical Subject Headings terms, including: 'multiple myeloma', 'myeloma', 'plasma cell myeloma', 'autologous stem cell transplantation', 'autologous transplant', 'autograft', 'stem cell transplant', 'hematopoietic stem cell transplantation', 'tandem transplant', 'double transplant' and 'high-dose therapy'. Boolean operators (AND, OR) were applied to combine search terms appropriately. Restrictions on publication type were not applied. In addition to examining published trials, the World Health Organization International Clinical Trials Registry Platform (www.trialsearch.who.int) was also searched for any relevant registered trials. To ensure a broad scope, the review incorporated clinical guidelines from several countries. Moreover, in an effort to minimize publication bias, grey literature sources, including conference abstracts and academic dissertations, were also considered (20).

*Study selection*. The present study exclusively included RCTs to minimize selection bias and confounding factors, thereby providing the highest level of evidence on efficacy. Studies were considered eligible for inclusion if they met all of the following criteria: i) RCTs; ii) enrolled patients had a confirmed diagnosis of symptomatic or progressive, previously untreated MM; iii) participants were randomized to undergo either a single HDT/ASCT or a double HDT/ASCT within 6 months after the first ASCT; iv) reported data on response rates, OS, EFS and/or progression-free survival (PFS) and treatment-related mortality (TRM) for both treatment arms; and v) published in the English language. Studies were excluded if they met any of the following criteria: i) Non-randomized study designs (such as observational studies, case series or case reports); ii) studies enrolling patients with relapsed or refractory MM; iii) studies comparing transplantation strategies other than single vs. double HDT/ASCT; iv) studies that did not report at least one of the prespecified outcomes of interest; v) duplicate publications reporting exactly the same patient cohort and identical outcomes without providing any new information (conference abstracts that supply additional subgroup analyses or long-term follow-up data not available in the corresponding full-text articles were considered complementary and were included after confirming no overlap in the extracted patient data); and vi) reviews, editorials, commentaries or guidelines without original data.

*Data extraction*. A total of two independent reviewers assessed each article against the eligibility criteria. A third reviewer was consulted to arbitrate any discrepancies that arose. Another pair of reviewers were responsible for extracting the following data from the studies that were included: i) General study information (first author, year of publication, study design and sample size); ii) baseline patient characteristics (diagnosis, prior treatments, sex and age); iii) details of the treatment protocols (patient groups, pre-treatment regimens, treatment plans, duration and follow-up period); and iv) outcomes measured for each group. The endpoints of primary interest were OS and PFS. Secondary outcomes encompassed response rate and TRM. Where available, data on adverse events were also extracted to evaluate safety.

For conference abstracts that provided additional subgroup or long-term follow-up data not reported in the corresponding full-text articles, only those unique estimates were extracted. It was verified that the same patient cohort was not counted twice for the same outcome in any meta-analysis.

The potential for bias in the included RCTs was evaluated using the Cochrane Risk of Bias tool, version 2 (RoB 2) (21).

A summary of this assessment is presented in Table SI, with detailed domain-level judgments for each included study. Whilst the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework is another important system for evaluating evidence certainty, the principal evaluation of methodological quality and bias risk was grounded in the Cochrane RoB 2 tool. This method is specifically tailored and extensively validated for use with RCTs. Consequently, a formal GRADE assessment was not performed for this analysis.

*Data synthesis*. A table was constructed to summarize the characteristics of the included studies, which helped identify the data available for synthesis. For comparing categorical outcomes (such as response rate and TRM) between intervention groups, the risk ratio (RR) was employed. Estimates of the RR were calculated using Review Manager 5.3 software (The Cochrane Collaboration). Pairwise meta-analyses were performed, and the results are displayed as forest plots. A random-effects model was applied for all meta-analyses to incorporate potential heterogeneity arising from variations in study populations, protocols and clinical settings across the included trials. Heterogeneity was assessed using the Q test and the $I^2$ statistic for descriptive purposes.

For time-to-event data (OS, EFS and PFS), hazard ratio (HR) was used for inter-group comparisons. HR estimates were derived employing the inverse variance method in Stata 16.0 (StataCorp LP). In cases where HRs and their confidence intervals (CIs) were not directly reported in the publications, they were approximated from published Kaplan-Meier curves using established methodological approaches (22).

A network meta-analysis was performed to assess the relative effects of different treatment strategies (23), utilizing a mixed-effects model in R software, version 4.2.1 (https://www.R-project.org/). This methodology enabled the simultaneous comparison of multiple interventions, even in the absence of direct head-to-head trials, thus yielding a hierarchical ranking of treatment efficacy and improving the clinical relevance of the results. Inconsistency within the network was also assessed using Cochran's Q statistic and a design-by-treatment interaction model (24). The effects of each treatment regimen relative to single HDT/ASCT alone are presented in a forest plot with 95% CIs.

*Reporting bias assessment*. Publication bias was assessed using Egger's test for PFS and OS, and Harbord's test for overall response rate and treatment-related mortality (25,26). Additional methods for detecting publication bias have been described by Jin *et al* (27). For the network meta-analysis of OS, a funnel plot was generated.

## Results

*Study selection*. The process of study identification is detailed in Fig. 1. Initially, 1,101 records were identified. Following a review of titles and abstracts, 18 records were selected for a full-text assessment based on the inclusion criteria. A total of 8 studies were considered potentially relevant. In the final selection, 6 full-text articles and 2 conference abstracts met the eligibility criteria. The 6 full-text articles (11,12,14,17,28,29) provided data for the conventional pairwise meta-analysis, encompassing 2,173 unique patients from the arms directly comparing double vs. single ASCT. The two conference abstracts (30,31) did not introduce additional patient cohorts; instead, they supplied supplementary subgroup analyses and extended follow-up data derived from the same trial populations already represented in the included full-text articles. No double counting of patients occurred in any meta-analysis. Among the 8 studies, 5 categorized patients into different risk groups according to adverse prognostic factors, and 3 were incorporated into the subgroup meta-analysis focusing specifically on high-risk patients.

*Characteristics of the included studies*. The key features of the included studies are summarized in Table I. The median duration of follow-up across these studies varied from 38-134 months. The patient population in each treatment arm ranged between 76-501 individuals. All studies provided a direct comparison of single vs. double ASCT in patients with MM.

