SCIENTIFIC REVIEW



Outcomes of Laparoscopic Splenectomy for Treatment of Splenomegaly: A Systematic Review and Meta-analysis

María Rita Rodríguez-Luna^{1,2} · Carmen Balagué² · Sonia Fernández-Ananín² · Ramon Vilallonga³ · Eduardo María Targarona Soler²

Accepted: 11 October 2020/Published online: 11 November 2020 © Société Internationale de Chirurgie 2020

Abstract

Objectives To review the evidence regarding the outcomes of laparoscopic techniques in cases of splenomegaly. *Background* Endoscopic approaches such as laparoscopic, hand-assisted laparoscopic, and robotic surgery are commonly used for splenectomy, but the advantages in cases of splenomegaly are controversial.

Review methods We conducted a systematic review using PRISMA guidelines. PubMed/MEDLINE, ScienceDirect, Scopus, Cochrane Library, and Web of Science were searched up to February 2020.

Results Nineteen studies were included for meta-analysis. In relation to laparoscopic splenectomy (LS) versus open splenectomy (OS), 12 studies revealed a significant reduction in length of hospital stay (LOS) of 3.3 days ($p = \langle 0.01 \rangle$) in the LS subgroup. Operative time was higher by 44.4 min (p < 0.01) in the LS group. Blood loss was higher in OS 146.2 cc ($p = \langle 0.01 \rangle$). No differences were found regarding morbimortality. The global conversion rate was 19.56%. Five studies compared LS and hand-assisted laparoscopic splenectomy (HALS), but no differences were observed in LOS, blood loss, or complications. HALS had a significantly reduced conversion rate (p < 0.01). In two studies that compared HALS and OS (n = 66), HALS showed a decrease in LOS of 4.5 days (p < 0.01) and increase of 44 min in operative time (p < 0.01), while OS had a significantly higher blood loss of 448 cc (p = 0.01). No differences were found in the complication rate.

Conclusion LS is a safe approach for splenomegaly, with clear clinical benefits. HALS has a lower conversion rate. Higher-quality confirmatory trials with standardized splenomegaly grading are needed before definitive recommendations can be provided.

Prospero registration number: CRD42019125251.

Eduardo María Targarona Soler etargarona@santpau.cat

- IRCAD, Research Institute against Digestive Cancer, France
 Place de l'Hôpital, 67000 Strasbourg, France
- ² Gastrointestinal and Hematological Surgical Unit, Service of General and Digestive Surgery, Hospital de la Santa Creu I Sant Pau, Autonomous University of Barcelona (UAB) Medical School, Carrer Sant Antoni Ma Claret, 167, 08025 Barcelona, Spain
- ³ Endocrine, Metabolic and Bariatric Unit, Center of Excellence for the EAC-BC, Vall d'Hebron University Hospital, Universitat Autònoma de Barcelona, Passeig de la Vall d'Hebron 119-129, 08035 Barcelona, Spain

Introduction

The laparoscopic approach is considered the gold standard surgical technique for diseases requiring removal of the spleen [1, 2]. Since the first laparoscopic splenectomy (LS) was performed by Delaitre et al. [3] in 1991, laparoscopy has proven to be especially useful for surgical treatment of diseases associated with a normal-sized or slightly enlarged spleen, but some diseases requiring splenectomy are associated with a marked increase in the organ's volume. Splenomegaly entails a significant technical difficulty due to the complex maneuvers involved with potential intraoperative complications and a high conversion rate.

The definition of splenomegaly varies. Some authors have categorized spleen weights below 600 g as "non-massive," weights between 600 and 1600 g and between 17 and 22 cm in length as "massive, and weights over 1600 g or 22 cm as "supramassive" [4, 5].

Splenomegaly was initially considered a contraindication for a minimal invasive approach. In a series of 108 patients, Patel et al. reported that spleen weight was the most powerful predictor of morbidity during LS [6]. In 1999, Targarona et al. found that the morbidity rate after LS was higher for patients with spleens weighing more than 400 g, that LS in spleen weight exceeding 1 kg had a 23% conversion rate, and that all spleens over 3.2 kg required conversion. These findings questioned the potential advantages of LS for splenomegaly [4]. According to the clinical practice guidelines of the European Association for Endoscopic Surgery (EAES), LS is the standard of care in children and in adults, but its recommendation in patients with splenomegaly is still under discussion [7]. Nevertheless, with the implementation of new technological devices and increasing experience, recent trials have shown that LS can be performed safely in enlarged spleens [4, 8]. We conducted the present study to analyze and clarify the best evidence in relation to the minimal invasive approach in splenomegaly and to evaluate relevant clinical outcomes. To our knowledge, this is the first meta-analysis to compare endoscopic techniques in the splenomegaly setting.

Objective

The objective was to systematically evaluate the evidence and the potential advantages of laparoscopy splenectomy (LS), hand-assisted laparoscopic splenectomy (HALS), and robotic splenectomy (RS) as the approach for treatment of splenomegaly in comparison with open splenectomy (OS). We also compared these three minimally invasive techniques.

Methods

The methods of analysis and inclusion criteria were specified in advance (Prospero registration number CRD42019125251). Studies were searched in PubMed/ MEDLINE, ScienceDirect, Scopus, Cochrane Library, and Web of Science from the inception of LS in 1992 to February 2020 to identify potential eligible studies in which the primary objective was to describe efficacy, safety, and complications. Searches used the following Medical Subject Headings (MeSH) terms in combination with Boolean operators (AND, OR, NOT): "laparoscopy" [MeSH Terms] OR "minimal invasive" [All Fields] OR "hand assisted" [All Fields] OR "laparoscop*" [All Fields] OR "robotic surgical procedures" [All Fields] OR "robot*" [All Fields] OR "Vinci" [All Fields] OR "hand" [MeSH Terms] AND "splenectomy" [MeSH Terms] OR "splenectomy" [All Fields] OR "splenectomies" [All Fields] OR "splenomegalies" [All Fields] OR "splenomegaly" [MeSH Terms] OR "splenomegaly" [All Fields] NOT "paediatrics" [All Fields] OR "pediatrics" [MeSH Terms] OR "pediatrics" [All Fields] OR "paediatric" [All Fields] OR "pediatric" [All Fields] OR "animals" [MeSH Terms:noexp] OR "animals" [All Fields] OR "injuries" [MeSH Subheading] OR "injuries" [All Fields] OR "trauma" [All Fields] OR "wounds and injuries" [MeSH Terms] OR "wounds" [All Fields] AND "injuries" [All Fields] OR "wounds and injuries" [All Fields] OR "traumas" [All Fields].

The research was restricted to full-text studies published in English. Reference lists were also screened in order to find potential articles. Previous meta-analyses were identified and cross-checked to compare included studies.

The groups were constructed based on the surgical approach. The primary aim of the study was LS versus OS, LS versus HALS, HALS versus OS, RS versus LS, and RS versus OS or HALS as the secondary aims.

The review was carried out in accordance with the PRISMA statement [9]. Studies were considered eligible if they met the following criteria: (1) observational, retrospective, prospective, randomized, and non-randomized clinical studies that included laparoscopic, open, hand-assisted laparoscopic, or robotic splenectomy; (2) a clear defined comparator group; (3) data concerning (operative time, excess blood loss, length of hospital stay, conversion rate, morbidity, and mortality); and (4) grade of splenomegaly reported either by spleen weight or spleen size. Reviews, conference abstracts, editorials, and pediatrics journal were excluded. Studies that include patients <18 years were excluded and trauma as an indication for splenectomy. Studies that include merged information with splenomegaly and any other abdominal condition such as previous abdominal surgery were also excluded.

Data collection and outcome definition

Titles and abstracts were screened independently by two authors (R.R. and E.T). After screening for title and abstract, we assessed the full-text versions of each study for eligibility. Data on the study were extracted independently by two authors (R.R and E.T). Study characteristics included author, date of publication, study design, study period, and number of patients in each group. Patient



Group (2009). Preferred Reporting Items for Systematic Reviews and Meta- Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. https://doi.org/10.1371/journal.pmed1000097. For more information, visit https://www.prisma-statement.org

characteristics were age, sex, body mass index (BMI), malignant rate, spleen weight, and spleen size. Outcomes evaluated were length of hospital stay, excess blood loss, conversion rate, morbidity, and mortality. Disagreements between reviewers were resolved by consensus.

The authors Rosen M, Pietrabissa A, Zhong W, and Grahn S were contacted by e-mail in order to clarify information and decide whether or not to include their studies for the analysis.

Methodological quality of included studies

All studies were assessed for methodological quality using the Newcastle–Ottawa Scale (NOS) [10]. This scale evaluates the methodology quality in three domains: patient selection, comparability, and outcome, with the maximal grade being nine points. Studies with a score of 8 or higher were classified as high quality, 4–8 as moderate, and less than 4 as low. To evaluate the randomized control trial, we used the revised tool to assess risk of bias in randomized trials (RoB 2.0) [11].

