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Review

Do anemia treatments improve quality of life and physical function in patients with myelodysplastic syndromes (MDS)? A systematic review

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ABSTRACT

Anemia is common in Myelodysplastic Syndromes (MDS). Different anemia treatments have been tested in clinical studies, but the full impact on patients' health-related quality of life (HRQoL) and physical function is unknown. The main aim of this review was to assess whether improvements in anemia are associated with changes in HRQoL/physical function.

Twenty-six full-text publications were identified, enrolling 2211 patients: nine randomized trials (RCTs), fourteen non-randomized studies of interventions and three cross-sectional studies. Interventions included: growth factors/erythropoiesis-stimulating agents (n = 14), red cell transfusion (n = 9), erythroid maturation agents (n = 1), or a combination (n = 2). Five RCTs reported no changes in HRQoL despite erythroid response to the intervention, raising the question of whether anemia treatment alone can effectively improve HRQoL. Many studies were considered at high risk of bias for assessing HRQoL. There is a pressing need for future clinical trials to better define the nature of the relationship between anemia and HRQoL/functional outcomes.

1. Introduction

Myelodysplastic syndromes (MDS) are clonal bone marrow failure disorders characterised by cytopenias and ineffective hematopoiesis. Predominantly affecting older individuals (median age 79 years) [1], many patients cannot receive the only curative therapy (allogeneic stem cell transplantation) due to age and comorbidities. Anemia is common and associated with poorer health-related quality of life (HRQoL) [2]. HRQoL is a multi-dimensional concept commonly used to examine the impact of health status on quality of life. Interventions targeting anemia in MDS include red blood cell (RBC) transfusion, erythropoiesis-stimulating agents (ESAs), and more recently, erythroid maturation agents (EMAs). Over half of MDS patients will require at least one RBC transfusion during their disease, and one-third are RBC transfusion-dependent [1].

.Maintaining physical function is also a key consideration for MDS patients, who are often older individuals. Studies of elderly cancer patients show reduced physical function, which can impact on activities of daily living [3]. Anemia in older individuals has been associated with functional decline [4], decreased mobility [5], reduced handgrip strength [6] and poorer performance on tests of physical function [7]. However, it is unclear whether transfusion or other supportive care treatments in patients with MDS improves physical function and which tests are most appropriate to measure this effect.

The objectives of this systematic review, which extends a previous review [8], were, firstly, to identify and describe the instruments that

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have been used to assess HRQoL and physical function in clinical studies of MDS patients receiving supportive care (including transfusion) treatments for anemia. The second objective was to assess whether improvements in anemia outcomes are associated with changes in measures of HRQoL and physical function. Our review focuses on blood transfusion and other supportive care interventions for MDS-related anemia, and excludes studies of disease-modifying agents (e.g. hypomethylating or immunomodulatory agents), which have more direct treatment effects on the disease.

2. Methods

This review was registered in the PROSPERO international prospective register of systematic reviews (registration CRD42019125866).

2.1. Search strategy

Comprehensive searches of the following databases were conducted from inception until 18 July 2022: MEDLINE, Embase, CINAHL, PubMed, the Cochrane Library, PsycINFO and Transfusion Evidence Library. Ongoing clinical trial databases were also searched: ClinicalTrials.gov, WHO International Clinical Trial Registry Platform and ISRCTN. PROSPERO and Epistemonikos were searched for ongoing or completed systematic reviews. Searches were undertaken on 27 September 2021 and updated on 18 July 2022.

The MEDLINE search strategy was developed by an Information Specialist with expertise in systematic review searching, reviewed by the project team and then adapted by the Information Specialist for other databases. No restrictions on study design or publication year were applied. Due to resource limitations, we excluded non-English language studies at the screening stage. All search strategies are presented in Appendix 1.

2.2. Criteria for inclusion of studies

Eligible study designs included randomized controlled trials (RCTs), controlled clinical trials, cohort studies, case-control studies and cross-sectional studies. We excluded case reports, narrative reviews, conference abstracts without an associated publication, and interim reports of ongoing trials.

Inclusion criteria for studies:

- >50% of patients aged ≥18 years, with MDS or myelodysplastic/myeloproliferative neoplasm (MDS/MPN) (including chronic myelomonocytic leukemia [CMML]), acute myeloid leukemia with <30% blasts); and, for studies including other patient groups, the study included a subpopulation of eligible patients in whom the outcome data were presented separately
- at least one supportive treatment targeted for anemia or increasing hemoglobin levels, including: RBC transfusion, ESAs, other growth factors, EMAs and iron. We excluded disease-modifying therapies (e.g. hypomethylating agents, chemotherapy, stem cell transplantation), due to their potential wider impacts on HRQoL outside of their effect on anemia [9]
- included HRQoL and/or physical functional assessment as a primary or secondary outcome measure.

2.3. Study selection, risk of bias assessment and data collection

Four reviewers (AM, NS, EL, MP) screened all citations for eligibility. A fifth reviewer (ZM) resolved any discrepancy. Data extraction of all eligible studies was performed by three reviewers (AM, NS, MP). Risk of bias assessment was performed by three reviewers (AM, NS, MP) using the Cochrane RoB1 [10] tool for randomized studies, or the Cochrane ROBINS-I tool for non-randomized studies [11].

2.4. Data analysis

2.4.1. Objective 1: to identify and describe the instruments and tests used to assess HRQoL and physical function in clinical studies of patients with MDS

All eligible studies were included to describe the instruments. This analysis was narrative, with findings tabulated.

2.4.2. Objective 2: to assess whether improvements in anemia outcomes are reflected in measures of HRQoL and physical function

Due to the possibility of bias with non-RCT study designs (e.g. confounding factors, selection bias), included studies were divided into two groups: randomized trials and non-randomized studies of interventions (NRSIs) for data analysis. NRSIs were defined as any quantitative study evaluating treatment effectiveness, without randomization of patients to treatment groups [12]. This includes cohort, case-control or controlled before-and-after studies [12].

Group 1: Randomized trials

Randomized trials were used to address the question – *Do HRQoL and physical function outcomes mirror Hb outcomes*? Non-randomized trials were not included in this analysis due to potential bias from the lack of a comparator arm for Hb and HRQoL/ physical function outcomes. Meta-analysis of the results was planned if sufficient data were available. If multiple HRQoL or physical functional outcome instruments were identified, then pooled analysis of the results was planned using Hedge's g, which provides an estimate of the standardised mean difference weighted according to the relative size of each sample and allows for different HRQoL/physical function instruments to be included in a pooled analysis [13].

Group 2: Non-randomized studies of interventions (NRSIs) and non-randomized comparisons based on Hb response

NRSIs and non-randomized comparisons of subgroups in RCTs based on Hb response (e.g. ESA responders versus non-responders; or high versus low Hb groups), were extracted to address the question – *Is there a greater improvement in HRQoL/ physical function for subgroups defined by Hb response to therapy?*

Such subgroup analyses of RCTs were not included in the Group 1 analysis above due to inherent biases in patient selection. A descriptive analysis was planned for this comparison. Studies were excluded from data analysis if no data on Hb or erythroid response to treatment were reported. These are detailed in Appendix 2.

2.5. Quality assessment using SPIRIT-PRO Extension guidelines

In addition to risk of bias assessment, studies were examined for other key features as recommended by the SPIRIT-PRO Extension [14] guidelines on the use of patient reported outcomes (PROs) in clinical trials. Of the 16-item SPIRIT-PRO Extension checklist, we particularly focused on: pre-specification of the PRO domains of interest, pre-specification of analysis plan, defining timepoints for PRO measurement, describing missing data, and sample size definition where the PRO is the primary endpoint [14]. Although SPIRIT-PRO Extension is primarily designed for clinical trials, many of the items may also be useful for cohort or non-randomized studies [14].

Further, we assessed for inclusion of a minimal clinically important difference (MCID) in reported studies. Given HRQoL and physical function are both patient-centred outcomes, it is important that the MCID, which reflects the smallest benefit of value to patients, is reported in addition to any statistically significant findings, to enhance its clinical relevance [15].

3. Results

The search strategy identified 6656 citations (Fig. 1), of which 6515 titles and abstracts were screened for eligibility. The PRISMA diagram of included studies is shown in Fig. 1.

