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Drivers of Transfusion Decision Making and Quality of the Evidence in Orthopedic Surgery: A Systematic Review of the Literature

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Reasons for variation in transfusion practice in orthopedic surgery are not well understood. This systematic review identified and appraised the quality of the literature in this area to assess the impact of factors associated with the use of allogeneic red blood cell (RBC) transfusion in orthopedic procedures. MEDLINE and EMBASE databases were searched for relevant English language publications. Articles containing a range of MeSH and text terms regarding "blood transfusion," "predictors," and "multiple logistic regression" were retrieved. Articles that focused on patients undergoing orthopedic procedures and that met prespecified inclusion criteria were appraised in terms of potential bias and the appropriateness of statistical approach. A total of 3641 citations were retrieved, and 29 met the inclusion criteria for the review. Articles reported on a range of orthopedic procedures including total hip arthroplasty; total knee arthroplasty, total shoulder arthroplasty, and spinal surgery. Most studies were conducted in the United States (n = 12) or Canada (n = 5). Study quality was moderate; 50% or more of the quality criteria were assessed in 15 articles. Particular areas of concern were the lack of prospective studies, lack of clarity in defining the time interval between risk factor assessment and transfusion outcome, and lack of model validation. A narrative synthesis found that 2 factors consistently influenced the use of RBC transfusion—decreased hemoglobin (n = 25) and increased patient age (n = 18). Increased surgical complexity (n = 12), low body weight (n = 9), presence of additional comorbidities (n = 9), and female sex (n = 7) were also important factors. The general quality of the studies in the field is weak. However, low hemoglobin and increasing age were consistently identified as independent risk factors for RBC transfusion in orthopedic practice. Additional or alternative analytical approaches are required to obtain a more comprehensive, holistic understanding of the decision to transfuse RBCs to patients undergoing orthopedic surgery.

ORTHOPEDIC SURGERY ACCOUNTS for a considerable amount of red blood cells (RBCs) transfused.[1-3] Variation in the use of RBCs has been well documented in many specialties,[4-8] including orthopedics.[9-11] For example, Murphy et al[11] recently found that RBC use in patients undergoing primary total hip replacement in the UK ranged from 23% to 58%. Reasons for such variation are unclear and do not appear to be the result of case mix, surgical technique, or anesthetic practices.[7,12] With concerns regarding the future supply of RBCs and transfusion safety, reducing variation in RBC use is of the utmost importance.

Transfusion guidelines have been produced in an attempt to standardize RBC use; these tend to set an upper threshold for hemoglobin of 10 g/dL, above which transfusion is not indicated, and a lower hemoglobin threshold of between 6 and 7 g/dL, below which transfusion is recommended.[13,14] However, the evidence base for upper and lower hemoglobin transfusion thresholds is weak.[15] A review of the literature on transfusion triggers concluded that the limited evidence available supported the use of a restrictive transfusion threshold in patients without cardiac comorbidity.[16] A more recent trial found that there were no significant differences in postoperative ambulation, length of hospital stay, or achievement of independent ambulation between patients managed using liberal (10 g/dL) or restrictive (8 g/dL) RBC transfusion thresholds when undergoing hip fracture repair. Patients in the restrictive transfusion threshold group experienced significantly more cardiac events and higher mortality, however, the authors urged caution in interpretation because the study was not powered to investigate mortality and because there were significantly more patients with an American Association of Anesthesiologists (ASA) score of 3 in the restrictive group.[17]

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Furthermore, evidence to support practice within the "grey zone" between upper and lower transfusion thresholds where transfusion decisions are informed by other factors, for example, the presence of cardiovascular comorbidity or patient age, is lacking.

Because guideline implementation is highly dependent on the clinician's perceptions of the evidence base for guidelines,[18] deficiency in the evidence base and lack of consensus between guidelines are likely to contribute to the variation in practice observed.[19-21]

A better understanding of those factors that influence the need for RBC transfusion may facilitate better guideline development and transfusion decision making. A systematic review examined studies of the predictors of RBC transfusion in any clinical specialty.[22] Preoperative anemia, advanced age, female sex, and small body size were associated with an increased risk for transfusion. However, the review did not address the methodological quality of the studies included; the transfusion component considered as the outcome of interest varied across the studies; and the review did not discriminate between risk factors established through descriptive analysis, multiple linear regression analysis, or multiple logistic regression analysis. The latter is important because descriptive analyses do not account for the influence of other potential confounding factors that may lead to inaccurate results; multiple linear regressions examine factors associated with the number of units transfused, rather than the decision to transfuse itself, a question that requires the use of multiple logistic regression. Combining results from these different types of study is potentially misleading.

The aim of the systematic review reported here was to address these methodological shortcomings to provide an improved understanding of the factors influencing the decision to transfuse allogeneic RBCs in orthopedic practice.

METHODS

Search Strategy and Data Sources

The population, intervention, comparison, and outcome[23] criteria for the review were as follows: population of interest, adult patients, defined as 18 years or older, who had undergone an orthopedic procedure; intervention, allogeneic RBC transfusion in a hospital setting (inpatient/outpatient); comparison, patients who did not receive an allogeneic RBC transfusion; and outcomes, the patient, disease, and health service setting variables that may be associated with the use of allogeneic RBCs, as determined through multiple logistic regression methods.

Data sources and search terms. The electronic databases MEDLINE and EMBASE were searched using terms highlighted in Appendix 1 (available online). Searches were restricted to studies on humans, written in the English language, and on adult populations published between 1950 and August 2010. The reference sections of studies selected for full article review were hand searched for additional studies.

Study eligibility. The inclusion and exclusion criteria listed in Table 1 were applied. Articles with titles that appeared to meet the criteria for relevance, or that were ambiguous, went forward for abstract review. Articles with abstracts that appeared to meet the criteria or were ambiguous, or that had missing abstracts, were reviewed in full. At full article review, the articles that met the inclusion criteria were retained, and review data were extracted. An important inclusion criterion in the current review was the use of multiple logistic regression analyses. Multiple logistic regression is a common statistical method for assessing the association between a risk factor (eg, age, sex, hemoglobin) and an outcome (eg, probability of transfusion), while adjusting for potential confounding effects of other covariates. To avoid including studies that were likely to have produced a confounded estimate of an association between a risk factor and RBC transfusion, our review excluded those studies that did not use multiple logistic regression analysis.