Statistical analysis

Meta-analyses were conducted on each continuous and binary outcome. For each criterion, the heterogeneity between all studies was studied and measured. Statistical heterogeneity between the studies was assessed using the I^2 value and Chi-square test. If the I^2 was less than 50% or the p value was >0.05, heterogeneity was not taken into account, and a model with a fixed effect was used. If I^2 was >50% or if p < 0.05, the heterogeneity between studies

Table 1 Overvie	sw of	the studies in	ncluded										
Author	N	Mean age	Gender M/F	BMI	Malignant %	Spleen weight	Spleen size	Operative time	Excess blood loss	Length of hospital stay	Conversion%	Complication%	Mortality %
A. Laparoscopic vers	obe.	n splenectomy i	n splenomega	ly									
Terrosou [12] Laparoscopic	~	50 (21–60)	4 (50)	I	75	1762 ± 1150 (500-3680)	I	$197 \pm 65)110-300)$	393 ± 239 (100-800)	6 ± 3 (4−12)	0	1 (12.5)	0
Open	15	50 (31–64)	11 (73.33)	Ι	100	$27,138 \pm 1097$ (800–3850)	1	110 ± 21 (85–150)	393 ± 239 (100-800)	9 ± 3 (6-14)	I	5 (33)	0
Targarona et al. [13]	21	58 (12)	9 (42.85)	I	80.95	1600 (586)	I	176 (56)	I	6 (3)	23	28	0
Laparoscopic													
Open	20	56 (12)	10 (50)	I	80	1973 (713)	ļ	111 (19)	I	12 (5)	Į	55	0
Boody et al. [14] Laparoscopic	Π	64 (43–76)	10 (90.9)	I	I	2000 (1000–3530)	I	90 (45–225)	800 (20–5120)	6 (2–8)	6 (54.5)	2 (18.2 5)	1 (9.1)
Open	18	67 (29–81)	10 (55.5)	I	I	2447.5 (1025–6000)	I	45 (25–85)	65 (0–1635)	7 (5-44)	I	2 (11.1)	0
Owera et al. [15]	15	63 (53–67)	10	I	66.66	1300	I	175 (120–270)	I	2 (2-40)	6.6	2 (13.3)	0
Laparoscopic			(00.1%)			(0005-0001)							
Open	13	53 (31–65)	4 (30.8%)	I	61.4	1100 (100–3800)	I	90 (70–120)	1	10 (6-20)	I	4 (30.76)	1 (7.7)
Feldman et al.[16]	18	64 (55–71)	6 (33.33)	25 (24–28)	<i>TT.TT</i>	1051 (833–1325)	20 (18–22)	135 (116–145)	350 (163–750)	3 (3-5)	9	7 (39)	0
Laparoscopic													
Open	11	52 (44–63)	8 (72.72)	26 (24–28)	72.72	1645 (940–2250)	20 (18–23)	100 (116–145)	375 (100–863)	6 (5–7)	I	6 (55)	0
Zhou et al. [17]	33	48.2 (14.8)	17 (51.51)	I	I	1450.8 (345.7)	22.5 (4.8)	219.9 (43.3)	163 (56.2)	7.5 (.17)	1 (3.03)	3 (9.1)	0
Laparoscopic													
Open	29	44.5 (13.0)	16 (55.17)	I	I	1554.6 (283.8)	21.5 (4.8)	182.3 (66.8)	420 (177.3)	10.1 (2.4)	I	10 (34.5)	0
Koshenkov et al. [5]	10	48	3 (30)	I	30	611 (277–1268)	19 (17–20)	160 (115–315)	425 (59–1500)	3 (1-6)	30	20	0
Massive laparoscopic													
Open	7	53	6 (85.71)	I	43	624 (470–1459)	17 (15–20)	140 (45–245)	500 (100-800)	6 (4–14)	I	43	0
Koshenkov et al. [5]	12	64	9 (75)	I	92	1808 (988–2681)	25 (24–30)	195 (120–350)	308 (150–1000)	1 (1–13)	25	17	0
Supramassive laparoscopic													
Open	14	61	7 (50)	I	79	1712 (660–5039)	28 (22-40)	105 (45–310)	400 (100-6000)	4.5 (2–7)	I	14	0
Wu et al. [18]	18	46.6 (10.6)	12 (66.6)	1	I	1	23.7 (4.8)	203.6 (48.3)	70.3 (36.9)	6.3 (1.3)	0	2 (11.1)	0
Laparoscopic													
Open	16	45.7 (7.9)	11 (68.75)	I	I	I	26.3 (3.7)	162.8 (56.9)	300 (254.2)	8.8 (1.9)	I	3 (18.75)	0
Bo et al. [19]	40	38.8 (15.6)	25 (62.5)	1	I	I	22.4 (3)	150 (30)	150 (110)	6.1 (2.2)	2 (5)	8 (20)	0
Laparoscopic													
Open	4	40.3 (17.2)	27 (67.5)	I	I	I	23.8 (3.7)	100 (30)	140 (50)	11.3 (2.3)	0	7 (17.5)	0
Tsamalaidze et al. [6]	27	60.3 ± 15.42 (22-85)	20 (74.1)	28.7 ± 6.51 (18.7-48.4)	16	I	33 ± 2 (31–359	$153 \pm 70-58$ (76-328)	100 ± 110.77 (10-400)	3.2 ± 1.63 (1-7)	3 (11.1)	9 (33.33)	0
Laparoscopic													

🖄 Springer

Author	N	Mean age	Gender M/F	BMI	Malignant %	Spleen weight	Spleen size	Operative time	Excess blood loss	Length of hospital stay	Conversion%	Complication%	Mortality %
Open	47	60.5 ± 13.58 (19-82)	27 (57.44)	26.3 ± 4.41 (17.6-36.2)	26	I	33.3 ± 4.68 (30-45)	131 ± 58.38 (38-346)	278 ± 563 (29-2300)	5.4 ± 3.09 (2-21)	I	6/17.02)	1 (2.1)
HALS	12	56 ± 22.25 (16-80)	8 (66.7)	27.6 ± 8.43 (17.8-49.5)	7	I	23.7 ± 4.08 (20-29)	168 ± 92.86 (55-418)	162 ± 297 (20-1000)	4.9 ± 3.14 (2-12)	1 (8.3)	1 (8.3)	0
Shin et al. [20] Moderate laparoscopic	22	60.8 (37–82)	11 (59)	27.1 (14.8–39.7)	I	677.6 (570–984)	I	178.4 (114–296)	I	5.5 (2–25)	3 (14)	9 (41)	1 (5)
Open	4	52.2 (25–77)	23 (52.2)	26.4 (17.9–36.9)	I	689 (508–1000)	I	107.21 (38–288)	367 (50–2200)	6.5 (3-48)	I	10 (23)	2 (5)
Shin et al. [20] Massive laparoscopic	26	58.5 (25–87)	9 (40.9)	27.9 (20.4–39.3)	I	1754.9 (1032–3800)	I	170.8 (70–291)	606.6 (5–2400)	4.6 (2–12)	9 (35)	11 (42)	0
Open	52	60.6 (29.3–83)	14 (26.92)	25.4 (18.8–30.9)	I	1755.6 (10,434–3850)	I	112.1 (45–322)	588.5 (5–9500)	5.7 (3–27)	I	14 (27)	1 (2)
Cassacia et al. [21] Laparoscopic	25	53 (15)	9 (76)	24.8 (2.9)	I	I	24 (3.3)	143 (31)	278 (302)	6 (3)	0	4 (16%)	0
Open	40	58 (11) ic splenectomy i	27 (67.5) n_snlenomead	23 (3.4) hv	I	1	27.9 (5.3)	112 (40)	574 (583)	9 (4)	I	9 (22.5)	4 (10)
Targarona et al. [26]	36	58 (13) 19–82	24 (66.6)	5	66.66	1425 (884) 400–700	25 (5) 19–34	177 (52) 95–300	I	6.3 (3.3) 3–14	7 (20)	13 (36)	0
HALS	20	58 (16) 16–84	10 (50)	I	85	1753 (1124) 720–4500	26 (8) 16-42	135 (52) 85–270	I	4 (1.2) 2–5	1 (5)	2 (10)	0
Rosen et al. [25]	31	54	22 (70.96)	28	54.83	1031	I	186	376	4.2	7 (23)	6 (19.35)	0
HALS	14	57	7 (50)	25	71.42	1516	I	177	602	5.4	1 (7)	5 (35.71)	0
Ke-Xin et al. [27] Laparoscopic	16	38 (12) 15–61	7 (43.75)	I	18.75	1185 (536) 720–3900	24 (5) 16–31	195 (71) 110–320	138 (80) 60–550	5.3 (3.8) 3–13	4 (25)	2 (12.5)	0
HALS	20	43 (14) 17–65	12 (60)	I	5	1346 (735) 750-4800	27 (7) 18-40	141 (64) 95–280	86 (45) 30–350	7.4 (1.6) 5–9	0	0	0
Wang et al. [32] Massive laparoscopic	~	51 (10)	4 (50)	I	I	I	21 (1)	94 (19)	63 (26)	7.9 (3.8)	0	1 (13)	0
HALS	10	47 (11)	2 (25)	I	I	I	20 (1)	162 (24)	66 (20)	7.7 (1.7)	0	2 (20)	0
Wang et al. [32] Supramassive	11	45 (12)	4 (36.36)	I	I	I	32 (6)	146 (40)	113 (78)	7.5 (1.8)	0	3 (27)	0
laparoscopic													
HALS	10	48 (12)	7 (70)	I	I	I	28 (3)	229 (29)	272 (122)	9.3 (2.5)	0	7 (70)	0
Tsamalaidze et al. [6]	27	60.3 (15.42) 22–85	20 (74.1)	28.7 (6.51) 18.7–48.4	59.3	I	24.2 (3.92) 20–35	153 (70.58) 76–328	$100 (110.77) \\ 10-400$	3.2 (1.63) 1–7	3 (11.1)	9 (33.33)	0
Laparoscopic													
Open	47	60.5 (13.58) 19–82	27 (20)	26.3 (4.41) 17.6–36.2	55.3	I	26.6 (5.58) 20-45	131 (58.38) 38–346	278 (563.06) 20–2300	5.4 (3.09) 2–21	I	28 (59.57)	1 (2.1)