One non-English study was excluded [16]. 375 studies were

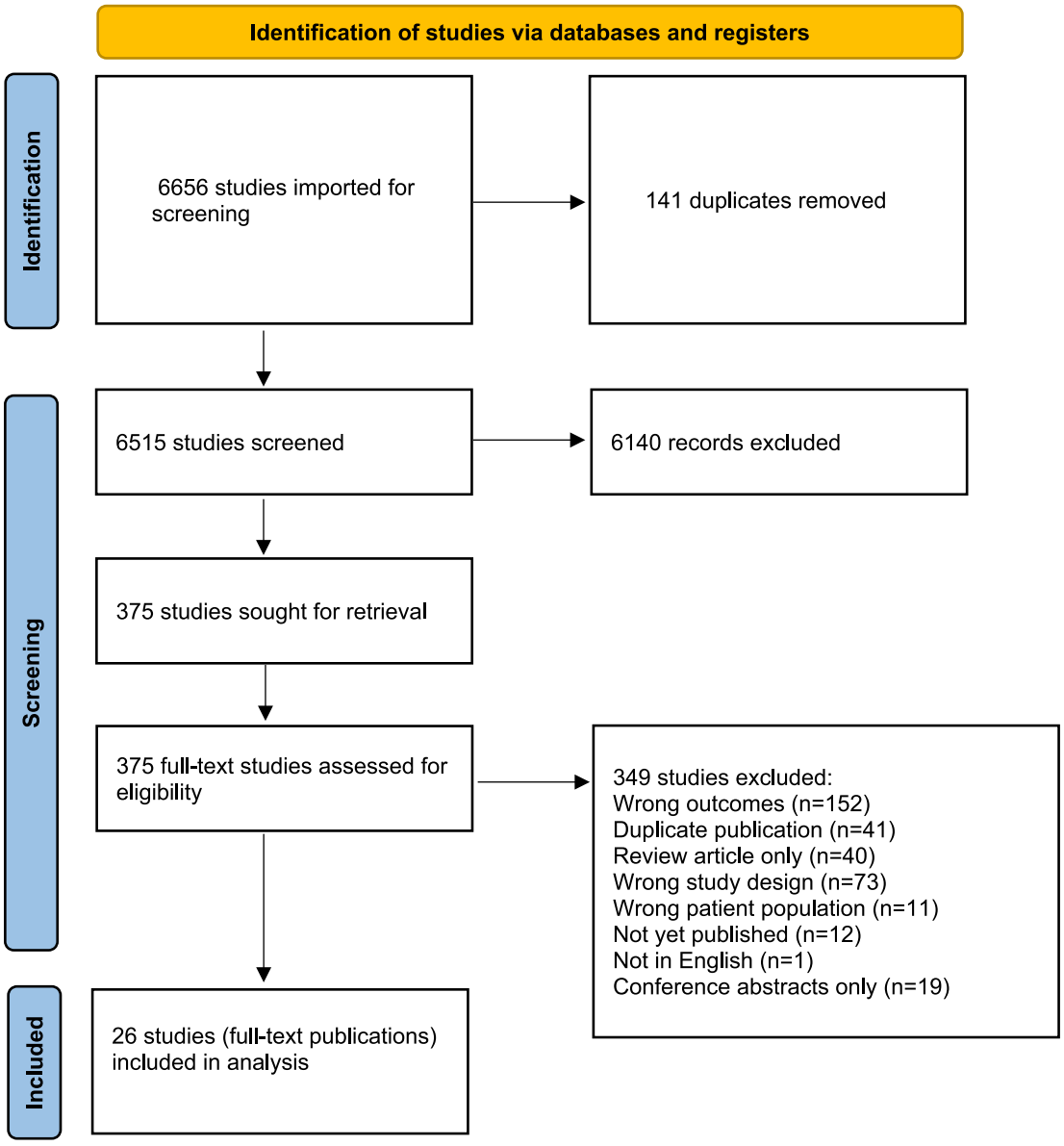

Fig. 1. PRISMA diagram of screening results.

retrieved for full-text review. The majority of studies ($n = 349$) did not meet inclusion criteria and were excluded (wrong outcomes, review article or expert opinion only, wrong study design, wrong intervention). Twenty-six studies met the eligibility criteria for this review.

3.1. Study characteristics

The 26 included studies (Table 1) enrolled 2211 patients. There were nine RCTs [17–25], fourteen NRSIs [26–39] and three cross-sectional studies [40–42]. The study publication dates ranged from 2004 to 2022.

3.2. Risk of bias

Of the nine RCTs, seven [17–21,23,24] had high risk of bias for HRQoL and physical functional outcomes in at least one domain, including inadequate blinding of participants/personnel/assessors for outcomes, incomplete outcome data for all outcomes or selective outcome reporting (Supplementary Table 1).

Of the 14 NRSIs and three cross-sectional studies, 15 [26–36,38–42] had at least one high risk of bias for HRQoL/ physical functional outcomes in at least one domain, including bias due to missing data, outcome measurement, confounding, study participant selection, deviation from intended intervention, or selective outcome reporting (Supplementary Table 1).

3.3. Randomized controlled trials

Of the nine RCTs, five investigated the effects of ESAs (with or without G-CSF) [17–19,21,22], three investigated the effect RBC transfusion [20,23,24] and one investigated an EMA (luspatercept) [25]. One study included only patients with low risk (International Prognostic Scoring System [IPSS] or IPSS-Revised [IPSS-R]) MDS [18], two included both low and intermediate risk MDS [22,25], four included low, intermediate and high risk MDS [17,19,21,24]. Risk category was not reported in two trials [20,23] including one study enrolling transfusion-dependent patients due to any aetiology, of whom 65% ($n = 13/20$) had MDS or CMML [20].

Two RCTs [18,20] included HRQoL as a primary outcome. Balleari et al. evaluated HRQoL and hematological response in anaemic low-risk MDS patients randomly assigned to either ESA or ESA with GCSF [18].

Table 1
Summary of included study designs and findings.

Author, study design	N	MDS subtypes, IPSS/R-IPSS scores	Baseline Hb; transfusion dependence (TD) %	Main aim or intervention	Outcome measures	HRQoL outcome result	Physical function outcome result
RCTs							
Balleari, 2006 [18] RCT	30	RA 10 (33.3%) RARS 5 (16.7%) RCMD 7 (23.3%) RA with <10% blasts 5 (16.7%) Del 5q 3 (10%) All IPSS <1	rHuEPO arm: median Hb 83 g/L (range 70–98); TD 40% rHUEPO + G-CSF arm: median Hb 86 g/L (range 76–100); TD 33%	rHuEPO 10,000 IU 3×/ week x8/52, additional 8/52 for responders Comparator: rHuEPO 10,000 IU 3× / plus G-CSF 1-2×/week x8/52 additional 8/52 for responders	Hematological response, HRQoL (FACT-An)	Post-hoc analysis: Total FACT-An score improved from baseline to final evaluation in most responders to haematopoietic growth factor whereas it did not change for non-responders.	Nil
Casadevall, 2004 [17] RCT	60	RA 33%; RARS 43%; RAEB with <10% blasts 23% IPSS: Low 38%; int-1 38%; int-2 3%; high 3%; unknown/non-evaluable 17%	Arm A 86+/− 12 g/L (mean, SEM) Arm B 86+/− 11 g/L (mean, SEM)	Arm A: rHuEPO and G-CSF X 12/52 + additional 40/52 rHuEPO for responders. Arm B: supportive care x 52/52, including RBC transfusion to maintain Hb > 80 g/L	Erythroid response, HRQoL (FACT-An), cost	No difference in HRQoL scores for the 2 groups, despite Arm A having higher erythroid response rates.	Nil
Fenaux, 2018 [22] RCT	130	RA 62.3%, RARS 8.5%, RCMD 43.8%, RCMD-RS 13.1%, RAEB-1 8.5%, RAEB-2 0.8%, MDS-U 0.8%, del 5q 3.8%, Not available 3.8% IPSS low 44.6%, int-1 54.6%, missing 0.8%	Placebo mean 90 g/L SD 8.48 g/L Epoetin-α 90 g/L SD 9.39 g/L	Randomized 2:1 to epoetin- α or placebo 450 IU/kg. Increase dose at week 8 for non responders.	Primary endpoint: Erythroid response 24/52 Secondary endpoints: duration of Erythroid response 48/52, time to RBC transfusion, n of RBC units transfused, HRQoL (FACT-An, EQ-5D-3L)	No significant differences in HRQoL between ESA versus placebo arm at any timepoint. EQ-5D scores at week 24 was significantly better for responders in the ESA group compared to responders in the placebo group.	Nil
Gerard Jansen, 2020 [23] RCT	19	Restrictive group (n = 10): RA 2, RARS 4, RCMD 4 Liberal group (n = 9): RA 1, RARS 1, RAEB 2, RCMD 5 IPSS/IPSS-R not stated	Restrictive group mean 97 g/L, liberal group 97 g/L All patients TD	Compared a restrictive (Hb transfusion trigger <4.5 mmoL/L, <7.3 g/dL) with a standard (liberal) transfusion policy (Hb transfusion trigger <6.0 mmoL/L,<9.7 g/dL) in patients with MDS	Fatigue (multidimensional fatigue inventory [MFI]) and HRQoL (EQ-5D)	Improved HRQoL scores and physical fatigue scores in liberal group.	Nil
Greenberg, 2009 [19] RCT	110	RA 38%, RARS 34%, RAEB 26%, CMML 2% IPSS: Low/Int-1 83%, Int-2/High 17%	Baseline Hb not stated 63% TD	Arm A: Supportive care Arm B: EPO 150 U/kg daily plus supportive care For 4/12, then arm A patients crossed over to arm B. Non-responders had G-CSF added +/− increased EPO dose.	Primary outcome: erythroid response Secondary outcomes: toxicity, incidence of AML, overall survival, HRQoL (FACT-G, FACT-Fatigue)	No difference in HRQoL for supportive care vs EPO groups. Patients who had an erythroid response at 4 months reported significant improvement from baseline in physical, emotional and functional well-being on the FACT-G, as well as fatigue and overall HRQOL.	Nil
Hsia, 2016 [20] RCT, n-of-1 trial	20	11 (55%) MDS, 2 (10%) CMML-2 IPSS/R-IPSS not stated	Hb not stated All patients were TD	n-of-1 trial of chronically transfusion dependent patients, each consisting of up to 8 randomly allocated transfusions of fresh versus standard RBCs	Primary outcome: difference in change in HRQoL scores (FACT-An)	No difference in HRQoL scores for fresh versus standard RBCs	Nil

