SYSTEMATIC LITERATURE REVIEW (SLR) TO IDENTIFY THE BURDEN OF ILLNESS AND TREATMENT EFFECTIVENESS IN ESA-REFRACTORY OR RELAPSED, TRANSFUSION-DEPENDENT, LOWER RISK MDS

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MDS-261

Background

- Myelodysplastic syndromes (MDS) result in abnormal blood cell development, cytopenias, and risk of progression to acute myeloid leukemia (AML).[1]
- MDS are orphan diseases with a US incidence rate of 4.6 per 100,000 in the general population and rates increasing to 26.9 and 59.3 per 100,000 in ages 65+ and 75+ respectively.[2,3]
- 75% of MDS patients are classified as lower risk MDS according to IPSS criteria.[4] Per the 2008 WHO classification, 7.6% of US MDS patients have ring sideroblast (RS+) disease, in which ≥15% RS cells are found in the bone marrow or ≥5% RS cells in the bone marrow with the presence of SF3B1 mutation. Rates of RS positivity vary and have been found to be as high as 17% in Germany using the 2016 WHO classification.[6]
- Lower risk MDS can progress to higher risk MDS or transform to AML; RS- patients are more likely to progress to higher risk MDS or AML compared to RS+ patients.[7]
- Approximately 50% of lower risk MDS patients develop transfusion-dependent (TD) anemia, irrespective of RS status, which is associated with fatigue, reduced quality of life, and increased hospitalization and mortality.[8] Patients with moderate to severe anemia have significantly worse survival outcomes (30 and 26 months respectively) than patients with mild anemia (63 months).[9]
- Initial therapy for anemia in lower risk MDS consists of erythropoietin stimulating agents (ESAs) and blood transfusions.
- Anemic (or TD) lower risk MDS patients who failed ESA therapy (ESA relapsed/refractory) and require ≥2 units of RBCs over 8 weeks may receive luspatercept if RS+, or potentially be treated with hypomethylating agents (HMAs) such as azacytidine (AZA), decitabine (DEC), or the immunomodulatory agent lenalidomide (LEN).[10] There are no approved treatments that specifically target RS- lower risk MDS patients.

Objective and Methods

To identify the burden of illness, treatment patterns, and costs for ESA-refractory or relapsed (ESA-r/r) lower risk MDS by conducting real-world evidence (RWE), economic, and patient-reported outcomes/health-related quality of life (PRO/HRQoL) systematic literature reviews (SLRs).

- Three SLRs were conducted in line with the requirements of National Institute for Health and Care Excellence (NICE) and the Preferred Reporting Items for Systematic Review and Meta Analyses (PRISMA) (Figure 1).

Figure 1. Summary of searches for RWE, Econ and PRO/HRQoL SLRs

Original SLRs: 2011 - September 2021; Update SLRs: 2011 – June 2022

Search database: Ovid platform
Conference proceedings: ASCO, EHA, ISPOR, ESMO, ASH
Bibliography searches: SLRs and meta-analyses

Publications included based on the following PICOS criteria:

Population:	Interventions/Comparators:	Outcomes:	Study Design:
RWE: lower risk MDS, ESA refractory Econ: lower risk MDS, TD PRO/HRQoL: lower risk MDS, TD	RWE: ESAs, HMAs, lenalidomide, imetelstat, luspatercept, roxadustat, rigosertib, ruxolitinib Econ: Any PRO/HRQoL: Any	RWE: clinical outcomes Econ: resource use, costs PRO/HRQoL: quality of life outcomes, utilities, patient reported outcomes	RWE: real world evidence studies Econ: economic evaluations PRO/HRQoL: RWE, clinical trials, economic evaluations

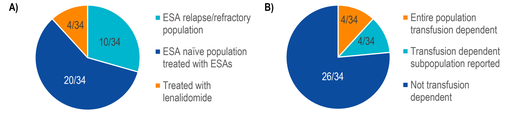
Results

Included records†: RWE: 34 PRO/HRQoL: 24 Econ: 16

Total studies†: RWE: 34 PRO/HRQoL: 16 Econ: 15

- 34 studies were included from the RWE SLR, 24 from the PRO/HRQoL SLR, and 16 from the Econ SLR. Figure 2 depicts lower risk MDS patient populations reported in the RWE SLR.

Figure 2. Number of studies with **A)** ESA-r/r populations and **B)** TD* populations found in the RWE SLR.