Table 1 continued

Table 1 continue	pa												
Author	Ν	Mean age	Gender M/F	BMI	Malignant %	Spleen weight	Spleen size	Operative time	Excess blood loss	Length of hospital stay	Conversion%	Complication%	Mortality %
HALS	12	56 (22.25) 16–80	8 (66.7)	27.6 (8.43) 17.8–49.5	58.3	1	23.7 (4.08) 20–29	168 (92.86) 55–418	162 (297) 20–1000	4.9 (3.14) 2–12	1 (8.3)	5 (41.66)	0
Sun et al. [24]	46	57 (17)	38 (82.6)	1	I	I	22.7 (4.8)	172 (43)	230 (130-740)	6.7 (3)	9 (19.56)	12 (26.08)	1 (2.17)
Laparoscopic													
HALS	45	55 (16)	34 (75.5)	1	I	I	23.5 (5.4)	141 (46)	215 122–332	6.4 (2.8)	1 (2.22)	15 (33.33)	0
C. HALS versus open	n spler.	vectomy in splen	omegaly										
Barbaros et al. [23] HALS	13	48 (13–68)	7 (53.84)	24 (20–29)	46.15	1200 (480–2110)	I	90 (30–150)	200 (200–800)	3 (2–10)	0	1 (7.69)	0
Open	14	50 (24–75)	8 (57.14)	23 (19–28)	78.57	1800 (600-3050)	I	97 (80–150)	300 (100–900)	6 (4-12)	I	1 (7.14)	0
Swanson et al. [22] HALS	20	55.2 (15.9)	15 (75)	I	09	I	22.9 (2.5)	163 (50)	375 (227)	4.2 (3)	-	7 (35)	0
Open	19	53.8 (12)	15 (78.94)	I	68.4	I	25.3 (3.7)	115 (40)	935 (877)	8.9 (5)	I	6 (32)	0
D. Robotic versus la	parosc	opic splenectom	y in splenome	galy									
Cavalier et al. [28]	27	56 (42–64)	Į	24.1 24.5 27 7	66.6	I	20 (18–23)	180 (146–238)	350 (100-800)	6 (4–8)	4 (14.8)	3 (11.1)	1 (3.7)
Laparoscopic				(21.8-21.1)									
Robotic	12	54 (46–60)	I	26 (23.9–32.1)	9.99	I	21 (17–23)	270 (190–300)	100 (100-250)	6 (5–6)	0	0	0
N indicates number of	of patie	ents; BMI body	mass index, H.	ALS hand-assisted	l laparoscopic :	splenectomy							

was taken into account for the modelization. We then added a random effect to model a supplementary variance source that we called an inter-study variation. For continuous variables, the mean difference between two groups was measured and estimated (using the inverse variance weighting correction) and the 95% confidence intervals were calculated. For binary variables, odds ratios were evaluated in their 95% asymptotic confidence interval. The adjusted results and the associated forest plot for each criterion are given. We set the first risk error alpha at 5%, and a p value <0.05 was then considered statistically significant. The statistical analysis was performed using R Software version 3.6.1, with all the packages necessary to perform the meta-analysis.

Results

Literature search

A total of 3382 papers were identified through the literature research. After removing duplicated articles, 2703 were retained for screening and 52 were potentially eligible for full-text evaluation. Thirty-two of these were excluded. The systematic review therefore included 20 studies, 19 of which were finally pooled into the meta-analysis (Fig. 1).

Study characteristic and quality assessment

The LS versus OS group included 12 studies [5, 8, 12–21] (one ambidirectional cohort, five prospective cohorts, and six retrospective cohorts, with a total of 652 patients). The HALS versus OS [22, 23] group included two studies (one retrospective cohort and one prospective randomized control trial with a total of 398 patients), and the LS versus HALS [8, 24–27] group included five studies (four retrospective cohorts and one prospective cohort, with a total of 306 patients). The RS versus LS [28] group included only one retrospective cohort. We found no studies comparing RS versus OS or RS versus HALS (Tables 1a, b, c, d, 2).

Synthesis of results

Primary aim: comparison between LS and OS

A comparison of LS versus OS showed that LOS was significantly shorter after LS: -3.3 days [-4.2; -2.4] (p < 0.01). However, operative time was shorter for OS: 44.4 min [36.4; 52.5] (p < 0.01). Blood loss was significantly lower in LS -146.2 cc [-276.4; -16.1] (p < 0.01) than in OS, with a global OR of 0.66 [0.19; 2.27]. Differences between the two groups regarding

mortality and complications were not significant OR = 0.95 [0.65; 1.39] (p = 0.8) (Fig. 2a–e).

Subanalysis according to the splenic weight and size The meta-analysis of spleen weight and size showed no differences between the LS and OS groups : -121.2 g [-250.6; 8.1] (p = <0.05), -0.9 cm [-2.5; 0.6] (p = 0.2485), respectively.

In the LS subgroup, the median of weights was 1450.8 g (611; 2000), SD 644.2 g (345; 4293). In the OS subgroup, the median of weights was 1554.6 g (624; 2738), SD 3780 g (283; 6716.25).

In the LS subgroup, the median of sizes was 22.5 cm (19.0; 33.0), SD 4.8 cm (3.0–10.8). In the OS subgroup, the median of sizes was 23.8 cm (17.0; 33.3), SD 5.3 cm (3.7; 24.3) (Fig. 2f, g).

Secondary aim: comparison between LS and HALS

The model did not identify any statistically significant difference between LS and HALS regarding LOS mean difference: -0.4 days [-1.9; 1.2] (p = 0.9), operative time mean difference -7.1 min [-57.3; 43.1] (p > 0.05), or excess blood loss -35.9 cc [-106.3; 34.4] (p = 0.32). Neither did we find any difference in the complication rate: OR 0.78 [0.44; 1.37] (p = 0.38). The conversion rate was significantly reduced OR 4.92 [1.75; 13.89] (p < 0.01) in the HALS group. We were unable to analyze mortality as only one event was reported among all the studies (Fig. 3a–f).

Subanalysis of splenic weight and size The meta-analysis revealed no statistically significant differences between the groups in spleen weight – 218.8 g [– 554.9; 117.2] (p > 0.05) or spleen size 0.6 cm [– 0.2; 1.4] (p = 0.123). In the LS subgroup, the median of weights was 1425 g (1185; 1425), SD 884 g (536; 884). In the HALS subgroup, the median of weights was 1549.5 g (1346.0; 1753.0), SD 929.5 g (735.0; 1124.0).

The median of sizes was 24.2 cm (21.0; 32.0), SD 4.8 cm (1.0; 6.0). In the HALS subgroup, the median of sizes was 23.7 cm (20.0; 28.0), SD 5.4 cm (1.0; 8.0) (Fig. 3 g, h).

Secondary aim: comparison between HALS and OS

LOS was significantly lower after HALS than after OS, with a mean difference of 4.5 days [2.1; 7] (p < 0.01). Operative time was significantly lower after OS, with a mean difference of 44 min [-71.3; -16.7] (p < 0.01). Moreover, excess blood loss was lower after HALS: 448 cc [94.3; 801.7] (p = 0.01). The model did not find any

significant difference in the complication rate OR = 0.87 [0.26; 2.91] (p = 0.82) (Fig. 4a–d).

We were unable to perform a subanalysis for splenic weight and size in this group because values were lacking in all the studies.

We found only one study comparing RS with another technical approach [28]. The authors compared RS versus LS in a retrospective study of 12 versus 27 patients. They found a longer operative time in the RS group (p = 0.007). However, blood loss was lower (100 vs. 350 cc) (p = 0.032) in RS group. The series reported four cases of conversion from RS to LS due to intraoperative bleeding.

Our search did not identify any studies that compared RS and OS.

The quality of included studies

Twelve studies that compared LS and OS were considered high quality, and one was moderate quality according to NOS. In the HALS versus LS subgroup, five were considered high quality and one had some concerns according to the RoB 2.0 tool. One study in the HALS versus OS analysis was considered high quality, and one presented some concerns according to RoB 2.0. The RS versus LS study was of high quality according to NOS (Table 2).

