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Total versus partial splenectomy in pediatric hereditary spherocytosis: a systematic review and meta-analysis

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Title: Total versus partial splenectomy in pediatric hereditary spherocytosis: a systematic review and meta-analysis

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Abbreviations:

HS	hereditary spherocytosis
OPSS	overwhelming post-splenectomy spherocytosis
TS	total splenectomy
PS	partial splenectomy

Abstract

To compare the clinical effectiveness of total (TS) or partial (PS) splenectomy in pediatric hereditary spherocytosis, a systematic review and meta-analysis was performed (PROSPERO registration CRD42015030056). There were 14 observational studies comparing pre- and post-operative hematologic parameters. Secondary outcomes include in-hospital infections, surgical complications, symptomatic recurrence and biliary disease. TS is more effective than PS to increase hemoglobin (3.6 g/dL vs 2.2 g/dL) and reduce reticulocytes (12.5% vs 6.5%) after one year; outcomes following PS are stable for at least 6 years. There were no cases of overwhelming post-splenectomy sepsis. A population-based patient registry is needed for long-term follow-up.

Introduction

Hereditary spherocytosis (HS) is a rare genetic disease affecting the erythrocyte cell membrane, producing characteristically spherical erythrocytes (spherocytes). The worldwide prevalence of HS is approximately 1 in 2,000 people [1–3]. The main molecular defects in HS arise from a heterogeneous set of mutations to cytoskeletal proteins facilitating linkage to the lipid bilayer [4], Weakening the mechanical integrity of the cell membrane. Signs and symptoms of HS may include splenomegaly, severe anemia, jaundice, reticulocytosis, fatigue, abdominal discomfort [5]. These symptoms are widely recognized to be caused by hemolysis of immature reticulocytes undergoing conditioning in the spleen.

The degree of splenomegaly is a generally reliable indicator of the severity of hemolysis, anemia and risk of developing gall stones. An enlarged spleen is also vulnerable to traumatic rupture. If the degree of anemia is too great, surgical management of HS by splenectomy remains the only intervention. Management of HS by splenectomy has historically been focused on total splenectomy (TS) which was performed through a laparotomy incision. In the early 1990s, the laparoscopic approach was successfully adopted for splenectomy in HS patients [6], and became a more popular choice of technique. The spleen is a major lymphoid organ in the body and the risk of infection caused by staphylococci and Gram-negative enteric organisms is high in the early post-operative period. Following TS, there is increased susceptibility for many years to potentially fatal overwhelming post-splenectomy sepsis (OPSS; otherwise called overwhelming post-splenectomy infection) from these encapsulated bacteria such as pneumococci, *Neisseria meningitides*, *Haemophilus influenzae* and staphylococci [7]. The risk of OPSS from these organisms has been reduced as most centres across North America and Europe use prophylactic

vaccinations and prophylactic antibiotics prior to elective splenectomy, and if possible, delay the surgery until the patient over five years old [4]. It is suggested that PS confers some residual immune competence against encapsulated organisms. The level of circulating IgM memory B cells after splenectomy and the percentage of pitted erythrocytes have been used as surrogate markers for immune competence against encapsulated organisms or residual splenic function [8, 9]. However, these observations need further validation through prospective, controlled studies. This review aims to determine how PS and TS compare when performed for pediatric HS.

Methods

Systematic Review Protocol

Methods of the present systematic review and meta-analysis were pre-specified and documented in a protocol (PROSPERO registration CRD42015030056). The study question was translated into a PICO-formatted grid and was developed to guide the selection of appropriate search terms (**Table I**), in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [10] (**Supplemental Table SI**).

The population of interest (P) were children, 18 years of age or younger, diagnosed with HS. The intervention (I) was a PS as compared (C) to TS, performed to correct anemia, the primary indicator of HS severity. While PS can be performed as one of two surgical procedures, a less aggressive PS and a more aggressive near-total splenectomy, both are treated as PS for this review. The former leaves between a splenic remnant of about 15-30% in size; the latter leaves a splenic remnant supplied by a single pedicle, of about 10-15% [11]. This choice is left to the experience of surgeon. The specific surgical technique was not considered here. Primary outcomes (O), chosen based on a pilot search, were pre- and post-operative hemoglobin concentration (g/dL) and

percent reticulocytes because these are the most commonly reported outcomes, and often only with one year of follow-up; these were of primary interest because they are a marker of anemia and erythropoiesis, respectively. Secondary outcomes included in-hospital infections, surgical complications, biliary disease, OPSS, recurrence of symptoms and splenosis. All study designs (S) were included for initial screening except case-series with less than five cases.

Search Strategy

A systematic literature search protocol was conducted with the help of a research librarian using the PubMed, EMBASE, Web of Science and CINAHL databases up to Oct. 1, 2015 for studies published with English full-text. Search terms regarding the population of interest, intervention and indication, and comparator and outcome were used to identify eligible studies (**Table I**). The reference lists of relevant articles were then manually searched for additional studies.

Grey literature are publications produced by individuals or organizations, considered to be outside of the traditional commercial or academic publishing and distribution channels; sources searched using "spherocytosis" or "splenectomy" include: clinical trial databases (UK Clinical Trials Gateway; ClinicalTrials.gov), systematic review registries (Cochrane Library; PROSPERO), thesis depositories (Library and Archives Canada; NTLTD, EThOS), health service agencies (WHO; US CDC, Health Canada; CADTH) and grey literature-specific databases (OpenGrey; Grey Literature Report). One clinical trial was identified (NCT01276561) but excluded for lack of relevance and have not yet published any results. Some authors were contacted by e-mail to provide further details, yet was supplied in only one case [12].

Study screening

All retrieved studies from database searches were included in the screening process to create a systematic, precise, and validated search strategy. Records were imported into EPPI-Reviewer (version 4.5), duplicates removed, and remaining entries were screened on title and abstract for relevance, and full-text for full consideration. Additionally, eligible studies were included after reading relevant review articles and their reference lists. A complete list of inclusion and exclusion criteria is presented in **Table II**. Studies were not included if they failed to report on a relevant outcome.