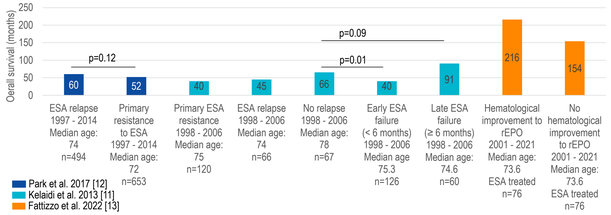
Abbreviations: ESA-r/r: erythropoietin stimulating agent relapsed/refractory; TD: transfusion-dependent

Results of RWE SLR

ESA r/r lower risk MDS patients have worse overall survival compared with ESA responding lower risk MDS patients

- Only 1/34 studies included a transfusion-dependent, ESA refractory population (Figure 2).
- 9/28 RWE studies included ESA-r/r populations in September 2021 SLR, 10/34 studies in June 2022 update.
  - Overall survival (OS) was longer for patients when ESA failure occurred at later time points (Figure 3).[11-13]

Figure 3. OS following ESA treatment in TD and TI subpopulations.



Abbreviations: ESA: erythropoietin stimulating agent; OS: overall survival; rEPO: recombinant erythropoietin; TD: transfusion-dependent; TI: transfusion-independent.

- 20/34 studies reported on ESA naïve populations treated with ESAs.
  - One study reported a significantly lower OS at 5-years for patients that did not respond to ESAs according to International Working Group (IWG 2006) criteria (OS 60.9%; 95% CI 35.9 – 78.6) compared with responding patients (OS 75%; 95% CI 12.8 – 96.1, p=0.008).[14]
    - Of 47 included lower risk MDS patients, 46% were responders and 53% were non-responders (IWG 2006 criteria).

ESA-treated TD patients have worse outcomes and survival when compared to ESA-treated transfusion independent (TI) patients

- 6/28 RWE studies included a TD population in the September 2021 SLR; 8/34 studies in the June 2022 SLR included a TD population (including subpopulations).
  - 4/34 studies reported TD and transfusion-independent (TI) subpopulations in ESA treated lower risk MDS patients (Figure 2). [13,15-17]
  - 4/34 studies reported a TD overall population (Figure 2).[18-21]
  - In three studies that compared TD and TI populations treated with ESAs, hematologic improvement (HI) was 25 to 55 percentage points greater in TI patients compared to TD populations (Figure 4).[15-17]
  - One study found that OS was 30 months shorter in patients with TD lower-risk MDS treated with recombinant erythropoietin compared to TI patients (Figure 5).[13]

Figure 4. % HI-E following ESA treatment in TD and TI subpopulations.[15-17]

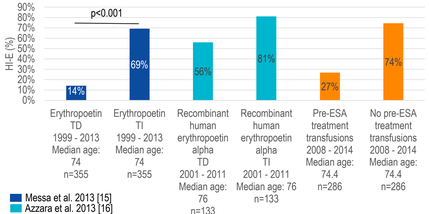
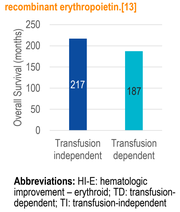


Figure 5. OS in TI and TD subpopulations of lower-risk MDS patients treated with recombinant erythropoietin.[13]

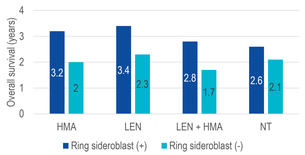


Abbreviations: HI-E: hematologic improvement – erythroid; TD: transfusion-dependent; TI: transfusion-independent

Worse prognosis and more frequent transfusions occur in anemic lower risk MDS patients, irrespective of RS status

- No RWE studies reported an RS+, TD population.
  - Only 2 studies reported an RS- and RS+ population in the RWE SLR.[22,23]
    - Park et al. 2012 found refractory anemia (RA) and refractory anemia with ring sideroblasts (RARS) populations had similar % HI-E in non-del5q lower risk MDS patients treated with ESAs (70% vs. 68%).[22]

Figure 6. OS in RS+ and RS- populations treated with HMA, LEN, LEN + HMAs, or no treatment (NT).[23]



  - Wang et al. 2019 found significantly longer OS in RS+ lower risk MDS (non-del5q) patients treated with HMA, LEN, or no treatment (NT) (Figure 6). There was no significant impact of HMA treatment on transfusion independence at 8 weeks (RS[+] HMA treated TI 53.8%; RS[-] HMA treated TI 57.3%).[23]
  - While RS status did not impact TI, OS was significantly longer in RS+ populations (2.8 vs. 2.1 years, p<0.01; US SEER Medicare-linked database), highlighting the unmet need in RS- populations.[23]

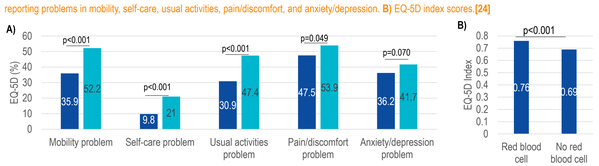
Abbreviations: HMA: hypomethylating agent; LEN: lenalidomide; OS: overall survival; RS: ring sideroblast; TD: transfusion-dependent; TI: transfusion-independent

Results of PRO/HRQoL SLR

Transfusion-dependent lower risk MDS patients have lower HRQoL compared to TI patients