Discussion

The outcome of the current meta-analysis helps us better understand the clinical impact of minimally invasive surgery (MIS) in this challenging situation of splenomegaly.

Following the pooled meta-analysis, our model did not find differences between LS and OS regarding morbimortality. The operative time was higher in the LS group, but it was also associated with a lower blood loss and a shorter hospital stay. These results, along with the well-known rapid postoperative recovery in laparoscopic procedures, can be considered as potentially cost-effective [29] despite the need for conversion to OS in some cases. The median global conversion rate in the LS subgroup was 19.56% [11.11; 25]. The highest conversion rate was that of Boddy et al. [14] with 54.55% [mean spleen weight: 2000 g (1000–3530)], followed by that of Shin et al. [20] with 34.62% in the subgroup of massive splenomegaly [mean splenic weight of 1754.9 g (1032-3800)], and Targarona et al. [13] with 23.81% [mean weight of 1616 ± 651 g (1000-2950)]. However, in a cohort with 25 patients, Cassacia et al. [21] reported a 0% conversion rate [mean splenic diameter of 24.0 ± 3.3] in cases of massive splenomegaly.

After demonstrating that spleen size was not an obstacle for successful LS despite its association with a variable and

 Table 2 Quality overview of the studies included

A. Studies quality assessment for prin	nary and secondary aims		
Outcome	Author	Type of study	Quality assessment NOS/RoB 2.0
LS versus OS	1998 Terrosou [12]	Retrospective cohort	9
LS versus OS	1999 Targarona [13]	Retrospective cohort	8
LS versus OS	2006 Boddy [14]	Ambidirectional cohort	8
LS versus OS	2006 Owera [15]	Retrospective cohort	8
LS versus OS	2008 Feldman [16]	Retrospective cohort	8
LS versus OS	2011 Zhou [17]	Prospective cohort	9
LS versus OS	2012 Koshenkov [5]	Retrospective cohort	8
LS versus OS	2012 Wu [18]	Prospective cohort	8
LS versus OS	2013 Bo [19]	Prospective cohort	8
LS versus OS	2017 Tsamaliadze [6]	Retrospective cohort	7
LS versus OS	2018 Shin [20]	Retrospective cohort	8
LS versus OS	2019 Casaccia [21]	Prospective cohort	8
LS versus HALS	2001 Targarona [26]	Prospective cohort	9
LS versus HALS	2002 Rosen [25]	Retrospective cohort	8
LS versus HALS	2007 Xin [27]	Retrospective cohort	8
LS versus HALS	2012 Wang [32]	Retrospective cohort	8
LS versus HALS	2017 Tsamaliadze [6]	Retrospective cohort	8
LS versus HALS	2019 Sun [24]	Prospective randomized control trial	Some concerns (RoB 2.0)
HALS versus OS	2007 Barbaros [23]	Prospective randomized control trial	Some concerns (RoB 2.0)
HALS versus OS	2011 Swanson [22]	Retrospective cohort	8
RS versus LS	2018 Cavaliere [28]	Comparative retrospective cohort	8
B. Revised Cochrane risk of bias tool	for randomized trials (Rol	B 2.0)	
Variable	2007 Barbaros [23]	2019 Sun [24]	
Random sequence generation	+	+	
Allocation concealment	?	?	
Blinding of participant and personal	+	+	

+

+

+

high conversion rate, the logical next step was to introduce HALS in the treatment of an enlarged spleen. HALS has been described as a middle option between LS and OS. The tactile feedback allows surgical and facilitates intra-abdominal manipulation [30]. It has also been suggested that HALS can be a starting point in the advanced laparoscopic learning curve and serve as a bridge in the armamentarium for difficult cases before conversion. These advantages could explain the lower conversion rate in HALS than in LS and also the conversion rates in the literature of around 5% [26], which is similar to findings found in this systematic review [mean 5% (0-8.3)].

+

+

+

In our analysis, when comparing LS and HALS, seven studies met the inclusion criteria and statistical differences were found, with a significant increase in the conversion rate in the LS group. However, we did not find statistical

Incomplete outcome data

Selective reporting

Other bias

differences in relation to the length of hospital stay, excess blood loss during surgery, or complications. Six studies reported the spleen size and only three studies reported the spleen weight, but we did not find any significant differences between groups (p = > 0.05).

Yong Huang et al. recently published a meta-analysis comparing HALS versus LS in cases of splenomegaly and splenectomy plus upper stomach devascularization. In the pure splenomegaly subanalysis, the authors included nine trials with 486 patients and they did not find differences between the groups in splenic weight (0.6, 95% CI - 0.12 to 1.32; p = 0.1). The operative time was significantly shorter and blood loss volume and conversion rate were significantly lower in the HALS group, with no significant differences in length of hospital stay, blood transfusion, time to food intake, or morbidity and mortality rate [31]. In

Â		Lapar	oscopic			Open	Mean difference			
Study	Total	Mean	SD	Total	Mean	SD		MD	95%-CI	Weight
							-1			
1998 Terrosou	8	6.00	3.0000	15	9.00	3.0000		-3.00) [-5.57;-0.43]	7.2%
1999 Targarona	21	6.00	3.0000	20	12.00	5.0000	-	-6.00	[-8.54; -3.46]	7.4%
2006 Boddy	11	6.00	8.1000	18	7.00	52.6500		-1.00	[-25.79; 23.79]	0.1%
2006 Owera	15	2.00	51.3000	13	10.00	18.9000		-8.00) [-35.92; 19.92]	0.1%
2008 Feldman	18	3.00	2.7000	11	6.00	2.7000		-3.00) [-5.03;-0.97]	9.6%
2011 Jing Zhou	33	7.50	1.7000	29	10.10	2.4000	-	-2.60) [-3.65; -1.55]	15.6%
2012 Koshenkov Massive	10	3.00	6.7500	7	6.00	13.5000		-3.00	[-13.84; 7.84]	0.6%
2012 Koshenkov Suprammasive	9 12	1.00	16.2000	14	4.50	6.7500	<u> </u>	-3.50	[-13.32; 6.32]	0.7%
2012 Zhong Wu	18	6.30	1.3000	16	8.80	1.9000	÷	-2.50	[-3.61; -1.39]	15.2%
2013 Wang Bo	40	6.10	2.2000	40	11.30	2.3000	+	-5.20) [-6.19: -4.21]	16.0%
2017 Tsamalaidze	27	3.20	1.6300	47	5.40	3.0900	1 m	-2.20	[-3.28: -1.12]	15.4%
2018 Shin Massive	26	4.60	13,5000	52	5.70	32,4000		-1.10	[-11.32: 9.12]	0.7%
2018 Shin Moderate	22	5 50	31 0500	44	6 50	60 7500		-1.00	[-23, 15, 21, 15]	0.2%
2010 Casaccia	25	6.00	3 0000	40	0.00	1 0000		-3.00	[-20.10, 21.10]	11 3%
2019 Casaccia	20	0.00	3.0000	40	9.00	4.0000		-5.00	[-4.71, -1.23]	11.576
Pandom offects model	286			366				-3 30	Γ_A 17· _2 AA1	100 0%
Hotorogonoity $l^2 = 52\%$ $n = 0.01$	200			300				-5.50	, [-4.17, -2.44]	100.076
Heterogeneity: $T = 52\%$, $p = 0.01$							30 30 10 0 10 30	20		
							-30 -20 -10 0 10 20	30		
В						•	••			
Study	Total	Lapare	oscopic	Total	Meen	Open	Mean difference	MD	05% CL	Noight
Study	lotal	wean	30	rotar	wean	30		ND	95%-01	weight
1998 Terrosou	8 1	97 00	65 0000	15 1	10.00	21 0000		87.00	[40 72· 133 28]	3.0%
1990 Targarona	21 1	76.00	56 0000	20 1	11 00	10,0000	-	65.00	[30 64· 00 36]	10.0%
2006 Roddy	11		43 0000	18	45.00	81 0000		45.00	103 40. 103 401	0.3%
2006 Owers	15 1	75 00 2	43.0000	12	40.00	67 5000		45.00	22 95: 102 951	0.5%
2000 Owera	10 1	75.00 Z	20 1500	10	90.00	20,1500		25.00 [[-23.65, 193.65]	7 40/
2000 Feldman	10 1	10.00	39.1500	20.1	00.00	39.1500 66.9000	1	35.00		7.4%
2011 Jing Zhou	33 Z	19.90	43.3000	29 1	40.00			37.60		7.9%
2012 Koshenkov Massive	10 1	00.00 2	10.0000	1 1	40.00	270.0000		20.00 [-	-240.79, 260.79]	0.1%
2012 Rosnenkov Suprammasive	12 1	95.00 Z	48.3000	14 1	62.00	56,0000		— 90.00 [-	· 102.22; 342.22]	0.1%
	10 2	03.60	46.3000	10 1	02.00	56.9000	1	40.80		5.0%
2013 Wang Bo	40 1	50.00	30.0000	40 1	00.00	30.0000		50.00		37.2%
2017 Isamalaidze	27 1	53.00	70.0000	4/ 1	31.00	59.3800	1	22.00		0.5%
2018 Shin Massive	26 1	70.80 2	98.3500	52 1	12.10	373.9500		58.70 [-94.54; 211.94]	0.3%
2018 Shin Moderate	22 1	78.40 2	45.7000	44 1	07.21	337.5000	·	71.19 [[-/1.94; 214.32]	0.3%
2019 Casaccia	25 1	43.00	31.0000	40 1	12.00	40.0000		31.00	[13.64; 48.36]	21.3%
Pandom offects model	296			366				11 15	1 26 A2+ 52 A61 -	100.0%
Heterogeneity: $I^2 = 0\%$, $p = 0.51$	200			300				44.45	[30.43, 32.40]	100.0 %
Herefogeneity. $T = 0.8$, $p = 0.51$							-300-200-100 0 100 200 30	00		
							-500-200-100 0 100 200 50			
С										
		Laparos	copic			Open	Mean difference			
Study Tot	tal Me	an	SD To	otal Me	ean	SD		MD	95%-0	I Weight
1998 Terrosou		~~ ~~		45 000				0.00		10.40
1999 Targarona	8 393.	00 239	9.0000	15 393	3.00	239.0000	3	0.00	[-205.08; 205.08	3] 13.1%
2006 Boddy								705 00 1	0450 50. 4000 50	0.0%
2006 Owera	11 800.	00 666	5.0000	10 00	5.00 Z	207.2500		- 735.00 [-3459.53, 4929.53	0.1%
2008 Feldman		. 70'	. 4500					25.00	[610 41: 560 44	0.0%
2011 Jing Zhou	10 300.	00 794	2.4500	11 3/3	0.00	177 2000	1	-25.00	[204 22: 100 60	J 3.0%
2012 Koshenkov Massive	33 103. 10 425	00 104	5.2000	29 420	0.00	045.0000		-257.00	1460 21. 1210 24	
2012 Koshenkov Suprammasive	10 420.	00 194	7 5000	14 400	0.00 7	945.0000		-75.00 [-1409.21, 1319.21	J 0.0%
2012 Zhong Wu	12 300.	30 114	3000	16 200	00 /	254 2000		-92.00 [-4014.40, 4130.40	0.1.70
2013 Wang Bo	10 /0.	00 110	0000	10 300	0.00	50 0000	10	-229.70	[-303.42; -103.98 [-27.45: 47.44	10.4%
2017 Tsamalaidze	40 100. 27 100	00 110	7700	40 140	2 00	563 0000		178.00	[-21.40, 47.40	1 1/ 70/
2018 Shin Massive	26 606	60 222	3 2500	52 599	2 50 12	818 2500		-1/0.00	2680 00 2717 40	1 0 10/
2018 Shin Moderate	20 000.	50 201	5.0000	14 267	200 2	010.2000		352 50 1	-1403 61. 2200 64	0.1%
2019 Casaccia	25 279	00 391	2 0000	40 574	100 2	583 0000		-296.00 [[=512 00· _80 00	1 12 7.%
	20 210.	50 502		40 014		000.0000		-230.00	[-012.00, -00.00	1 12.170
Random effects model 2	50		2	333				-146.24	[-276.43: -16.05	1 100.0%
Heterogeneity: $I^2 = 82\%$, $p < 0.01$,
							-4000 -2000 0 2000 4000)		