Data extraction. Articles were reviewed and data extracted (Table 2) by two members of the research team (P.B. and K.B.) using a predesigned form. Where the information available to apply the inclusion criteria was ambiguous, a final decision was made by consensus within the study team.

Study Quality and Analysis

Study quality. A plethora of tools designed to assess study quality and scoring systems to summarize study quality have been created.[24,25] Although there is no "gold standard method" or tool for assessing study quality,[25] two recent systematic reviews of critical appraisal tools for observational

Table 1. Inclusion and Exclusion Criteria Used in This Study

Inclusion criteria	Exclusion criteria
Adult humans undergoing an orthopedic procedure.	Patients under the age of 18 y.
The decision to prescribe an allogeneic RBC transfusion occurred within a hospital setting (inpatient/outpatient).	The decision to prescribe an allogeneic RBC transfusion occurred outside the hospital or orthopedic setting (eg, general practice, home transfusion, or other specialty).
Multiple logistic regression analysis was used to determine the influence of the risk factors on the likelihood of receiving an allogeneic RBC transfusion.	The RBC transfusion was not allogeneic in nature (eg, autologous blood use), or if the outcome was a combination of all blood products transfused. (such as fresh frozen plasma, platelets and cryoprecipitate).
Primary research (the authors have conducted the study as an original piece of primary research).	A multiple logistic regression model was not used to determine predictors of transfusion.
	The outcome of interest was massive transfusion (eg, predicting the need for ≥3 units of allogeneic RBCs).
	The study was not a primary piece of research; for example, letters, reviews, or editorials would be excluded.

studies[25,26] provide some common themes among the many critical appraisal tools available. Guided by these reviews and materials from The Centre for Review and Dissemination,[27] The Critical Appraisal Skills Program,[28] the American Heart Association scientific statement "Standards for Statistical Models Used for Public Health Reporting of Health Outcomes,"[29] and characteristics directed toward the statistical quality of the multiple logistic regression models,[30,31] we selected eight items with which to assess the quality of the included studies (Appendix 2, available online). Each item was assessed as either present (✓) or absent (✗). The higher the number of items assessed as "yes," the higher was the assumed quality of the study.

Data Analysis. The key characteristics of the studies and the quality of the studies were combined in a narrative summary and tabulated according to The Centre for Review and Dissemination guidelines (Appendices 2–4, available online).[27]

Source of Funding

The study was funded by the Research and Development Office of the Northern Ireland Health and Social Services.

RESULTS

Studies Selected

A total of 3641 citations were identified by the search strategy (Fig 1). Of these, 264 abstracts were reviewed, and 69 met the criteria for full article review. After a hand search of the reference sections, a further 44 studies were added for full article review. To ensure that articles were not being rejected inappropriately, an abstract check was conducted on a sample of articles excluded on the basis of title only, and a full article check was conducted on a sample of articles excluded at abstract review. There were no articles that had their exclusion reversed by this process. A total of 29 studies met the inclusion criteria.[9,32-59] A description of each study and an assessment of study quality are provided in Table 2 and Appendix 2 (available online), respectively. Due to the differences between studies, in terms of the patient population studied and the risk factors included in the regression models, (Table 2 and Appendix 3. available online), a meta-analysis was not considered to be appropriate. A detailed narrative summary was the most pragmatic method to provide a meaningful description and appraisal of the literature.[60,61]

Description of Studies

The 29 studies that met the inclusion criteria concerned patients undergoing one of the following orthopedic procedures: total hip arthroplasty (THA) and total knee arthroplasty (TKA)[35,37,39,43-46,48,53-56,58]; THA alone[32,41,50,59]; hip fracture with surgical repair[9,33,38,52]; TKA alone[36,40,47]; and total shoulder arthroplasty (TSA) alone,[42,57] spinal surgery,[34,49] and hip, knee, or spinal surgery.[51] Twelve studies were based in the United States,[34-36,41,42,44,45,47,50,52,57,59] five in Canada,[39,46,48,53,54] three in the UK,[9,32,55] two in France,[49,58] and one study in each of Ireland,[38] Israel,[33]

Italy,[37] Holland,[51] Japan,[40] and Spain.[56] One study was conducted across Ireland and Scotland.[43]

The median proportion of patients transfused was 24.5% (range, 7.5%-51.9%). The percentage of transfused patients within each of the categories of surgical procedure varied: 9.7% to 39.5% (THA/TKA), 16% to 49.9% (THA alone), 15.8% to 47.6% (THA alone with fracture), 7.5% to 51.9% (TKA only), 19.6% to 43% (TSA), and 19% to 32% (spinal surgery). Several studies included patients who were enrolled in an autologous transfusion program but who had also received an allogeneic transfusion.[35,36,41,44,45,47,48,59,62] In these cases, the percentage of patients transfused allogeneic RBCs was much lower, from as little as 7.5%[47] to 37%.[35]

The median age of the patients studied was 67 years (range, 53-83 years), and the median proportion of male patients was 41% (range, 23%-82%). The youngest patients were those undergoing spinal surgery, with the oldest being those admitted with hip fracture. Two of the 4 studies including hip fracture admissions were restricted to patients of 60 years or older.

The time frame during which factors associated with transfusion were assessed included the perioperative (n = 14)[9,33,36,41,42,44,46,47,50-53,55,59] and preoperative (n = 14)[32,34,35,37-39,43,45,48,49,54,56-58] periods. The time frame during which transfusion assessment was undertaken also varied: 11 studies identified transfusions occurring postoperatively,[9,35,36,41-44,48,56,58,59] seven used the perioperative period,[32,37,42,46,51,52,55] and four included transfusions occurring during the entire hospitalization.[34,38,53,54] The time frame for transfusion assessment was not clearly stated in 6 studies.[33,39,40,45,47,50]

Study Quality

Only 15 of the studies assessed 50% or more of the predefined study quality items[9,32-34,37,39,43,49,52-55,57-59] (Appendix 2, available online). Most studies were retrospective case series, with a relative dearth of prospective studies (item 3). There was a lack of clarity in defining the time interval between risk factor assessment and transfusion outcome (item 5) and limited attempts at validation of statistical models (item 8).