- 3/16 HRQoL studies (5 records) found TD lower risk MDS patients had lower HRQoL than TI patients (QOL instruments used: EQ-5D, FACT-Anemia, EORTC-QLQ-C30).[24-28]
  - Evidence from the MDS-CAN registry suggested that transfusion burden negatively affects HRQoL in RS+ lower risk MDS‡.[29]
  - HRQoL as measured by the EQ-5D index or VAS was significantly impaired in patients with increased transfusion burden compared to those with lower transfusion burden (multi- and univariate analysis) (Figure 7).[24-26]
  - In a study of newly diagnosed MDS patients, EORTC QLQ-C30 scores were lower (indicating worse HRQoL) in lower risk TD patients compared to TI patients. Clinically meaningful differences in EORTC QLQ-C30 scores were only found between TI and TD patients who had higher risk disease, but not in lower risk disease patients‡.[28]

Figure 7. EQ-5D was reported for patients with lower risk MDS receiving red blood cell transfusions and those not. **A)** EQ-5D dimension scores reporting problems in mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. **B)** EQ-5D index scores.[24]



- Luspatercept reduced transfusion burden while HRQoL remained stable over 25 weeks in the MEDALIST trial (as measured using the EORTC-QLC-C30 and the QOL-E instruments).[27]
  - ESA-r/r, RS+, lower risk MDS patients had higher disease burden (physical functioning, role functioning, social functioning, fatigue, dyspnea) relative to the general population.[27]
  - Luspatercept did not lead to clinically meaningful changes in patients' HRQoL over 25 weeks compared to placebo as measured by the EORTC QLQ-C30 or QOL-E.[27]

Results of Econ SLR

Transfusion burden negatively impacts the HRQoL of lower risk MDS patients and substantially contributes to the overall costs of lower risk MDS

- 9/15 studies investigated the costs or economic burden of illness associated with transfusions.[28-37]
- RS+, TD populations are associated with 3-fold higher costs compared to TI populations [33], increased risk of hospitalization (OR 1.3 95% CI 1.15 – 1.46)[29], and lower HRQoL in France and Canada.[29]
- In the US, ambulatory care (51%) and inpatient care (48%) made up most of the transfusion-related costs in a study from 2008 to 2013.[31]
- Over 2 years, patients with transfusions ≤28 days apart had higher mean total costs ($19,498) than those with transfusions >28 days apart ($12,717) (Figure 8).[31]
- Patients that became TI had their monthly costs reduced by half after 3 months, and costs continued to decrease over time.[31]
- Transfusion-related costs in lower risk MDS patients increased with severity of disease (Italy; 2011, 2018; very low, low, intermediate-1 risk MDS)[35,38] (Figure 9) and transfusion dependence (Italy; very low, intermediate, very high-risk MDS) (Figure 10).[35]

Figure 8. Averaged adjusted monthly medical and pharmacy costs by transfusion frequency. US$ per patient-month. **A)** Transfusion frequency of ≤28 days between infusions. **B)** Transfusion frequency of >28 days between infusions.[31]

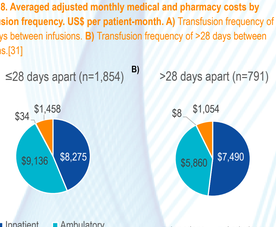


Figure 9. Cost of illness in patients with MDS in Italy. Individuals stratified by IPSS.[38]

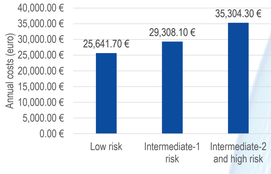


Figure 10. Average number of transfusions in very low, low, intermediate, high, and very high risk MDS patients over 4-years follow-up. Revised IPSS categories determined at diagnosis.[35]



Conclusions

- Management of anemia is one of the major challenges in treating lower risk MDS patients.
- Transfusion dependency is associated with an increased risk of mortality in lower risk MDS.
- Transfusion burden negatively impacts the HRQoL of lower risk MDS patients and substantially contributes to the overall costs across all subtypes of MDS.
- Treatment options remain suboptimal in lower risk MDS patients who are not eligible or who no longer respond to ESAs. **New therapies that reduce transfusions and improve durability regardless of RS status may improve HRQoL and outcomes.**
- Our findings are limited by the lack of comparative outcomes data among lower risk MDS patient subgroup populations (TD vs. TI, ESA-r/r vs. non-ESA-r/r, and RS+ vs. RS-) in the current literature.

Acknowledgments

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†There were 6 additional records (6 studies) included from the June 2022 SLR update for RWE, 2 additional records (1 study) for Econ, and 2 additional records (1 study) for PRO/HRQoL SLRs. *Definition of transfusion dependence varied between publications. Anwar et al. 2019 reported a mean of 2 units/4 weeks for transfusion dependent patients [20], while three studies did not report a definition [15,18,19] and four studies reported transfusion dependent groups has having any RBC within the last 8 weeks.[11,13,16,21] ‡Summary sentences but no values were reported in the record.