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**Association Between Transfusion Status and Overall Survival in Patients With Myelodysplastic Syndromes: A Systematic Literature Review and Meta-Analysis**

**Running head:** Transfusion Independence and OS in Patients With MDS

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**Abstract**

Introduction: Multiple studies show transfusion independence (TI) in myelodysplastic syndrome (MDS) has a positive impact on overall survival (OS). To assess this, a systematic review and meta-analysis of the association between TI and OS in patients with MDS was conducted (PROSPERO ID: CRD42014007264). Methods: Comprehensive searches of five key bibliographic databases were conducted and supplemented with additional search techniques. Included studies recruited adults aged >18 years with MDS and examined the impact of transfusion status on OS. Results: 55 studies (89 citations) were included. The vast majority reported a statistically significant HR for OS in favour of TI patients, or patients who acquired TI after treatment. A random effects meta-analysis was conducted. Patients classed as TI at baseline showed a 59% decrease in the risk of death compared with transfusion dependent (TD) patients (HR 0.41; 95% credible interval (CrI): 0.29, 0.56), and this effect did not appear to interact significantly with illness severity (interaction coefficient HR 1.3895% CrI: 0.62, 3.41). Meta-analysis of studies where patients acquired TI was not possible, but consistently reported a survival benefit for those who acquired TI. Conclusion: The findings revealed a 59% pooled reduction in mortality among TI patients when compared with TD patients.

**Keywords:** Myelodysplastic syndrome; transfusion dependence; overall survival; systematic review; meta-analysis

**Introduction**

Primary myelodysplastic syndromes (MDS) are heterogeneous clonal disorders characterized by bone marrow failure manifesting as cytopenia(s) and varying propensity to transformation to acute myeloid leukemia (AML). The prognostic importance of anemia and subsequent transfusion status in patients with MDS has been recognized. In 2007, Malcovati et al[1] proposed the World Health Organization (WHO) classification–based prognostic scoring system which replaced the International Prognostic Scoring System (IPSS) cytopenia category with transfusion dependence (TD). The depth of anemia correlates with TD and poor outcomes in MDS[2]. The precise reasons for the impact of transfusion status remain unclear, although it may be an indicator of underlying disease severity[3] and transfusions may lead to iron overload, which can cause organ dysfunction and death.[4;5]

Although the prognostic significance of TD is widely acknowledged, no systematic review has assessed the impact of transfusion status on overall survival (OS) in patients with MDS. It is also unclear whether the association varies by illness severity (although isolated studies have provided some analysis of this)[6-9] and whether the association holds for patients who achieve transfusion independence (TI) through treatment. This study aimed to conduct a systematic review and meta-analysis of the association between OS and TI in patients with MDS. It further aimed to assess whether the association is modified by patient risk category and to assess the association in those who acquired TI through treatment.

**Methods**

The systematic review followed the principles recommended in the PRISMA statement.[10] The protocol is published in the PROSPERO database (http://www.crd.york.ac.uk/PROSPERO; record CRD42014007264).

Searches

Comprehensive electronic searches were conducted in 5 key bibliographic databases (MEDLINE, EMBASE, Cochrane Library, CINAHL, Science Citation Index), from inception through January 13, 2014, and updated in MEDLINE only on May 7, 2014. Sensitive key word strategies using free text and thesaurus terms were developed. Boolean operators and database-specific syntax were used to combine synonyms related to MDS and TD. Terms related to survival outcomes were not used because a scoping search found these were too restrictive due to a lack of survival outcome reporting in abstracts. Searches were limited to human studies only. An example of the search strategy used (from MEDLINE) is available as a supplementary appendix online. Relevant conference proceedings were searched electronically, experts were contacted for additional studies, grey literature (guidelines, unpublished and unindexed studies) was searched online, and reference lists of relevant reviews and guidelines were checked to ensure data saturation.

Study selection

Studies were included if they recruited adults aged > 18 years with a confirmed diagnosis of MDS and reported OS for TI patients vs TD patients. Studies recruiting > 20% pediatric or primary AML patients were excluded. Studies were not excluded on the basis of changes in MDS definitions. Studies with any proportion of patients with AML secondary to MDS were

included. Studies recruiting any patients with conditions other than these were excluded. Transfusion status expressed (or calculable) as units transfused per unit time was acceptable; however, total units transfused was not acceptable because this is not an indicator of degree of dependence. Studies comparing patients who acquired TI (eg, through treatment) with those who did not were included but analyzed separately. Any expression of OS was acceptable, although only hazard ratios (HRs) were included in the meta-analysis. Studies only reporting predicted survival, progression-free survival, or composite outcomes such as "survival or progression to AML" were excluded. Studies with follow-up of < 6 months were excluded because short follow-ups may miss effects of transfusion status. Studies with unclear follow-up length were included to avoid excluding potentially relevant studies on the basis of poor reporting. Randomized controlled trials (RCTs), cohort studies, consecutive case series of ≥ 10 cases, before-after studies, and case-control studies were included. Non–English-language studies were included if an English-language abstract described study type, population, and outcome in sufficient detail.

Data extraction

A standardized data extraction form was developed following the recommendations in the Centre for Reviews and Dissemination handbook[11] and piloted on studies of different designs. Data were extracted by one reviewer and checked by another. Disagreements were resolved through discussion or involvement of a third reviewer.

Quality assessment

Study quality was assessed using the validated Quality in Prognosis Studies (QUIPS) tool[12] adapted for this review. All items were included, and scored as low risk, high risk, or unclear risk (moderate and unclear risk as defined in the QUIPS guidelines). These included assessment of: representativeness of study sample (selection bias), difference in key patient characteristics between those excluded or lost and those included (attrition bias), differences in TD measurement in those who survived vs those who did not (prognostic factor measurement bias), differences in OS measurement in TD vs TI patients (detection bias), how potential confounders were dealt with (confounding), and appropriateness of statistical analysis (statistical analysis and reporting bias). Potential confounders of highest priority were IPSS or cytogenetics, WHO stage, and age. Studies were scored for confounding according to whether some (unclear risk), all (low risk), or none (high risk) of these characteristics were accounted for in analysis. For the statistical analysis item, studies scored unclear when the Kaplan-Meier curves or multiple cox regression analyses were not conducted or high risk when neither were conducted.

Narrative synthesis

A narrative synthesis, including tabulation of results and a consideration of clinically meaningful patterns, was conducted. Data were grouped by risk category of included patients and study type. Cohorts were classed as high risk if inclusion was restricted to IPSS int-2[13], patients with high-risk disease, or those in WHO MDS subgroups[14] with excess blasts. Conversely, low-risk cohorts comprised studies that restricted inclusion to IPSS low- or int-1–risk categories or WHO MDS subgroups without excess blasts. When both classifications were reported, the IPSS was preferred. Cohorts including both patients with high- and low-risk disease were classed as "unselected."

Meta-analysis

Meta-analyses were conducted for studies that presented HRs. A Bayesian Markov chain Monte Carlo approach was conducted in WinBUGS, with a random-effects model to allow heterogeneity in the effect of TI on OS across studies. When HRs were expressed for TD rather than TI, the ratio was converted by dividing 1 by the reported HR.

Multiple Cox regression analyses were selected when presented because these corrected for confounding variables. To avoid double counting, only nonoverlapping cohort studies were included. When studies overlapped each other, 1 study was selected for inclusion in the meta-analysis by excluding studies with the narrowest patient spectrum (eg, studies that only recruited patients who had an allogeneic stem cell transplant); studies with less adequate covariate adjustments in multiple Cox regression analysis (see definition in quality assessment section); studies in which another study included additional patients (eg, 2 extra years of data, abstracts when a full journal article was available); studies lacking of recruitment date or location information which prevented an assessment of overlap. For studies with unreported standard error, 95% CI, or exact P value (eg, only reported P < .001), the P value was treated as the exact P value in the analysis (eg, P = .001 when P < .001 was reported).

Sensitivity analyses were conducted which included univariate Cox regression analyses when multiple Cox regression analyses were not presented and included studies that only reported Kaplan-Meier curves. For the latter, Kaplan-Meier curves were digitized and patient-level data were reconstructed using the approach published in Guyot et al[15] to obtain the

estimated HR. A meta-regression was conducted to investigate whether the effect of TI on OS differed according to patient risk category.