Articles were screened by two independent reviewers in three levels (title, abstract and full-text) and differences were resolved by consensus. Level 1 (title) screening was based on relevance, level 2 (abstract) screening ruled in studies based on patient population and outcomes, and level 3 (full-text) screening was carried out on studies that might satisfy all criteria of the PICOS. Level 3 screening inter-rater agreement was 83% (kappa=0.64). Then each article was critically appraised and a risk of bias assessment was made using Downs and Black checklist [13], which was originally validated for appraising surgical interventions. Downs and Black score ranges were given corresponding quality levels as previously outlined: excellent (26–28); good (20–25); fair (15–19); and poor (≤14) [14]. Articles rated as poor were excluded for severe risk of bias. In total, 14 studies met the sufficient quality criteria and were included in this meta-analysis (**Table III**) [12, 15–26].

Meta-analysis and publication bias

Data were extracted into a spreadsheet for analysis. Hemoglobin and percent reticulocytes were compared using the pre- to post-op difference. When the standard deviation of an estimate was not reported, it was calculated where possible or estimated from individual patient data. A

fixed-effects model was used to explore the overall effect of surgery, where each study was weighted by the inverse variance method (**Figure 1**). To assess heterogeneity between studies, the chi-square test and I^2 statistic were calculated; an I^2 value greater than 75% suggested high heterogeneity among studies. Publication bias was assessed by inspecting the funnel plot and Egger's method.

Results

Study Characteristics

From the initial search there were 23 studies included after full-text screening for quality review (**Figure 1**). In total, 14 observational studies were included after risk of bias assessment with a total of 2,224 patients, including one cross-sectional study (**Table III**) and no identified trials. The primary reason for exclusion of studies was incomplete data reporting or a high perceived risk of selection and reporting bias. The funnel plot of hemoglobin concentration suggested publication bias (**Figure 3**). However, it is difficult to determine whether this asymmetry represents a true publication bias, or if there is a true heterogeneity of intervention effects. It is more likely caused by the small number of studies having few observations. Within each outcome, the studies do not overlap in patient population based on reported methodology.

Hemoglobin

All studies reported qualitative resolution of anemia, often increasing hemoglobin to clinically normal values. One year following splenectomy, eight studies reported post-operative hemoglobin changes for TS and PS, then only four reports concerned PS followed for at least three to four years (**Figure 2**). PS significantly increased the hemoglobin concentration by an average of 2.20 g/dL (95% CI: 1.96 g/dL to 2.45 g/dL; $P<0.001$) and following TS resulted in an average

increase of 3.60 g/dL hemoglobin (95% CI: 3.08 g/dL to 4.12 g/dL; P<0.001) (**Figure 2A**). Three to four years following PS, there was an average increase of 3.22 g/dL (95% CI: 2.49 g/dL, 3.94 g/dL; P<0.001) (**Figure 2B**), and after five to six years, there was a significant increase of 2.21 g/dL (95% CI: 1.42 g/dL, 2.99 g/dL; p<0.001) (**Figure 2C**). A single report followed PS patients for a decade [15], finding a similar plateau effect.

Reticulocytes

Four studies reporting percent reticulocyte were included for meta-analysis [20–22, 26] (**Figure 4**). Absolute reticulocyte counts could not be used for lack of comparison among children of different ages. Following splenectomy, there is a significant decrease in percent reticulocytes, though values typically remained above the normal range (1.5%) in both TS and PS at all time points (**Figure 4**). Following PS, percent reticulocytes decreased from baseline by an average decrease of 6.5% (95% CI: -7.4% to -5.6%) after one year (**Figure 4A**), 12.5% (95% CI: -12.7% to -12.2%) after three to four years (**Figure 4B**), and 7.8% (95% CI: -10.7% to -4.9%) after five to six years (**Figure 4C**). Percent reticulocytes remain persistently decreased from baseline by about half to a final value around 4-6%. The profile for TS is more limited but also greater in magnitude after one year, decreasing by an average of 12.5% (95% CI: -12.7% to -12.2%) to about 2-3% after one year (**Figure 4A**). This magnitude of effect of TS is heterogeneous, and could be a result of selection bias if those children undergoing TS had larger spleens or more severe hemolysis. It is expected that erythropoiesis correlates with the degree of hemolysis and therefore TS should have a greater effect than PS. The largest study of TS in this review does not include lab or clinical values [27].

Infections and Mortality

Fatal events were extremely rare across all reported studies. One 4-year old female died due to unrelated splenic necrosis 8 weeks following PS [11, 24], in a total of 2,119 reported patients across 13 studies, and no reported cases of OPSS. The study of 1,657 TS patients [27] used the Agency for Healthcare Research and Quality's Pediatric Quality Indicators to profile the safety of the procedure. The found in-hospital pneumonia was extremely rare (<0.6%). A study of similar magnitude for PS has yet to be conducted.

Presence of Accessory Spleens

Four studies reported that 4.5% of HS patients have accessory spleen(s) (80/1,770) but the best estimate in this review is about 3.6% (59/1,657) [27]. This is likely to be underestimated due to a lack of reporting, but is on the low end of the estimated 4-27% reported for other conditions ([28, 29] and references within). When present, surgeon preferences affect the decision to remove accessory spleens, where some choose to remove them routinely [26], whereas others do not [18], with no completion splenectomy after two years in these patients.

Splenic remnant regrowth

The volume of regrowth is highly heterogeneous, ranging from 0-170% of its initial size [20, 24], consistent with others [30]. Remnant regrowth is does not appear to be associated with recurring anemia [24, 30], however, regrowth is lowest at younger age and severe disease [24].

Splenomegaly, recurrence of symptoms and secondary splenectomy

Splenomegaly was reported in 241 of 1,716 individuals (14.0%). Only with excessively large spleens (greater than 1,500 g), do laparoscopic techniques become cumbersome. Recurrence of symptoms (anemia, jaundice, fatigue or abdominal pain) was not common (5-10%), and in some, secondary splenectomy was indicated (5%) [15, 16, 20, 23, 24].

In-hospital complications and adverse surgical events

Paralytic ileus was the most common in-hospital complication (1.5%), followed by urinary and respiratory complications (1% each), acute pancreatitis and accidental puncture or laceration during surgery (<1% each) [27]. One HS patient had a sequestration crisis following splenectomy [21].

Cholelithiasis and cholecystitis

Biliary disease is among the most common associated problem with long-standing hemolysis. Among TS patients, cholecystectomy was the most common concurrent procedure (26.7%), of which, 40% suffered from cholelithiasis [27]. The role of prophylactic cholecystectomy performed during splenectomy in children suffering from HS was questioned in the late 1990s [31], who found that this was indicated when symptomatic gall stones were present. The degree of splenectomy does not seem to be associated with cholecystectomy and cholelithiasis.