The study by Attal *et al* (11) involved previously untreated patients classified with Durie-Salmon stage I, II or III myeloma. All participants received 3-4 cycles of vincristine, doxorubicin, dexamethasone (VAD) induction chemotherapy prior to transplantation. The conditioning regimen for the single ASCT arm consisted of melphalan (140 mg/m$^2$) combined with total-body irradiation. For the double transplant group, the first procedure used melphalan (140 mg/m$^2$) alone, and the second procedure employed the same regimen as the single-transplant group. Maintenance therapy with interferon-α (IFN-α) was administered to all patients. Cavo *et al* (12) (the Bologna 96 trial) enrolled previously untreated patients with symptomatic MM. All participants received VAD induction therapy. The conditioning regimen for the initial transplant was melphalan (200 mg/m$^2$). Patients assigned to the double transplantation group underwent a second transplant 3-6 months later, which utilized melphalan (120 mg/m$^2$) combined with busulfan (12 mg/kg). IFN-α served as the maintenance therapy. This study also performed an analysis of outcomes specifically for patients who failed to achieve at least a near-CR after a single transplant. Both Mai *et al* (14) (the GMMG-HD2 trial) and Stadtmauer *et al* (17) (the BMT CTN 0702 trial) used high-dose melphalan (200 mg/m$^2$) as the conditioning regimen. However, these trials did not include subgroup analyses focused on high-risk patients. Cavo *et al* (28) (the EMN02/HO95 MM trial) also reported outcomes for participants with high-risk cytogenetic profiles. Straka *et al* (29) analyzed pooled data from two clinical trials (NCT00416273 and NCT00416208), proposing that double ASCT may extend EFS in newly diagnosed MM. Finally, two conference abstracts (30,31) also provided data on EFS and OS for the overall patient population and for subsets with adverse prognostic factors.

*Risk of bias in the studies*. The results of the risk of bias assessment are presented in Table SI, with detailed domain-level judgments for each included study. Whilst all studies described their randomization procedures, a high risk-of-bias related to deviations from the intended interventions was identified. This was primarily due to the inherent difficulty, if not impossibility, of blinding both participants and healthcare providers to the transplantation assignment.

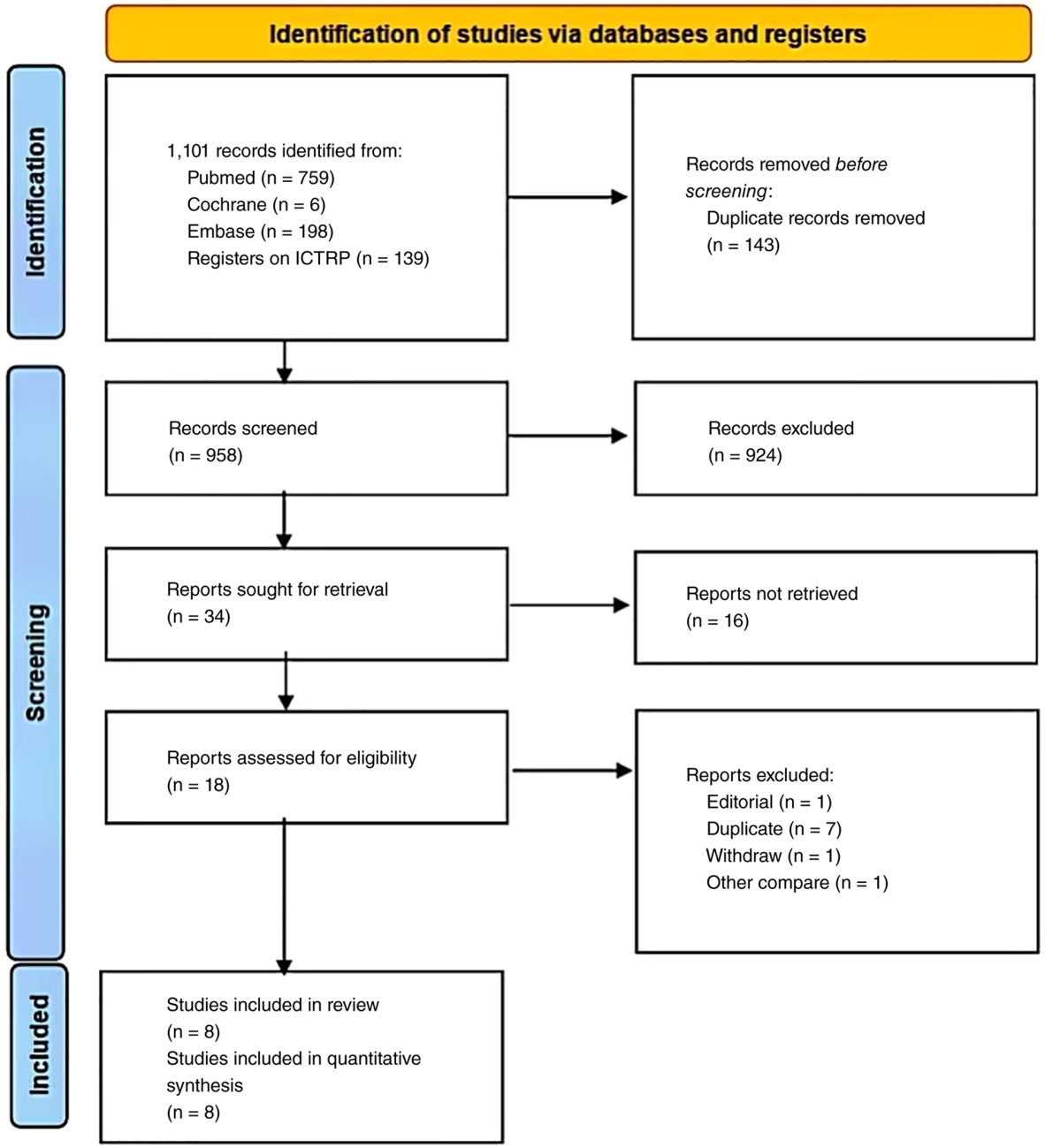


Figure 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses flow diagram of the study selection process outlining the systematic process for identifying, screening and including studies in the systematic review and meta-analysis comparing double vs. single ASCT in patients with multiple myeloma. A total of 1,101 records were identified through systematic searches of electronic databases (PubMed, n=759; Cochrane Library, n=6; and Embase, n=198) and the World Health Organization ICTRP (n=139). After removing 143 duplicate records, 958 unique records underwent title and abstract screening. Of these, 924 records were excluded as irrelevant. The full text of 34 reports was sought for retrieval; 16 reports could not be retrieved. The remaining 18 reports were assessed for eligibility based on the predefined inclusion criteria. A total of 10 reports were excluded for the following reasons: Editorial material (n=1), duplicate publication (n=7), withdrawn study (n=1) and comparison of other interventions (n=1). Ultimately, 8 studies (comprising 6 full-text articles and 2 conference abstracts) met all eligibility criteria and were included in the qualitative synthesis (systematic review). All 8 studies also provided sufficient data for quantitative synthesis (meta-analysis). ACT, autologous stem cell transplantation; ICTRP, International Clinical Trials Registry Platform.

In certain instances, participants did not adhere to the study protocol, partly due to their awareness of the assigned intervention and partly due to disease progression. All studies reported performing intention-to-treat analyses. The two conference abstracts (30,31) lacked detailed information on random sequence generation and the handling of missing data. Overall, the risk-of-bias for all included studies was judged to entail 'some concerns'. A detailed account of the methodological quality assessment is provided in Table SI.

*Meta-analyses*. Fig. 2 shows response rates and TRM and Fig. 3 presents survival outcomes for high-risk patients.