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Table 1 (*continued*)

Author, study design	N	MDS subtypes, IPSS/R-IPSS scores	Baseline Hb; transfusion dependence (TD) %	Main aim or intervention	Outcome measures	HRQoL outcome result	Physical function outcome result
Oliva, 2022 [25] RCT	225	IPSS-R risk category: very low or low 82.7%, intermediate 16.9%, missing 0.4%	Baseline Hb not stated 100% patients were RBC-TD	Randomized 2:1 to receive luspatercept (1.0–1.75 mg/kg) or placebo every 3 weeks for 24 weeks. Best supportive care including RBC transfusion at investigator's discretion.	Primary endpoint: transfusion independence ≥ 8 weeks, in weeks 1–24 Secondary: transfusion independence ≥12 weeks during weeks 1–24 and 1–48; HRQoL (EORTC QLQ-C30, QOL-E)	No clinically meaningful within- or between-group differences in HRQoL for the 2 groups, except one item of QOL-E MDS-spcific disturbances domain: luspatercept patients reported improvement in daily life due to reduce transfusion burden, relative to placebo.	Nil
Platzbecker, 2017 [21] RCT	146	RA 22 (15.1%), RARS 21 (14.4%), RCMD 64 (43.8%), RCMD 64 (43.8%), MDS-U 2 (1.4%), del 5q 13 (8.9%), RAEB-1 23 (15.8%), unknown 1 (0.7%) IPSS-R Very low 14 (10%), low 89 (60.9%), int 33 (22.6%), high 4 (2.7%)	Hb median 9.3 g/dL (IQR 8.8–9.7) TD not specified	2:1 randomization to 24/52 darbepoetin alfa or placebo Followed by 48/52 open-label darbepoetin alfa for all patients	Primary endpoint: transfusion incidence Secondary: erythroid response, HRQoL (EQ-5D, FACT-Fatigue)	No clinically significant differences in change in HRQoL between the two treatment arms.	Nil
Stanworth, 2020 [24] RCT	38	RCUD-A 5, RARS 3, RCMD 18, RCMD-RS 6, RAEB-1 1 RAREB-2 1, MDS-U 2, MPNS 2 IPSS-R Very low 7, low 17, int 4, high 4, N/A 6	100% patients RBC TD	Compared restrictive (Hb 85-100 g/L) vs liberal (Hb 110-125 g/L) transfusion thresholds	Primary outcomes: feasibility (% of pre-transfusion Hb below target range; ≥20g/L difference in pre-transfusion Hb for the 2 groups Secondary: HRQoL (EORTC QLQ-C30, EQ-5D-5L), enrolment rates, % transfusions given correctly, compliance HRQoL surveys, blinding, blood usage, adverse events	All HRQoL domains improved for liberal group compared to the restrictive group.	Nil
Non-RCTs							
Abel, 2021 [26] Prospective cohort study, no control arm	62	Not stated	Mean 80.5 g/L SD 6 g/L	Peri-transfusion HRQoL assessment (PTQA) in MDS patients receiving RBC transfusion. A report was sent to each patient and provider before the next transfusion.	HRQoL (QUALMS) Follow-up questionnaire to assess whether patients perceived their PTQA data were used for future transfusion decisions.	35% patients experienced a clinically significant increase in QoL score after transfusion. 46% no change, 19% decrease. For those with increase in QUALMS score, the mean increase was 14 points (SD 4.8), with greatest change for physical burden symptoms. For those who had a decrease, the mean decrease was 7 points (SD 1.6). 23% of patients reported that the PTQA results were discussed by their provider when considering repeat transfusion	Nil

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Table 1 (*continued*)

Author, study design	N	MDS subtypes, IPSS/R-IPSS scores	Baseline Hb; transfusion dependence (TD) %	Main aim or intervention	Outcome measures	HRQoL outcome result	Physical function outcome result
Caocci, 2007 [27] Prospective cohort study, no control arm	32	RA 64%, RA with <10% blasts 36% 90% had low or int-1 IPSS	Baseline not stated. Mean Hb during the study 90 g/L (range 78–123 g/L)	RBC transfusion when Hb < 80 g/L, or EPO 10,000 units SC three to five times a week	HRQoL (EORTC QLQC30) and association with the variation in Hb	Transfusion free patients reported better QoL and less fatigue than transfused patients. Significant association between lower variation in Hb and better QoL score and a lower fatigue score. No correlation between mean Hb level and QoL or fatigue.	
Castelli, 2014 [37] Retrospective cohort study, no control arm	24	RA 63%, RARS 13%, RACMD 8%, RCMD 8%, RCMD-RS 4%, RAEB-1 4% All had IPSS low (46%) or int-1 (54%)	Median Hb pre-treatment 85 g/L. TD rates not stated.	Biosimilar epoetin α 40,000 IU weekly for 12 weeks. Responsive patients continued for further 12 weeks.	Erythroid response, HRQoL (FACT-An), cognitive function (Mini Mental State Examination; MMSE) after 12/52	Positive and significant correlation between the variations in Hb scores and FACT-An scores.	Nil
Clavio, 2004 [28] Prospective cohort study, no control arm	11	RA 36%, RARS 46%, RAEB 18% IPSS/ IPSS-R not stated	Not stated	rHuEPO 40,000 IU two times a week for 12/52. After 12/52, rHuEPO withheld in patients without erythroid response. Responsive patients had maintenance therapy for further 12/52	HRQoL (FACT-An), brain function	Erythroid response associated with positive changes in HRQoL, which exceeded the predefined clinically significant criteria.	Nil
Gabrilove, 2008 [38] Prospective cohort study, no control arm	206	RA 58%, RARS 35%, RAEB 6%, missing 0.5% IPSS low 67%, int-1 28%, missing 5%	TD 1.5%	Darbepoetin alfa 500 microg every 3-weeks. Dose escalation at week 7 for non-responders.	Primary endpoint: erythroid response at 13 weeks Secondary: erythroid response, Hb change to week 53/55, RBC transfusions, HRQoL (FACT-F, EQ-5D, 3 additional patient-related outcome questions concerning energy, activity, overall health), safety endpoints	FACT-F score improved from baseline to week 13 for ESA-naïve patients (mean 5.6 points increase, 95% CI 3.5–7.7). No change for prior ESA-treated patients (mean 2.4; 95% CI -0.9-5.8 points). Increases in FACT-F scores associated with changes in Hb levels from baseline (statistical significance not given). No trends over time for other HRQoL measures.	Nil
Kelaidi, 2013 [29] Prospective cohort study, no control arm	95	RA 25%, RARS 33%, RCMD 16% RCMD-RS 7%, del 5q 2%, RAEB-1 15% CMML 2% All had IPSS low (54%) or int-1 (46%)	92 g/L(range 62–100 TD not defined but 46% of the patients had received at least one RBC transfusion during the previous 8 weeks	Darbepoetin alfa 500 μg every 2/52 for 12/52. Non-responders had GCSF added at 12/52.	Primary endpoint: erythroid response after 12/52 Secondary: erythroid response at 24/52, safety, HRQoL (SF-36, FACT-An), physical functioning (VO2 max, 6-min walk test, short performance battery test), AML incidence, response duration, overall survival	Greater improvement in FACT-An for responders vs non-responders. Some SF-36 domains (physical functioning scales) correlated positively with erythroid response.	Significant difference over time in VO_2max for ESA responders (improved) vs non-responders (declined). No significant difference over time in 6MWT or short battery test results for ESA responders vs non-responders.

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Table 1 (*continued*)