Patient health measures and quality of life

Following splenectomy, abdominal pain was improved [19, 20], sleep quality improved [32] and two studies noted growth spurts in children [15, 32]. Lastly, three studies reported that quality of life improved using a composite score of some or all of pain, chronic fatigue, or return to physical exercise [15, 16, 32]. These quality of life metrics were not described using standard assessment tools and are open to interpretation. Clinical experience would suggest splenectomy is favourably improves pain and quality of life, despite the residual risk of PS for recurrent anemia.

Length of hospital stay and duration of surgery

While duration of hospital stay and duration of surgery have been reported to be different

between TS and PS, these data suggests that they are comparable. The length of stay for TS is between 2-4 days [27]. However, more recent studies on TS find shorter stays of 1-4 days. Likewise, length of stay for PS was 2-4 days. Surgeries that are uncomplicated and performed without additional procedures are typically 50-75 minutes. Both length of stay and duration of surgery will be influenced by the surgeon's technical proficiency and experience.

Discussion

This meta-analysis finds that both total and PS adequately resolve short-term anemia in pediatric HS patients. There is a general theme that there is longer follow-up data available for PS patients, and the extent of detailed reporting varies. In the short-term post-operative period, splenectomy is generally safe and well tolerated, with extremely low risk of death and no reported cases of OPSS. This agrees with a meta-analysis which included adult hemolytic anemia patients [33].

Consensus guidelines for which data should be collected during routine monitoring of the HS patient are needed. For instance, hemoglobin concentration and reticulocytes are inexpensive and worthwhile to collect. For this reason and based on a pilot search of the literature, they were used in this review because of their relation to anemia and splenic function, and also that anemia is an independent risk factor of future cardiovascular disease [34]. The best way forward would be a discussion among experts with the patient and their family, in order to confirm what are important and clinically relevant outcomes for the managing clinician and the patient. Ideally, such information can be collected at regular clinic visits.

Several quality of life instruments measuring of pain, health and functioning exist. A few examples are the Pediatric Quality of Life Inventory (PedsQL™), WHO International

Classification of Functioning or the Brief Pain Inventory. A standard inventory should be used during follow-up visits to better allow for comparison across institutions. Improvement in abdominal pain and return to physical activity were infrequently described, but can be quickly and easily determined using a standardized questionnaire. The goal of a related, on-going clinical trial is to examine the patients' perception of scar formation, suggesting that cosmesis is an important factor to some patients and their families.

Measures of splenic function need also to be collected and validated prospectively. Pitted erythrocytes, measured by phase microscopy, are the gold standard of phagocytic function and is widely available. The normal clinical range is 0–4%, but may increase to 70% in clinically relevant splenomegaly. Data from sickle cell patients suggest a value of 15% or less is associated with immune competence and fewer instances of sepsis [35–37]. In contrast, Howell-Jolly bodies poorly correlate with other measurements [8]. Imaging modalities may be used for functional assessment. MRI can measure splenic volume in HS [23] and splenosis [29]. Scintigraphic scans using 99m-technetium labelled heat-damaged, autologous erythrocytes measure splenic function due to (mostly) splenic sequestration of the cell membranes, and splenic volume. However, scintigraphy is unlikely to be a cost-effect or common option in the pediatric population, and is only available in specialized centres. There is the possibility that sequestration-based measures in HS patients are at risk of increased false positives and could diminish its diagnostic utility [38]. Finally, ultrasonography can assess splenic size, portal hypertension, and gallstones, which may be an economical, safe, first-line imaging approach.

The extent of splenectomy positively correlates with hematologic improvement. All studies agreed that TS adequately resolves anemia to normal or near-normal hemoglobin concentrations.

Hematologic values following PS remain stable for at least five years, and this should also be expected following TS. There is less erythropoiesis following splenectomy, though percent reticulocytes remain abnormally elevated due to residual hemolysis. It seems prudent to consider PS when modest improvements in hemoglobin and reticulocytes are required, and to consider TS in more severe instances.

Following splenectomy, residual hemolysis increases the risk of gallstone formation, and symptomatic gall stones or cholecystitis, especially with severe disease or delayed splenectomy [20]. Secondary TS is indicated when symptoms recur following PS, and is more likely to be required in severe disease. The genotypic and phenotypic severity of HS should be characterized to help predict patient outcome, as disease severity is a cumulative effect of spectrin and band 3 protein deficiency, or a relative imbalance in their abundance [39]. The level of methemoglobin bound to the erythrocyte membrane negatively affects the post-splenectomy hemoglobin concentration, another possible marker of outcome [39].

An often cited concern for avoiding TS is that the risk of OPSS was perceived to be greater than that of PS. An older review of 5,902 TS cases produced an estimated post-operative sepsis rate of 4.4% and a mortality rate of 2.2% [40]. One meta-analysis observed post-operative sepsis rates of 5-12% for TS and 0–11% for PS [33]. However, these mortality rates included both adult and pediatric patients across several hemolytic disorders. The reason for the significantly reduced mortality in pediatric HS over the past two decades is mostly influenced by prophylactic antibiotics and vaccinations, and to delay elective splenectomy until age five [4, 41]. This delay is even reflected in the patient demographics (**Table III**). Furthermore, no case of OPSS in a pediatric HS patient who has received prophylactic immunization and antibiotics were found.

Whether the splenic remnant retains immune competency is uncertain. The resident population of IgM memory B cells in the spleen constitute a major defense against encapsulated bacteria. However, splenectomy severely reduces this B cell population [9]. Several documented cases of OPSS or serious bacterial infection in patients with splenosis or accessory spleen tissue have been documented [29, 42–44], and some cases of fulminant pneumococcal infections occur more than 20 years after splenectomy [45]. There is no clear correlation that the volume of splenic regrowth or splenosis offers immune protection, and preliminary findings exacerbate this risk as immune protection declines with age independent of splenectomy [29, 46]. The immunogenic response to pneumococci and meningococci vaccination are also less than ideal following splenectomy performed for congenital hemolytic disorders [46–48]. This scanty data supports the extra concern noted in a recent review of vaccination guidelines for the care of hyposplenic individuals [49]. It remains unknown if splenectomized children experience more frequent bacterial infection in later adulthood.