*Meta-analysis of response rates*. Data on response rates were available from 5 studies (11,12,14,17,28). The meta-analysis of response rates [achievement of at least very good partial response (VGPR)] included 4 studies that provided sufficient data for pooling, with results shown in Fig. 2A. Cavo *et al* (12) reported a significant increase in the CR/near-CR rate from ~33% with single ASCT to ~47% with double ASCT (P=0.008).

Table I. Baseline characteristics of the randomized controlled trials included in the systematic review and meta-analysis.

| First author/s, year | Publication type | Total patients, n | Intervention, n | Induction (dose) | Consolidation | Median follow-up, months (range) | More effective procedure according to outcome[a] | | | | (Refs.) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | OS | PFS | Response rate | TRM | |
| Attal *et al*, 2003 | Full text | 399 | ASCT, 200; S-ASCT, 199 | Melphalan (140 mg/m$^2$) | Neither | 75 (36-93) | Neither | D-ASCT | Neither | Neither | (11) |
| Cavo *et al*, 2007 | Full text | 321 | D-ASCT, 158; S-ASCT, 163 | Melphalan (200 mg/m$^2$) | Neither | 70 (32-112) | D-ASCT | D-ASCT | D-ASCT | Neither | (12) |
| Cavo *et al*, 2013 | Abstract | 606 | D-ASCT, 352; S-ASCT, 254 | Not reported | Neither | Not reported | D-ASCT | D-ASCT | Not reported | Not reported | (30) |
| Mai *et al*, 2016 | Full text | 358 | D-ASCT, 181; S-ASCT, 177 | Melphalan (200 mg/m$^2$) | Neither | 134 | Neither | Neither | Neither | Not reported | (14) |
| Rocchi *et al*, 2019 | Abstract | 909 | D-ASCT, 408; S-ASCT, 501 | Not reported | Neither | 117 (91-126) | D-ASCT | D-ASCT | Not reported | Not reported | (31) |
| Stadtmauer *et al*, 2019 | Full text | 758 | D-ASCT, 247; S-ASCT, 257; S-ASCT + C, 254 | Melphalan (200 mg/m$^2$) | RVD | 38 | Neither | Neither | Neither | Neither | (17) |
| Cavo *et al*, 2020 | Full text | 419 | D-ASCT, 210; S-ASCT, 209 | Melphalan (200 mg/m$^2$) | Neither | 60 (52-68) | D-ASCT | D-ASCT | Not reported | Not reported | (28) |
| Straka *et al*, 2021 | Full text | 340 | D-ASCT, 96; S-ASCT, 76; S-ASCT + C, 76; D-ASCT + C, 92 | Melphalan (140 or 200 mg/m$^2$) | V | 51 | Neither | D-ASCT | Not reported | Not reported | (29) |

This table summarizes the key design and demographic features of the 8 randomized controlled trials comparing the efficacy of D-ASCT vs. S-ASCT in patients with newly diagnosed multiple myeloma. [a]Denotes the treatment arm associated with superior outcomes for each endpoint [OS, PFS, response rate (best achieved response) and TRM] as reported by the primary analysis of each individual study. 'Neither' indicates that no statistically significant difference was demonstrated between the intervention groups for that specific endpoint. ASCT, autologous stem cell transplantation; D-ASCT, double (tandem) ASCT; S-ASCT, single ASCT; + C, treatment followed by consolidation therapy; OS, overall survival; PFS, progression-free survival; TRM, treatment-related mortality; RVD, lenalidomide, bortezomib and dexamethasone; V, bortezomib.