**Results**

The total number of unique records considered for inclusion was 1842 (Figure 1). Of these, 1641 were identified through electronic searching, of which 80 were included in the review. Expert sources and chance find articles contributed 4 additional articles. The reference lists of 45 reviews were checked for titles not retrieved by electronic searches, and 186 additional unique titles were considered for inclusion. Of these, 5 met the inclusion criteria and were selected for the review. No further unique titles were identified from the final reviews checked thus achieving data saturation. In total 89 articles were included in the review, representing 55 separate, but often overlapping, data sets. All studies and their parallel publications (in which no unique patients were analyzed) are listed in Table 1.

Risk of bias

Measurement of TD and OS was consistent in most studies, and statistical analyses were appropriate in most cases (ie, log-rank test in univariate analyses, with multiple Cox regression models for > 1 covariate) (Figure 2). There was a low risk of attrition bias in approximately 50% of studies, with unclear reporting of attrition being a common issue. Many studies exhibited issues with cohort representativeness (eg, studies only including participants with available bone marrow biopsies) and covariate adjustment. A diagrammatic representation of the risk of bias assessment for each study is included in the online appendix (Supplementary Figure 1).

Narrative synthesis

Three main study types were identified: A) studies that recruited both TD and TI patients at baseline and compared OS between these 2 groups (generally retrospective cohort studies), B) studies that recruited only TD patients and compared the OS of those who became TI after treatment with those who remained TD (generally RCTs), and C) studies that recruited only TD patients at baseline and compared the OS of those with a high transfusion burden with those with a low transfusion burden (generally retrospective cohort studies); the same cutoff point was sometimes used to categorize patients as low burden in these studies as was used to categorize TI in type A studies, but patients with no transfusions were missing from these studies. Most data sets (n = 43, reported across 70 publications) were type A, 4 were type B (reported across 9 publications), and 5 were type C (Table 1). Three studies were not study type A, B, or C: Rojas et al[16] recruited all TI patients at baseline and compared OS in those who became TD with those who did not, whereas both Jädersten et al[17;18] and List et al[17;18] analyzed transfusion status as a continuous variable.

The studies were conducted in different countries and settings, most commonly in the United Sates, followed by Italy and Germany. Several included patients from > 1 country or center. Most (n = 36) did not select patients on the basis of risk (unselected cohorts), although 16 were conducted with patients with low-risk disease only and 3 with high-risk disease only. Two unselected cohorts[6;19] reported a low-risk subgroup analysis, and 1 study[9] reported both high- and low-risk subgroup analyses in separate publications.[7;8] The risk group was unclear in 1 study and was categorized as unselected.[20] Study cohort size ranged from 37[21] to 9820.[22] However, the total number of patients included in the review is unclear because

multiple studies drew patients from the same locations over overlapping time periods, and cohorts or parts of cohorts were often included in several studies (Table 1).

Results from each study are presented in Tables 2-5. To minimize impact of double counting participants on the narrative synthesis, studies that drew data from patient cohorts that were entirely independent from each other are listed first. Studies that drew data from overlapping (or potentially overlapping) patient cohorts are grouped together, and studies for which this could not be ascertained are also grouped together.

As seen from Tables 2-5, TI was consistently associated with an OS benefit for patients with MDS, and the effect was usually statistically significant, with only a few exceptions.

For study type A (Table 2), 34 studies reported HR or significance of HR in multiple Cox regression analyses. Usually expressed as TD vs TI (for which values > 1 indicated better survival for TI patients), HRs ranged from 1.04 (95% CI, not reported [NR]; P = .85)[7] to 10.95 (95% CI, 3.19-37.53; P < .001)[6]. Studies that recruited only patients with high-risk disease had a lower range of HRs in multiple Cox regression analyses (1.04; 95% CI n.r.; p=0.85 and 1.9; 95% CI 1.4-2.6; p≤0.0001)[7;23] than studies that recruited only patients with low-risk disease (HR range, 1.548 [95% CI, 1.092-2.195; P = .014] to 10.95 [95% CI, 3.19-37.53; P < .001]),[6;24] and in 2 of the 3 high-risk studies, the HR was nonsignificant.[7;25] Of the 34 studies, only 7 did not report a statistically significant HR.[7;26-31]

Other analyses reported in type A studies included mean and median survival times, mortality rates at a point in time, and univariate Cox regression analyses. In all cases, a numerically favorable survival was reported for TI. Of 37 studies for which statistical significance was reported, only 5 studies reported a nonsignificant difference.[26;28-30;32]

All but 2 type B studies drew patient data from one or both of the lenalidomide trials, MDS-003 and MDS-004, and recruited del(5q) patients with low-risk disease. The HRs from multiple Cox regression analyses, expressed as TI vs TD (for which values < 1 indicated better survival for TI patients) ranged from 0.3584 (95% CI, NR; P < .001)[33] to 0.53 (95% CI, 0.31-0.91; P = .021)[34] and were statistically significant, apart from 1 that drew a small sample of patients with bone marrow samples available (n = 39) from the MDS-003 trial[35]. Other analyses of the MDS-003/004 trials reflected a survival advantage for patients achieving TI. Of the two studies that were not an analysis of MDS-003/004, one recruited patients with high-risk disease and treated them with azacitidine [36] and the other was a reanalysis of two decitabine trials [62]. Both studies reported that achieving TI was associated with a lower risk of death (table 3).

All type C studies, whether low risk or all risks, reported that low-burden TD was associated with better OS compared with high-burden TD (Table 4). HRs were sometimes unexpectedly high (78.1 [95% CI, NR; P < .05][21], although this particular analysis had only 14 patients. Large differences in the HRs reported for patients with low-risk disease (range, 1.056-78.1) prevented drawing any meaningful observations about whether the association between low-burden TD and OS was different in low- or all-risk studies. The re-analysis of MDS-003/004 data[37] showed only a small HR between low-burden and high-burden TD patients.

Meta-analysis
Analysis 1: meta-analysis of all eligible studies (study type A)
Ten studies[6;9;19;24;38-43] were included in the meta-analysis of type A studies (regardless of risk category) reporting the multiple Cox regression analysis HR for OS of TI patients compared

with TD patients. Analyzed cohort size ranged from 63[6] to 840.[40] Only low- and all-risk subgroups were included in the analysis because none of the 3 studies that recruited patients with high-risk disease were eligible for inclusion due to 1) overlap of the patient cohort with other studies,[23] 2) multiple Cox regression analysis in Komrokji et al[7] had already corrected for transfusion status, and 3) data were not reported for univariate or multiple Cox regression analyses (Table 4)[25] Two of 10 studies[24;39] selected only patients with low-risk disease, whereas the rest selected patients with any severity or risk disease. The meta-analysis showed that TI was associated with a 59% decrease in the risk of death compared with TD (HR, 0.41 [95% credible intervals (CrI), 0.29-0.56]; Figure 3). The estimated between-study SD was 0.39 (95% CrI, 0.18-0.83), implying moderate heterogeneity between studies in the effects of TI.

A sensitivity analysis was conducted to check the robustness of the estimates by including studies that had reported univariate Cox regression analyses but not a multiple Cox regression analysis[44] and studies that had only published Kaplan-Meier curves[26;45-47]. In it TI was associated with a 59% decrease in the risk of death compared with TD (HR, 0.41 [95% CrI, 0.32-0.51]; Figure 4). The estimated between-study SD was 0.32 (95% CrI, 0.16-0.59).

Analysis 2: meta-regression for different patient risk categories (study type A)

A random-effects meta-regression analysis was conducted to assess whether the effect of TI on OS depended on the risk group of the patients included. The same 10 studies used in analysis 1 were included.

The estimated coefficient of the interaction term was HR of 1.38 (95% CrI, 0.62-3.41), which indicated the possibility of no interaction. Hence, the meta-regression suggested that the magnitude of the benefit on OS from TI was higher for all risk groups, but this was inconclusive.

The analysis also showed that TI was associated with a 62% decrease in the risk of death compared with TD for the all-risk groups (HR, 0.38 [95% CrI, 0.25-0.55]) and with a 47% decrease in the risk of death compared with TD for low-risk groups (HR, 0.53 [95% CrI, 0.25-1.12]). The estimated between-study SD was 0.41 (95% CrI, 0.19-0.92), which implied moderate heterogeneity between studies in the effects of TI.