There are limitations to this review. First, there is a limited length of follow-up. Second, these reports mostly represent experiences of single institutions, and are often based on a small patient sample. While these patients experience moderate to severe disease, this review focused on reports which endeavoured to use systematic collection procedures, such as institutional reviews, so as to limit some forms of selection bias. While the recovery of hemoglobin, resolution of hemolysis, prevention of cholelithiasis and the consequent hepatobiliary disease and future risk of vascular disease in HS patients are all important issues for both the clinician and the patient, the choice of TS vs PS in achieving an optimal outcome is not yet clear.

This review identifies key opportunities for improving pediatric patient care. First,

establishing a population-based disease registry for tracking outcomes of HS. Efforts in this direction have been started by the Splenectomy in Congenital Hemolytic Anemia [21]. Such a multi-institution collaboration, prospectively following patients, should be able to address questions of long-term questions of recurrent hemolysis, gall bladder and liver disease, as well as estimate burden of morbid bacterial infections. It appears feasible based on available data to conduct a clinical trial comparing PS to TS to examine these outcomes. Second, functional splenic assessments should be made regularly, possibly incorporating diagnostic imaging to monitor splenic function and splenic regrowth, gall stones and liver disease. Third, careful monitoring for history of bacterial infection and vaccination history should continue. Data on serious infection incidence, lab results and clinical imaging can be incorporated into such a patient registry. Finally, individualized intervention is advocated with continued surveillance; the optimal choice of treatment and outcomes should clinically relevant and but confirmed with the patient.

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Figure Legends

Figure 1. Flow diagram of study selection

Figure 2. Meta-analysis of absolute post-operative difference in hemoglobin concentration (g/dL) from pre-operative baseline. Mean pre- and post-operative hemoglobin concentrations and the pooled standard deviation are listed. (*A*) After 6 months to 1 year follow-up, average hemoglobin concentration increased following PS by 2.20 g/dL (95% CI: 1.96 g/dL to 2.45 g/dL; heterogeneity I^2=65.3%) and following TS by 3.60 g/dL (95% CI: 3.08 g/dL to 4.12 g/dL; heterogeneity: I^2=0.0%). (*B*) After 3 to 4 years follow-up, average hemoglobin concentrations increased following PS by 3.22 g/dL (95% CI: 2.49 g/dL to 3.94 g/dL; heterogeneity I^2=0.0%). (*C*) After 5 to 6 years follow-up, average hemoglobin concentrations increased following PS by 2.21 g/dL (95% CI: 1.42 g/dL to 2.99 g/dL; heterogeneity I^2=44.8%).

Figure 3. Funnel plot of absolute mean difference of measured hemoglobin.

Figure 4. Meta-analysis of post-operative difference in percent reticulocytes from pre-operative baseline. Mean pre- and post-operative percent reticulocytes concentrations and the pooled standard deviation are listed. (*A*) After 6 months to 1 year follow-up, average percent reticulocytes decreased following PS by 6.5% (95% CI: -7.4% to –5.6%; heterogeneity I^2=0.0%) and following TS by 12.5% (95% CI: -12.7% to -12.2%; heterogeneity I^2=98.7%). (*B*) After 3 to 4 years follow-up, average percent reticulocytes decreased following PS by 7.8% (95% CI: -10.7% to -4.9%; heterogeneity I^2=0.0%). (*C*) After 5 to 6 years follow-up, average hemoglobin concentrations increased following PS by 7.7% (95% CI: -10.7 % to 4.7%; heterogeneity I^2=0.0%).

Table Legends

Table I. Search terms
Table II. Inclusion and exclusion criteria.
Table III. Characteristics of included studies.

Supplemental Files

Supplemental Table SI. MOOSE Checklist for Meta-analyses of Observational Studies

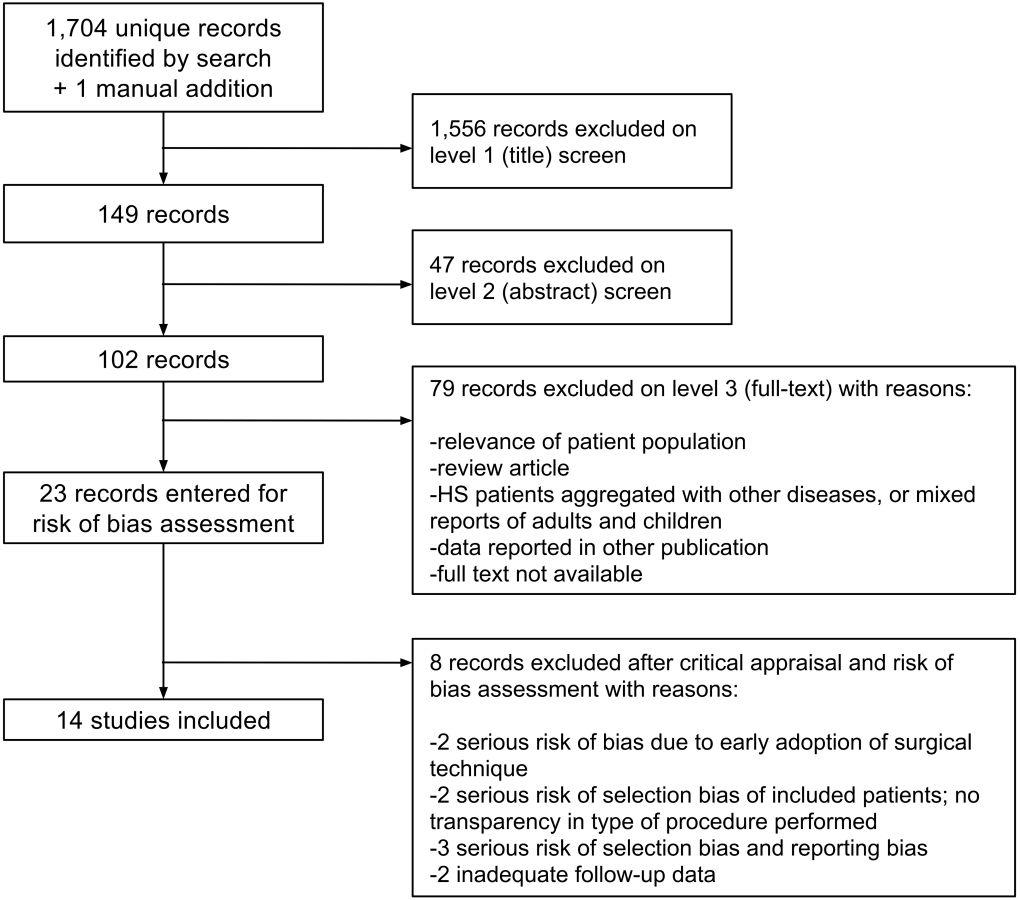
1,704 unique records identified by search + 1 manual addition
1,556 records excluded on level 1 (title) screen
149 records
47 records excluded on level 2 (abstract) screen
102 records
79 records excluded on level 3 (full-text) with reasons:
-relevance of patient population
-review article
-HS patients aggregated with other diseases, or mixed reports of adults and children
-data reported in other publication
-full text not available
23 records entered for risk of bias assessment
8 records excluded after critical appraisal and risk of bias assessment with reasons:
-2 serious risk of bias due to early adoption of surgical technique
-2 serious risk of selection bias of included patients; no transparency in type of procedure performed
-3 serious risk of selection bias and reporting bias
-2 inadequate follow-up data
14 studies included