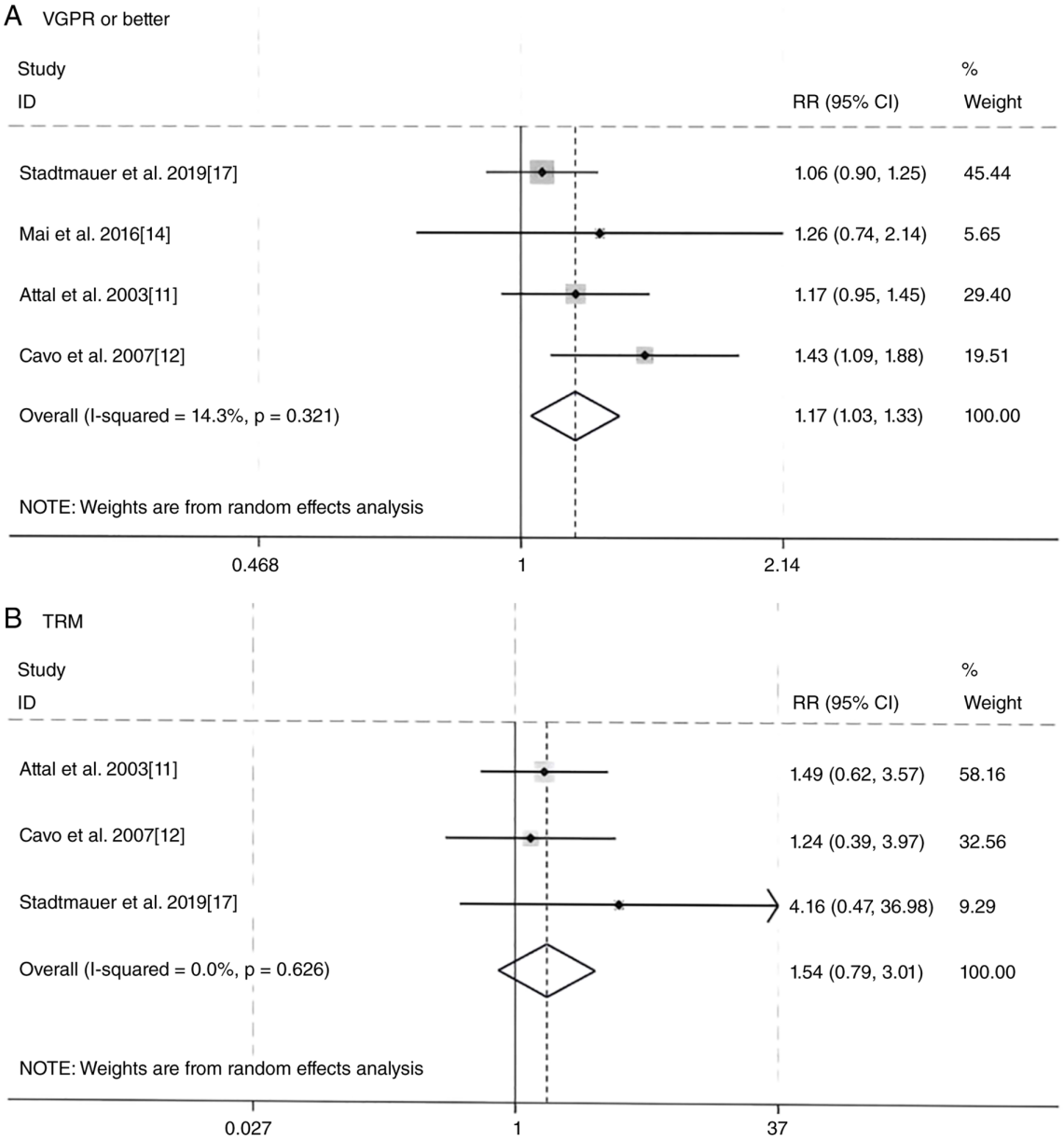


Figure 2. Forest plots for meta-analysis of response rates and TRM. (A) Forest plot comparing the achievement of at least a VGPR between double and single HDT/ASCT. The combined RR demonstrates a statistically significant benefit in favor of double HDT/ASCT (RR, 1.17; 95% CI, 1.03-1.33; P=0.02). Heterogeneity was low ($I^2$=14.3%; P=0.321). (B) Forest plot comparing TRM between double and single HDT/ASCT. The combined RR shows no statistically significant difference between the two strategies (RR, 1.54; 95% CI, 0.79-3.01; P=0.17). No heterogeneity was observed ($I^2$=0%; P=0.626). A random-effects model was used for both meta-analyses. TRM, treatment-related mortality; RR, risk ratio; VGPR, very good partial response; HDT, high-dose therapy; ASCT, autologous stem cell transplantation; CI, confidence interval.

Mai *et al* (14) also reported a significant rise in CR rates from the first to the second HDT/ASCT procedure (P=0.04). By contrast, Attal *et al* (11) reported no statistically significant difference in the CR/VGPR rates between the single and double transplant groups (42 vs. 50%; P=0.10). Similarly, Stadtmauer *et al* (17) reported no significant advantage for achieving a response of at least a VGPR with double vs. single HDT/ASCT (P=0.37). The pooled RR for the ORR (defined as at least partial response) showed no significant difference between the treatment groups (RR, 1.03; P=0.42; data not shown). However, using a random-effects model, the combined RR for achieving a response of at least a VGPR was 1.17 (95% CI, 1.03-1.33; P=0.02), demonstrating a statistically significant advantage for the double HDT/ASCT approach (Fig. 2A). The analysis indicated no significant heterogeneity among the studies ($I^2$=14.3%; P=0.321).

*Meta-analysis of TRM*. A total of 3 studies provided data on TRM (11,12,17). The corresponding forest plot is presented in Fig. 2B. No heterogeneity was detected among these studies ($I^2$=0%; P=0.626). Furthermore, the results indicated no statistically significant difference in the risk of TRM between the double and single HDT/ASCT groups (RR, 1.54; 95% CI, 0.79-3.01).

*Meta-analysis of double vs. single transplantation only in patients with adverse prognostic factors*. For this specific analysis, patients were classified into a high-risk category if they possessed at least one of the following adverse prognostic factors: i) Failure to achieve at least a near CR or

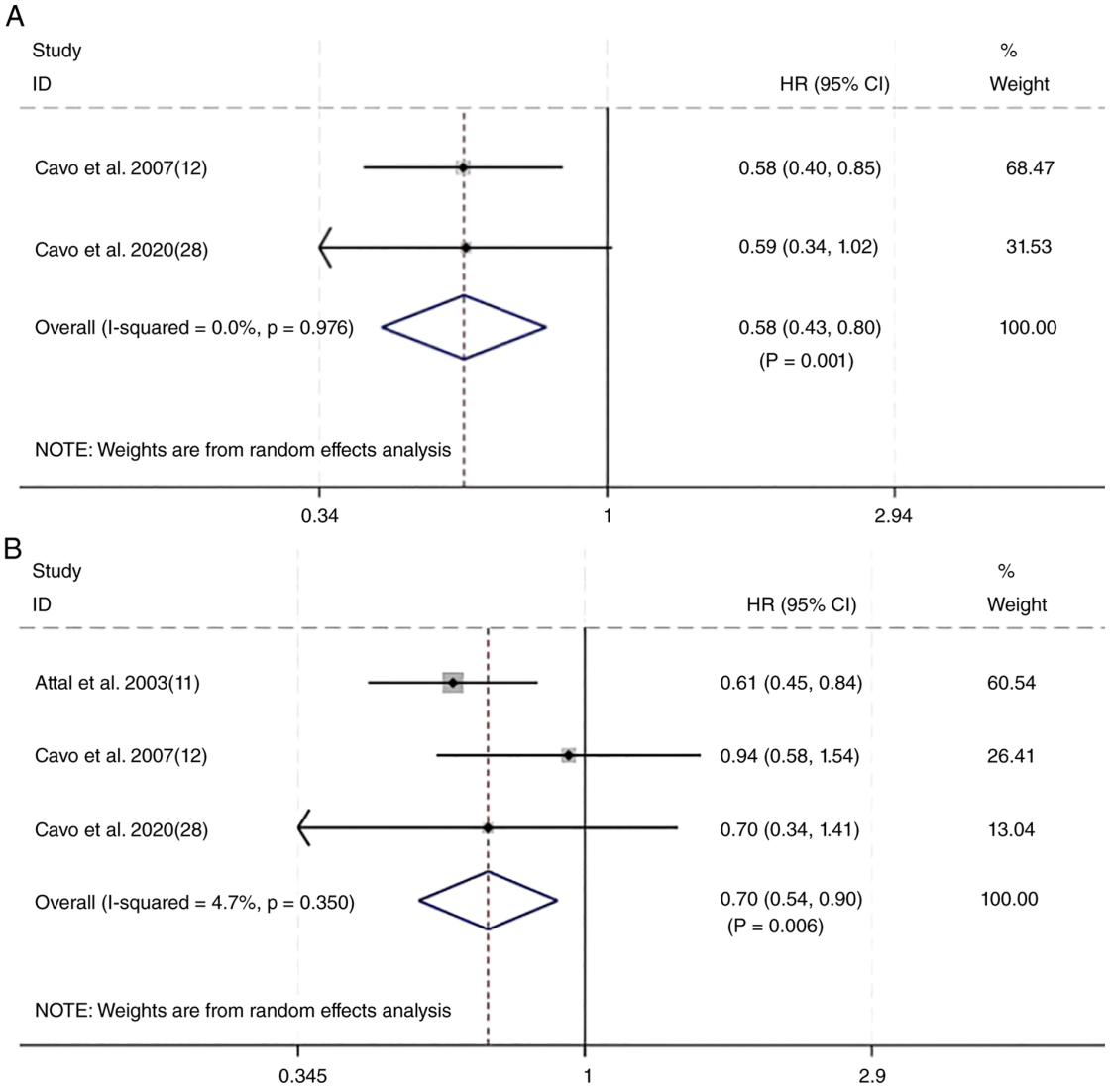


Figure 3. Forest plots of PFS and OS for high-risk patients. (A) Forest plot comparing PFS between double and single HDT/ASCT in patients with at least one adverse prognostic factor. The combined HR demonstrates a statistically significant PFS benefit in favor of double HDT/ASCT (HR, 0.58; 95% CI, 0.43-0.80; P=0.001). (B) Forest plot comparing OS between double and single HDT/ASCT in the same high-risk patient population. The combined HR shows a statistically significant OS benefit for double HDT/ASCT (HR, 0.70; 95% CI, 0.54-0.90; P=0.006). For the purpose of this analysis, high-risk was defined by the presence of at least one of the following: Failure to achieve at least a very good partial response after induction or first transplant, high-risk cytogenetics or International Staging System stage II/III disease. A random-effects model was used for both meta-analyses. PFS, progression-free survival; OS, overall survival; HDT, high-dose therapy; ASCT, autologous stem cell transplantation; HR, hazard ratio; CI, confidence interval.