The sensitivity analysis including studies that did not use multiple Cox regression showed that TI may have had more benefit on OS among the all-risk groups, but again the effect was inconclusive (HR of low-risk group vs all-risk group, 1.45 [95% CrI, 0.87-2.50]). It also showed that TI was associated with a 62% decrease in the risk of death compared with TD in the all-risk groups (HR, 0.38 [95% CrI, 0.29-0.48]) and with a 45% decrease in the risk of death compared with TD in the low-risk groups (HR, 0.55 [95% CrI, 0.35-0.87]). The estimated between-study SD was 0.31 (95% CrI, 0.16-0.59).

Analysis 3: patients who achieved TI during the course of the study (study type B)

A meta-analysis was also planned to assess the impact on OS of becoming TI for patients who were TD at baseline potentially including 3 studies.[33;34;48] However, there was too much overlap in the study cohorts to permit a meta-analysis.

**Discussion**

This systematic review is the first to investigate the benefits of being (study type A) or becoming TI (study type B) on OS among patients with MDS. The narrative synthesis of findings revealed a consistent reduction in mortality among TI patients compared with TD patients, in both those who were TI at recruitment and those who achieved TI through treatment. In this meta-analysis,

the reduction in mortality was estimated to be 59% for those who were TI at recruitment compared to those who were TD at recruitment, when all risk categories were included (analysis 1). No meta-analysis was possible for studies in which patients achieved TI through treatment (analysis 3), but the 59% estimate for those who were TI at recruitment falls within the range of reductions for those who achieved TI through treatment (47% to 64% [HR range, 0.53-0.36]).

The meta-regression of different risk categories was limited by the small number of studies reporting HRs in high- (n = 0), low- (n = 2), and all (n = 9) risk categories for study type A. The test for an interaction between risk group and the effect of TI on OS suggested the possibility of no interaction by risk group because the CrI for the interaction was inconclusive. Narrative results for high-risk studies suggested a much lower range of HRs compared with all-risk and low-risk studies, but the range of CI cross over between low- and high-risk groups (Table 2). Hence, it is currently impossible to determine whether there is a differential effect of TI on OS depending on risk category of patients. Compounding this, 1 limitation for both analysis 1 and 2 is that the all-risk group studies were treated the same regardless of the proportions of risk categories within each study because not all studies reported these data.

Studies that recruited all TD patients at baseline and compared those with higher transfusion burden with those with lower (type C studies) had a very wide range of HRs, preventing any meaningful conclusions being drawn. Among these were 2 re-analyses of MDS-003/004 data, which reported the smallest HRs in this analysis set. This may be a product of lenalidomide treatment, which may alter the relative risk of death between high- and low-burden patients compared with untreated patients.

A small number of studies (n = 8)[7;25-29;31;35] reported that the survival difference between TD and TI patients did not reach statistical significance in multiple Cox regression

analyses. These studies had some unusual characteristics. Komrokji et al[7] and Cermak et al[25] were both conducted in patients with high-risk disease, in whom the expected OS may have been too short to show a significant benefit. Platzbecker et al[28] and Cermak et al[25] selected patients who had undergone allogeneic stem cell transplant, with Platzbecker et al[28] suggesting that this intervention may be protective against the prognostic disadvantage of transfusion requirement. Buesche et al[35] selected a small subsample of del(5q) patients with available bone marrow samples from the MDS-003 trial, which may have resulted in underpowering, or spectrum bias, both of which could have contributed to the nonsignificant result. Wallvik et al[26] treated anaemic (TD and TI) patients with epoetin and corrected for epoetin response. However, a greater proportion of TI patients responded (54%) than TD patients (21%), therefore, correcting for response is in part correcting for transfusion status. Rojas et al[16] was unique because it recruited all TI patients at baseline and followed them through disease progression, whether treated or untreated. The comparison was median survival, which at last follow-up had not been reached in the TI group, and therefore, the analysis may not reflect the true survival difference between groups. Finally, the patients in Lim et al[29] had been treated with antithymocyte globulin, an intervention that aims to promote hematologic response. Indeed, it appears that the analysis in this study was for baseline TI, which may be confounded by the $\approx 30\%$ of TD patients who became TI during treatment. The impact of these treatments and patient characteristics on the relationship between TI and OS, however, remains under-researched and is worth exploring in future trials and cohort studies. One further study reported nonsignificant results in 1 analysis[32] in which only those with < 5% blasts and $\geq 1\%$ ring sideroblasts were selected but a significant HR in the 2 other analyses in which all patients were selected[31] and only those with > 15% ring sideroblasts were selected.[49]

This systematic review has been conducted to high standards following an a priori protocol published in the PROSPERO database. It included comprehensive search techniques that reached data saturation, validation of study selection and data extraction, quality assessment of included studies, an inclusive narrative synthesis, and bespoke meta-analysis. It represents the first formal meta-analysis of this association using a systematic review, and care was taken to avoid double-counting within a very challenging data set.

Study limitations and future research

The definition of TI varied across the literature and was frequently unreported. This may have affected the meta-analysis results, and the potential impact of TI definition on HRs is worthy of further investigation. Due to a lack of suitable data, no meta-analysis was performed for high-risk cohorts and the meta-analysis for low-risk disease included only 2 studies, meaning that the effect of TI within this group was associated with considerable uncertainty. The exclusion of non–English-language studies may have resulted in relevant data being missed. Additionally, the search strategies and study selection process relied on terms included in the abstract. This potential problem was mitigated through the checking of references from a large number of relevant reviews (n = 45) to data saturation, which yielded 6 additional included studies. It is therefore likely that most relevant studies were included.

In conclusion, previous studies have suggested that patients with MDS who are TI have better survival relative to those who are TD, but no meta-analysis had been conducted to date. Our findings revealed a consistent, substantial reduction in mortality among TI patients compared with TD patients, confirming the positive TI-OS association. A meta-regression

indicated that the impact of TI was higher in all-risk cohorts vs low-risk cohorts, but this effect was inconclusive. A similar association was seen for those who acquired TI through treatment.

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**Table 1. Study and Participant Characteristics**

| Author/Year | Location/Setting | Overlap and Recruitment Dates | No. of Patients Analyzed | Risk Category | Specific Inclusion/ Exclusion Criteria | Prevalence of TD |
|---|---|---|---|---|---|---|
| | | | | **Inclusion Criteria** | | |
| | | | | Risk Category | Specific Inclusion/ Exclusion Criteria | |
| **Study Type A** | | | | | | |
| **Unselected by Risk** | | | | | | |
| **Italian Cohorts** | | | | | | |
| Alessandrino 2010[59] 1 parallel publication[80] | Italy: multiple sites | O: 1997-2007 | Unclear if 325 or 328 | All | With ASCT | 68% or 69% |
| Crisa 2012[6][a] | Italy: Torino | I: 2001-2007 | Unclear | All | Not eligible for ASCT | 70% |
| Malcovati 2011[40] 6 parallel publications[1;81-85] | Italy: Pavia | O: 1992-2007 | 840 | All | | 35% |
| Salvi 2007[54] | Italy: Piedmont | I: 1999-2004 | 202 | All | | 65% |
| Voso 2013[42] | Italy: Rome (multiple sites) | U: 2001-2011 | 380 | All | Available data | 72% |
| **US Cohorts** | | | | | | |
| Goldberg 2009[51] 1 parallel publication[41] | Hackensack, NJ | I: 2003 | 585 | All | > 65 years | 39% |
| Johnson 2013[20] | Stanford, CA | I: NR | 64 | Unclear | | NR |
| Lulla 2011[45] | Houston, TX | I: 2000-2008 | 88 | All | Veterans (mostly men) | 65% |
| Uno 2013[22] | United States | U: 2001-2007 | Unclear (9820 identified) | All | | NR |
| Wong 2005[56] | Texas | I: NR | 51 | All | | 65% |
| Komrokji 2012[9][a,b] 4 parallel publications[7;8;57;86] | Tampa, FL (Moffitt Cancer Center) | O: 2001-2009 | 775 | All | | 46% |
| Pardanani 2012[44] | Rochester, MN (Mayo Clinic) | U: NR | 78 | All | MDS with bone marrow and plasma samples | 51% |
| Patnaik 2012[32] | | U: NR | 200 | All | With bone marrow samples and cytogenic evaluation, < 5% blasts and ≥ 1% RS | 17% |
| Patnaik 2012[31] 1 parallel publication[87] | | O: 2000-2005 | 277 | All | With bone marrow samples and cytogenic evaluation | 19% |
| Patnaik 2012[49] 1 parallel publication[88] | | U: NR | 107 | All | With bone marrow samples and cytogenic evaluation, > 15% RS | 27% |
| Quintás-Cardama, 2011[58] | Houston, TX (MD Anderson Cancer Center) | O: 1998-2007 | 279 | All | MDS secondary to treatment | NR |
| Tong 2012[27] | | O: 1993-2007 | 169 | All | MDS and < 20% bone marrow blasts | 53% |
| Kadia 2011[62][c] | | U: NR | 96 | All | Excluding erythropoietin treated | 49% |