Author, study design	N	MDS subtypes, IPSS/R-IPSS scores	Baseline Hb; transfusion dependence (TD) %	Main aim or intervention	Outcome measures	HRQoL outcome result	Physical function outcome result
Nilsson-Ehle, 2011 [30] Prospective cohort study, no control arm	36	RA 16.7%, RARS 22.2%, RCMD 33.3%, RAEB-1 11.1%, RAEB-2 2.8%, del 5q8.3%, MDS-U 2.8%, CMML 2.8% IPSS low 38.9%, int-1 33.3%, int-2 8.3%	47.2% TD	All patients received darbepoetin alfa with addition of GCSF in patients with TD RARS or those with no response by 9/52. If Hb reached 120 g/L at 16/52, treatment was maintained until 26/52. All other patients had RBC transfusion aiming for Hb 120 g/L.	Erythroid response, HRQoL (EORTC QLQC30), exercise spirometry (VO2 max), cardiac MRI, MRI of the heart	Hb increase associated with improved HRQoL, whether induced by growth factor treatment or transfusion. (However, study not powered to study subgroups). The actual change in Hb did not correlate with function or symptom changes.	8 patients showed an improvement in VO2max. 7 of these had achieved Hb 126-138 g/L. Another 6 patients with Hb ≥120 g/L showed unchanged or decreased VO2 max, 4 of whom were transfused. Cardiac iron overload detected in 2 patients however without association with ferritin levels.
Oliva, 2005 [40] Cross-sectional study	39	Not stated	12/27 (44.4%) TD	Comparing cardiac remodelling and HRQoL in TD vs transfusion free (TF) MDS patients	Echocardiographic measurements, HRQoL (QOL-E, EORTC QLQ-C30)	Improvements in Hb correlated with changes in QOL-E domains. In TF patients, Hb values correlated with changes in MDS-specific scores, physical scores. In TD patients, changes in transfusion requirements correlated with changes in functional well-being. Transient improvements during first 8 weeks in EORTC QLQ-C30 in physical functioning, emotional well-being, fatigue.	Higher rates of cardiac remodelling in TD group. Cardiac remodelling was associated with lower mean Hb levels and older age. Each unit of Hb increase predicted a 49% reduction in the risk of remodelling
Oliva, 2010 [31] Prospective cohort study, no control arm	41	RA 59%, RCMD 27%, RARS 4.9%, del5q 4.9%, RAEB 1 2.4%, unclassified MDS 2.4% All had low or int-1 IPSS MDS 71% had IPSS low-risk	Mean Hb + SD (g/L) 90 + 10 59% TD	All patients received weekly DPO 150microg for 24/52 with dose increase for non-responders	Response to DPO, erythroid response, Hb level, HRQoL (QOL-E, EORTC QLQ-C30), safety, apoptotic progenitor cells and CD34+ cells	Response to treatment was associated with improvements in HRQoL.	Nil
Oliva, 2012 [32] Prospective cohort study, no control arm	148	RA 48 (40.3%), RARS 4 (3.4%), 5q-6 (5.0%), RCMD 29 (24.4%), RCMD RS 1 (0.85%), RAEB1 21 (17.6%), RAEB2 7 (5.9%), CMML 3 (2.5%), MDS-U 29 Low 56 (41.8%), Int-1 64 (47.8%), Int-2 14 (10.4%), NA 14	Mean Hb 103 g/L, SD 20.6 g/L TD % not defined	Investigating the effects of transfusion on HRQoL, predictors of HRQoL in MDS patients and correlations between patient and physician perceived HRQoL.	HRQoL (QOL E, Linear analogue self assessment scales [LASA]), comparing physician-assessed scores with patients' scores	TD patients had worse HRQoL scores. Hb, comorbidities were major determinants of HRQoL. Physicians' and patients HRQoL scores correlated but physicians underestimated some specific components.	Nil
Ramos, 2017 [33] Prospective cohort study, no control arm	30	Refractory cytopenia 3.3%, RARS 20.0% RCMD 63.3%, Unclassifiable MDS 3.3%, Other MDS/MMN 10%, CMML-2 6.6%, RAEB-1 3.3% All had low-risk MDS (IPSS<1.5)	Mean (SD) 101 g/L (13 g/L) TD ranged from 20 to 23% during the study	Observational study of low-risk MDS patients (IPSS<1.5) to assess changes in HRQoL and cardiac remodelling during one-year follow-up	HRQoL (SF-36, EORTC QLQ-C30, FACT-An), functional outcomes (short physical performance battery [SPPB], ECG, echocardiogram)	Overall HRQoL remained stable, except for slight reduction in SF-36 physical function and FACT-An score during the 12-months. HRQoL not correlated to changes in Hb or gait speed. Patients and physicians had similar perceptions for need for transfusion on the LASA survey, in all visits but the first.	Significant reduction (slower) in SPPB gait speed at 12 months associated with increase in serum ferritin levels, with no other SPPB changes. No significant changes in left ventricular function.

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Table 1 (*continued*)

Author, study design	N	MDS subtypes, IPSS/R-IPSS scores	Baseline Hb; transfusion dependence (TD) %	Main aim or intervention	Outcome measures	HRQoL outcome result	Physical function outcome result
Ryblom, 2015 [34] Prospective cohort study and qualitative study, no control arm	16	Subtypes not stated. IPSS risk category: low 3/16 (18.8%), intermediate-1 8/16 (50%), intermediate-2 3/16 (18.8%), high 2/16 (12.5%)	Baseline Hb 90 (64–114) g/L (median, range) 100% patients were RBC TD	Investigate symptoms of anemia immediately before and in the 7 days post transfusion	HRQoL (FACT-An) Interview responses	FACT-An score increased after blood transfusion. A positive correlation was found between increments in the FACT-An score and Hb value ($r = 0.66$, $p = 0.02$). Interviews confirmed the FACT-An results, also showed patients experienced severe fatigue that negatively affected interpersonal relationships.	Nil
Spiriti, 2005 [35] Prospective cohort study, no control arm	133	RA 62%, RARS 24%, RAEB 14% All patients had low risk MDS	85.7 ± 10.3 g/L (mean SD) 54/133 (40.6%) TD	Epoetin alfa 40,000 IU twice weekly; dose reduction to weekly after 4/52 weeks in responders.	Erythroid response HRQoL (FACT-An)	Improvement in HRQoL scores overall with treatment. FACT-An scores were positively associated with Hb values.	Nil
Stasi, 2005 [36] Prospective cohort study, no control arm	53	RA 58.5%, RCMD 18.9%, RAEB-1 15.1%, RARS 5.6%, RCMD-RS 1.9% All patients had low or IPSS intermediate-1 risk MDS IPSS risk group Low risk 54.7% Int-1 45.2%	median 79 g/L Range 68-93 g/L 86.8% TD	24-weeks of DA weekly (150 μg) with dose increase if suboptimal response	Erythroid response, apoptosis measurement, HRQoL(LASA, FACT-An/ FACT-G)	HRQoL scores improved for responders, but no change for non-responders. Positive correlation between change in HRQoL domains and change in Hb.	Nil
Trudeau, 2020 [41] Cross-sectional qualitative study	16	RARS 43.8%, RCMD 37.5%, MDS-U 12.5%, RCUD 6.3%, del 5q 6.3% IPSS int-1 56.2%, low risk 43.8%	Hb not stated All patients were TD	Qualitative study of lower-risk MDS patients to evaluate the content validity of the QUALMS and FACT-An instruments, in transfusion dependent MDS patients	Qualitative interviews consisting of concept elicitation (exploring symptoms and impacts important to patients) and cognitive debriefing (assessing understanding and relevance of QUALMS and FACT-An)	Commonest symptoms: fatigue (100%), shortness of breath (87.5%), weakness (81.2%), low energy (75%) These impacted on HRQoL domains including: activities of daily living (100%), physical functioning (93.8%), emotional wellbeing (81.3%), social functioning (75%). QUALMS and FACT-An are appropriate to assess symptoms and functioning in patients with lower-risk MDS	Nil
Villegas, 2011 [39] Prospective cohort study, no control arm	44	RA 31.8%, rARS 61.4%, RAEB 6.8% IPSS low 77.3%, int-1 22.7%	Mean Hb (SD): 92 g/L (0.8) 27% TD	Darbepoetin alfa 300microg weekly for 8 weeks. At 8 weeks, changed to every 2-weeks for patients with major erythroid response or GCSF started concomitantly for minor or no response. At 16 weeks, patients with minor or no response withdraw from study. Patients with major response continued darbepoetin alfa (dosing at clinician discretion) for additional 8 weeks.	Primary: % patients with major erythroid response at 8, 16, 24 weeks. Secondary: Hb, RBC transfusion incidence, HRQoL (FACT-F)	FACT-F score increased mean 2.23 points (95% CI 0.04–4.42) from baseline to last observation (paried *t*-test, $p = 0.046$). Significant correlation between change in Hb levels change in FACT-F score from baseline to week 24 ($p = 0.0024$), and from baseline to last observation ($p = 0.008$).	Nil

(*continued on next page*)

Table 1 (*continued*)

Author, study design	N	MDS subtypes, IPSS/R-IPSS scores	Baseline Hb; transfusion dependence (TD) %	Main aim or intervention	Outcome measures	HRQoL outcome result	Physical function outcome result
Vijenthira, 2022 [42] Cross-sectional study	447	(Self-reported by patients) MDS-SLD 1%, MDS-MLD 7%, MDS-RARS 16%, del (5q) 11%, MDS-EB1 6%, MDS-EB2 4%, MDS-U 13%, CMML-1 1%, CMML-2 < 1%, unknown 40% MDS risk category (self-reported) Low 45%, high 27%, unknown 28%	Hb unknown 100% patients were RBC-TD	Cross-sectional survey to audit real-world transfusion practices and understand the experiences and preferences of TD MDS patients	Transfusion-related characteristic and patient experiences via survey (patient perceptions of transfusion, transfusion-related symptoms, impact of transfusion process, transfusion preferences)	The most commonly experienced symptoms were fatigue (91%), shortness of breath (72%), weakness (69%), dizziness (43%). The symptoms with the largest impact on patients' lives were fatigue (46%) and shortness of breath (24%).	Nil

Hsia et al. assessed the effect of fresh versus standard-issue RBCs on HRQoL in an n-of-1 trial design involving nine patients [20]. For the remaining seven RCTs, HRQoL was a secondary outcome. The primary outcomes in these trials included: five trials [17,19,21,22,25] which evaluated erythroid response or transfusion incidence as the primary outcome when randomising to growth factor or EMA, versus supportive care/ placebo, one evaluating fatigue score as the primary outcome for restrictive versus liberal transfusion thresholds [23] and one trial evaluating the feasibility of the design of an RCT of restrictive versus liberal transfusion [24].