VGPR following induction therapy or the first transplant; ii) high-risk cytogenetic abnormalities, as defined by the original studies [such as the presence of t(4;14), t(14;16) or del(17p)]; and iii) International Staging System (ISS) stage II or III disease (32).

A total of 4 studies reported on PFS in patients characterized by the aforementioned adverse factors (12,28,30,31). However, only 2 studies (28,30) provided extractable HR estimates with CIs suitable for quantitative pooling. Cavo *et al* (12) reported subgroup findings without providing usable HRs and Rocchi *et al* (31) presented median PFS values without HRs. To avoid potential double-counting of patients from overlapping cohorts in the conference abstracts, the most complete and non-duplicative data were prioritized. Therefore, data from Cavo *et al* (28) and Cavo *et al* (30) were pooled in the meta-analysis (Fig. 3A). Cavo *et al* (30) reported that double HDT/ASCT was associated with a significantly longer PFS for patients possessing one or two adverse factors (HR, 0.70; P=0.006). Rocchi *et al* (31) reported a significant PFS benefit from double ASCT in patients with high-risk cytogenetics (median PFS, 36 months for double ASCT vs. 20 months for single ASCT; P=0.032). The other 2 studies reported findings consistent with these results. The pooled HR was 0.58 (95% CI, 0.43-0.80; P=0.001; Fig. 3A), indicating that double HDT/ASCT significantly extended PFS in patients presenting with at least one adverse prognostic factor.

OS data for patients with adverse factors were available from 4 studies (12,28,30,31). Cavo *et al* (30) reported that patients with two adverse factors who received double HDT/ASCT had a significantly longer OS compared with those planned for single HDT/ASCT (HR, 0.32; P=0.001). The OS advantage was particularly notable for patients who failed to achieve a CR after induction and who also had high-risk cytogenetics (HR, 0.22; P=0.001) or ISS stage III

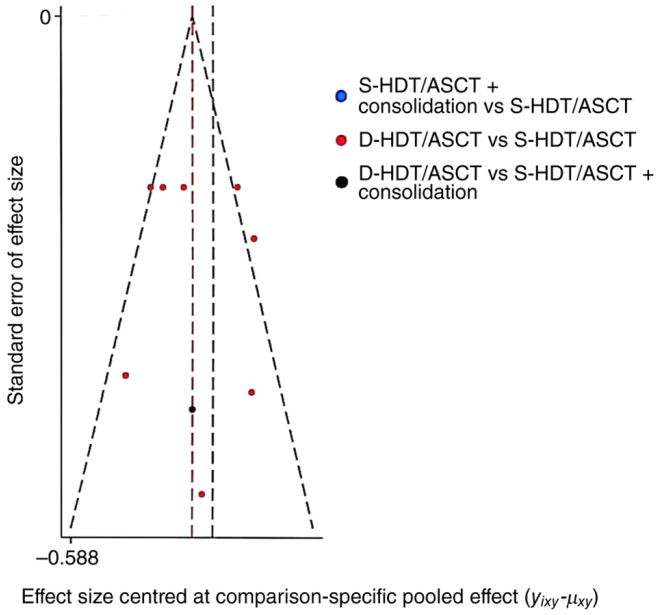


Figure 4. Funnel plot for assessment of publication bias in the network meta-analysis for overall survival. The standard error of the effect size is plotted against the effect size centered at the comparison-specific pooled effect. Different symbols represent different treatment comparisons. Symmetrical distribution of points around the vertical line (null effect) suggests a low risk of publication bias. S-, single; D-, double; HDT, high-dose therapy; ASCT, autologous stem cell transplantation.

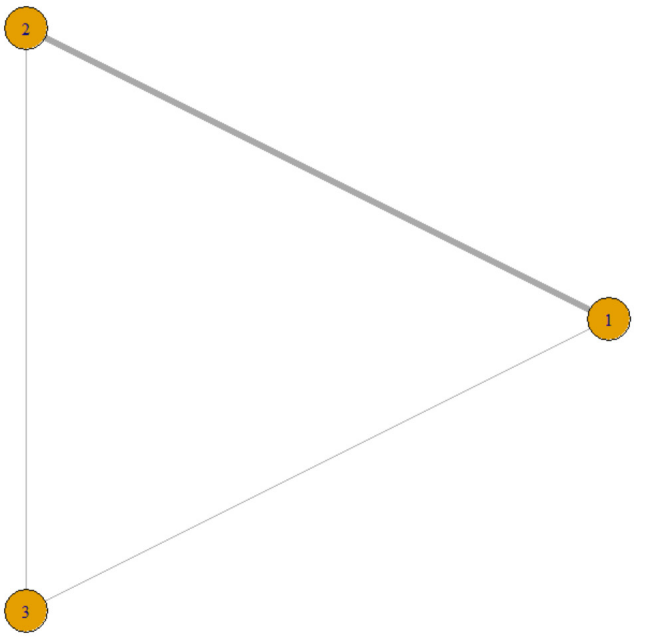


Figure 5. Network plot of treatment comparisons for progression-free survival. Treatments are represented as nodes: 1=D-HDT/ASCT, 2=S-HDT/ASCT, 3=S-HDT/ASCT with consolidation therapy. Lines denote the availability of direct comparisons in the included studies for the PFS outcome. S-, single; D-, double; HDT, high-dose therapy; ASCT, autologous stem cell transplantation.

MM (HR, 0.42; P=0.033). Rocchi *et al* (31) reported an OS benefit with double HDT/ASCT in the subgroup with high-risk cytogenetics (10-year OS rates, 51% for double ASCT vs. 34% for single ASCT; P=0.004). A subgroup meta-analysis for OS was performed using the 3 studies that provided extractable HRs with CIs for patients with adverse prognostic factors (12,28,30). Rocchi *et al* (31) reported 10-year OS rates but did not provide an HR suitable for pooling and was therefore excluded from the quantitative synthesis. The pooled analysis demonstrated no significant heterogeneity ($I^2$=4.7%; P=0.350). Moreover, the combined HR revealed a statistically significant OS benefit favoring double ASCT for patients with at least one adverse prognostic factor (HR, 0.70; 95% CI, 0.54-0.90; P=0.006; Fig. 3B).

*Reporting biases*. For the pairwise meta-analyses, each outcome included <10 studies; therefore, funnel plots were not generated. Instead, quantitative tests were used to assess publication bias. Egger's test detected no significant bias for PFS (P=0.437) or OS (P=0.725). Harbord's test showed no significant bias for overall response rate (P=0.947) or treatment-related mortality (P=0.470). For the network meta-analysis of overall survival, a funnel plot is presented in Fig. 4; the symmetrical distribution of points suggests a low risk of publication bias across the network.