| **European Cohorts** | | | | | | |
|---|---|---|---|---|---|---|
| Damm 2013[38] | France: Paris, Marseille (Hôpital Cochin) | O: 1999-2011 | 209 | All | | 48% |
| Kulasekararaj 2013[43] | United Kingdom: London (King's College) | U: 2004-2010 | 318 | All | With bone marrow samples | 55% |
| Lim 2007[29] | United Kingdom, Germany, Italy | U: NR | 96 | All (80% low risk) | Treated with ATG | 82% |
| Platzbecker 2008[28] 2 parallel publications[89;90] | Germany, Austria, United States | U: NR | 172 | All | De novo MDS with HSCT and GCSF | 76% |
| Thol 2011[63] 2 parallel publications[91;92] | Germany | U: NR | 154 | All | | 81% |
| Arnan 2011[60] 1 parallel publication[61] | Spain: Catalan | U: NR | 479 | All | | 31% |
| Sanz 2008[64] | Spain | U: NR | 902 | All | De novo MDS | 37% at diagnosis (23% during follow-up; 60% at any point) |
| Savic 2012[65] | Serbia | U: 1990-2009 | 67 | All | With bone biopsies | NR |
| Wallvik 2002[26] | Sweden, Denmark | I: 1989-1995 | 64 | All | Anemic only | 64% |
| **Other Areas** | | | | | | |
| Awidi 2009[46] | Jordan | I: 1985-2007 | 66 | All | | 76% |
| Demirkan 2007[50] | Turkey: Izmir | I: 1992-2005 | 113 | All | | NR |
| Hiwase 2013[19] | Australia: Darwin, Adelaide, Bedford Park | I: NR | 182 | All | De novo MDS, excluding ASCT and other treatments | 63% |
| Kim 2010[52] | South Korea: 12 sites | I: 2006-2007 | 113 | All | Treated with azacitidine | 76% at baseline |
| Park 2008[53] | South Korea | I: 1995-2006 | 149 | All | With cytogenetic results | 68% |
| Li 2008[66] | Hong Kong | U: 1994-2007 | 142 | All | Excluding RAEB-T | NR |
| Wei 2009[55] | China | I: 2002-2007 | 100 | All | De novo MDS | 60% |
| **Low Risk** | | | | | | |
| **US Cohorts** | | | | | | |
| Chee 2008[67] | United States | U: NR | 115 | Low | | 38% |
| Patnaik 2010[70] | Rochester, MN (Mayo Clinic) | O/I[c]: 1989-2009 | 88 | Low | del(5q) | 69% |
| Komrokji 2012[8] | Tampa, FL (Moffitt Cancer Center) | O/I[c]: 2001-2009 | 479 | Low | | 42% |
| **European Cohorts[d]** | | | | | | |
| Cermak 2009[30] 3 parallel publications[93-95] | Czech Republic | I: 1982-2004 | 137 | Low | TI after erythropoietin treated excluded | >0.1 units/month: 87% >1.1 units/month: 66% >2.1 units/month: 44% >3.0 units/month: 28% |
| de Swart 2011[68] | EUMDS network | U: 2008-2010 | Unclear (1000 | Low | | 43% |

| 2 parallel publications[96;97] | | | identified) | | | |
|---|---|---|---|---|---|---|
| Durairaj 201 [47] | Scotland | I: 2000-2010 | 159 | Low | | 31% |
| Falantes 2013[24]<br>1 parallel publication[98] | Spain | I: 1990-2010 | 332 | Low | | 53% |
| Germing 2012[39] | Germany, Austria, Switzerland, Greece, Czech Republic, United States, Australia, France | U: NR | 327 | Low | del(5q) | 42% |
| Kelaidi 2013[69] | France: multiple sites | U: 2006 to 2009 | 95 | Low | All anemic | 46% |
| **Other Areas** | | | | | | |
| Hiwase 2013[19] | Australia: Darwin, Adelaide, Bedford Park | O/I[c]: NR | NR | Low | De novo MDS, excluding ASCT and other treatments | 51% |
| **High risk** | | | | | | |
| Cermak 2010[25]<br>1 parallel publication[95] | Czech Republic | O/I[c]: 1990-2010 | 43 | High | With ASCT | NR |
| Itzykson 2011[23]<br>1 parallel publication[71] | France: multiple sites | U/I[c]: 2004-2009 | 282 | High | Treated with AZA | 45% |
| Komrokji 2011[7] | Tampa, FL (Moffitt Cancer Center) | O/I[c]: 2001-2009 | 139 | High | none | 58% |
| **Study Type B** | | | | | | |
| **Low Risk** | | | | | | |
| **MDS 003 Trial** | | | | | | |
| Buesche 2011[35] | Germany | O: NR | 39 | Low | del(5q), with bone marrow samples | 100% (54% became TI during treatment) |
| **MDS 004 Trial** | | | | | | |
| Fenaux 2011[34]<br>3 parallel publications[33;48;99] | 37 sites in United Kingdom, Belgium, France, Italy, Germany, Spain, Netherlands, Sweden, Israel | O: 2005-2007 | 139 | Low | del(5q) | 100% at baseline (39% became TI during treatment) |
| | | O: 2005-2007 | 138 | Low | del(5q) | NR |
| | | O: 2005-2007 | 135 | Low | del(5q) | 100% (33% TI during treatment) |
| **MDS 003 and MDS 004 Trials** | | | | | | |
| Fenaux 2011[72] | United States, United Kingdom, Belgium, France, Italy, Germany, Spain, Netherlands, Sweden, Israel | O: 2003-2007 | 148 | Low | del(5q), < 65 years | 100% (56% TI became during treatment) |
| Sekeres 2011 [33] [e-g] | Multicenter European sites only | O: 2003-2007 | 268 | Low | del(5q), low risk | 100% (% achieving TI NR) |
| **Crossover With MDS 004** | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Sánchez-García 2014[74] | Spain: multiple sites (17 patients from MDS 004) | O: unclear | 215 | Low | Low or int-1 IPSS score, with cytogenic evaluation, no previous chemotherapy or radiotherapy | 100% at baseline (42% became TI during treatment) |
| **High Risk** | | | | | | |
| Seymour 2010[36] 1 parallel publication[100] | Australia, Italy, France, Germany, Spain | O/I[c]: 2004-2006 | 111 | High | | 100% at baseline (55% became TI during treatment) |
| **Study Type C** | | | | | | |
| **Unselected by Risk** | | | | | | |
| Chan 2011[21][a] | Canada | I: 1998-2011 | 37 | All | | 100% (low: 65%; high: 35%) |
| Musto 2010[76] 1 parallel publication[77] | Italy | U: 1998-2002 | 192 | All | No previous chemotherapy, no CMML and RAEB-T | 100% |
| **Low Risk** | | | | | | |
| Kuendgen 2011[37] 1 parallel publication[79] | Europe, United States, Australia (MDS 003 and MDS 004 plus other registry data) | O/U: NR (assume 2003-2007) | 420 | Low | | 100% |
| Rose 2010[78] | France: multiple sites | O/U: May-June 2005 | 97 (only low risk included) | Low | | 100% |
| Delforge 2014[75] | Belgium: multiple sites | U: NR | 127 | Low | Low-risk patients, treated with various treatments and no treatment | NR (assume 100%) |
| **Other Study Types** | | | | | | |
| Jädersten 2008[17] | Sweden, Italy, Norway (comparison of RCT cohort with Italian database) | I: 1990-1999 | 358 | All | Some exclusions | 48% (transfusion status analyzed as continuous variable) |
| List 2008[18] | Germany | O: 2003-2004 | 155 | Low | | NA (transfusion status analyzed as continuous variable) |
| Rojas 2014[16] | Spain: multiple sites | O: September-November 2008 | 84 | Low | Low-risk patients with del(5q) and TI at baseline | 61% became TD during treatment |

ASCT, autologous stem cell transplant; ATG, antithymocyte globulin; AZA, azacitidine; CMML, chronic myelomonocytic leukemia; EUMDS, European LeukemiaNet MDS registry; GCSF, granulocyte colony-stimulating factor; HSCT, hematopoietic stem cell transplant; I, independent cohort; IPSS, International Prognostic Scoring System; MDS, myelodysplastic syndromes; NA, not available; NR, not reported; O, overlapping cohort; RAEB-T, refractory anemia with excess blasts in transition; RCT, randomized controlled trial; RS, ringed sideroblasts; TD, transfusion dependence; TI, transfusion independence; U, extent to which cohort is independent or overlapping is unknown.