Fig. 2 Meta-analysis of main aim. LS versus OS. a Length of hospital stay, b operative time, c excess blood loss, d mortality, e complications, f spleen weight, g spleen size

contrast with the result from Huang et al., in our analysis the operative time was not lower in HALS than in the LS group. Regarding conversion rates, both meta-analyses found differences favoring the HALS subgroup. Ailawaidi et al. in our meta-analysis was not included because the authors mixed the results of laparoscopy in cases of

D		Laparos	copic		Open	OR			
_	Study	Events	Total	Events	Total		OR	95%-CI	Weight
	1998 Terrosou	0	8	0	15				0.0%
	1999 Targarona	0	21	0	20				0.0%
	2006 Boddy	1	11	0	18		5.29 [0	0.20; 141.74]	14.1%
	2006 Owera	0	15	1	13		0.27	[0.01; 7.19]	14.1%
	2008 Feldman	0	18	0	11				0.0%
	2011 Jing Zhou	0	33	0	29				0.0%
	2012 Koshenkov Massive	0	10	0	7				0.0%
	2012 Koshenkov Suprammasive	e 0	12	0	14				0.0%
	2012 Zhong Wu	0	18	0	16				0.0%
	2013 Wang Bo	0	40	0	40				0.0%
	2017 Tsamalaidze	0	27	1	47		0.56 [0.02; 14.32]	14.6%
	2018 Shin Massive	0	26	1	52		0.65 [0.03; 16.45]	14.6%
	2018 Shin Moderate	1	22	2	44		1.00 [0.09; 11.67]	25.3%
	2019 Casaccia	0	25	4	40		0.16	[0.01; 3.09]	17.3%
	Random effects model		286		366		0.66	0.19; 2.27]	100.0%
	Heterogeneity: $I^2 = 0\%$, $p = 0.73$						·		
	0					0.01 0.1 1 10	100		
Е									
		Laparoso	copic		Open	OR			
	Study	Events	Total	Events	Total		OR	95%-CI We	ight
	1998 Terrosou	1	8	5	15		0.29 [0.0	03; 3.01] 3	.8%
	1999 Targarona	6	21	11	20		0.33 [0.0	09; 1.19] 8	.6%
	2006 Boddy	2	11	2	18		1.78 [0.2	1; 14.86] 4	.5%
	2006 Owera	2	15	4	13		0.35 [0.0	05; 2.31] 5	.3%
	0000 Faldman	7	40	0	4.4		0 50 10 4	10. 0 401 7	40/

Chudu	Laparos	copic	Evente	Open	OR		0.5% (1)	Waight
Study	Events	Total	Events	Total		UR	95%-01	weight
1998 Terrosou	1	8	5	15		0.29	[0.03; 3.01]	3.8%
1999 Targarona	6	21	11	20		0.33	[0.09; 1.19]	8.6%
2006 Boddy	2	11	2	18		1.78	[0.21; 14.86]	4.5%
2006 Owera	2	15	4	13		0.35	[0.05; 2.31]	5.3%
2008 Feldman	7	18	6	11		0.53	[0.12; 2.42]	7.1%
2011 Jing Zhou	3	33	10	29		0.19	[0.05; 0.78]	7.8%
2012 Koshenkov Massive	2	10	3	7		0.33	[0.04; 2.87]	4.4%
2012 Koshenkov Suprammasive	e 2	12	2	14		1.20	[0.14; 10.12]	4.4%
2012 Zhong Wu	2	18	3	16		0.54	[0.08; 3.74]	5.1%
2013 Wang Bo	8	40	7	40		1.18	[0.38; 3.63]	9.9%
2017 Tsamalaidze	9	27	6	47		3.42	[1.06; 11.03]	9.5%
2018 Shin Massive	11	26	14	52	÷	1.99	[0.74; 5.36]	11.1%
2018 Shin Moderate	9	22	10	44	÷	2.35	[0.78; 7.10]	10.1%
2019 Casaccia	4	25	9	40		0.66	[0.18; 2.41]	8.5%
Random effects model		286		366		0.85	[0.51; 1.42]	100.0%
Heterogeneity: $I^2 = 40\%$, $p = 0.06$								
					0.1 0.5 1 2 10			

F

		Lap	paroscopic			Open
Study	Total	Mean	SD	Total	Mean	SD
1998 Terrosou	8	1762.00	4293.0000	15	2738.00	4117.5000
1999 Targarona	21	1600.00	586.0000	20	1973.00	713.0000
2006 Boddy	11	2000.00	3415.5000	18	2447.50	6716.2500
2006 Owera	15	1300.00	3510.0000	13	1100.00	3780.0000
2008 Feldman	18	1051.00	664.2000	11	1645.00	1768.5000
2011 Jing Zhou	33	1450.80	345.7000	29	1554.60	283.8000
2012 Koshenkov Massive	10	611.00	1337.8500	7	624.00	1335.1500
2012 Koshenkov Suprammasive	12	1808.00	2285.5500	14	1712.00	5911.6500
2012 Zhong Wu						
2013 Wang Bo						
2017 Tsamalaidze						
2018 Shin Massive	26	1754.90	3736.8000	52	1755.60	3801.6000
2018 Shin Moderate	22	677.60	558.9000	44	689.00	664.2000
2019 Casaccia						
Fixed effect model Heterogeneity: $l^2 = 0\%$, $p = 0.96$	176			223		

Mean difference				
	MD	9	5%-CI	Weight
	-976.00	[-4608.01; 26	56.01]	0.1%
	-373.00	[-773.57;	27.57]	10.4%
	-447.50	[-4148.93; 32	253.93]	0.1%
	200.00	[-2516.12; 29	16.12]	0.2%
	-594.00	[-1683.21; 4	95.21]	1.4%
i i i i i i i i i i i i i i i i i i i	-103.80	[-260.58;	52.98]	68.0%
	-13.00	[-1303.67; 12	277.67]	1.0%
	96.00	[-3259.82; 34	51.82]	0.1%
				0.0%
				0.0%
				0.0%
	-0.70	[-1770.09; 17	68.69]	0.5%
+	-11.40	[-316.46; 2	93.66]	18.0%
				0.0%
· · · ·	-121.24	[-250.56;	8.08]	100.0%
-4000 -2000 0 2000 40	000			