*Network meta-analysis*. A network meta-analysis incorporating 6 studies evaluated PFS across three strategies: Double HDT/ASCT, single HDT/ASCT augmented with consolidation therapy and single HDT/ASCT alone (11,12,14,17,28,29). The network structure for these comparisons is illustrated in Fig. 5 (PFS network) and Fig. 6 (OS network). Figs. S1-S3 provide network meta-analysis forest plots for PFS with different references. When double HDT/ASCT was used as

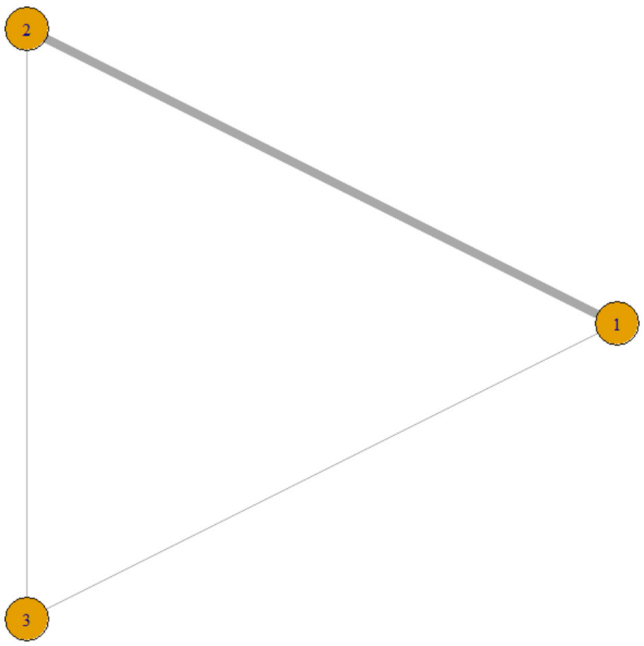


Figure 6. Network plot of treatment comparisons for overall survival. Treatments are represented as nodes: 1=D-HDT/ASCT, 2=S-HDT/ASCT, 3=S-HDT/ASCT with consolidation therapy. Lines connecting the nodes indicate that direct head-to-head comparisons between those treatments were available in the included studies. The plot visually represents the evidence base for the network meta-analysis. S-, single; D-, double; HDT, high-dose therapy; ASCT, autologous stem cell transplantation.

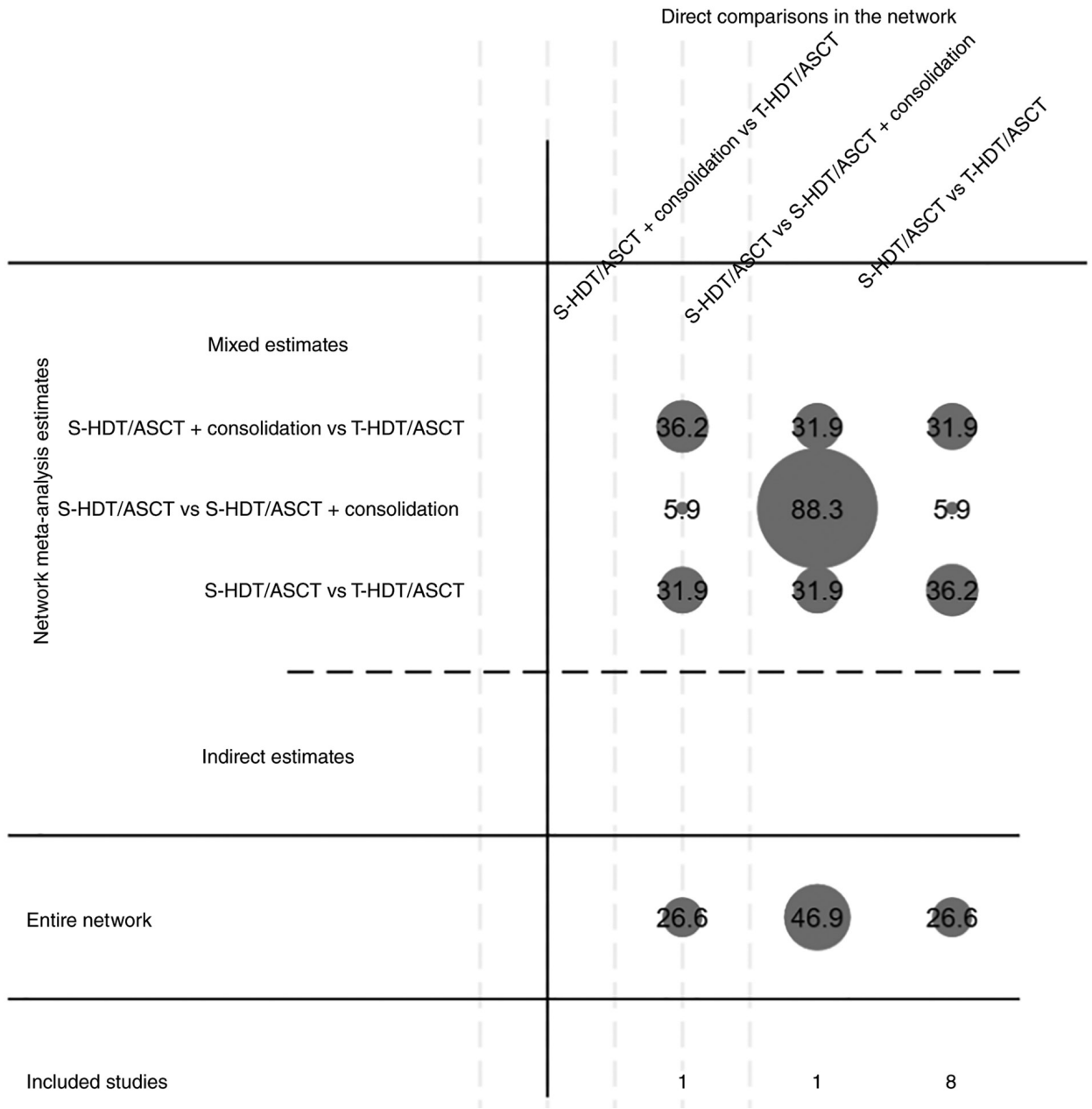


Figure 7. Contribution plot for the network meta-analysis for OS. This plot illustrates the proportional contribution of direct comparisons, indirect evidence and their mixture (mixed estimates) to the network meta-analysis estimate for each treatment comparison in the OS network. OS, overall survival; S-, single; D-, double; HDT, high-dose therapy; ASCT: autologous stem cell transplantation.

the reference (Fig. S1), single HDT/ASCT alone (HR, 1.2; 95% CI, 1.1-1.4) and single HDT/ASCT with consolidation therapy (HR, 1.0; 95% CI, 0.8-1.4) did not show a PFS benefit. With single HDT/ASCT alone as the reference (Fig. S2), double HDT/ASCT demonstrated a significant PFS benefit (HR, 0.83; 95% CI, 0.72-0.94), whereas single HDT/ASCT with consolidation therapy did not (HR, 0.84; 95% CI, 0.6-1.1). When single HDT/ASCT with consolidation therapy was used as the reference (Fig. S3), no significant difference was observed for double HDT/ASCT (HR, 0.99; 95% CI, 0.7-1.3) or single HDT/ASCT alone (HR, 1.2; 95% CI, 0.9-1.6).