Figure 1

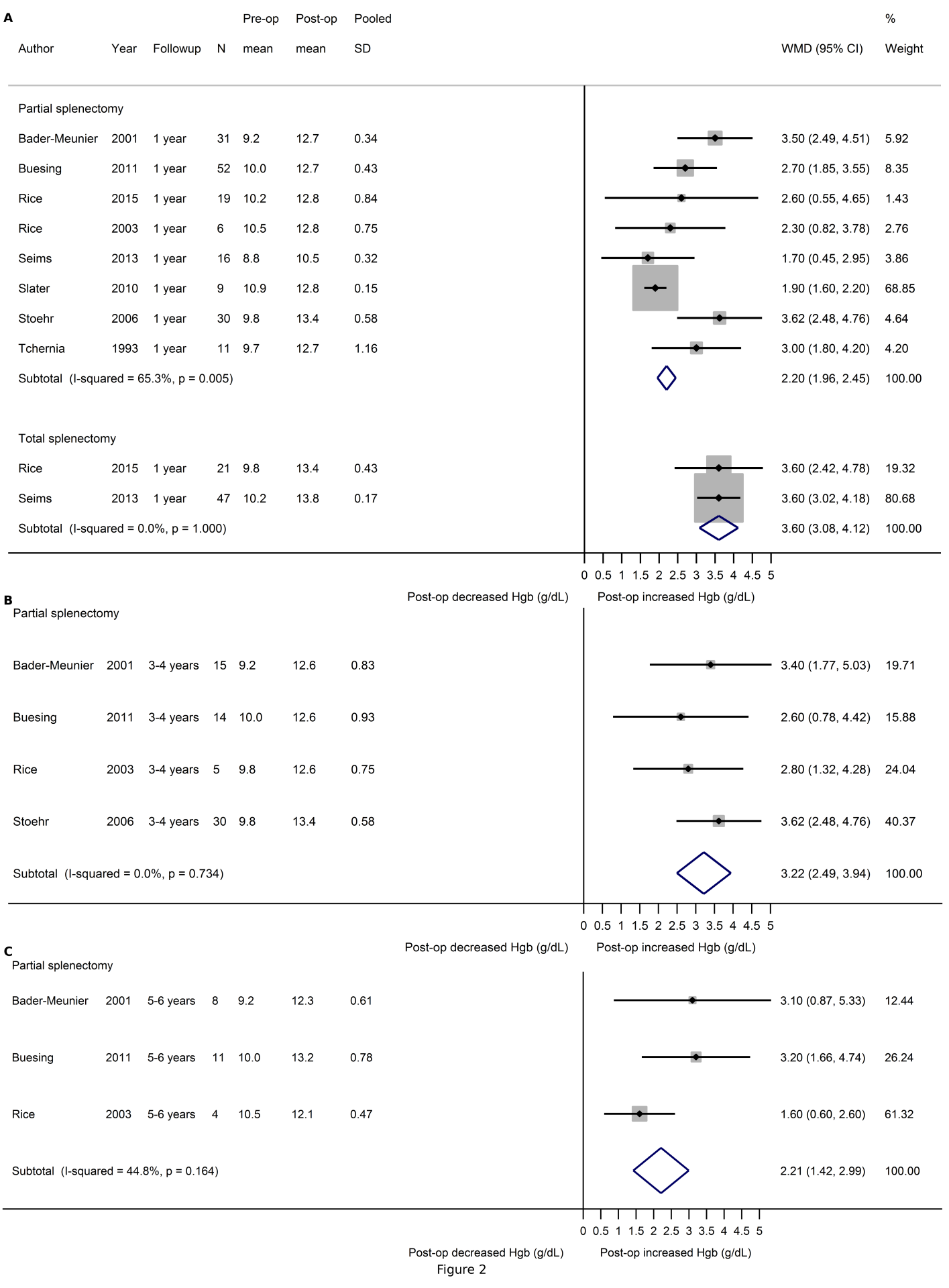
A
Author
Year
Followup
N
Pre-op mean
Post-op mean
Pooled SD
WMD (95% CI)
% Weight
Partial splenectomy
Bader-Meunier 2001 1 year 31 9.2 12.7 0.34 3.50 (2.49, 4.51) 5.92
Buesing 2011 1 year 52 10.0 12.7 0.43 2.70 (1.85, 3.55) 8.35
Rice 2015 1 year 19 10.2 12.8 0.84 2.60 (0.55, 4.65) 1.43
Rice 2003 1 year 6 10.5 12.8 0.75 2.30 (0.82, 3.78) 2.76
Seims 2013 1 year 16 8.8 10.5 0.32 1.70 (0.45, 2.95) 3.86
Slater 2010 1 year 9 10.9 12.8 0.15 1.90 (1.60, 2.20) 68.85
Stoehr 2006 1 year 30 9.8 13.4 0.58 3.62 (2.48, 4.76) 4.64
Tchernia 1993 1 year 11 9.7 12.7 1.16 3.00 (1.80, 4.20) 4.20
Subtotal (I-squared = 65.3%, p = 0.005) 2.20 (1.96, 2.45) 100.00
Total splenectomy
Rice 2015 1 year 21 9.8 13.4 0.43 3.60 (2.42, 4.78) 19.32
Seims 2013 1 year 47 10.2 13.8 0.17 3.60 (3.02, 4.18) 80.68
Subtotal (I-squared = 0.0%, p = 1.000) 3.60 (3.08, 4.12) 100.00
0 0.5 1 1.5 2 2.5 3 3.5 4 4.5 5
Post-op decreased Hgb (g/dL)
Post-op increased Hgb (g/dL)
B
Partial splenectomy
Bader-Meunier 2001 3-4 years 15 9.2 12.6 0.83 3.40 (1.77, 5.03) 19.71
Buesing 2011 3-4 years 14 10.0 12.6 0.93 2.60 (0.78, 4.42) 15.88
Rice 2003 3-4 years 5 9.8 12.6 0.75 2.80 (1.32, 4.28) 24.04
Stoehr 2006 3-4 years 30 9.8 13.4 0.58 3.62 (2.48, 4.76) 40.37
Subtotal (I-squared = 0.0%, p = 0.734) 3.22 (2.49, 3.94) 100.00
0 0.5 1 1.5 2 2.5 3 3.5 4 4.5 5
Post-op decreased Hgb (g/dL)
Post-op increased Hgb (g/dL)
C
Partial splenectomy
Bader-Meunier 2001 5-6 years 8 9.2 12.3 0.61 3.10 (0.87, 5.33) 12.44
Buesing 2011 5-6 years 11 10.0 13.2 0.78 3.20 (1.66, 4.74) 26.24
Rice 2003 5-6 years 4 10.5 12.1 0.47 1.60 (0.60, 2.60) 61.32
Subtotal (I-squared = 44.8%, p = 0.164) 2.21 (1.42, 2.99) 100.00
0 0.5 1 1.5 2 2.5 3 3.5 4 4.5 5
Post-op decreased Hgb (g/dL)
Post-op increased Hgb (g/dL)