G			Lonor	accorio			Onen	Maan difference			
	Study	Total	Mean	SD	Total	Mean	SD	mean difference	MD	95%-CI	Weight
	2006 Owera	13	25.00	5.4000	13	21.00	8.1000	÷	4.00	[-1.29; 9.29]	6.7%
	2008 Feldman	18	20.00	5.4000	11	20.00	6.7500		0.00	[-4.70; 4.70]	8.0%
	2011 Jing Zhou	33	22.50	4.8000	29	21.50	4.8000		1.00	[-1.39; 3.39]	16.8%
	2012 Koshenkov Massive	10	19.00	4.0500	7	17.00	6.7500		2.00	[-3.60; 7.60]	6.2%
	2012 Koshenkov Suprammasive	12	25.00	8.1000	14	28.00	24.3000		-3.00	[-16.53; 10.53]	1.3%
	2012 Zhong Wu	18	23.80	3.7000	16	26.30	3.7000		-2.50	[-4.99; -0.01]	16.3%
	2013 Wang Bo	40	22.40	3.0000	40	23.80	3.7000		-1.40	[-2.88; 0.08]	22.1%
	2017 Tsamalaidze	27	33.00	10.8000	47	33.30	20.2500	H	-0.30	[-7.38; 6.78]	4.2%
	2019 Casaccia	25	24.00	3.3000	40	27.90	5.3000		-3.90	[-5.99; -1.81]	18.5%
	Random effects model Heterogeneity: $l^2 = 50\%$, $p = 0.04$	196			217				-0.93	[-2.51; 0.65]	100.0%
								-15 -10 -5 0 5 10 15			