In the few studies that attempted to validate their statistical model, the performance of the models in predicting the need for transfusion was relatively poor. For example, Feagan et al[39] found that their model had a poor specificity, 22.8%, which decreased in the validated model to 21.3%, although the sensitivity of their model was more than 90%.

Risk Factors Identified

The studies reported a median of four independent risk factors (range, 1-13) that were associated with the risk of receiving an RBC transfusion. The reported odds of receiving an RBC transfusion varied dramatically between studies (Appendix 3, available online).

Decreasing hemoglobin and older age were the most common associated factors. Hemoglobin remained in the final adjusted model in the majority of studies where it was considered[9,32,33,35-40,42-50,52-58] (25/27 studies); age was considered in all but one of the studies and remained in the final adjusted model 18 times[34,36,38,39,42,44-47,49,50,52-55,57-59] (18/28 studies).

Additional factors that were associated with an increased risk for transfusion were comorbidity (n = 9/21 studies)[34-36,39,40,46,52,54,57]; low body weight (n = 9/16 studies)[12,32,39,47,48,53,54,56,59]; increased complexity of surgery (n = 12/23 studies),[37,39,40,42,44-46,48,49,53,55,59] for example, revision surgery[37,39,44,46,48,53,55]; and female sex (n = 7/27 studies).[34,42,46,47,53,54,59] Specific comorbidities found to increase the risk of receiving a transfusion, including rheumatoid arthritis,[36,39] history of anemia,[35,52] diabetes,[34] cardiovascular disease,[52] renal failure,[46] and metastases.[34] An ASA physical status classification of 3 (indicating severe systemic disease) or greater was also found to be a risk factor impacting on transfusion decision making in one study.[54]

One study did not have any of the aforementioned variables in the adjusted model. This study was investigating the potential link between serotonergic antidepressants and transfusion risk. Despite collecting information on hemoglobin, this variable did not appear in the analysis presented, and no explanation for this decision was offered.[51]

Fourteen studies mentioned explicitly that transfusion criteria were used to guide transfusion decisions (Appendix 4, available online).[9,32,37,40-42,44,46,47,49,52,56,59] The main transfusion criterion in these cases was the hemoglobin level. The precise hemoglobin threshold for transfusion was modulated by the presence of symptoms of anemia, when a higher hemoglobin threshold ranging from 8.5 to

Table 2. Studies Evaluating the Factors Associated With RBC Transfusion in Orthopedic Surgery

Author, year, and country	Patient population	Eligible patients included (validation set); average age (y); male (%)	Sampling method (recruitment dates)	Prespecified transfusion criteria	% of patients receiving RBC transfusion (n) in analysis	Interval used to identify risk factor	Transfusion period	Factors associated with RBC transfusion after adjustment					
								↓ HB	↑ Age	↓ Weight	Complexity of surgery	Comorbidity	Female
THA/TKA													
Borghi and Casati (2000), Italy[37]	Elective THA/TKA and hip revision (autotransfusion program)	n = 2884; age: 63; male: 34%	Prospective case series (N/S)	Yes	9.7% (278/2884)	Preoperative	Perioperative	✓	✗	✗	✓	✗	✗
Larocque et al (1997), Canada[48]	THA/TKA (unilateral and bilateral)	n = 599; age: 68; male: 43%	Random (1990-1994) and prospective cases-series (1994-1995)	None stated	14.9 % (89/599)	Preoperative	Postoperative	✓	✗	✓	✓	✗	✗
Hatzidakis et al (2000), USA[44]	THA/TKA (unilateral/bilateral and primary/ revision)	n = 489; age: 65; male: 59%	Prospective case series (02/1994-01/1997)	Yes	16.8% (82/489) any patient. 8% (22/264) PAD patients	Perioperative	Postoperative	✓	✓	N	✓	✗	✗
Saleh et al (2007), UK[55]	TKA /THA (primary /revision)	n = 816; age: 68; male: N/S	Retrospective linkage. (08/2000-07/2001)	None stated	21% (225/1059)	Perioperative	Perioperative	✓	✓	N	✓	N	✗
Guerin et al (2007), Ireland/ Scotland[43]	THA /TKA (elective unilateral)	n = 162; age: 67; male: 53%	Prospective case series (N/S)	None stated	25% (41/162)	Preoperative	Postoperative	✓	✗	✗	N	N	✗
Feagan et al (2001), Canada[39]	THA/TKA (primary/revision and bilateral/ unilateral)	n = 984 (981); age: 70; male: 42%	Retrospective case series (01/1995-12/1996)	None stated	25% (246/984)	Preoperative	Not stated	✓	✓	✓	✓	✓	✗
Rashiq et al (2004), Canada[54]	THA/TKA (primary and revision)	n = 884 (934); age: 67; male: 41%	Retrospective case series (01/2000-12/2000)	None stated	27% (239/884)	Preoperative	Hospitalization	✓	✓	✓	✓	✓	✓
Rashiq and Finegan (2006), Canada[53]	THA/TKA (primary and revision)	n = 1875; age: 67; male: 41%	Retrospective case series (01/2000-12/2000)	None stated	28% (517/1875)	Perioperative	Hospitalization	✓	✓	✓	✗	✗	✓