Figure 2

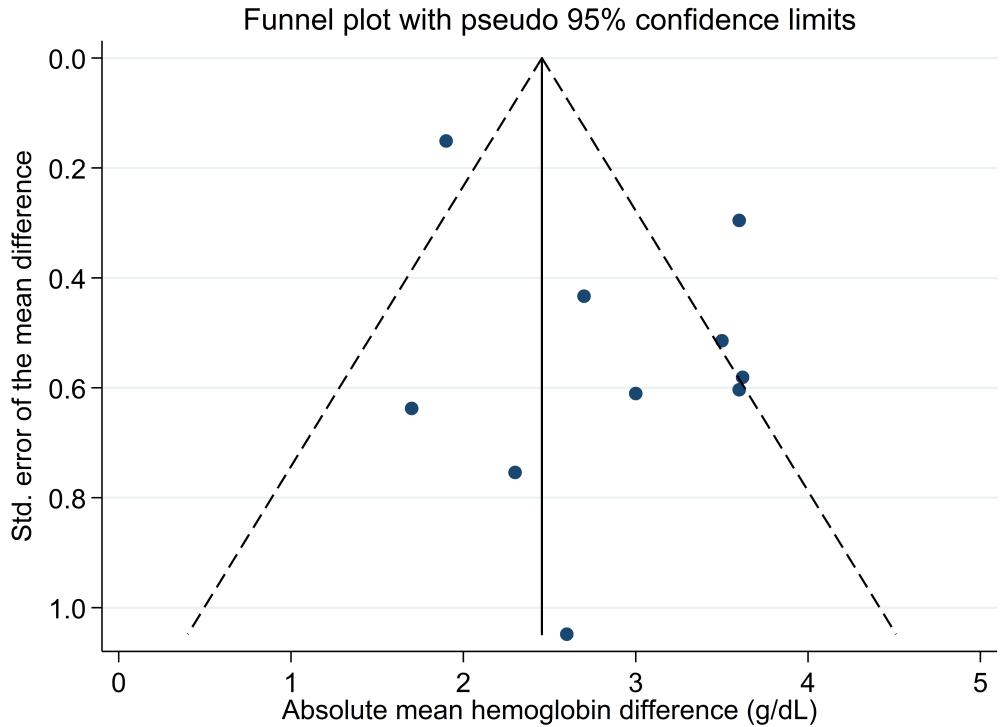
Funnel plot with pseudo 95% confidence limits
Std. error of the mean difference
0.0
0.2
0.4
0.6
0.8
1.0
0
1
2
3
4
5
Absolute mean hemoglobin difference (g/dL)