Fig. 2 continued

A		Laparo	scopic			Open		Mean diffe	erence					
Study	Total	Mean	SD	Total	Mean	SD				MD		95%-CI	Weight	
2001 Targarona	36	6.30	3,3000	20	4.00	1,2000		:	-	2.30	[1.1	0: 3.501	19.2%	
2002 Rosen	31	4.20	0.0000	14	5.40				_	-1.20	L	0, 0.00]	0.0%	
2007 Wang Ke Xin	16	5.30	3.8000	20	7 40	1 6000				-2.10	[-4.0	9: -0 111	16.0%	
2012 Xin Wang massive	8	7 90	3 8000	10	7 70	1 7000				0.20	[-2.6	4.3.041	12.6%	
2012 Xin Wang suppremasive	11	7.50	1 8000	10	9 30	2 5000	_			_1.80	[-3.6	8. 0.081	16.5%	
2017 Teamalaidze	27	3 20	1.6300	12	J.00 ⊿ Q∩	3 1400	_			-1.00	[-3.5	8. 0.181	16.5%	
2019 Xiangyu Sun	46	6.70	3.0000	45	6.40	2.8000			-	0.30	[-0.8	9: 1.49]	19.3%	
		0.1.0	0.0000		0.10	210000								
Random effects model	175			131			_		>	0.39	[-1.94	4; 1.16]	100.0%	
Heterogeneity: $I^2 = 80\%$, $p < 0.0^{\circ}$	1						-4	-2 0	2	4				
B							-4	-2 0	2	4				
0		Lana	rosconi			Onen		Moon	difference					
Study	Total	Mean	S) Tota	I Me	an SD		Wearr	umerence		MD		95%-CI	Weight
2001 Targarona	36	177.00	52.000) 20) 135.	00 52.0000			: — • —	4	2.00	[13.58;	70.42]	17.2%
2002 Rosen	31	186.00		. 14	177.	. 00			· _		9.00			0.0%
2007 Wang Ke Xin	16	195.00	71.000) 20) 141.	00 64.0000				- 5	64.00	[9.31;	98.69]	15.9%
2012 Xin Wang massive	8	94.00	19.000) 10) 162.	00 24.0000				-6	68.00	[-87.86;	-48.14]	17.7%
2012 Xin Wang suppramasive	11	146.00	40.000) 10	229.	00 29.0000				-8	3.00	[-112.70:	-53.301	17.1%
2017 Tsamalaidze	27	153.00	70.5800) 12	2 168	00 92.8600			<u></u>	-1	5.00	[-73.90	43,901	14.5%
2019 Xiangyu Sun	46	172.00	43.000) 4	5 141.	00 46.0000				3	1.00	[12.70:	49.301	17.7%
2010 Mangya Can	10		10.000									[12.10,	10.00]	
Random effects model	175			13	1						7.08	[-57.28;	43.12]	100.0%
Heterogeneity: $I^2 = 95\%$, $p < 0.01$	1								1 1					
								-100 -50	0 50	100				
C														
C														
Study	Total	Lapa Mean	roscopio SE	c) Tota	l Mea	an SD		Mean	difference		MD		95%-CI	Weight
														0
2001 Targarona														
-														0.0%
2002 Rosen	31	376.00		. 14	602.0			I.		-2	26.00			0.0% 0.0%
2002 Rosen 2007 Wang Ke Xin	31 16	376.00 138.00	80.000	. 14) 20	602.0 86.0	 00 . 00 45.0000		1		-2	26.00 52.00	[8.12	2; 95.88]	0.0% 0.0% 29.2%
2002 Rosen 2007 Wang Ke Xin 2012 Xin Wang massive	31 16 8	376.00 138.00 63.00	80.0000 26.0000	. 14) 20) 10	602.0 86.0 66.0	 00 . 00 45.0000 00 20.0000				-2	26.00 52.00 -3.00	[8.12 [-24.87	2; 95.88] 7; 18.87]	0.0% 0.0% 29.2% 31.9%
2002 Rosen 2007 Wang Ke Xin 2012 Xin Wang massive 2012 Xin Wang suppramasive	31 16 8 11	376.00 138.00 63.00 113.00	80.0000 26.0000 78.0000	. 14) 20) 10) 10	602.0 86.0 66.0 272.0					-2 -1	26.00 52.00 -3.00 59.00	[8.12 [-24.87 [-247.56	2; 95.88] 7; 18.87] 5; -70.44]	0.0% 0.0% 29.2% 31.9% 21.6%
2002 Rosen 2007 Wang Ke Xin 2012 Xin Wang massive 2012 Xin Wang suppramasive 2017 Tsamalaidze	31 16 8 11 27	376.00 138.00 63.00 113.00 10.00	80.0000 26.0000 78.0000 110.7700	. 14) 20) 10) 10) 12	602.0 86.0 66.0 272.0 2162.0					-2 -1 -1	26.00 52.00 -3.00 59.00 52.00	[8.12 [-24.87 [-247.56 [-325.16	2; 95.88] 7; 18.87] 5; -70.44] 5; 21.16]	0.0% 0.0% 29.2% 31.9% 21.6% 11.0%
2002 Rosen 2007 Wang Ke Xin 2012 Xin Wang massive 2012 Xin Wang suppramasive 2017 Tsamalaidze 2019 Xiangyu Sun	31 16 8 11 27 46	376.00 138.00 63.00 113.00 10.00 230.00	80.0000 26.0000 78.0000 110.7700 823.5000	. 14) 20) 10) 10) 12) 45	602.0 86.0 66.0 272.0 2162.0 5215.0					-2 -1 -1	26.00 52.00 -3.00 59.00 52.00 15.00	[8.12 [-24.87 [-247.56 [-325.16 [-235.71	2; 95.88] 7; 18.87] 5; -70.44] 5; 21.16] ; 265.71]	0.0% 0.0% 29.2% 31.9% 21.6% 11.0% 6.4%
2002 Rosen 2007 Wang Ke Xin 2012 Xin Wang massive 2012 Xin Wang suppramasive 2017 Tsamalaidze 2019 Xiangyu Sun	31 3 16 8 11 27 46 3	376.00 138.00 63.00 113.00 10.00 230.00	80.0000 26.0000 78.0000 110.7700 823.5000	. 12) 20) 10) 10) 12) 45 111	602.0 86.0 66.0 272.0 2162.0 5215.0					-2 -1 -1	26.00 52.00 -3.00 59.00 52.00 15.00	[8.12 [-24.87 [-247.56 [-325.16 [-235.71	2; 95.88] 7; 18.87] 5; -70.44] 5; 21.16] 5; 265.71]	0.0% 0.0% 29.2% 31.9% 21.6% 11.0% 6.4%
2002 Rosen 2007 Wang Ke Xin 2012 Xin Wang massive 2012 Xin Wang suppramasive 2017 Tsamalaidze 2019 Xiangyu Sun Random effects model Heterogeneity: $l^2 = 81\%$, $p < 0.01$	31 3 16 8 11 27 46 3	376.00 138.00 63.00 113.00 10.00 230.00	80.0000 26.0000 78.0000 110.7700 823.5000	. 14) 20) 10) 10) 12) 45 11	602.0 86.0 66.0 272.0 162.0 5215.0			- 		-2 -1 -1 -1	26.00 52.00 -3.00 59.00 52.00 15.00 35.94	[8.12 [-24.87 [-247.56 [-325.16 [-235.71 [-106.31	2; 95.88] 7; 18.87] 5; -70.44] 5; 21.16] 5; 265.71] ; 34.44]	0.0% 0.0% 29.2% 31.9% 21.6% 11.0% 6.4%
2002 Rosen 2007 Wang Ke Xin 2012 Xin Wang massive 2012 Xin Wang suppramasive 2017 Tsamalaidze 2019 Xiangyu Sun Random effects model Heterogeneity: <i>I</i> ² = 81%, <i>p</i> < 0.01	31 : 16 8 11 27 46 : 139	376.00 138.00 63.00 113.00 10.00 230.00	80.0000 26.0000 78.0000 110.7700 823.5000	. 14 0 20 0 10 0 10 0 12 0 45 11 1	602.0 86.0 66.0 272.0 162.0 5 215.0			-300 -200 -100	0 100 20	-2 -1 -1 -1 0 300	26.00 52.00 -3.00 59.00 52.00 15.00 35.94	[8.12 [-24.87 [-247.56 [-325.16 [-235.71 [-106.31	2; 95.88] 7; 18.87] 6; -70.44] 6; 21.16] 7; 265.71] 7; 34.44]	0.0% 0.0% 29.2% 31.9% 21.6% 11.0% 6.4% 100.0%
2002 Rosen 2007 Wang Ke Xin 2012 Xin Wang massive 2012 Xin Wang suppramasive 2017 Tsamalaidze 2019 Xiangyu Sun Random effects model Heterogeneity: <i>I</i> ² = 81%, <i>p</i> < 0.01	31 : 16 8 11 27 46 2 139	376.00 138.00 63.00 113.00 10.00 230.00	80.0000 26.0000 78.0000 110.7700 823.5000	. 14 0 20 0 10 0 10 0 12 0 45 11 1	602.0 86.0 66.0 272.0 162.0 215.0	00 45.0000 00 45.0000 00 20.0000 01 122.0000 00 297.0000 00 270.0000		-300 -200 -100	0 100 20	-2 -1 -1 -1 -1 0 300	26.00 52.00 -3.00 59.00 52.00 15.00 35.94	[8.12 [-24.87 [-247.56 [-325.16 [-235.71 [-106.31	2; 95.88] 7; 18.87] 5; -70.44] 5; 21.16] ; 265.71] ; 34.44]	0.0% 0.0% 29.2% 31.9% 21.6% 11.0% 6.4%
2002 Rosen 2007 Wang Ke Xin 2012 Xin Wang massive 2012 Xin Wang suppramasive 2017 Tsamalaidze 2019 Xiangyu Sun Random effects model Heterogeneity: / ² = 81%, <i>p</i> < 0.01	31 16 8 11 27 46 139	376.00 138.00 63.00 113.00 10.00 230.00	80.0000 26.0000 78.0000 110.7700 823.5000	. 14 0 20 0 10 0 10 0 12 0 45 11 1	602.0 86.0 66.0 272.0 215.0 C	00 45.0000 00 20.0000 00 122.0000 00 297.0000 00 270.0000			0 100 20	-2 -1 -1 -1 -1 0 300	26.00 52.00 -3.00 59.00 52.00 15.00 35.94	[8.12 [-24.87 [-247.56 [-325.16 [-235.71 [-106.31	2; 95.88] 7; 18.87] 5; -70.44] 5; 21.16] ; 265.71] ; 34.44]	0.0% 0.0% 29.2% 31.9% 21.6% 11.0% 6.4%
2002 Rosen 2007 Wang Ke Xin 2012 Xin Wang massive 2012 Xin Wang suppramasive 2017 Tsamalaidze 2019 Xiangyu Sun Random effects model Heterogeneity: / ² = 81%, p < 0.01 D Study	31 : 16 : 8 : 11 : 27 : 46 : 139	376.00 138.00 63.00 113.00 230.00 230.00	80.0000 26.0000 78.0000 110.7700 823.5000	. 14 0 20 0 10 0 10 0 12 0 45 111	602.0 602.0 66.0 272.0 2162.0 215.0 C nts 1	00 45.0000 00 20.0000 00 122.0000 00 297.0000 00 270.0000		-300-200-100	0 100 20	-2 -1 -1 0 300	26.00 52.00 -3.00 59.00 52.00 15.00 35.94	[8.12 [-24.87 [-247.56 [-325.16 [-235.71 [-106.31	2; 95.88] 7; 18.87] 5; -70.44] 5; 21.16] 5; 265.71] 7; 34.44]	0.0% 0.0% 29.2% 31.9% 21.6% 11.0% 6.4% 100.0%
2002 Rosen 2007 Wang Ke Xin 2012 Xin Wang massive 2012 Xin Wang suppramasive 2017 Tsamalaidze 2019 Xiangyu Sun Random effects model Heterogeneity: / ² = 81%, p < 0.01 D Study 2001 Targarona	31 : 16 : 8 : 11 : 27 : 46 : 139	138.00 63.00 113.00 10.00 230.00	80.0000 26.0000 78.0000 110.7700 823.5000 s Copic s Tota 3 36	. 14 0 20 0 10 0 10 0 12 0 45 111	602.0 602.0 66.0 272.0 2162.0 5215.0 C nts 1 2	00 45.0000 00 20.0000 00 122.0000 00 297.0000 00 270.0000 00 270.0000		-300 -200 -100	0 100 20	-2 -1 -1 0 300	26.00 52.00 -3.00 59.00 52.00 15.00 35.94 OR 5.09	[8.12 [-24.87 [-247.56 [-325.16 [-235.71 [-106.31	2; 95.88] 3; 18.87] 3; -70.44] 3; 21.16] 3; 265.71] 34.44] 95%-CI 25.49]	0.0% 0.0% 29.2% 31.9% 21.6% 11.0% 6.4% 100.0% Weight 14.9%