[a] Also reports low-risk subgroup data.
[b] Also reports high-risk subgroup data.
[c] Also reports results for study type B.

[d] All European cohorts may overlap with de Swart et al 2011 (85).
[e] Data cohort does not overlap with other high- or low-risk studies of the same study type but may (U) or does (O) overlap with all-risk studies.
[f] Also reports results for study type C.
[g] Also analyzes transfusion status as a continuous variable for low-risk patients (see "other study types").

**Table 2. Study Type A Results**

| Risk | Author/Year | Estimate of TD Effect HR From Multiple Cox Regression(95% CI; P value; TD vs TI unless otherwise stated) | Other Analyses | |
|---|---|---|---|---|
| | | | Comparison (TD vs TI unless otherwise stated) | Results |
| Unselected by Risk | **Independent Cohorts** | | | |
| | Awidi 2009[46] | NR | Mean OS (months) | 32 (SE, 4.17) vs 56 (SE, 8.42) (P = .023) |
| | Crisa 2012[6] | 6.55 (2.26-18.97; P = .001) | Univariate analysis (HR) Median OS (months) | 3.13 (95% CI, 1.55-6.31; P = .001) 37.5 vs 78 (P = .001) |
| | Damm 2013[38] | 2.6 (1.5-4.6; P = .001) | Univariate analysis (HR) | 3 (95% CI, 1.7-5.1; P < .001) |
| | Demirkan 2007[50] | NR | Median OS (months) WHO groups FAB groups | 19 vs 77 (P = .0001) 22 vs 90 (P = .0001) |
| | Goldberg 2009[41;51] | 2.14 (1.67-2.73; P < .01) | 3-year OS | 63.2% vs 32.8% (P < .0001) |
| | Hiwase 2013[19] | 3.17 (NR; P < .0001) | NR | NR |
| | Johnson 2013[20] | NR (NR; P = .001) | Univariate analysis (HR) | P < .001 |
| | Kim 2010[52] | NR | 1-year OS | 66.7% vs 94.4% (P = .041) |
| | Park 2008[53] | NR | Univariate analysis (HR) | 2.08 (95% CI, 1.24-3.49; P = .01) |
| | Salvi 2007[54] | NR | OS | Significantly worse in TD vs TI |
| | Wallvik 2002[26] | NR (NR; P = .067) | Median OS (months) | 15 vs 38 (P = .067) |
| | Wei 2009[55] | NR (NR; P = .0009) | Mean OS (months) | 24 vs 43 (P = .00049) |
| | Wong 2005[56] | NR | OS | Significantly worse in TD vs TI |
| | **Overlapping Cohorts** | | | |
| | **Moffitt Cancer Center Cohorts (Tampa, FL) With Probable Overlap** | | | |
| | Komrokji 2012[9] Corrales-Yepez 2010[57] | 1.3 (1-1.7; P = .06) | Univariate analysis (HR) Median OS (months) | NR; favored TI (P < .05) 17 (95% CI, 14-19) vs 29 (95% CI, 23-35) (P < .005) |
| | **Mayo Clinic Cohorts (Rochester, MN) With Probable Overlap** | | | |
| | Pardanani 2012[44] | NR | Univariate analysis (HR) | 2.3 (95% CI, 1.3-4.2, P = .006) |
| | Patnaik 2012[31] | HR (NR) favored TI (P = .002) | Univariate analysis (HR) | NR; favored TI (P = .0053) |
| | Patnaik 2012[32] | NR (NS) | 3-year OS, by IPSS category | Int-1: 50% vs 62% (P = .38) Int-2: 59% vs 61% (P = .48) High: 36 vs 50% (P = 0.6) |
| | Patnaik 2012[49] | P = .0025 | Univariate analysis (HR) | P < .0001 |
| | **MD Anderson Cohorts (Houston, TX) With Probable Overlap** | | | |
| | Quintás-Cardama, 2011[58] | 1.59 (NR; P ≤ .05) | Univariate analysis (HR) | P < .001 |

| | | | |
|---|---|---|---|
| | Tong 2012[27] | NR (NS) | Median OS (months) | 13.8 vs 26.7 |
| | **Italian Cohorts With Some Overlap** | | | |
| | Malcovati 2011[40] | 2.89 (NR; P < .001) | Univariate analysis (HR) | 4.09 (95% CI, NR; P < .001) |
| | Alessandrino 2010[59] | 1.48 (NR; P = .017) | Univariate analysis (HR) | 1.68 (95% CI, NR; P ≤ .001) |
| | **Studies for Which Possible Overlap Could Not Be Ascertained** | | | |
| | Arnan 2011[60] Arnan 2013[61] | 69[a] (NR; P = .002) | Standardized mortality ratio (in comparison with Catalan population) (> 2 vs < 2 RBC units/ month) (> 3 vs < 3 RBC units/month) | 6.7 vs 3.8 9.1 vs 4 |
| | Kadia 2011[62] | NR | Univariate analysis (HR) Median OS (months): TD at baseline and became TI vs those who remained TD Median OS (months): TI at baseline and became TD vs those who remained TI | 0.33 (95% CI, NR; P = .012) 19.2 (95% CI, 14.7-21.6) vs 9.4 (95% CI, 5.8-13.0) 6.8 (95% CI 0.99- not evaluable) vs 19.8 (95% CI 12.9- not evaluable) |
| | Platzbecker 2008[28] | 1.68 (0.76-3.7; P = .2) | 3-year OS: (TI vs TD) | Whole cohort: 60% vs 49% (P = .1) RAEB only: 56% vs 36% (P = .1) IPSS int-1: 62% vs 50% (P = .38) IPSS int-2: 61% vs 59% (P= .48) IPSS high: 50% vs 36% (P = .6) |
| | Thol 2011[63] | 3.19 (1.45-7.06; P = .004) | Univariate analysis (HR) | 3.72 (95% CI, 1.7-8.14; P = .001) |
| | Sanz 2008[64] | 8.8 (NR; p<0.0001) | Median OS (months) TD at diagnosis TD development TI | 19 60 96 (P < .0001) |
| | Uno 2013[22] | NR (significant) | NR | NR |
| | Kulasekararaj 2013[43] | 2.166 (1.3-3.4; P = .001) | NR | NR |
| | Savic 2012[65] | NR (NR; P = .007) | Median OS (months) | 21 vs endpoint not reached (P = .00003) |
| | Lulla 2011[45] | NR (NR; P = .003) | Univariate analysis (HR) | HR (95% CI, NR; P < .0001) |
| | Li 2008[66] | NR | Univariate analysis (HR) | HR (95% CI, NR; P < .001) |
| | Lim 2007[29] | NR (NS) | Univariate analysis (HR) | 7.03 (95% CI, 0.95-51.75; P = .06) |
| | Voso 2013[42] | 0.213 (0.12-0.379; P < .001)[b] | NR | NR |
| **Low Risk** | **Independent Cohorts** | | | |
| | Cermak 2009[30] | ≥ 0.1 units/month: P = .0017 ≥ 1.1 units/month: P = .0004 ≥ 2.1 units/month: P = .0001 ≥ 3 units/month: P = .001 | Univariate analysis (HR) of TD vs TI at different cutoffs to define TD/TI | ≥ 0.1 units/month: NR (P = .018) ≥ 1.1 units/month: NR (P = .001) ≥ 2.1 units/month: NR (P = .001) ≥ 3 units/month: NR (P = .032) |
| | Durairaj 2011[47] | NR | Logistic regression coefficient Median OS (months) | 2.36 (SE, 0.8; P = .0035) 19 vs 32 (P = .0056) |
| | Falantes 2013[24] | 1.548 (1.092-2.195; P = .014) | Univariate analysis (HR) | P = .001 |