Vuille-Lessard et al (2010), France[58]	THA/TKA primary or revision. 3 hospitals	n = 701; age: 67; male: 35%	Retrospective case series (2002-2006)	None stated	29% (202/701)	Preoperative	Postoperative	✓	✓	✗	✗	✗	✗
Bierbaum et al (1999), USA[35]	THA/TKA (unilateral and bilateral)	n = 3471 (non- PAD); age: 67; male: 41%	Prospective case series (09/1996-06/1997)	None stated	29.7% (1031/3471)	Preoperative	Postoperative	✓	✗	✗	✗	✓	✗
Karkouti et al (2005). Canada[46]	THA and TKA. Hb<13 g/dL and not PAD given	n = 770; age: 69; male: 82%	Prospective case series (07/1999-06/2003)	Yes	31.2% (503/1611)	Perioperative	Perioperative	✓	✓	✓	✓	✓	✓
Salido et al (2002), Spain[56]	THA/TKA, partial hip arthroplasty, with arthritis (excluding surgery for hip fracture)	n = 296; age: 67; male: 69%	Retrospective, not clear. (1994-1998)	Yes	39.5% (117/296)	Preoperative	Postoperative	✓	✗	✓	✗	N	✗
Jain and Jain (2005), USA[45]	THA/TKA zpatients' part of blood salvage program.	n = 152 TKA; age: 70; male: 57% n = 77 THA; age: 67; male: 40%	Retrospective case series (1997-2000)	None stated	TKA 19% (29/152) THA 31% (24/77)	Perioperative	Not stated	✓	✓	N	✓	N	✗
THA only													
Grosvenor et al (2000), USA[41]	Unilateral elective THA with blood salvage program	n = 156; age: 64; male: 40%	Retrospective case series (N/S)	Yes	16% (25/156)	Perioperative	Postoperative	✗	✗	N	N	N	✗
Aderinto and Brenkel (2004) UK[32]	Primary THA (unilateral)	n = 1016; age: 68; male: 38%	Prospective case series (1998-2002)	Yes	24% (244/1016)	Preoperative	Perioperative	✓	✗	✓	N	N	✗
Marx et al (2001), USA[50]	THA	n = 140; age:N/S*; male: 31%	Retrospective case series (N/S)	None stated	30.7% (43/140)	Perioperative	Not stated	✓	✓	N	✗	✗	✗
Walsh et al (2007), USA[59]	Primary THA (bilateral/ unilateral)	n = 1035; age: 60; male: 43%	Retrospective (N/S)	Yes	All patients 22.5% (232/1031); no PAD 49.9% (185/371)	Perioperative	Postoperative	✗	✓	✓	✓	✗	✓

(*continued on next page*)

Table 2. (*continued*)

Author, year, and country	Patient population	Eligible patients included (validation set); average age (y); male (%)	Sampling method (recruitment dates)	Prespecified transfusion criteria	% of patients receiving RBC transfusion (n) in analysis	Interval used to identify risk factor	Transfusion period	Factors associated with RBC transfusion after adjustment					
								↓ HB	↑ Age	↓ Weight	Complexity of surgery	Comorbidity	Female
THA for hip fracture													
Gul et al (2007), UK[9]	Hip fracture (hemiarthroplasty/ DHS repair). Preoperative Hb >8 g/dL excluded	n = 310; age: 83; male: 23%	Retrospective case series (02/2003-02/2005)	Yes	15.8% (49/310)	Perioperative	Postoperative	✓	✗	N	✗	N	✗
Dillon et al (2005), Ireland[38]	Hip fracture, DHS/ hemiarthroplasty	n = 124; age: 75; male: 27%	Retrospective case series (2001-2002)	None stated	30% (37/124)	Preoperative	Hospitalization	✓	✓	N	✗	✗	✗
Poses et al (1998), USA[52]	Hip fracture (age, ≥60 y)	n = 8776; age: 80; male: N/S	Retrospective case series (1982-1993)	Yes	42.1% (3691/8776)	Perioperative	Within 7 d preoperative or post op	✓	✓	N	✗	✓	✗
Adunsky et al (2003), Israel[33]	Hip fracture (age, ≥60y) emergencies	n = 296; age: 82; male: 24%	Retrospective case series (N/S)	None stated	47.6% (141/296)	Perioperative	Not stated	✓	✗	N	✗	✗	✗
TKA only													
Fujimoto et al (2003), Japan[40]	TKA	n = 274; age: N/S; male: N/S	Not clear. Consecutive (1998-1999)	Yes	19% (51/274)	Preoperative and intraoperative	Not stated	✓	N	N	✓	✓	N
Bong et al (2004), USA[36]	Primary TKA (unilateral and bilateral)	n = 1402 unilateral (1194) and bilateral (208); age: 67; male: 23%	Retrospective case series (09/1997-11/2001)	Yes	Unilateral 22% (263/1194); bilateral 51.9% (118/208)	Perioperative	Postoperative	✓	✓	✗	N	✓	✗
Keating et al (1998), USA[47]	Unilateral and bilateral TKA	Unilateral n = 279; age: 70; male: 36%; bilateral n = 280; age: 71; male: 46%	Retrospective case series (N/S)	Yes	Unilateral 7.5% (21/279); bilateral 24% 68/280	Perioperative	Not stated	✓	✓	✓	N	N	✓*

TSA only													
Schumer et al (2010), USA[57]	Total shoulder arthroplasty; humeral hemiarthroplasty	n = 266 (109); age: 66; male: N/S	Retrospective case series 01/2001-12/2004 (01/2007-12/2007)	None stated	19.6% (55/266)	Preoperative	Intraoperative or postoperative	✓	✓	N	✗	✓	✗
Gruson et al (2009), USA[42]	Any shoulder arthroplasty (primary/revision)	n = 196; age: 67; male: 58	Consecutive (N/S)	Yes	43% (84/196)	Perioperative	Postoperative	✓	✓	✗	✓	✗	✓
Spinal surgery													
Berenholtz et al (2002), USA[34]	Primary spinal procedure	n = 3988; age: 53; male: 55%	Retrospective linkage (07/1997-06/2000)	None stated	19% (763/3988)	Preoperative	Hospitalization	N	✓	N	✗	✓	✓
Lenoir et al (2009), France[49]	Elective thoracolumbar spinal surgery	n = 230 (125); age: 58; male: 40%	Retrospective case series 01/2006-03/2007	Yes	32% (74/230)	Preoperative	Intraop-5 days Postoperative	✓	✓	✗	✓	✗	✗
Hip, knee, and spine													
Movig et al (2003), Holland[51]	Hip, knee, or spine implants	n = 520; age: 68; male: 30%	Consecutive (01/1999-31/2000)	None stated	11% (59/520)	Perioperative	Perioperative	N	✗	N	N	✗	✗

NOTE. ✓, Present; ✗, absent; N, not considered in model; N/S, not stated; Hb, hemoglobin; TKA, total knee arthroplasty; THA, total hip arthroplasty; PAD, pre-operative autologous donation; op, operative; DHS, deep hip screw; n = number of patients analyzed.