Figure 3

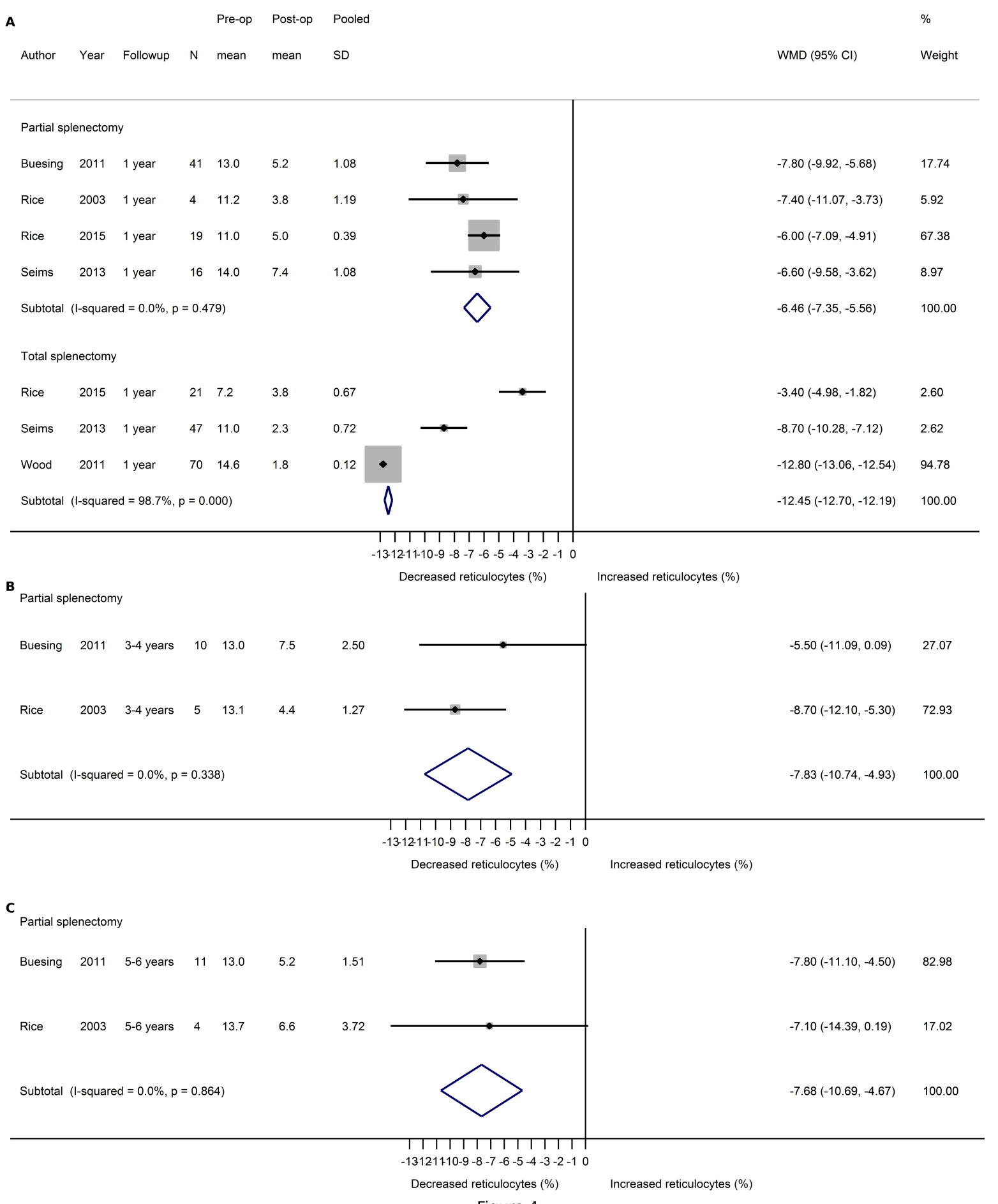
A
Pre-op
Post-op
Pooled
%
Author
Year
Followup
N
mean
mean
SD
WMD (95% CI)
Weight
Partial splenectomy
Buesing 2011 1 year 41 13.0 5.2 1.08 -7.80 (-9.92, -5.68) 17.74
Rice 2003 1 year 4 11.2 3.8 1.19 -7.40 (-11.07, -3.73) 5.92
Rice 2015 1 year 19 11.0 5.0 0.39 -6.00 (-7.09, -4.91) 67.38
Seims 2013 1 year 16 14.0 7.4 1.08 -6.60 (-9.58, -3.62) 8.97
Subtotal (I-squared = 0.0%, p = 0.479) -6.46 (-7.35, -5.56) 100.00
Total splenectomy
Rice 2015 1 year 21 7.2 3.8 0.67 -3.40 (-4.98, -1.82) 2.60
Seims 2013 1 year 47 11.0 2.3 0.72 -8.70 (-10.28, -7.12) 2.62
Wood 2011 1 year 70 14.6 1.8 0.12 -12.80 (-13.06, -12.54) 94.78
Subtotal (I-squared = 98.7%, p = 0.000) -12.45 (-12.70, -12.19) 100.00
-13 -12 -11 -10 -9 -8 -7 -6 -5 -4 -3 -2 -1 0
Decreased reticulocytes (%)
Increased reticulocytes (%)
B
Partial splenectomy
Buesing 2011 3-4 years 10 13.0 7.5 2.50 -5.50 (-11.09, 0.09) 27.07
Rice 2003 3-4 years 5 13.1 4.4 1.27 -8.70 (-12.10, -5.30) 72.93
Subtotal (I-squared = 0.0%, p = 0.338) -7.83 (-10.74, -4.93) 100.00
-13 -12 -11 -10 -9 -8 -7 -6 -5 -4 -3 -2 -1 0
Decreased reticulocytes (%)
Increased reticulocytes (%)
C
Partial splenectomy
Buesing 2011 5-6 years 11 13.0 5.2 1.51 -7.80 (-11.10, -4.50) 82.98
Rice 2003 5-6 years 4 13.7 6.6 3.72 -7.10 (-14.39, 0.19) 17.02
Subtotal (I-squared = 0.0%, p = 0.864) -7.68 (-10.69, -4.67) 100.00
-13 -12 -11 -10 -9 -8 -7 -6 -5 -4 -3 -2 -1 0
Decreased reticulocytes (%)
Increased reticulocytes (%)

Figure 4

Table I. Search terms.

Domain	Concept	Search terms
Population of interest	Children (0-18 yrs)	"Child"&, "Child, Preschool"&, "Infant"&, "Adolescent"&, youth*, juvenile*, teen*, pediatric*, paediatric*, child*, preschool*, pre-school, infant*
Indicator	Hereditary Spherocytosis	"Spherocytosis, Hereditary"&, "Anemia"&, "Anemia, Hemolytic"&, "Anemia, Hemolytic, Congenital"&, "Hemolysis"&, "Hemoglobin"&, "Splenomegaly"&, "Splenectomy"&, "Hypersplenism"&, "Jaundice"&, spherocyt*, microspherocyt*, splenomega*, splenect*, accessor*, hypersplen*, anemi*, anaemi*,hemoly*, haemoly*, hemoglobin*, haemoglobin*, jaundice*
Intervention	Splenectomy (Total vs Partial)	"Spleen"&, "Splenectomy"&, "Laparotomy"&, "Laparoscopy"&, "Hand-Assisted Laparoscopy"&, splenectom*, asplen*, ablat*, laparotom*, laparoscop*, total, complete, partial, subtotal, sub-total
Outcome	Lab parameters, adverse events, morbidity, mortality, quality of life	"Treatment Outcome"&, "Hospitalization"&, "Morbidity"&, "Mortality"&, "Postoperative Complications"&, "Intraoperative Complications"&, followup* OR follow-up*, comparison*, morbid*, mortal*, outcome*, complication*, adverse*

Notes: Terms within domains were combined using the OR Boolean operator, while combinations of domains were combined using the AND operator.
& denotes MeSH major headings. All other search terms were text searches.
* denotes a wildcard.

Table II. Inclusion and exclusion criteria.