| | | Median OS (months) | 22 vs 60 |
|---|---|---|---|
| | | 4-year OS (months) | 27.6% vs 59.9% |
| Hiwase 2013[19] | NR | Median OS (months) | 52.7 vs 122.5 (P = .001) |
| **Cohorts for Which Possible Overlap Could Not Be Ascertained** | | | |
| Chee 2008[67] | NR | Univariate analysis (HR) | HR (95% CI, NR; P = .001) |
| Crisa 2012[6] | 10.95 (3.19-37.53; P < .001) | Univariate analysis (HR) | 3.37 (95% CI, 1.52-7.47; P = .001) |
| de Swart 2011[68] | 4.11 (2.61-6.46; P = .0001) | Univariate analysis (HR) Patients who progressed within 24 months (defined as increase in bone marrow blasts to higher WHO category) | 4.12 (95% CI, 2.65-6.4; P = NR) |
| | | Patients who did not progress within 24 months | 1.51 (95% CI, 0.64-3.56; P = NR) |
| Germing 2012[39] | Whole cohort: NR (1.52-3.61; P = .0001) Subgroup with RAEB excluded: 2.26 (1.41-3.63; P = .001) | Whole cohort: Median OS (months) Correlation coefficient and exp(coefficient) Correlation coefficient and exp(coefficient) (RAEB patients excluded) | 44 vs 97 (P < .001) 0.8523 (2.344) 0.8155 (2.260) |
| Kelaidi 2013[69] | NR | Narrative data only | "baseline transfusion dependence… accurately predicted OS from treatment onset" |
| Komrokji 2012[8] | NR | Univariate analysis (HR) | "significant" (P = NR) |
| Patnaik 2010[70] | NR (P = .04) | Univariate analysis (HR) | NR (P = .04) |
| **Independent Cohorts** | | | |
| Cermak 2010[30] | NR (NS) | Narrative data only | "TD did not affect survival" |
| Itzykson 2011[23;71] | 1.9 (1.4-2.6; P ≤ .0001) | Median OS (months) | 10.3 vs 19.2 (P = .0001) |
| Komrokji 2011[7] | 1.04 (NR; P = .85) | Univariate analysis (HR) | Significant (P = NR) |

AZA, azacitidine; FAB, French American British; HR, hazard ratio; IPSS, International Prognostic Scoring System; NR, not reported; NS, not significant; OS, overall survival; RAEB, refractory anemia with excess blasts; RBC, red blood cell; TD, transfusion dependence; TI, transfusion independence; WHO, World Health Organization.

[a] As was reported in the source document.

[b] TI vs TD.

**Table 3. Study Type B Results**

| Risk | Author/Year | Estimate of TD Effect HR From Multiple Cox Regression (95% CI; P value; achieving TI vs remaining TD unless otherwise stated) | Other Analyses | |
|---|---|---|---|---|
| | | | Comparison (achieving TI vs remaining TD unless otherwise stated) | Results |
| Unselected | **Independent Cohort** | | | |
| | Kadia 2011[62] | NR | Median OS (months) | 19.2 (95% CI 14.7-21.6) vs. 9.4 (95% CI 5.8-13.0) |
| Low Risk | **Overlapping Cohorts—All Drew From MDS 003 and/or MDS 004 Trials** | | | |
| | Buesche 2011[35] | NR (NS) | | |
| | Fenaux 2011[34] | 0.53 (0.31-0.91; P = .021)[a] | Univariate analysis (HR) | 0.47 (95% CI, 0.28-0.78; P = .003)[a] |
| | Fenaux 2010[48] | 0.49 (NR; P = .008)[a] | Risk ratio OS | 51% RR (P = .008) |
| | Fenaux 2011[72] | NR | Median OS (years) TI ≥ 26 weeks vs not | 4.9 vs 2.0 |
| | Giagounidis 2013[73] | NR | OS | P = .007 |
| | Sánchez-García 2014[74] | NR | Median OS (months) | Not reached vs 31 (log-rank P < .001) |
| | Sekeres 2011[33] | 0.3584 (NR; P < .001)[a] | Univariate analysis (HR) | 0.333 (95% CI, NR; P < .001)[a] |
| High Risk | **Independent Cohort** | | | |
| | Seymour 2010[36] | NA | 2-year death risk ratio<br>Median OS (months) | 0.244 (P = NR)<br>Not reached (95% CI, 25.1-not reached) vs 7.3 months (95% CI, 4.8-10.5) (P < .0001) |

HR, hazard ratio; NA, not applicable; NR, not reported; OS, overall survival; TD, transfusion dependence; TI, transfusion independence; RR, risk ratio/relative risk
[a] TI:TD.

**Table 4. Study Type C Results**

| Risk | Author/Year | Estimate of High- vs Low-Burden TD From Multiple Cox Regression (95% CI; P value; high burden vs low burden unless otherwise stated) | Other Analyses | |
|------|-------------|---|---|---|
| | | | Comparison (high burden vs low burden unless otherwise stated) | Results |
| Unselected | **Independent Cohorts** | | | |
| | Chan 2011[21] | 18.6 (NR; P = .0001) | 100-week OS rate | 27% vs 73.2% (P = NR) |
| | **Unclear if Overlaps** | | | |
| | Delforge 2014[75] | NR | Univariate analysis (HR) | Transfusion burden significantly associated with survival (P = .023) |
| | Musto 2010[76;77] | 2.62 (1.21-5.69; P = .015) | Univariate analysis (HR) (< 2 vs > 2 RBC units/ month) | 3.87 (95% CI, 2.21-6.76; P < .0001) |
| Low Risk | **Independent Cohorts** | | | |
| | Chan 2011[21] | 78.1 (NR; P < .05) | | |
| | Fenaux 2010[48] | | Univariate analysis (HR) | 0.54 (95% CI, NR; P = .185)[a] |
| | Rose 2010[78] | 2.516 (1.37-4.61; p = .0028) | | |
| | **Overlapping Cohorts—Some Patients From MDS 003 and MDS 004 Trials** | | | |
| | Kuendgen 2011[37;79] | 1.056 (NR; P = .037) | | |

HR, hazard ratio; NR, not reported; OS, overall survival; TD, transfusion dependence; TI, transfusion independence; RBC, red blood cell.
[a] Low burden:high burden.

**Table 5. Other Study Types**

| Risk | Author/Year | Estimate of TD Effect HR From Multiple Cox Regression HR (95% CI; P value) | Other Analyses | |
| --- | --- | --- | --- | --- |
| | | | Description of Outcome | Results |
| Unselected | **Independent Cohort** | | | |
| | Jadersten 2008[17] | NR | TS analyzed as continuous variable (RBC units/month) in multiple Cox regression analysis | 1.1 (95% CI, 1.01-1.2; P = .034) per unit |
| Low Risk | **Overlapping Cohorts—Some or All Patients From MDS 003 or MDS 004 Trial** | | | |
| | Sekeres 2011[33] | NR | TS analyzed as continuous variable (RBC units/8 weeks) in multiple Cox regression analysis | 1.0643 (P = .013) |
| | List 2008[18] | NR | TS analyzed as continuous varible (RBC units/month) multiple Cox regression analysis | 1.1 (95% CI, 1.01-1.18; P = .02) per unit |
| | Rojas 2014[16].[a] | NR | Median survival time (months) for TD vs TI | 66 vs not reached (P = .527) |
| HR, hazard ratio; NR, not reported; RBC, red blood cell; TD, transfusion dependence; TI, transfusion independence; TS, transfusion status [a] Recruited all TI patients at baseline and compared overall survival in those who became TD with those who did not. | | | | |