* Unilateral & bilateral procedures analyzed separately: Female only a factor in Unilateral analysis.

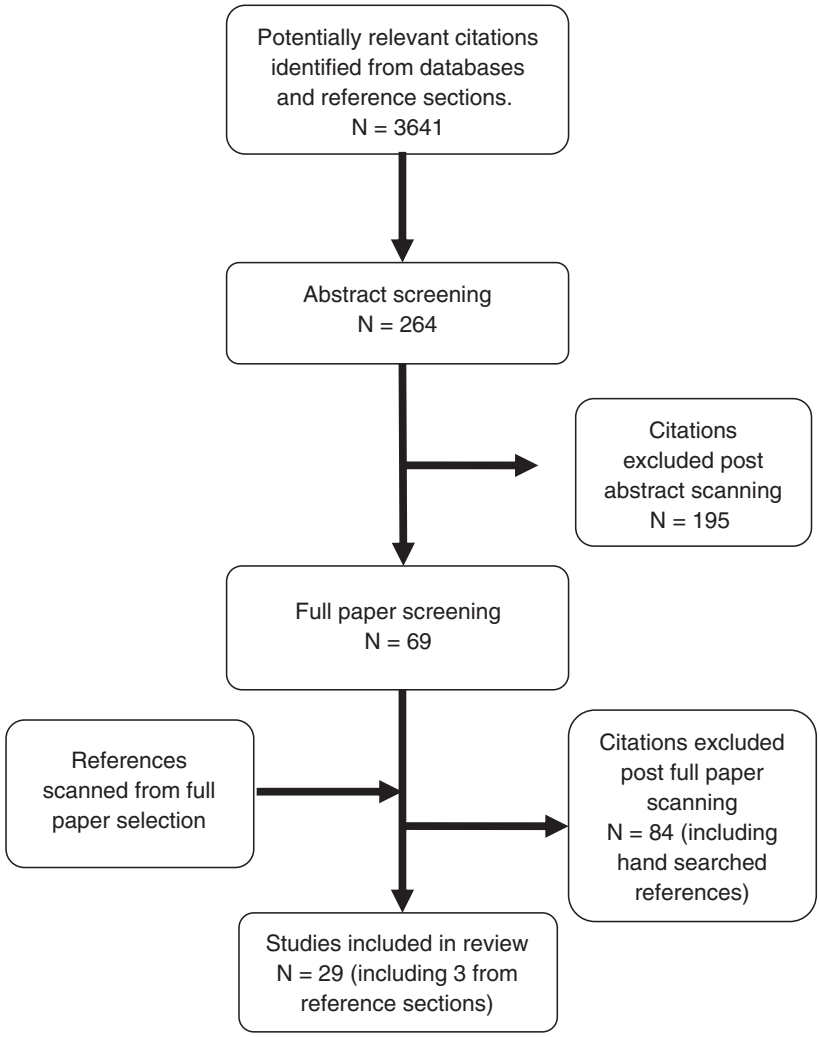

Fig 1. Flowchart describing the different stages of study selection from initial title scanning to full article selection.

12 g/dL was deemed appropriate, whereas in the absence of symptoms, the acceptable hemoglobin was between 6 and 9 g/dL. Several of the authors mentioned that the criteria were for guidance only and that the transfusion decision was down to the clinician.[36,41,42,52,59]

DISCUSSION

The current systematic review is the first to investigate the predictors of RBC transfusion in orthopedic practice. Despite the presence of marked heterogeneity among the included studies with regard to patient populations, surgical procedures, study design, and study quality, it was possible to discern some common themes using a narrative approach.

There was marked variation in the proportion of patients transfused, some of which could be explained by differences in case mix and the nature of the surgical procedures studied. For example, the lowest percentage of patients transfused (9.7%) was observed in the subgroup of studies focusing on THA/TKA; however, these patients were also included in an aggressive autotransfusion program.[37] In two other studies with low transfusion rates, preoperative autologous donation (PAD) was also offered at the study centers, which may have contributed to the lower rates of allogeneic RBC transfusion observed.[44,48]

High rates of transfusion (>40%) were observed in two studies involving patients undergoing THA for hip fracture[33,63] that included only patients older than 60 years. Increased complexity of surgery may be related to an increase in the amount of surgical bleeding and therefore exposure to transfusion risk.[9,32,44,52]

The use of clinical transfusion guidelines may be expected to reduce variation; however, differences between guidelines and variable implementation could have the opposite effect. The acceptable hemoglobin threshold for transfusion that is recommended for otherwise healthy patients is between 6 and 7 g/dL. However, hemoglobin on its own may be a poor indicator of tissue hypoxia,[64] and current thinking suggests that each individual patient has an "acceptable" hemoglobin level, and it is this that should be maintained through transfusion. Given this complexity, the absence of a consistent relationship between the presence of liberal or restrictive guidelines and the proportion of patients transfused (Appendix 4, available online) is not surprising.