Inclusion Criteria
Studies report hereditary spherocytosis patients undergoing any form of splenectomy with pre- and post-operative hematological parameters or markers of hemolysis, specifically: hemoglobin concentrations and peripheral reticulocyte proportion.
Studies report adverse events, surgical complications or mortality.
Studies followed a cohort, case-control or case series study design. When case series were reported, the chart review was conducted in an unbiased manner, such as an institutional review reporting on all cases of hereditary spherocytosis over a specified period of time.
Data were reported with the value of relative risk (RR), odds ratio (OR) or difference scores with 95% confidence intervals (CI); or the raw data needed to calculate these statistics.
Studies with English title and abstract (for searching), but whose full-text is available in English, Italian or French were included.
Exclusion Criteria
Single case reports or case series describing <4 patients. or studies that describe a single familial experience with HS.
Letters to the editor or commentaries that did not include full data of the splenectomized patients.
Splenectomies were performed secondary for any other indication than hereditary spherocytosis, including blunt trauma, thrombocytopenia purpura, sickle cell anemia, or cholelithiasis.
Data are reported in aggregate of hemolytic anemias, and the spherocytosis-specific data could not be obtained either from the article text or by correspondence with the author.
Studies which exclusively focus on only “mild” cases of spherocytosis, or adult cases, which are less likely to require surgical intervention.
Studies that include adult patients, but for which the individual data or subgroup data are not reported by age.

Table III. Characteristics of included studies.

Study (Ref)	Study Design	Sample Size	Setting & Location	Period	Splenectomy & Procedure	M:F	Age at Surgery	Follow-up	Risk of Bias[a]
Abdullah 2009 [27]	Retrospective cross-section	1,657	National registry; USA	1988-2004	TS, open	830/819	median: 8.0 y range: 5-12 y	NR	Fair
Bader-Meunier 2001 [15]	Institutional case series	39	Single institution; France	1985-1998	PS, open	22/17	8.1 ± 4.3 y (sd)	12-168 mo.	Good
Buesing 2011 [16]	Retrospective cohort	24	5 pediatric centres; Canada & USA	1990-2008	PS, laparoscopy	12/12	7.4 ± 4.2 (sd)	19 mo.	Fair
		38			PS, open	19/19	8.2 ± 3.8 y (sd)	48 mo.	
Mariani 2008 [12]	Institutional case series	121	Single institution; Italy	1980-2008	TS, open	NR	NR	NR	Fair
Mattioli 2007 [17]	Selected case series	50	9 pediatric centres; Italy	Jan 1999 - Dec 2003	TS, laparoscopy	NR	mean: 10.0 y range: 2-10 y	7-56 mo.	Fair
Morinis 2008 [18]	Retrospective cohort	9	Single institution; Canada	2000-2006	PS, laparoscopy	7/2	9.5 ± 4.2 y (sd)	25 mo.	Good
		9			TS, laparoscopy	7/2	8.6 ± 3.8 y (sd)	25 mo.	
Wood 2011 [26]	Institutional case series	70	Pediatric centre; USA	Jan 2000 - July 2008	TS, laparoscopy (mostly)	41/29	mean: 8.9 y range: NR	29-100 d	Good
Rescorla 2007 [19]	Prospective cohort	111	Single institution; USA	Aug 1995 - Nov 2006	TS (mostly), laparoscopy	NR	mean: 7.7 y range: 9 mo. - 19 y	NR	Fair
Rice 2003 [20]	Prospective cohort	16	Two pediatric institutions; USA	1993-2000	PS, open	NR	7.0 ± 3.4 y (sd)	7-72 mo.	Fair
Rice 2015 [21]	Retrospective cohort	19	16 institutions; Canada & USA	2005-2013	PS, mixed	19/21	< 18 yr	NR	Fair
		21			TS, mixed		< 18 yr	NR	
Seims 2013 [22]	Retrospective cohort	87	Single institution; USA	2002-2012	PS, laparoscopy	NR	5.5 ± 2.8 y (sd)	24 mo.	Fair
					TS, laparoscopy	NR	7.1 ± 3.6 y (sd)	13 mo.	
Slater 2010 [23]	Selected case series	9	Single institution; USA	May 2005 - Sept 2009	PS, laparoscopy	5/4	mean: 11.0 y range: 5-15 y	12-42 mo.	Fair
Stoehr 2006 [24]	Prospective cohort	31	Single institution; Germany	Nov 1996 - Dec 2004	PS, open	17/14	mean: 8.7 y range: 3-21 y	9-98 mo.	Fair
Tchernia 1993 [25]	Selected case series	11	Single institution; France	NR	PS, open	NR	7.9 ± 3.1 y (sd)	6-48 mo.	Fair

[a]denotes risk of bias assessment using the Downs and Black critical appraisal checklist [13]. Qualitative descriptors are: excellent (26–28), good (20–25), fair (15–19) and poor (<=14) [14]. Studies with a "poor" score were excluded during the risk of bias assessment.
TS/PS denotes total or partial splenectomy. NR denotes not reported by author.

Supplemental Table S1. MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	2-3
2	Hypothesis statement	3
3	Description of study outcome(s)	3-4
4	Type of exposure or intervention used	4
5	Type of study designs used	3
6	Study population	3-4
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	3
8	Search strategy, including time period included in the synthesis and key words	4-5
9	Effort to include all available studies, including contact with authors	4-5
10	Databases and registries searched	4
11	Search software used, name and version, including special features used (eg, explosion)	5
12	Use of hand searching (eg, reference lists of obtained articles)	4
13	List of citations located and those excluded, including justification	Fig. 1, pp. 5-6
14	Method of addressing articles published in languages other than English	Table 2
15	Method of handling abstracts and unpublished studies	Table 2
16	Description of any contact with authors	5
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Table 2, pp. 5-6
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	4
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	4
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	5-6
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	5-6
22	Assessment of heterogeneity	pp. 6-7, Table 4
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	6
24	Provision of appropriate tables and graphics	Yes
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Yes, where appropriate See Fig. 2&4 and Table 3
26	Table giving descriptive information for each study included	Tables 3
27	Results of sensitivity testing (eg, subgroup analysis)	Figures 2 and 4, and pp. 7-8, 10
28	Indication of statistical uncertainty of findings	Fig 2, Table 4, and in descriptions of results

Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	pp 6-7 and Fig 3
30	Justification for exclusion (eg, exclusion of non-English language citations)	Table 2
31	Assessment of quality of included studies	Table 3
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	Yes
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	Yes
34	Guidelines for future research	12-14
35	Disclosure of funding source	No sources

From: Stroup *et* al. *JAMA*. 2000.

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