3.4. Non-randomized studies

Of the 14 NRSIs, nine investigated ESAs (with or without G-CSF) [28–31,35–39], three investigated RBC transfusion [26,32,34], one investigated both RBC and ESAs [27] and one was an observational study of HRQoL and cardiac remodelling in MDS patients including correlations with Hb levels [33]. Of the three cross-sectional studies, one investigated the symptoms, impacts on HRQoL domains and content validity of HRQoL instruments in transfusion-dependent MDS patients [41], one compared transfusion-dependent versus transfusion-free patients [40] and one was a cross-sectional survey to audit transfusion practices and preferences of MDS patients [42]. Two included only low risk MDS [33,35], eleven included low and intermediate risk MDS [27,29–32,36–39,41], two included all MDS risk groups [34,42] and three did not report MDS risk category [26,28,40].

3.5. Objective 1: HRQoL and physical function instruments measured in clinical studies

3.5.1. HRQoL instruments

Within the 26 studies, 12 different HRQoL tools were used (Supplementary Table 2), the commonest being FACT-Anemia (FACT-AN) (used in 12 studies [17,18,20,22,28,29,33–37,41]), EORTC QLQC30 (used in seven studies [24,25,27,30,31,33,40]) and the EQ-5D (used in six studies [21–24,32,38]). Other tools used included: FACT-General (FACT-G), FACT-Fatigue (FACT-F), Visual Analogue Scale (VAS), Linear Analogue Self Assessment (LASA), QoL-E, Quality of Life in Myelodysplasia scale (QUALMS), SF-36. Two included other surveys [38,42]. Two studies included a physician survey [32,33] and two included qualitative interviews [34,41]. Six studies used an MDS-specific HRQoL instrument (QUALMS [26,41] or QOL-E [25,31,32,40]).

3.5.2. Physical functional instruments

Four studies reported physical function instruments [29,30,33,40]. None of these were randomized trials. A total of six different tools were used. Cardiac function testing [29,30,33,40] (echocardiography or MRI) and VO_2 max [29,30] were the most commonly used tools (Supplementary Table 3). One study assessed echocardiography in a cross-sectional study comparing transfusion-dependent versus transfusion-free patients [40]. Kelaidi et al. measured exercise ability via VO_2 max, 6-min walk tests (6MWT) or short performance battery (SPPB) tests, in addition to echocardiography, in a study of ESAs and G-CSF [29]. Ramos et al. assessed SPPB and cardiac function in a longitudinal study of HRQoL in low-risk anaemic MDS patients [33]. Nilsson-Ehle et al. measured VO_2max and cardiac MRI in a study using ESAs, GCSF or RBC transfusion targeting a Hb > 120 g/L. [30]

3.6. Objective 2: are improvements in anemia outcomes reflected in measures of HRQoL and physical function?

3.6.1. Group 1 studies (randomized trials): do HRQoL outcomes mirror Hb outcomes?

Table 2 shows the effects of treatments on Hb/erythroid response outcomes, HRQoL outcomes and the concordance between them, for the nine RCTs. These have been colour-coded in the table to illustrate the strength of evidence behind each finding.

Six (66.7%) RCTs showed statistically significant improvements in Hb or higher erythroid response rates associated with the treatment under investigation: four reported higher erythroid responses for growth factor versus supportive care/placebo (Casadevall [17], Feanux [22], Greenberg [19], Platzbecker [21]), one reported higher transfusion independence and erythroid response for EMA versus placebo [25]. Stanworth et al. [24] reported higher mean Hb for liberal versus restrictive transfusion. Two (25%) RCTs reported higher Hb/erythroid response rates, which did not reach statistical significance, or was of unclear significance: Balleari et al. [18] reported higher erythroid response rates in the ESA + G-CSF arm compared to ESA alone ($p = 0.065$); Gerard Jansen et al. [23] reported higher mean Hb in the liberal vs restrictive transfusion groups (no p-value reported). A randomized n-of-1 study investigating fresh versus standard RBC, and reported no difference in mean Hb [20].

Of these, only one study [24] reported improved HRQoL in the group with higher Hb (liberal transfusion arm), although not statistically significant. Five studies reported no difference in HRQoL scores for the two groups, despite differences in erythroid response rates: this included three studies [17,21,25] which had detailed data and statistical analysis, and two studies [19,22] which did not describe the data or statistical analysis. In the studies by Balleari [18] and Gerard Jansen [23], no statistical analysis was performed for the HRQoL results due to insufficient patient numbers.

Meta-analysis and pooled analysis of the results using Hedge's g was not possible due to insufficient data reported in the publications.

Table 2
Group 1 studies (Randomized trials): Do HRQoL outcomes or physical function outcomes mirror Hb outcomes?

Colour key:

Green	***Strong evidence of treatment effect*** *on Hb/HRQoL outcome (e.g. p<0.05); or* ***concordance*** *of Hb/HRQoL results*
Orange	*There* ***may be a positive*** *treatment effect of the treatment on Hb/HRQOL outcome; or concordance of Hb/HRQoL results with data provided to support this, but the results was not statistically significant, or statistical significance is unclear*
Red	***Strong evidence*** *that the* ***treatment did not result in any improvement*** *to Hb/HRQoL outcome****, or discordance*** *of Hb/HRQoL results. sufficient confidence of this finding (data presented in the paper such as differences in mean Hb/ HRQoL scores, statistical analyses)*
Grey	*For assessment of treatment effect on Hb/HRQoL outcome: authors report* ***no treatment effect but insufficient data*** *to assess strength of evidence (e.g no statistical analyses or further data provided) There* ***may be discordance*** *between Hb/HRQoL outcome but insufficient data to assess strength of evidence*
Brown	***Insufficient data*** *provided to make a judgement*

Author	N patients in the study	Comparator groups	Effect of treatment on Hb or erythroid response results	Effect of treatment on HRQoL outcome	Was a clinically significant change (e.g. minimally clinically important difference [MCID]) in HRQOL defined? If so, are these effects clinically significant?	Concordance of Hb/erythroid outcome with HRQoL outcome
Balleari, 2006[17]	30	rHEPO vs rHEPO+G-CSF	At 8 weeks, higher erythroid response in rhEPO+GCSF arm (11/15,73.3%) vs rHEPO arm (6/15, 40%) but did not reach statistical significance (p=0.065). Erythroid response (minor/major) defined as: increase in Hb ≥10g/L or ≥50% decrease in transfusion requirement for TD patients.	No HRQoL analysis performed for the 2 groups due to small number of patients with HRQoL available. Subgroup analysis performed (see table 3).	Not specifically defined in paper but reference provided. Unclear as no HRQoL data for the 2 groups provided.	Unclear as no HRQoL analysis performed for the 2 groups. Subgroup analysis is shown in table 3.
Casadevall, 2004[16]	60	Group A receiving ESA+GCSF vs group B receiving supportive care	At 12 weeks, group A 10/24 (41.7%) had erythroid response vs 0% in arm B (p=0.01) Erythroid response definition: Hb ≥115g/L or Hb increase ≥15g/L or remained stable without transfusion	No significant difference in HRQoL scores for the two groups, with scores remaining constant throughout the study. Mean HRQoL scores for the 2 arms reported in tabulated format for weeks 0, 12, 28 and 52.	Yes, defined as a minimal difference of: 7.0 (FACT-An score), 3.9 (fatigue subscale), 6.0 (anemia subscale), based upon previous studies. Results did not meet this criteria.	No statistically significant difference in HRQoL scores despite higher erythroid response in Group A (ESA+GCSF).
Fenaux, 2018[21]	130	ESA vs placebo	At 24 weeks, erythroid response was 45.9% (ESA) vs 4.4% (placebo) (p<0.001).	No significant differences in HRQoL between ESA versus placebo arm at any timepoint. Data/ statistical analysis not	Not defined	No significant difference in HRQoL between the 2 groups despite higher erythroid responses in ESA group.
			Erythroid response defined per IWG 2006 criteria (minor/major): For patients with pre-treatment Hb<110g/L, Hb increase ≥10g/L. For TD patients, >50% decrease in transfusion requirements. Modified in study to also include patients with Hb increase ≥15g/L lasting less than 8 weeks due to ESA discontinuation if Hb still increased ≥15g/L on restarting ESA.	provided, apart from p-value of subgroup analysis of responders vs non-responders (see table 3).		Differences observed during subgroup analysis (ESA responder vs non responders -see table 3).
Gerard Jansen, 2020[22]	19 (study terminated early due to slow recruitment)	Restrictive versus liberal transfusion thresholds	Higher mean Hb values at 12 months in the liberal group but high drop-out rates: 73g/L (restrictive group, n=3) vs 84 g/L (liberal group, n=2) (statistical significance not reported).	Unclear if HRQoL changes differed in the liberal group compared to the restrictive group. Mean/SD HRQoL score at baseline (T=0) for restrictive group was 57.5± 13.1; at T=12 months 58.3±-20.2. Mean/SD HRQoL scores for liberal arm at baseline 70.6±12.4, at 12 months 73.8±11.1. Study terminated early due to insufficient patient recruitment.	Specifically stated that as a non-inferiority study design, it was not powered to detect clinically relevant differences.	Unclear if HRQoL changed significantly, or if there was any difference, between the restrictive versus liberal groups despite higher Hb in the liberal group.
Greenberg, 2009[18]	110	ESA vs supportive care	Higher erythroid response rate in ESA vs supportive care arm (36% vs 9.6%) at 4 months (p=0.0002). Erythroid response defined as per IWG 2000 MDS response criteria: minor/major): For patients with pre-treatment Hb<110g/L, Hb increase ≥10g/L. For TD patients, >50% decrease in transfusion requirements.	No difference in scores for supportive care versus ESA treated patients at baseline or 4 months. HRQoL data not reported. Some differences in ESA responders vs non-responders (see table 3).	Not defined	Reports no difference in HRQoL in the two arms despite higher erythroid response rate in the ESA arm, however HRQoL data not presented. For subgroup analysis of ESA responders vs non-responders, see table 3.
Hsia, 2016[19]	20	Patients receiving fresh vs standard RBC	No difference in mean Hb for fresh vs standard RBCs.	No difference in the HRQoL symptom scores for fresh vs standard RBCs. Reported HRQoL scores for all participants in the n-of-1 trials.	Not defined	Correlation – no difference in Hb change observed, and no difference in HRQoL scores.
Oliva, 2021[24]	225	Luspatercept + best supportive care (BSC) vs placebo + BSC	As reported in the primary MEDALIST trial results paper: Higher rates of transfusion independence for ≥ 8 weeks in luspatercept +BSC arm (38%)	No clinically meaningful within-group or between-group differences across all domains of the EORTC QLQ-C30 or QOL-E for the 2 groups.	Yes. Defined as ≥10-point change in score for QLQ-C30 or ≥0.5 standard deviations of the baseline domain score for QOL-E domains and summary scales.	No correlation between improved erythroid responses on luspatercept with changes in HRQoL