The observation that reduced hemoglobin, older age, and low body weight are influential drivers of transfusion decision making in an orthopedic setting is in keeping with the findings reported from other clinical specialties.[22]

Because the transfusion of RBCs will increase hemoglobin levels, a lower level of hemoglobin, or anemia, would be expected to be a key risk factor for RBC transfusion.[22,65] The older patients are less likely to tolerate a lower hemoglobin and hematocrit[13] and are therefore more likely to benefit from RBC transfusion. Furthermore, some of the risks associated with transfusion, such as transfusion-transmitted infection, have long latent periods and may therefore be of lesser importance in assessing the balance of risks and benefit in the older patients. For younger patients, the avoidance of transfusion because of the potential longer term risks may outweigh any short-term benefit of the transfusion in some circumstances.[66]

Lower body weight is associated with a smaller RBC volume,[22,67] and therefore lighter patients may be less able to compensate for blood loss.[22] Female sex appeared less influential than suggested in previous studies,[22,68] being found to be a risk factor for transfusion in only seven studies included in the current review. Because females tend to be lighter than males, the influence of sex may be partly explained by the relationship of weight/blood volume to the risk of transfusion as well as the tendency for females to have lower baseline hemoglobin than males.

Our review also found that the comorbidity was associated with an increased risk for transfusion. Although specific comorbidities varied, they appeared to be linked by the common theme of reduced capacity to tolerate anemia.

Overall, the assessed quality of articles in the current review was not high and potentially limits the strength of the findings. However, a limitation when making any quality assessment is the availability of relevant information in the published article; where such information is missing, studies may be misclassified with respect to quality. Study quality was not one of the inclusion or exclusion criteria for the current review but was viewed as an aid to understanding the methods of studies included in the review and their impact on the data obtained and the conclusions drawn. However, regardless of quality of the study, there did not appear to be a difference in findings. Yet, it is difficult to disentangle the impact of quality on the studies, from other factors that may have also affected study outcomes, for example, patient populations, study size, study setting, and guideline use.

The items that were used to assess the quality of the studies have not been validated as a stand-alone quality appraisal tool. However, the items were based on previously validated measures identified via a systematic review of tools used to assess the quality of appraisal tools[25-28] and covered the key areas of quality appraisal and specific items pertinent to the type of articles reviewed, such as selection bias (items 1 and 2) and statistical quality (items 6-8) as itemized in Appendix 2 (available only online).

The quality assessment revealed a lack of prospective studies and of model validation. Furthermore, many investigators failed to define the time period between risk factor assessment and transfusion outcome. The latter is an important design issue, because any relationship found between a risk factor and transfusion that infers importance in decision making means that the information on the "risk factor" must be relevant and available at the time the decision is taken. For example, admission hemoglobin may not be the most relevant hemoglobin measurement to consider in the context of postoperative transfusion. Authors

investigating the risk for transfusion among cardiac patients have also highlighted this issue.[12]

Although statistical modeling is useful in identifying some factors and their relative impact on the decision to transfuse, there are other factors that cannot be as readily accommodated within a statistical model because they are difficult to assess or measure, for example, physician beliefs and personality.[9] These factors may be particularly influential when the decision to transfuse is within the gray zone of hemoglobin, between 7 and 10 g/dL. The application of qualitative research methods to identify such drivers of transfusion practice or the use of heuristics in transfusion decision making are attractive options for further investigation of this issue.[69]

A meta-analysis was not possible because of the aforementioned heterogeneity among study populations and study design as well as the failure to present odds ratios (ORs) in the published articles. Furthermore, where ORs were presented, the variation in the number and type of factors included and how they were incorporated in the models influenced the actual figure reported (Appendix 3, available online).

CONCLUSIONS AND RECOMMENDATIONS

Although the variable design and quality of studies conducted in this area of practice precluded the conduct of a meta-analysis, this narrative review has confirmed that hemoglobin, age, and weight are independent risk factors for transfusion of RBC. In addition, comorbidity leading to a reduction in the capacity to tolerate anemia and complexity of the surgical procedure undertaken are also identified as risk factors for RBC transfusion in the orthopedic setting.

To improve the evidence base for RBC transfusion guidelines and practice, we suggest that future research attempts to capture additional factors that may influence clinical decision making but that cannot be readily categorized and included in a statistical model, by using a qualitative approach.

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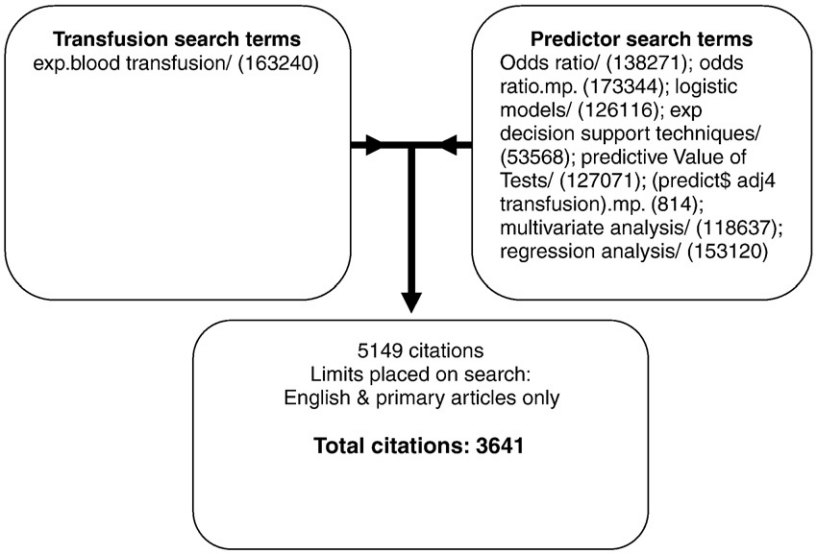
Appendix 1. Search Terms Used in This Study (Available Online Only)



adj4. Terms adjacent to each other; acceptable distance between terms was set at four words.

Exp. Term exploded to include all other subheadings

.mp. Term within title, subject heading word, abstract or instrumentation.