**Figure 1. PRISMA study selection flow chart. AML, acute myeloid leukemia; OS, overall survival; TI, transfusion independence.**
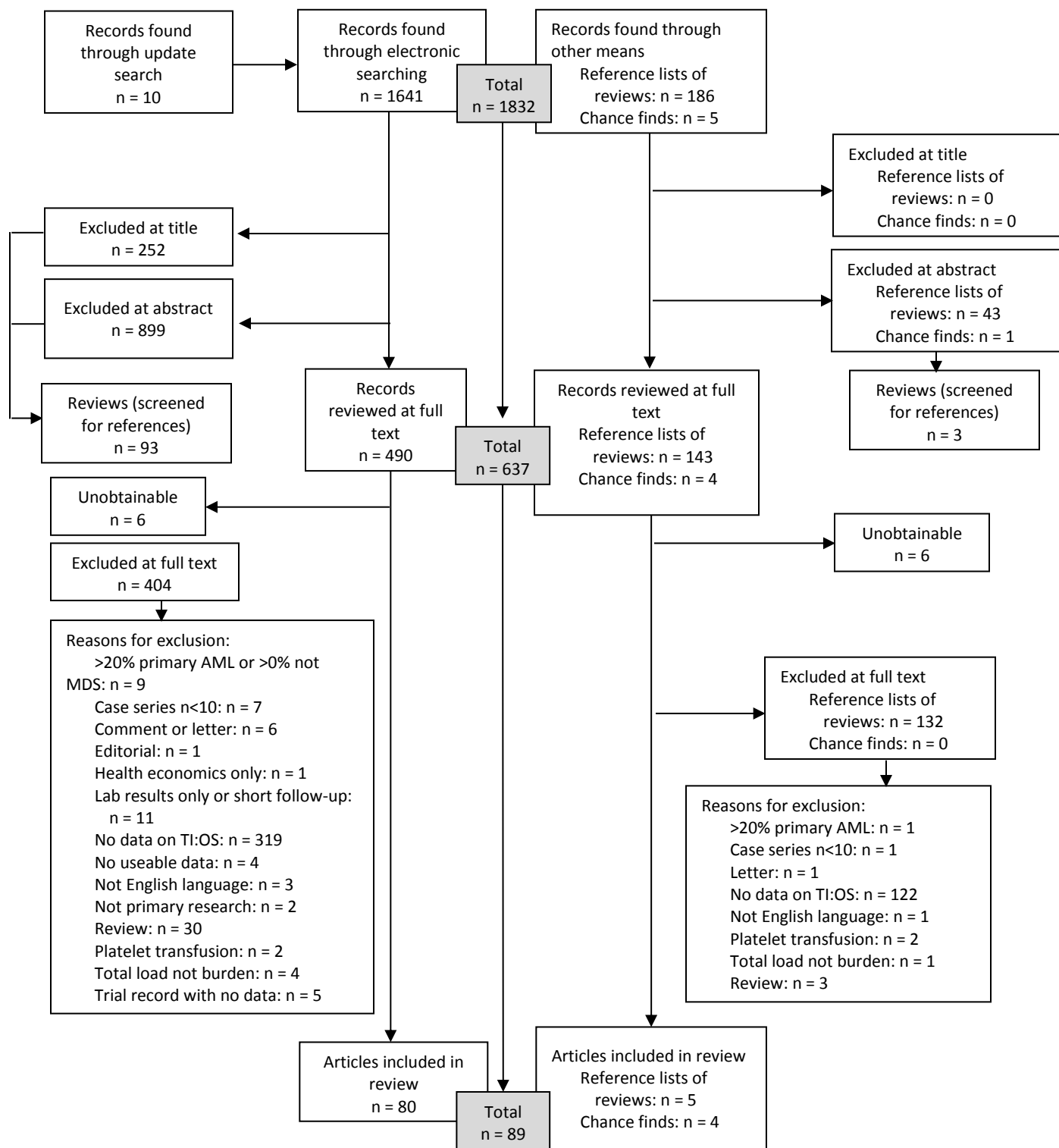
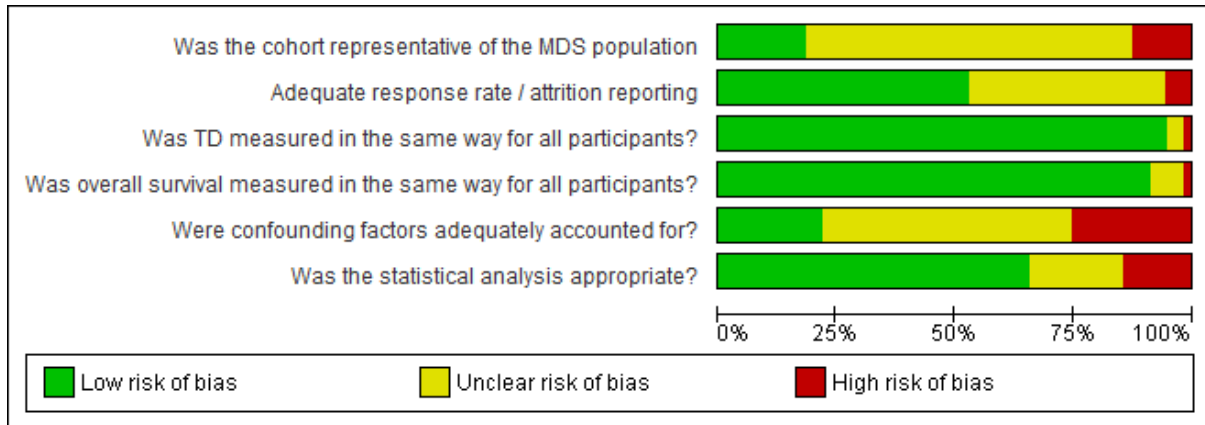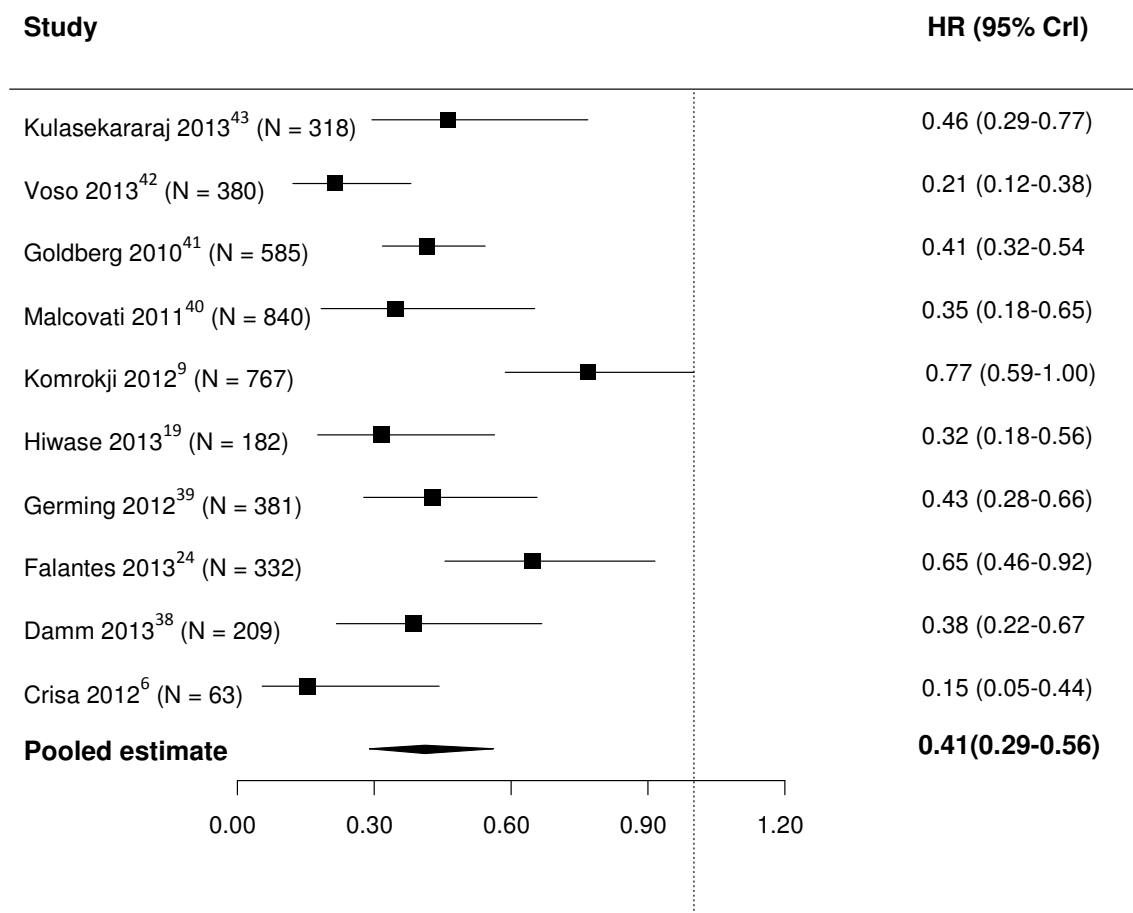**Figure 2. Risk of bias assessment across the included literature. MDS, myelodysplastic syndromes; TD, transfusion dependence.**