Another network meta-analysis, which included all studies, evaluated OS among the same set of treatment strategies (11,12,14,17,28-31). The contribution of direct and indirect evidence to the OS network estimates is illustrated in Fig. 7, and the forest plots for all pairwise OS comparisons are consolidated in Fig. 8. Assessment for potential publication bias within the OS network is presented in Fig. 4, and loop-specific inconsistency is shown in Fig. 9. Neither double HDT/ASCT (HR, 0.86; 95% CI, 0.71-1.10) nor single HDT/ASCT with consolidation therapy (HR, 0.76; 95% CI, 0.40-1.40) showed a statistically significant OS benefit compared with single HDT/ASCT alone (Fig. 8B). Furthermore, no significant difference in OS was demonstrated between double HDT/ASCT and single HDT/ASCT supplemented with consolidation therapy (HR, 1.10; 95% CI, 0.60-2.00; Fig. 8C). The funnel plot (Fig. 4) demonstrates symmetry around the vertical line, with points evenly distributed, suggesting a low risk of publication bias across the studies included in the network meta-analysis. The 95% CI of the odds ratios (1.00-3.07) from Fig. 9 included 1,

indicating no statistically significant inconsistency between the direct and indirect evidence within the network. This supports the consistency and validity of the network meta-analysis results.

## Discussion

The present meta-analysis offers a current and comprehensive assessment of the efficacy and safety of double vs. single HDT/ASCT, placing particular emphasis on patients with high-risk disease characteristics. The key findings revealed that, for patients harboring at least one adverse prognostic factor, double HDT/ASCT provided statistically significant and clinically meaningful enhancements in both PFS (HR, 0.58; P<0.001) and OS (HR, 0.70; P=0.006), without a concomitant increase in TRM. Additionally, although the ORR was similar between the two strategies, the double transplantation approach resulted in a significantly greater proportion of patients achieving a response level of at least a VGPR.

The therapeutic role of double HDT/ASCT in the management of MM has been a long-debated topic. The findings of the present study may help to resolve this controversy by demonstrating that the observable benefits of double transplantation are predominantly concentrated within a specific patient subgroup, namely those with high-risk disease. This crucial differentiation may account for the conflicting conclusions reported in earlier publications. For instance, the influential 2009 meta-analysis by Kumar *et al* (18), which included both randomized and non-randomized studies, concluded that double ASCT did not offer a marked OS advantage over single ASCT (relative risk, 1.01; 95% CI, 0.92-1.10). Similarly, a Cochrane systematic review by Naumann-Winter *et al* (6) reported no significant differences in OS or EFS between the two strategies. It is critical to recognize that these earlier analyses primarily evaluated the effects within the general MM population and were not sufficiently powered to performed detailed subgroup analyses based on risk stratification. By specifically aggregating data from high-risk subgroups across multiple RCTs, the present study provides evidence that the apparent absence of an OS benefit in an unselected population conceals a notable survival advantage for the high-risk cohort.

The biological basis for the aforementioned observation is sound. High-risk MM, often defined by aggressive disease biology and rapid clonal evolution (3,28,32), may not be adequately controlled by a single intensive therapy. A second, sequential high-dose treatment could potentially achieve a more notable level of tumor cell reduction (cytoreduction) and eliminate more therapy-resistant subclones, thereby postponing disease relapse and improving survival outcomes in this vulnerable group. This concept is reinforced by the finding of a superior VGPR rate in the double transplantation arm observed in the present study, suggesting that deeper therapeutic responses may be both achievable and clinically impactful.

Moreover, the conclusions of the present study are in agreement with post-hoc analyses from several major trials. For example, the EMN02/HO95 study (28) reported that double ASCT notably improved PFS compared with single ASCT, with the most pronounced benefit observed in high-risk patients, including those with high-risk cytogenetics or a suboptimal response to induction therapy. The integrated analysis of phase III European studies by Cavo *et al* (30) also strongly supported the use of double ASCT for patients with two adverse prognostic factors. In recent years, numerous meta-analyses and real-world investigations have further assessed the role of transplant strategies in MM, providing a wider context for the results of the present study. The finding of PFS and OS benefits with double ASCT in high-risk patients is corroborated by several of these contemporary studies. For example, the recent systematic review and meta-analysis by Chen *et al* (33) reported that double ASCT improved PFS and OS in high-risk individuals. Similarly, a retrospective propensity score-matching study by Wu *et al* (34) and a systematic review with meta-analysis by Li *et al* (35) both reported superior survival outcomes with double ASCT in selected patient subgroups, which aligns with the primary findings of the present study. Further bolstering the external validity of the results of the present study, real-world studies from diverse geographical regions, including the study by Dou *et al* (36) in China and Grieb *et al* (37) in Germany, reported that the survival benefit of double ASCT is especially notably in high-risk cases. However, the clinical context is continuously evolving. Venner *et al* (38) proposed that in the current era of effective maintenance therapy, the benefit of double ASCT for high-risk patients might be reduced. This nuance is consistent with the network meta-analysis finding of the present study, which revealed no significant difference between double ASCT and single ASCT combined with consolidation therapy. Other reviews have addressed related but distinct questions, such as the role of allogeneic transplantation (39-41) or sequential autologous-allogeneic strategies (42,43) or have provided

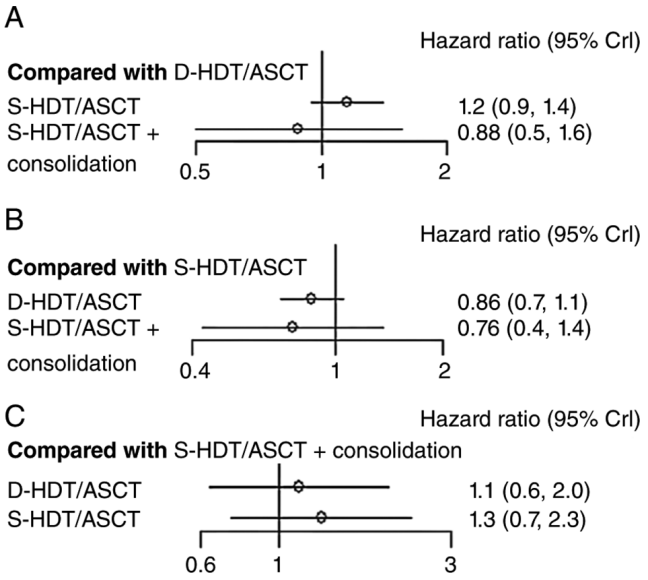


Figure 8. Forest plots for pairwise comparisons from the network meta-analysis of overall survival. Hazard ratios with 95% CrI are shown for each treatment comparison within the network. (A) Comparison of S-HDT/ASCT + consolidation vs. D-HDT/ASCT. (B) Comparison of S-HDT/ASCT vs. D-HDT/ASCT. (C) Comparison of S-HDT/ASCT + consolidation vs. S-HDT/ASCT. A hazard ratio <1 favors the first treatment listed in the comparison title. S-, single; D-, double; HDT, high-dose therapy; ASCT, autologous stem cell transplantation; CrI, credible interval.