			versus placebo + BSC arm (13%) (p<0.001). Higher erythroid response rates in luspatercept group compared to placebo (53% vs 12%). Erythroid response per IWG 2006 criteria. Higher rates of mean Hb increase of at least 10g/L in luspatercept vs placebo group (35% vs 8%).	On one item of the QOL-E MDS-specific disturbances domain, luspatercept patients reported improvements in daily life due to reduced transfusion burden, compared to placebo.	Changes were not clinically significant	
Platzbecker, 2017[20]	146	ESA (darbepoetin alfa) vs placebo	Higher erythroid response rates in ESA group vs placebo (14.7% vs 0%, p=0.016) at 24 weeks. Erythroid response defined as: ≥15g/L Hb increase	No difference in HRQoL changes between the 2 groups. No difference in EuroQol mean (SD) change from baseline: ESA 2.1(13.1) points vs placebo 0.8 (15.7) points. No difference in rates of clinically significant FACIT scale change in the 2 groups: fatigue subscale: ESA 35.6% vs placebo 31%	Yes, defined for FACIT as ≥3 points. The change in FACIT scores did not meet this criteria.	No difference in HRQoL despite higher erythroid response rates in the ESA group.
Stanworth, 2020[23]	38	Restrictive vs liberal transfusion thresholds	Higher mean pre-transfusion Hb in liberal arm vs restrictive arm (97g/L vs 80g/L, p<0.0001)	Higher number of participants achieving clinically meaningful improvements favouring the liberal group across some domains (EQ-5D-5L descriptive; EORTC QLQ-C30 : fatigue and global health score). In a post hoc analysis, all five main HRQoL outcomes were improved for the liberal arm compared to the restrictive arm. e.g. EQ-5D-5L area (median, IQR) under the curve: restrictive group 0.76 (0.51-0.81) vs liberal group 0.83 (0.69-0.86)	Yes – defined as QLQ-C30: 10 points and EQ-5D 0.08 points Yes – higher numbers of participants in the liberal group had clinically meaningful increase in the HR-QoL domains as listed.	Improved HRQoL reported in the liberal arm compared to restrictive arm though unclear if statistically significant.

3.6.2. *Group 2 studies (non-randomized comparisons of subgroups based on Hb response)*

If patients are split into groups according to their Hb response, is there a greater improvement in HRQoL for these subgroups?

Table 3 shows the effects of treatments on Hb/erythroid response outcomes, HRQoL outcomes and the concordance between them for studies comparing subgroups based on Hb response. This included subgroup analysis in three RCTs [18,19,22] and four [28,29,31,36] NRSIs. All seven studies investigated growth factor treatment for anemia, with the subgroup analysis comparing responders versus non-responders.

All seven studies showed higher Hb/erythroid response rates in the responders compared to non-responders. HRQoL was significantly improved in responders compared to non-responders in five studies [19,22,29,31,36], and the remaining two studies reported improved HRQoL in responders, but statistical significance was not provided [18,28].

3.6.3. *Are improvements in anemia outcomes reflected in physical function?*

One study included a subgroup analysis of Hb responders versus non-responders and is summarised in Table 4. Kelaidi et al. [29] compared growth factor responders versus non-responders within a single arm cohort study and found significantly greater VO_2max improvement in growth factor responders compared to non-responders, though there was no difference for two other tests (6MWT and SPPB) [29].

3.7. *Quality assessment of studies using SPIRIT-PRO Extension guidelines*

Key components of methodological analysis were assessed and found to vary between studies. These are summarised in Supplementary Tables 2 and 3.

Timing of HRQoL and physical function measurements was variable. For HRQoL instruments, 20/23 (74%) studies reported use at baseline [17–19,22,23,25,28–33,35–40,42] or pre-transfusion [20,24,26,34], however subsequent follow-up timepoints varied. For physical function instruments, one study involved a one-off measurement only [40]; the other three studies [29,30,33] all had baseline measurements, with subsequent variable follow-up timepoints.

Attrition rates were variable and generally increased with subsequent follow-up timepoints (Supplementary Tables 2 and 3), though the number of respondents over time was only reported in 12/23 studies (48%) [17–20,23,25–27,30,35,37,41]. Attrition rate was reported in 7/9 RCTs [17–20,23–25]: these ranged from 41.2% (7/17) [23] to 100% (9/9) [20] of patients having HRQoL/physical functional data at the end of study. Of the non-randomized studies, three studies [27,41,42] reported a one-off measurement of HRQoL data – of the remaining studies, attrition data was only reported in four studies [26,35,37,38], with 55% [38], 61% [26], 83.5% [35] and 100% [37] of patients having HRQoL/physical functional data at the end of study, respectively.

Two RCTs [18,20] had HRQoL as a primary outcome measurement but neither reported a power calculation based on HRQoL outcomes. One RCT was initially powered to detect HRQoL outcome but was terminated early due to slow recruitment [23].

Five RCTs [17,20,21,24,25] and all NRSIs reported an analysis plan for HRQoL outcomes.

A MCID in the HRQoL outcome in the study methodology [17,18,21,24,25] was defined in five RCTs; of these, one reported HRQoL outcomes meeting this criteria but notably the result was not statistically significant (possibly due to small sample size of 38 patients) [24], three reported the HRQoL score changes did not meet the criteria [17,21,25] and one study had insufficient HRQoL data for the two comparator groups [18]. (Table 2) Of the NRSIs in table 2, two studies defined a MCID in the methodology [28,36]; one study found HRQoL improvements which met these criteria and were also statistically significant [36] and the other also reported HRQoL changes meeting the criteria but statistical significance was unclear [28]. (Table 3) For physical function assessment, none of the studies defined a clinically significant change.

4. Discussion

Despite the importance of HRQoL and physical function for patients with MDS, we found that many studies investigating interventions in MDS-related anemia did not include assessment of HRQoL or physical function, as 152 studies were excluded in our screening for this reason. Of the 26 studies eligible for our review which did report HRQoL, many

Table 3
Group 2 (comparing subgroups based on Hb response): If patients are split into groups according to their Hb/erythroid response, is there a greater improvement in HRQoL for the subgroups?

Colour key:

Green	***Strong evidence of treatment effect*** *on Hb/HRQoL outcome (e.g. p<0.05); or* ***concordance*** *of Hb/HRQoL results*
Orange	*There* ***may be a positive*** *treatment effect of the treatment on Hb/HRQOL outcome; or concordance of Hb/HRQoL results with data provided to support this, but the results was not statistically significant, or statistical significance is unclear*
Red	***Strong evidence*** *that the* ***treatment did not result in any improvement*** *to Hb/HRQoL outcome****, or discordance*** *of Hb/HRQoL results. sufficient confidence of this finding (data presented in the paper such as differences in mean Hb/ HRQoL scores, statistical analyses)*
Grey	*For assessment of treatment effect on Hb/HRQoL outcome: authors report* ***no treatment effect but insufficient data*** *to assess strength of evidence (e.g no statistical analyses or further data provided)* *There* ***may be discordance*** *between Hb/HRQoL outcome but insufficient data to assess strength of evidence*
Brown	***Insufficient data*** *provided to make a judgement*