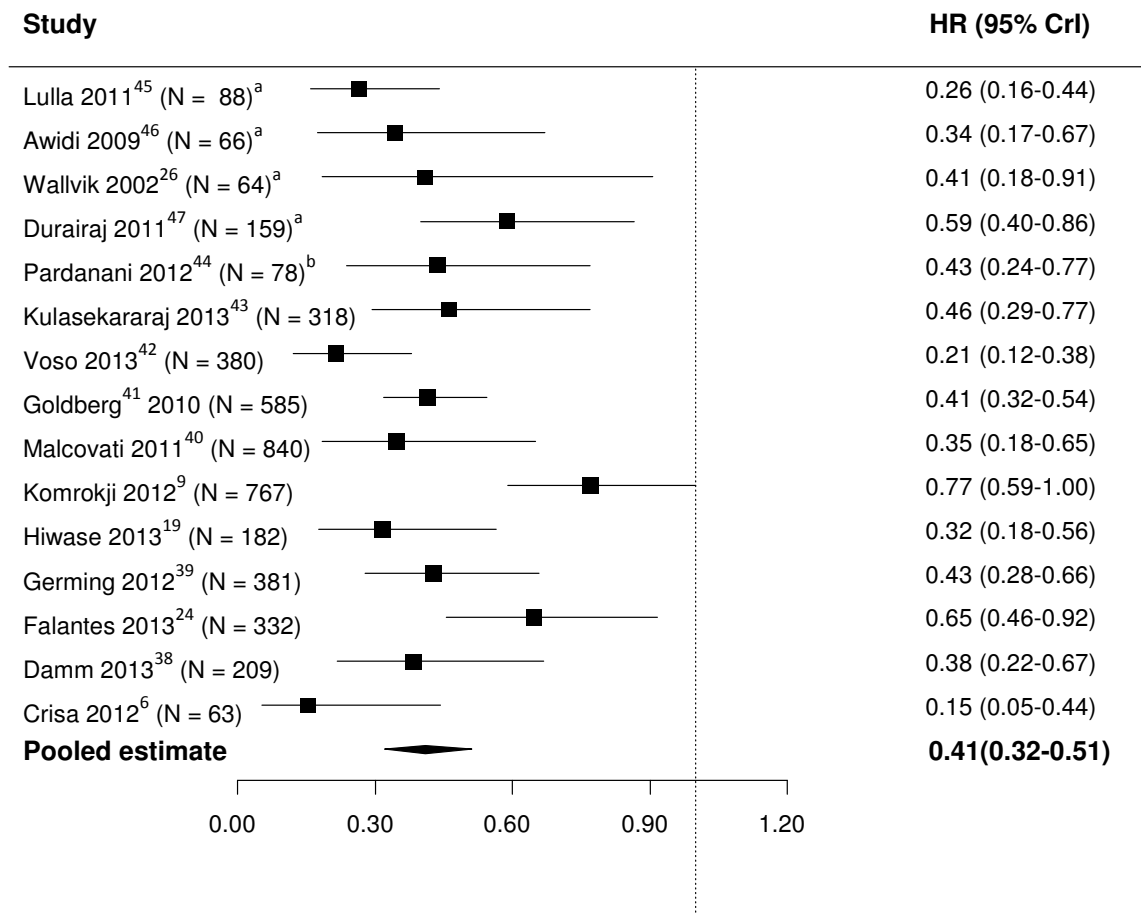**Figure 3. Forest plot for analysis 1 with all studies that used multiple Cox regression.**

| Study | HR (95% CrI) |
|---|---|
| Kulasekararaj 2013[43] (N = 318) | 0.46 (0.29-0.77) |
| Voso 2013[42] (N = 380) | 0.21 (0.12-0.38) |
| Goldberg 2010[41] (N = 585) | 0.41 (0.32-0.54 |
| Malcovati 2011[40] (N = 840) | 0.35 (0.18-0.65) |
| Komrokji 2012[9] (N = 767) | 0.77 (0.59-1.00) |
| Hiwase 2013[19] (N = 182) | 0.32 (0.18-0.56) |
| Germing 2012[39] (N = 381) | 0.43 (0.28-0.66) |
| Falantes 2013[24] (N = 332) | 0.65 (0.46-0.92) |
| Damm 2013[38] (N = 209) | 0.38 (0.22-0.67 |
| Crisa 2012[6] (N = 63) | 0.15 (0.05-0.44) |
| **Pooled estimate** | **0.41(0.29-0.56)** |



0.00    0.30    0.60    0.90    1.20

N indicates the cohort size.

CrI, credible intervals; HR, hazard ratio.

**Figure 4. Forest plot for analysis 1 with studies that used multiple Cox regression, univariate Cox regression, and published Kaplan-Meier curves.**

| Study | | HR (95% CrI) |
|---|---|---|
| Lulla 2011[45] (N = 88)[a] | | 0.26 (0.16-0.44) |
| Awidi 2009[46] (N = 66)[a] | | 0.34 (0.17-0.67) |
| Wallvik 2002[26] (N = 64)[a] | | 0.41 (0.18-0.91) |
| Durairaj 2011[47] (N = 159)[a] | | 0.59 (0.40-0.86) |
| Pardanani 2012[44] (N = 78)[b] | | 0.43 (0.24-0.77) |
| Kulasekararaj 2013[43] (N = 318) | | 0.46 (0.29-0.77) |
| Voso 2013[42] (N = 380) | | 0.21 (0.12-0.38) |
| Goldberg[41] 2010 (N = 585) | | 0.41 (0.32-0.54) |
| Malcovati 2011[40] (N = 840) | | 0.35 (0.18-0.65) |
| Komrokji 2012[9] (N = 767) | | 0.77 (0.59-1.00) |
| Hiwase 2013[19] (N = 182) | | 0.32 (0.18-0.56) |
| Germing 2012[39] (N = 381) | | 0.43 (0.28-0.66) |
| Falantes 2013[24] (N = 332) | | 0.65 (0.46-0.92) |
| Damm 2013[38] (N = 209) | | 0.38 (0.22-0.67) |
| Crisa 2012[6] (N = 63) | | 0.15 (0.05-0.44) |
| **Pooled estimate** | | **0.41(0.32-0.51)** |

0.00    0.30    0.60    0.90    1.20

[a] The study published Kaplan-Meier curves only.

[b] The study used univariate Cox regression.

N indicates the cohort size.

CrI, credible intervals; HR, hazard ratio.

**Supplementary Appendix.**

Example Search Strategy from MEDLINE

1. *Myelodysplastic Syndromes/
2. myelodysplas*.ti,ab.
3. MDS.ti,ab.
4. *Preleukemia/
5. 1 or 2 or 3 or 4
6. *Blood Transfusion/
7. (dependen* or independen* or status or require or requires or requiring or required or requirement).ti,ab.
8. 6 and 7
9. (transfusion* adj2 (dependen* or independen* or status or require or requires or requiring or required or requirement)).ti,ab.
10. 8 or 9
11. (transfusion adj2 need).ti,ab.
12. 10 or 11
13. 5 and 12
14. limit 13 to humans

**Supplementary Figure 1: Review authors' judgments for risk of bias in each included study.**

Red circle with minus sign: high risk of bias; yellow circle with question mark: unclear risk of bias; green circle with plus sign: low risk of bias. MDS, myelodysplastic syndromes; TD, transfusion dependence