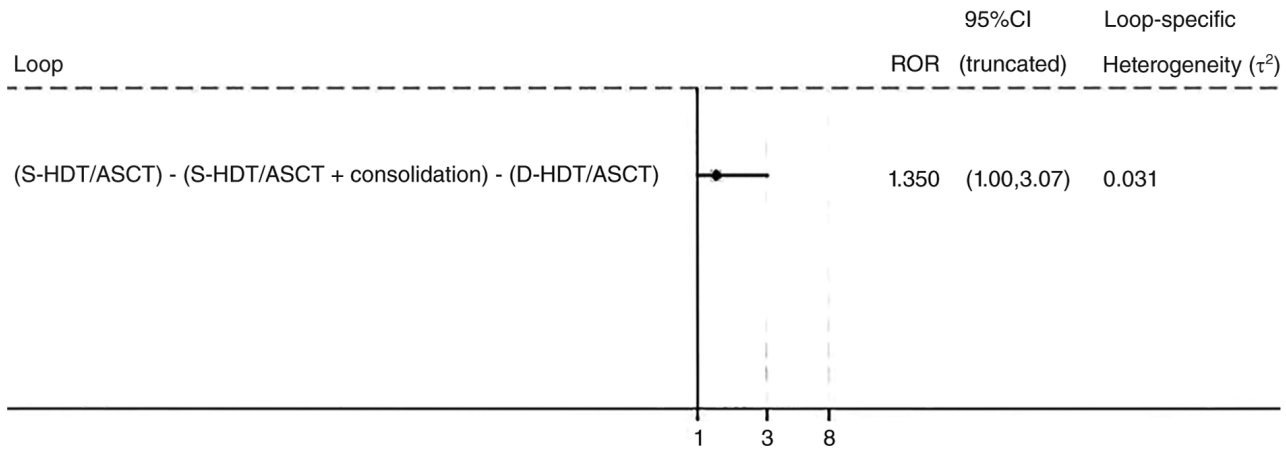


Figure 9. Loop-specific inconsistency test for the network meta-analysis for overall survival. The RORs with its 95% CI and the estimated heterogeneity ($\tau^2$) are presented for the closed loop: (S-HDT/ASCT)-(S-HDT/ASCT + consolidation)-(D-HDT/ASCT). An ROR of 1 indicates perfect consistency between direct and indirect evidence. S-, single; D-, double; HDT, high-dose therapy; ASCT, autologous stem cell transplantation; ROR, ratio of odds ratio; CI, confidence interval.

historical overviews of ASCT (44,45). Whilst these studies do not directly contradict the findings of the present study, they underscore the complexity of the treatment landscape in which the analysis is positioned. The collective evidence from these publications (33-45) confirms the ongoing relevance of the present work and its consistency with an expanding body of literature that advocates for a risk-adjusted approach to treatment intensification.

Notably, the network meta-analysis performed in the present study introduces a refined perspective to clinical decision-making. It was demonstrated that there was no statistically significant difference in the extension of PFS or OS between double HDT/ASCT and single HDT/ASCT followed by consolidation therapy. This implies that the strategy for intensifying treatment in high-risk patients may not be exclusively confined to a second transplant; potent, drug-based consolidation could represent an alternative method to improve clinical outcomes. This aligns with the evolving treatment paradigm wherein novel agents are being incorporated into all phases of MM therapy (3,4,28). However, it is imperative to acknowledge a marked limitation of the present analysis: The majority of the included trials were performed during a period when the use of contemporary induction regimens and maintenance therapy was limited. The BMT CTN 0702 trial (17), which integrated both consolidation and maintenance therapy into its design, did not demonstrate superior outcomes for double ASCT over single ASCT with consolidation, suggesting the potential for modern drug-based strategies to reduce the necessity for a second transplant. Consequently, a pivotal and still unresolved question is whether double ASCT remains superior to single ASCT followed by effective consolidation and maintenance therapy in high-risk patients who have been treated with modern triplet or quadruplet induction regimens. Therefore, there is a pressing need for future clinical trials that directly compare these two intensification strategies within the context of contemporary therapeutic protocols.

Beyond the evidence from randomized trials, several large real-world studies have also investigated the role of double ASCT. Although these analyses are susceptible to potential selection biases, they offer valuable insights into the effectiveness of this strategy in broader, more heterogeneous clinical practice settings. For example, a large registry analysis by Côté *et al* (46) reported superior survival outcomes with double ASCT compared with single ASCT in high-risk patients, particularly those with high-risk cytogenetic profiles. This finding aligns with the results of the present study and strengthens the generalizability of the conclusion that high-risk patients derive the most benefit from transplant intensification, defined as the administration of a second, sequential high-dose therapy followed by autologous stem cell transplantation (double ASCT) within 6 months of the first procedure (10). The convergence of evidence from both rigorous RCTs and extensive real-world data reinforces the potential value of double ASCT as a strategic option for this challenging patient population.

However, several limitations inherent in the present study should be considered. First, the number of studies available for the high-risk subgroup meta-analysis was relatively small, which prevented more detailed analyses, such as those based on the number of risk factors or specific types of high-risk features [such as del(17p) vs. t(4;14)]. Second, the definition of 'high-risk' was not uniform across the included trials, incorporating clinical, biochemical and cytogenetic factors, which introduced a degree of heterogeneity into the analysis. Third, the applicability of the findings to patients receiving current standard-of-care induction and maintenance therapy remains uncertain.

Notwithstanding the aforementioned limitations, the present study provides robust evidence to support the use of double ASCT for patients with MM with high-risk characteristics. Moreover, it helps to reconcile previously contradictory literature by emphasizing risk status as a pivotal factor determining which patients are most likely to benefit.

In conclusion, the results of the present study indicate that double HDT/ASCT exhibits a safety profile comparable with that of single HDT/ASCT. Patients with high-risk MM may obtain significant survival benefits from undergoing double HDT/ASCT, which should be considered a valuable therapeutic alternative for this specific population.

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**Availability of data and materials**

The data generated in the present study may be requested from the corresponding author.

**Authors' contributions**

WC and HC conceived the study and developed its design. SQ performed literature search and screening, data extraction from eligible studies, and prepared the initial draft of the manuscript. LZ conducted data extraction, quality assessment using the RoB 2 tool, and contributed to the preparation of summary tables. YL performed the formal meta-analysis and network meta-analysis, including all statistical analyses. QZ, PZ, FD, JC, XX and DL participated in data curation, verification of extracted data and critical review of the manuscript. SQ, YL and LZ confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

**Ethics approval and consent to participate**

Not applicable.

**Patient consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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