Author	N patients in the study / N of patients in the subgroup analysis (for RCTs)	Subgroups and definitions	Effect of treatment on Hb for responder vs non-responder groups	Effect of treatment on HRQoL outcome for responder vs non-responder groups	Was a clinically significant change (e.g. minimally clinically important difference [MCID]) in HRQOL defined? If so, are these effects clinically significant?	Concordance of HRQoL outcome change compared to Hb/erythroid response for responder vs non-responder groups
Randomised trials subgroup analyzes						
Balleari, 2006[17]	N in study: 30 N in subgroup analysis: 13	Responders to haematopoietic growth factors vs non-responders. Erythroid response defined as: Hb increase ≥10g/L or ≥50% decrease in transfusion requirement for TD patients.	By definition – 100% of responders and 0% of non-responders had erythroid response. Mean Hb or Hb changes for responders vs non-responders was not reported.	Total FACT-An score improved from baseline to final evaluation in most responders to haematopoietic growth factor whereas it did not change for non-responders. Mean increase (improvement) of 5.1-point (8-weeks) and 7.3-point (16-weeks) in responders. Non-responders had mean change in score <0 (only reported in a graphical format). No p-value provided.	Not specifically defined in paper but reference provided. Yes - the mean 5.1- and 7.3- point increases in the FACT-An score at 8 and 16 weeks respectively exceeded the changes required to reflect a clinically significant improvement in HRQoL.	Erythroid response appears to be correlated with HRQoL improvement.
Fenaux, 2018[21]	N in study: 130 N in subgroup analysis: not stated but 2 responders in placebo group and 39 in ESA group	Responders in the ESA group compared to responders in the placebo group. Response defined per IWG 2006 criteria (minor/major): For patients with pre-treatment Hb<110g/L, Hb increase ≥10g/L. For TD patients, >50% decrease in transfusion requirements. Modified in study to also include patients with Hb increase ≥15g/L lasting less than 8 weeks due to ESA discontinuation if Hb still increased ≥15g/L on restarting ESA.	45.9% erythroid response rate in the ESA group compared to 4.4% in placebo group (p<0.001). Mean Hb or Hb change for responders vs non-responders was not reported.	EQ-5D scores at week 24 was significantly better for responders in the ESA group compared to responders in the placebo group. (p=0.034)	Not defined.	Erythroid response was associated with improved HRQoL scores
Greenberg, 2009[18]	N in study: 110 N in subgroup analysis: not stated	Patients with an erythroid response compared to no erythroid response. Erythroid response defined as per IWG 2000 MDS response criteria: minor/major): For patients with pre-treatment Hb<110g/L, Hb increase ≥10g/L. For TD patients, >50% decrease in transfusion requirements.	By definition – 100% responders and 0% non-responders had erythroid response. Higher erythroid response rate in ESA vs supportive care arm (36% vs 9.6%) at 4 months (p=0.0002). Mean Hb changes for responders vs non-responders was not reported.	Patients who had an erythroid response at 4 months reported significant improvement from baseline in physical (p=0.007), emotional (p=0.05) and functional (p=0.005) well-being on the FACT-G, as well as fatigue (p=0.02) and overall QOL (p=0.02).	Not defined.	Patients with erythroid response had significantly improved HRQoL across multiple domains.
NRSIs						
Clavio, 2004[27]	N in study: 11	Prospective single arm study of ESA on HRQoL. Did compare patients with and without response to ESA. Erythroid response defined as per IWG 2000 MDS response criteria: minor/major): For patients with pre-treatment Hb<110g/L, Hb increase ≥10g/L. For TD patients, >50% decrease in transfusion requirements.	55% achieved erythroid response at 12 weeks (no comparator group). By definition – all responders achieved erythroid response vs 0% of non-responders, but mean changes in Hb not reported.	ESA responders had improvement of FACT-An score from baseline to final (mean increase 7.8 points at 12 weeks for responders), while it did not change in non-responders (score not provided; no p-value provided). Patients with greatest increase in Hb also had higher increases in HRQoL scores (data not provided). Responding patients maintained the improvement in HRQoL scores after 24 weeks therapy.	Referenced previous publication with a change of at least 4.2 points in Fact-An considered clinically significant. Yes, results in the ESA responder group reached clinical significance.	ESA responders appear to have greater improvements in HRQoL compared to non-responder though statistical significance not provided.
Kelaidi, 2013[28]	N in study: 99	Prospective single arm study of growth factor treatment (ESA for 12 weeks then	Erythroid response 48% at 12 weeks and 56% at 24	SF-36: Physical functioning scales correlated positively with	Not defined	Greater improvements in HRQoL in growth factor responders vs non-

		G-CSF added at week 12 in non-responders). Compared HRQoL in growth factor responders vs non-responders. Erythroid response defined by IWG 2006 criteria (minor/major): For patients with pre-treatment Hb<110g/L, Hb increase ≥10g/L. For TD patients, >50% decrease in transfusion requirements.	weeks (no comparator group). By definition – all responders achieved erythroid response vs 0% of non-responders but Hb change not reported.	erythroid response (mean difference over time in responders vs non responders: 9.6 vs -11.2, p=0.0002 for the interaction between group and time), bodily pain (7.9 vs -7.8, p=0.04), vitality (11.1 vs -7.1, p<0.0001). Scales evaluating mental health not significantly associated with erythroid response. Physical Component Summary improved over time in responders vs non-responders (mean difference 3 vs 0.4, p=0.04). FACT-An: steady and greater improvement in all scales over time for ESA responders vs non-responders (FACT-General mean difference over 6 months in responders vs non-responders 4.1 vs. -5.6, p=0.007), FACT-An Trial Outcome index (mean difference 14.4 vs -5.5, p=0.001), FACT-Anemia (mean difference 13 vs. -8.1, p=0.002).		responders, which were statistically significant.
Oliva, 2010[30]	41	Prospective single arm study of ESA. Compared HRQoL in ESA responders vs non-responders. Definition of response per 2000 IWG criteria (minor/major): Hb increase ≥10g/L or, for TD patients, >50% decrease in transfusion requirements.	73% (29/40) had a response (single arm study). By definition – all responders achieved erythroid response vs 0% of non-responders but Hb change not reported. Difference in Hb for responders vs non-responders not reported.	Improvements in Hb correlated with changes in QOL-E physical (r=0.429, p=0.036), functional (r=0.487, p=0.021), social (r=0.533, p=0.019) and general (r=0.845, p=0.034) domains.	Not defined	Hb improvements associated with HRQoL improvements which were statistically significant.
Stasi, 2005[35]	53	Prospective single arm study of ESA. Compared HRQoL between ESA responders vs non-responders Definition of response per IWG criteria (minor/major): Hb increase ≥10g/L or, for TD patients, >50% decrease in transfusion requirements.	At 24 weeks, erythroid response rate was 45%. (No comparator group). By definition – all responders achieved erythroid response vs 0% of non-responders.	LASA scores improved for responders. For none-responders, LASA energy levels, daily activities and overall assessment worsened. Positive correlation between change in HRQoL domains and change in Hb: LASA energy level	Yes – defined as a change in 2.54 in FACT-G and 4.24 in FACT-An fatigue subscale corresponds to a minimally important clinical difference	Hb improvements correlated with HRQoL improvements on both LASA and FACT-An scales, which were statically significant.
			Difference in Hb for responders vs non-responders not reported.	(r=0.0429, p=0.036, daily activities (r=0.653, p<0.001), overall wellbeing (r=0.457, p=0.024). Statistically significant (p<0.001) differences in mean score for all FACT scales in the responder group, but no significant change for the non-responders. In responders, Hb improvements correlated with improvement in FACT-An total score (r=0.247, p=0.025), FACT-G (r=0.315, p=0.013), anemia subscale (r=0.333, p=0.011), fatigue subscale (r=0.191, p=0.037).	Yes – the changes in FACT-An/FACT-G exceeded these	

different tools were reported: 12 HRQoL tools and six physical function tools were identified.

Overall, compliance with key aspects of the SPIRIT-PRO Extension guidelines was variable across the included studies, as there was variation in follow-up timepoints, and attrition rates were also generally either high or not reported. Few studies (5/9 RCTs [17,18,21,24,25] and 3/14 non-randomized studies [17,18,28,36]) defined a MCID for HRQoL outcomes in the study methodology and none defined it for physical function assessment. Similar to previous reports [44], there was a lack of MDS disease-specific HRQoL assessment tools used, which may more fully capture all the psychosocial and symptom burdens important to MDS patients (e.g. the QOL-E [45] and QUALMS [46] includes questions assessing the impacts of transfusion dependence and anemia symptoms). Taken together, all these limitations precluded more direct comparison of results between different studies or meta-analysis.

A recent literature review of HRQoL outcomes in patients with MDS highlighted the importance of measuring HRQoL in this patient cohort, given the lack of curative treatments available, and similarly identified the limitations of existing studies measuring such outcomes [44]. However, it was not a systematic review and, as such, did not include analysis of risk of bias of the included studies; in addition, studies were not evaluated against SPIRIT-PRO Extension guidelines. Additionally, physical functional outcomes were not included. The authors indicated that the benefits of ESAs on HRQoL overall in MDS patients is unclear, however did not directly correlate or analyse HRQoL changes with Hb outcomes [44].

In our analysis, across nine RCTs of a range of therapies including growth factors, EMAs, transfusion thresholds and fresh versus standard RBCs, we found that Hb outcomes might be associated with positive changes in HRQoL outcomes in only two studies. These two studies evaluated a liberal transfusion strategy that improved Hb and appeared to improve HRQoL, though this did not reach statistical significance [24], and another study showed no change in Hb or HRQoL for fresh compared to standard RBCs [20]. Five RCTs showed no change in HRQoL despite higher erythroid responses in patients treated with growth factors [17,19,21,22] or EMAs [25]. The exact nature of the relationship between anemia improvement and HRQoL therefore remains very unclear and raise the question of whether anemia treatment alone is effective in improving MDS patients' HRQoL and physical function. Previous research has shown that the major part of the negative impact of MDS on HRQoL, particularly in usual activities, self-care, and anxiety/depression, is not mediated via anemia [47]. Possible explanations for this include pathogenic factors causing reduced HRQoL beyond anemia or difficulties in measuring HRQoL accurately.