/ MeSH term

$ Wild card character

Appendix 2. Quality Criteria Checklist (Available Online Only)

Quality criteria		Rashiq et al[64]	Feagan[39]	Rashiq and Finegan[53]	Vuille-Lessard et al[58]	Borghi and Casati[37]	Guerin et al[43]	Saleh et al[55]	Bierbaum et al[35]	Karkouti et al[46]	Larocque et al[48]	Salido et al[56]	Hatzidakis et al[44]	Jain and Jain[45]		Grosvenor et al[41]	Aderinto and Brenkel[32]	Walsh et al[59]	Marx et al[50]
1. Was the sample-selected representative of the population of interest and sampling procedures fully described, that is, exclusion/inclusion criteria?	THA/TKA	✓	✓	✓	✓	✗	✓	✓	✗	✗	✓	✗	✗	✗	THA only	✗	✓	✓	✗
2. Were response rates reported and explained (follow-up of patients)?		✓	✓	✓	✓	✓	✓	✗	✗	✓	✗	✓	✓	✗		✓	✓	✓	✓
3. Was the data on the risk factors collected prospectively?		✗	✗	✗	✗	✓	✓	✗	✓	✓	✗	✗	✗	✗		✗	✓	✗	✗
4. Did the study report methods and procedures, which indicate good quality data collection of risk factors?		✓	✓	✓	✓	✓	✗	✓	✓	✗	✓	✗	✓	✓		✓	✓	✓	✓
5. Was the time interval between risk factor measurement and transfusion outcome clearly defined?		✓	✗	✓	✓	✗	✗	✗	✗	✗	✗	✗	✗	✗		✗	✗	✗	✗
6. Were there a sufficient number of events per variable included in the model?		✓	✓	✓	✓	✓	✓	✓	✓	✓	✗	✓	✗	✗		✗	✓	✓	✗
7. Were the ORs and confidence intervals of the significant risk factors in the final adjusted model provided?		✓	✓	✓	✓	✓	✗	✓	✗	✗	✓	✓	✗	✗		✓	✗	✓	✗
8. Was validation of the model also considered?		✓	✓	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗		✗	✗	✗	✗

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Appendix 2. (*continued*)

Quality criteria		Poses et al[52]	Adunsky et al[33]	Dillon et al[38]	Gul et al[9]		Bong et al[36]	Fujimoto et al[40]	Keating et al[47]		Schumer et al[57]		Gruson et al[42]	Lenoir et al[49]		Berenholtz et al[34]	Movig et al[51]
1. Was the sample-selected representative of the population of interest and sampling procedures fully described, that is, exclusion/inclusion criteria?	THA with fracture	✓	✗	✓	✓	TKA	✓	✗	✓	TSA	✓	✗	Spinal surgery	✓	✓	Hip, knee or, spine	✗
2. Were response rates reported and explained (follow-up of patients)?		✗	✓	✓	✗		✓	✓	✓		✓	✓		✓	✓		✗
3. Was the data on the risk factors collected prospectively?		✗	✗	✗	✗		✗	✗	✗		✗	✗		✗	✗		✗
4. Did the study report methods and procedures, which indicate good quality data collection of risk factors?		✓	✓	✓	✓		✓	✗	✓		✓	✓		✓	✓		✓
5. Was the time interval between risk factor measurement and transfusion outcome clearly defined?		✓	✗	✗	✗		✗	✗	✗		✓	✗		✓	✗		✓
6. Were there a sufficient number of events per variable included in the model?		✓	✓	✗	✓		✗	✓	✗		✗	✗		✓	✓		✗
7. Were the ORs and confidence intervals of the significant risk factors in the final adjusted model provided?		✓	✓	✗	✓		✗	✓	✗		✓	✓		✓	✓		✓
8. Was validation of the model also considered?		✗	✗	✗	✗		✗	✗	✗		✓	✗		✓	✗		✗

NOTE. ✓, present; ✗ , absent/not enough information in the study to determine.

Appendix 3. Adjusted ORs for RBC Transfusion for Hemoglobin, Age, Weight, and Sex (Available Online Only)

Study	Hb/Hct: OR (95% CI)	Age: OR (95% CI)	Weight: OR (95% CI)	Female sex: OR (95% CI)
Borghi and Casati[37]	>10 g/dL: 1.00 (ref. cat.) <10 g/dL: 8.8 (6.5-16.8)	–	–	–
Larocque et al[48]	>13 g/dL: 1.00 (ref. cat.) 11.1-13.0 g/dL: 4.1 (2.3-7.5) ≤11 g/dL: 12 (3.4-42.3)	–	>100 kg: 1.00 (ref. cat) 81-100 kg: 2.4 (0.6–9.2) ≤80 kg: 4.6 (1.3-16.5)	–
Hatzidakis et al[44]	>13 g/dL: 1.00 (ref. cat.) <13 g/dL: 5.7	<65 y: 1.00 (ref. cat.) >65 y: 2.8 (–)	N	–
Saleh et al[55]	13.1-15 g/dL: 1.00 (ref. cat.) 11.1-13 g/dL OR 2.42 (1.69-3.48) ≤11 g/dL: 13.9 (7.77-24.9)	Per year increase: 1.03 (1.02-1.05)	N	–
Guerin et al[43]	0.79 (N/S)	Per year increase: 1.08 (N/S)	N	0.89 (N/S)
Feagan et al[39]	>13 g/dL: 1.00 (ref. cat.) 12.1–13 g/dL: 2.2 (1.4-3.2) 11.1–12 g/dL: 4.6 (2.7-7.9) ≤ 11 g/dL: 9.2 (4.3-20)	<70 y: 1.00 (ref. cat.) 70-80 y: 1.8 (1.2-2.6) ≥80 y: 2.4 (1.5-3.9)	≥60 kg: 1.00 (ref. cat) <60 kg: 2.5 (1.5-4.1)	–
Rashiq et al[54]	>15 g/dL: 1.00 (ref. cat.) 14.1–15 g/dL: 3.49 (1.72-7.50) 13.1–14 g/dL:4.20 (2.07-8.53) 12.1–13 g/dL: 9.42 (4.54-19.57) ≤12 g/dL: 13.81(6.12-31.17)	<65 y: 1.00 (ref. cat) 65-69 y: 2.14 (1.29-3.56) 70-79 y: 1.83 (1.09-3.06) 80+ y: 2.75 (1.60-4.70)	>90kg: 1.0 (ref. cat) ≤60 kg: 6.27 (3.17-12.40) 61-70 kg: 3.92 (2.21-6.95) 71-80 kg: 2.44 (1.44-4.13) 81-90 kg: 2.19 (1.37–3.51)	1.74 (1.15-2.62)
Rashiq and Finegan[53]	Per 1.0 g/dL decrease: 1.05 (1.04-1.06)	Per year increase: 1.04 (1.02-1.05)	Per 1.0 kg decrease: 1.03 (1.02-1.04)	1.15 (1.02-1.97)
Vuille-Lessard et al[58]	Per 1.0 g/dL decrease: 1.22 (1.18-1.27)	Per year increase: 1.05 (1.02-1.08)	–	–
Bierbaum et al[35]	Per 1.0 g/dL decrease: Hip replacement: 1.5 (–) Knee replacement: Primary unilateral: 1.8 (–) Revision unilateral: 1.9 (–) Primary bilateral: 1.7 (–)	–	–	–
Salido et al[56]	Per 1.0 g/dL decrease: 2.51 (1.83-3.44)	–	Per 1.0 kg decrease: 1.05 (1.01-1.09)	–
Marx et al[50]	Per 1.0 g/dL decrease: 1.05 (1.03-1.09)	Per year increase: 1.01 (0.98-1.04)	N	–
Walsh et al[59]	–	(reference, <65) 75-84; OR, 3.51 (N/S)	(BMI <30 kg/m^2) BMI, +30 kg/m^2; OR, 0.54 (N/S)	1.9 (N/S)