Table 4
Effects of interventions on physical function.

Colour key:

Green	***Strong evidence of treatment effect*** *on Hb/physical function outcome (e.g. p<0.05); or* ***concordance*** *of Hb/physical function results*
Orange	*There* ***may be a positive*** *treatment effect of the treatment on physical function outcome; or concordance of Hb/physical function results with data provided to support this, but the results was not statistically significant, or statistical significance is unclear*
Red	***Strong evidence*** *that the* ***treatment did not result in any improvement*** *to Hb/physical function outcome;* ***or discordance*** *of Hb/physical function results. sufficient confidence of this finding (data presented in the paper such as differences in mean Hb/ physical function scores, statistical analyses)*
Grey	*For assessment of treatment effect on Hb/physical function outcome: authors report* ***no treatment effect but insufficient data*** *to assess strength of evidence (e.g no statistical analyses or further data provided)* *There* ***may be discordance*** *between Hb/physical function outcome but insufficient data to assess strength of evidence*
Brown	***Insufficient data*** *provided to make a judgement*

Author	N patients in the study	Comparator groups (responder vs non-responder)	Effect of treatment on Hb for responder vs non-responder groups	Effect of treatment on physical function outcome for responder vs non-responder groups	Was a clinically significant change (e.g. minimally clinically important difference [MCID]) in physical function defined? If so, are these effects clinically significant?	Concordance of physical function outcome change compared to Hb/erythroid response for responder vs non-responder groups
Kelaidi, 2013[28]	95	Prospective single arm study of growth factor treatment (ESA for 12 weeks then G-CSF added at week 12 in non-responders). Compared physical function outcomes in growth factor responders vs non-responders. Erythroid response defined by IWG 2006 criteria (minor/major): For patients with pre-treatment Hb<110g/L, Hb increase ≥10g/L. For TD patients, >50% decrease in transfusion requirements.	Erythroid response 48% at 12 weeks and 56% at 24 weeks (no comparator group). By definition – all responders achieved erythroid response vs 0% of non-responders but Hb change not reported.	Significant difference between baseline and 6 months in VO_2max for ESA responders (improved: mean difference 212.1mL/min) vs non-responders (declined: mean difference negative 89.5mL/min), p=0.01. No significant difference over time in 6MWT (mean difference between baseline and 6 months of 22.7 and 32.7m in responders and non-responders, p=0.81) or short battery test results for ESA responders vs non-responders.	Not defined	VO2max significantly improved for responders, who also had higher erythroid response rates. However, no difference for 6MWT or short battery test.

For example, older individuals might be cognitively and emotionally better prepared to accept illness [48] and hence less likely to report negative effects of anemia. Alternatively, other health and wellbeing factors may have a greater impact on HRQoL – for example, vulnerability in the elderly (defined as older persons at risk for health deterioration), was recently observed to have a detrimental effect on HRQoL in MDS patients, even in patients with lower-risk disease [49]. Another mechanism may be immune dysregulation. Studies in general populations show that inflammation may negatively impact on HRQoL in older individuals [50,51]. Inflammation can occur in MDS [52] and may also be modulated by transfusion [53].

HRQoL is difficult to measure, due to issues with loss to follow-up, the potential subjective nature of responses, and the difficulty in using standardised models with preselected domains to assess an aspect of health which is unique to different individuals. It has been proposed that currently used HRQoL tools are not patient centric due to the way in which the questions were generated, or the questionnaire format itself limits the responses or the scoring system may not be generalisable for all patients, and that more individualised (and complex) measures of HRQoL are required [54]. Further, most of these studies identified in this review were too small to detect realistic differences and the reporting is too limited to allow pooling of results to obtain a narrower confidence interval.

In contrast to the RCT results, when non-randomized and randomized studies that reported subgroup analyses of responders versus non-responders were reviewed, a greater and statistically significant improvement in HRQoL was observed in treatment responders in five studies [19,22,29,31,36] and an improvement in HRQoL observed in treatment responders, of unclear statistical significance, in two studies [18,28]. However, the strength of conclusions is limited by the inherent nature of observational research and risk of bias – lack of randomization leads to risk of confounding and lack of balancing of prognostic factors across treatment groups.

A major limitation to our analyses was the challenges of the study designs and reporting methodology. Missing data, for example, was a key problem identified in several included studies. It has been suggested that even a 10% or less rate of missing data may result in substantial bias [55]. Of the seven RCTs that reported attrition rates for HRQoL/physical functional outcomes, rates exceeded 10% in all but one study [20]. Additionally, it is unclear if the studies were adequately powered for the HRQoL/ physical function outcome. In the two RCTs with HRQoL as a primary outcome measurement, the power calculation for the PRO analysis was not described [18,20]. Other key data such as IPSS or IPSS-R was also not stated in five studies [20,23,26,28,40], or had missing IPSS/IPSS-R data of >10% in two studies [17,42]. For studies that did report IPSS/IPSS-R, the majority (3/7 RCTs and 13/15 NRSIs) included low or intermediate risk groups only. This is likely due to our exclusion of disease-modifying therapies, however may reduce the applicability of our findings to patients with higher risk disease.

Strengths of our review include capturing both HRQoL and physical function outcomes, the specific focus of our question (focusing on anemia supportive interventions) and the comprehensive search. We did not include disease modifying agents such as hypomethylating agents in this review, due to their potential impacts on HRQoL, independent of their effect on Hb; a previous study showed that patients receiving 5-azacitidine had greater improvement in several HRQoL domains compared to patients treated with supportive care only, with these differences maintained after controlling for the number of RBC transfusions [9]. Limitations of our review include exclusion of non-English studies. We were unable to make definitive conclusions about the effect of interventions on HRQoL and physical function, due to the limitations of the included studies.

The main implication of our paper is for future research. Larger studies are required to investigate the role of anemia and its treatment on HRQoL in patients with MDS. Studies investigating anemia-related interventions in MDS patients should consider inclusion of both HRQoL and physical function outcomes, which were lacking in many studies. Only one included study included a subgroup analysis of

physical function outcomes relating to erythroid response; which of interest showed improvements of VO_2 max in ESA responders [29]. The use of wearable devices to monitor physical outcomes is increasingly being explored and would also be of interest in MDS patients. Application of evidence-based guidelines, such as SPIRIT-PRO Extension, is important to ensure trials are well-designed and well-reported with respect to these outcomes.

5. Conclusion

This review highlights the lack of reported HRQoL and physical function outcomes in studies investigating anemia treatments for MDS patients and the limitations of such studies. We were unable to definitively conclude if anemia treatments improved HRQoL or physical function. In future, a more standardised approach and robust, clear and detailed reporting is essential to address the question of whether anemia treatments improve these important patient-centred outcomes, to ensure that higher quality data can be generated and used effectively in clinical practice.

Practice points

- HRQoL and physical function are important outcomes to assess as part of treatment response to anemia treatments in MDS patients, given that patients are frequently elderly and in whom MDS treatments are largely non-curative.
- Although supportive care treatments such as ESAs and transfusion may improve Hb, the effect on HRQoL and physical functional outcomes remains unclear. In particular, few data are available on physical functional outcomes.
- The current lack of a standardised approach to using HRQoL or physical functional tools in MDS patients makes comparison of different treatments and studies difficult.

Future considerations

- It is vital that the effects of anemia treatments on HRQoL and physical function in patients with MDS are further explored.
- There should be collaboration within the research and medical community to develop a standardised approach to use of HRQoL and physical function tools, so that these may be implemented in future clinical trials and used by clinicians on a day-to-day basis. The standardisation of symptoms, domains and timing of measurements may improve compliance and minimize missing data.
- Future studies of treatments for MDS related anemia should include HRQoL and physical function outcomes. These studies should be designed and reported in accordance with international guidelines such as SPIRIT-PRO Extension, to ensure results are robust and useful.

Research agenda

- More universal incorporation of HRQoL and physical function outcomes into future clinical trials of MDS therapies.
- Reporting of HRQoL and physical function outcome findings from randomized trials should ideally be standalone publications, and mandatory reporting of such findings should be considered for new therapies.
- Further research is needed to elucidate the relationship between anemia, Hb levels and HRQoL/physical functional outcomes.

Author contributions

AM did study protocol development, search strategy development, abstract and citation screening, full text screening and review, bias assessment, data extraction, data analysis, writing of final report.

MP did abstract and citation screening, full text screening and review, bias assessment, data extraction, data analysis, writing of final report.

EW did study protocol development, search strategy development, review of final report.

JS did study protocol development, search strategy development, review of final report.

SJB did study protocol development, search strategy development, data analysis, review of final report.

CD did study protocol development, search strategy development, search of databases, review of final report.

Jsa did statistical advice, review of final report.

NS did abstract and citation screening, full text screening and review, review of final report.

EL did abstract and citation screening, full text screening and review, review of final report.

SJS did study protocol development, search strategy development, review of final report.

ZM did study protocol development, search strategy development, abstract and citation screening, full text screening and review, data analysis, review of final report.

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Data availability

Data and study protocol may be made available by correspondence with the authors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.blre.2023.101114.

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