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Appendix 3. (*continued*)

Study	Hb/Hct: OR (95% CI)	Age: OR (95% CI)	Weight: OR (95% CI)	Female sex: OR (95% CI)
Gul et al[9]	Per 1.0 g/dL decrease: 1.65 (1.49–1.99)	–	N	–
Poses et al[52]	≥11 g/dL: 1.00 (ref. cat.) 10-10.9 g/dL: 1.9 (1.4-2.6) 9-9.9 g/dL: 12 (8.9-16) 8-8.9 g/dL: 65 (49-87) <8 g/dL: 300 (210-420)	Per year increase: 1.03 (1.02-1.04)	N	–
Adunsky et al[33]	>12 g/dL: 1.00 (ref. cat.) <12 g/dL: 4.88 (2.87-8.29)	–	N	–
Fujimoto et al[40]	>11 g/dL: 1.00 (ref. cat.) <11 g/dL; OR, 7.46 (3.10-17.86)	N	N	N
Bong et al[36]	>13 g/dL: 1.00 (ref. cat.) 10-13 g/dL: 1.83 (–) <10.0 g/dL: 4.17 (–)	<65 y: 1.00 (ref. cat.) 65-74 y: 1.54 (–) 75-84 y: 2.88 (–) ≥85 y: 4.5 (–)	–	–
Gruson et al[42]	Per 1.0 g/dL decrease: OR, 2.3 (1.67-3.33)	Per 5 year increase: 1.32 (1.12-1.56)	–	2.22 (1.03-4.81)
Berenholtz et al[34]	N	<41 y: 1.00 (ref. cat.) 41-53 y: – (–) 54-66 y: 1.6 (1.3-2.1) >66 y: 2.7 (2.0-3.5)	N	1.5 (1.3-1.9)
Lenoir et al[49]	>14 g/dL: 1.00 (ref. cat.) 12-14 g/dL: OR, 4.95 (2.04-12.5)	<50 y: 1.00 (ref. cat.) >50 y: OR, 5.14 (2.08-14.42)	–	–

Abbreviations: ref. cat, reference category; N, not stated/not clear if considered in analysis; –, not statistically significant in the final adjusted model; Hb, hemoglobin; Hct, hemtocrit.

Appendix 4. Explicit Transfusion Criteria Used in This Study (Available Online Only)

Author	Data collection date	Transfusion criteria	% of patients receiving an RBC transfusion
Lenoir et al[49]	01/2006-03/2007	ASA guidelines. Hemoglobin (Hb) <6 g/dL, transfuse Hb >10 g/dL, do not transfuse Hb 6-10 g/dL, decision based on patients risks for complications of inadequate oxygenation, organ ischemia, intravascular volume status, and potential or actual blood loss	32%
Gul et al[9]	02/2003-02/2005	Hb <8 g/dL	15.8%
Karkouti et al[46]	07/1999-06/2003	ASA guidelines (see above)	31.2%
Bong et al[36]*	09/1997-11/2001	Hb<9 and symptomatic = transfusion, but was left down to individual physician	22%-51.9%
Aderinto and Brenkel[32]	1998-2002	Postoperative Hb <8.5 g/dL Postoperative Hb 8.5-0 g/dL transfuse if symptomatic of anemia Hb >10 g/dL, never transfuse	24%
Fujimoto et al[40]	1998-1999	In postoperative period, Hb <8 g/dL and general condition (eg, general fatigue, dyspnea, severe vomiting, nausea)	19%
Grosvenor et al[41]*	1997-1998	General criteria only: dizzy; HCT <30%, angina, MI, tachycardia.	16%
Salido et al[56]	1994-1998	Hb <8.5 g/dL, transfuse	39.5%
Hatzadikas et al[44]	02/1994-01/1997	Hb <7 g/dL transfuse both intraoperatively and postoperatively Hb <12 g/dL and symptomatic of anemia	16.8%
Keating et al[47]	1993-1997	Hb<9 g/dL in otherwise healthy patients (unless there are cardiopulmonary risk factors) or acute blood loss of greater than 15% of blood volume	7.5-24%
Poses et al[52]*	1982-1993	Hb <8 g/dL likely to need blood Hb >10 g/dL unlikely to need blood	42.1%
Borghi and Casati[37]	Not stated	After all autoblood has been used: Hb <6 g/dL, transfuse if symptomatic anemia Hb <10 g/dL, transfuse in patients who are affected by cerebrovascular or coronary artery disease	9.7%
Walsh et al[59]*	Not stated	<9 g/dL and cardiac condition	22.5%
Gruson et al[42]*	Not stated	Symptomatic anemia	43%

*Criteria not strictly enforced.