2002 Rosen 2007 Wang Ke Xin 2012 Xin Wang massive 2012 Xin Wang suppramasive 2017 Tsamalaidze 2019 Xiangyu Sun Random effects model Heterogeneity: / ² = 81%, p < 0.01 D Study 2001 Targarona 2002 Rosen	31 : 16 : 27 : 46 : 139	376.00 138.00 63.00 113.00 230.00 230.00	80.0000 26.0000 78.0000 110.7700 823.5000 s Tota 3 36 6 31	. 14 0 20 0 10 0 10 0 12 0 45 111	602.0 602.0 86.0 272.0 215.0 Conts 1 2 5	00 45.0000 00 45.0000 00 122.0000 00 122.0000 00 297.0000 00 270.0000 00 270.0000		-300-200-100	0 100 20	-2 -1 -1 -1 0 300	26.00 52.00 -3.00 59.00 52.00 15.00 35.94 OR 5.09 0.43	[8.12 [-24.87] [-247.56 [-325.16 [-235.71 [-106.31] [-106.31] [-100.31]	2; 95.88] 5; 18.87] 5; -70.44] 5; 21.16] 5; 265.71] 7; 34.44] 95%-CI 25.49] 1 77]	0.0% 0.0% 29.2% 21.6% 11.0% 6.4% 100.0% Weight 14.9% 17.3%
2002 Rosen 2007 Wang Ke Xin 2012 Xin Wang massive 2012 Xin Wang suppramasive 2017 Tsamalaidze 2019 Xiangyu Sun Random effects model Heterogeneity: <i>I</i> ² = 81%, <i>p</i> < 0.01 D Study 2001 Targarona 2002 Rosen 2002 Rosen	31 : 16 : 11 : 27 : 46 : 139	138.00 63.00 113.00 10.00 230.00	80.0000 26.0000 78.0000 110.7700 823.5000 s Tota 3 36 6 31	12 20 10 10 10 10 12 111 111	602.0 602.0 86.0 272.0 215.0 Conts 1 2 5 2	00 500 500 500 500 500 500 500 500 500			0 100 20	-2 -1 -1 -1 0 300	26.00 52.00 59.00 52.00 15.00 35.94 OR 5.09 0.43	[8.12 [-24.87 [-247.56 [-325.16 [-235.71 [-106.31 [-106.31	2; 95.88] 3; 18.87] 3; -70.44] 3; 21.16] 3; 265.71] 34.44] 95%-CI 25.49] 1.77] 57.403	0.0% 0.0% 29.2% 31.9% 21.6% 11.0% 6.4% 100.0% Weight 14.9% 17.3%
2002 Rosen 2007 Wang Ke Xin 2012 Xin Wang massive 2012 Xin Wang suppramasive 2017 Tsamalaidze 2019 Xiangyu Sun Random effects model Heterogeneity: <i>I</i> ² = 81%, <i>p</i> < 0.01 D Study 2001 Targarona 2002 Rosen 2007 Wang Ke Xin	31 3 8 11 27 46 3 139	138.00 63.00 113.00 10.00 230.00	80.0000 26.0000 78.0000 110.7700 823.5000 s Tota 3 36 6 31 2 16	. 12 0 20 0 10 0 10 0 12 0 45 111	602.0 86.0 272.0 272.0 272.0 215.0 C nts 1 2 5 0	00 45.0000 00 20.0000 00 122.0000 00 297.0000 00 270.0000 00 270.0000 00 270.0000 00 270.0000			0 100 20	-2 -1 -1 -0 0 300	26.00 52.00 -3.00 59.00 52.00 15.00 35.94 OR 5.09 0.43 7.07	[8.12 [-24.87 [-247.56 [-325.16 [-235.71 [-106.31 [-106.31 [1.02 ; [0.11; [0.32; 1	2; 95.88] 7; 18.87] 5; -70.44] 5; 21.16] 5; 265.71] 7; 34.44] 9 5%-CI 25.49] 1.77] 58.49]	0.0% 0.0% 29.2% 31.9% 21.6% 11.0% 6.4% 100.0% Weight 14.9% 17.3% 5.8%
2002 Rosen 2007 Wang Ke Xin 2012 Xin Wang massive 2012 Xin Wang suppramasive 2017 Tsamalaidze 2019 Xiangyu Sun Random effects model Heterogeneity: / ² = 81%, p < 0.01 D Study 2001 Targarona 2002 Rosen 2007 Wang Ke Xin 2012 Xin Wang massive	31 : 16 : 8 : 11 : 27 : 46 : 139	138.00 63.00 113.00 10.00 230.00	80.0000 26.0000 78.0000 110.7700 823.5000 s Tota 3 36 6 31 2 16 1 8	. 14 0 20 0 10 0 10 0 12 0 45 111	602.0 602.0 60.0 272.0 2162.0 215.0 C nts 1 2 5 0 2	00 45.0000 00 122.0000 00 122.0000 00 297.0000 00 270.0000 00 270.0000 00 270.0000 00 270.0000 00 112 00 122.0000 00 297.0000 00 270.0000 00 200 00 200		-300-200-100	0 100 20	-2 -1 -1 -1 0 300	26.00 52.00 -3.00 59.00 15.00 35.94 OR 5.09 0.43 7.07 0.57	[8.12 [-24.87 [-247.56 [-325.16 [-235.71 [-106.31] [-106.31] [.1.02; [0.11; [0.32; 1 [0.32; 1 [0.04;	2; 95.88 7; 18.87 7; 70.44 3; 21.16 3; 265.71 34.44 95%-CI 25.49 1.77 58.49 7.74	0.0% 0.0% 29.2% 31.9% 21.6% 11.0% 6.4% 100.0% Weight 14.9% 17.3% 5.8% 7.7%
2002 Rosen 2007 Wang Ke Xin 2012 Xin Wang massive 2012 Xin Wang suppramasive 2017 Tsamalaidze 2019 Xiangyu Sun Random effects model Heterogeneity: / ² = 81%, p < 0.01 D Study 2001 Targarona 2002 Rosen 2007 Wang Ke Xin 2012 Xin Wang massive 2012 Xin Wang supprama	31 16 8 11 27 46 139	138.00 63.00 113.00 10.00 230.00	80.0000 26.0000 78.0000 110.7700 823.5000 s Tota 3 36 6 31 2 16 1 8 3 11	. 14) 20) 10) 10) 12) 45 111 ; I Eve	602.0 60	00 500 00 45.0000 00 122.0000 00 122.0000 00 297.0000 00 270.0000 00 270.0000 00 270.0000 00 270.0000 00 270.0000 00 270.0000 00 270.0000 00 20000 00 2000 00 2000 00 2000 00 2000 00 2000 00 200 00 200		-300 -200 -100	0 100 20	-2 -1 -1 -1 0 300	26.00 52.00 59.00 55.00 15.00 35.94 OR 5.09 0.43 7.07 0.57 0.16	[8.12 [-24.87 [-247.56 [-325.16 [-235.71 [-106.31 [-106.31 [.1.02; [0.11; [0.32; 1 [0.32; 1 [0.04; [0.02:	2; 95.88] 3; 18.87] 5; 21.16] 5; 265.71] 7; 34.44] 95%-CI 25.49] 1.77] 58.49] 7.74] 1.071	0.0% 0.0% 29.2% 31.9% 21.6% 11.0% 6.4% 100.0% Weight 14.9% 17.3% 5.8% 7.7% 12.2%
2002 Rosen 2007 Wang Ke Xin 2012 Xin Wang suppramasive 2012 Xin Wang suppramasive 2017 Tsamalaidze 2019 Xiangyu Sun Random effects model Heterogeneity: / ² = 81%, p < 0.01 D Study 2001 Targarona 2002 Rosen 2002 Rosen 2007 Wang Ke Xin 2012 Xin Wang massive 2012 Xin Wang supprama 2017 Tsamalaidze	31 16 8 11 27 46 139	138.00 63.00 113.00 10.00 230.00	80.0000 26.0000 78.0000 110.7700 823.5000 s Tota 3 36 6 31 2 16 1 8 3 11 9 27	14 14 10 10 10 10 11 111 111 11	602.0 602.0 602.0 602.0 20	00 500 00 45.0000 00 20.0000 00 122.0000 00 297.0000 00 270.0000 00 270.0000 00 270.0000 00 212.0000 00 122.0000 00 120.0000 00 120.00000 00 120.0000 00 120.0000 00 120.0000 00 120.0000		-300-200-100	0 100 20	-2 -1 -1 -1 0 300	26.00 52.00 59.00 59.00 15.00 35.94 OR 5.09 0.43 7.07 0.57 0.16 0.70	[8.12 [-24.87 [-247.56 [-235.10 [-235.71 [-106.31] [-106.31] [-106.31] [0.11; [0.11; [0.32; 1] [0.32; 1] [0.04; [0.02; [0.17]	2; 95.88] 3; 18.87] 3; -70.44] 5; 21.16] 5; 265.71] 34.44] 95%-CI 25.49] 1.77] 58.49] 7.74] 1.07] 2.841	0.0% 0.0% 29.2% 21.6% 11.0% 6.4% 100.0% Weight 14.9% 17.3% 5.8% 7.7% 12.2% 17.4%
2002 Rosen 2007 Wang Ke Xin 2012 Xin Wang massive 2012 Xin Wang suppramasive 2017 Tsamalaidze 2019 Xiangyu Sun Random effects model Heterogeneity: <i>I</i> ² = 81%, <i>p</i> < 0.01 D Study 2001 Targarona 2002 Rosen 2007 Wang Ke Xin 2012 Xin Wang massive 2012 Xin Wang supprama 2017 Tsamalaidze 2019 Xiangwu Sun	31 16 8 11 27 46 139		80.0000 26.0000 78.0000 110.7700 823.5000 5 Tota 3 36 6 31 2 16 1 8 3 11 9 27 2 46	14 14 12 10 10 11 11 11 11 11 11 11 11	602.(.) 86.(.) 272.(.) 272.(.) 2162.(.) 2162.(.) 215.(.) C T 5 2 5 2 1 2 5 2 1 5 1 2 5 1 5 2 1 5 1 5 1 5 1 5 1 1 5 1 1	00 45.0000 00 45.0000 00 122.0000 00 297.0000 00 270.0000 00 270.0000 00 270.0000 00 212.0000 00 227.0000 00 212.0000 00 20.0000 00 227.0000 00 212.0000 00 210.0000 00 2000 00 20000 00 2000 00 2000 00 20000 00 20000 00 2000 00 200		-300-200-100 C	0 100 20	-2 -1 -1 -1 0 300	26.00 52.00 -3.00 55.00 15.00 35.94 OR 5.09 0.43 7.07 0.16 0.70 0.71	[8.12 [-24.87 [-247.56 [-325.10 [-235.71 [-106.31 [-106.31 [-106.31 [-106.31 [-106.31 [-106.31 [-106.31 [-106.31] [-106.31 [-106.31] [-106.31] [-106.31]	2; 95.88] 3; 18.87] 3; -70.44] 5; 21.16] 5; 265.71] 34.44] 95%-CI 25.49] 1.77] 58.49] 7.74] 1.07] 2.84] 1.74]	0.0% 0.0% 29.2% 21.6% 11.0% 6.4% 100.0% Weight 14.9% 17.3% 5.8% 7.7% 12.2% 17.4% 24.7°
2002 Rosen 2007 Wang Ke Xin 2012 Xin Wang suppramasive 2012 Xin Wang suppramasive 2017 Tsamalaidze 2019 Xiangyu Sun Random effects model Heterogeneity: / ² = 81%, p < 0.01 D Study 2001 Targarona 2002 Rosen 2002 Rosen 2007 Wang Ke Xin 2012 Xin Wang massive 2012 Xin Wang supprama 2017 Tsamalaidze 2019 Xiangyu Sun	31 16 8 11 27 46 139		80.0000 26.0000 78.0000 110.7700 823.5000 s Tota 3 36 6 31 2 16 1 8 3 11 9 27 2 46	14 14 10 10 10 10 11 111 111 11	602.() 602.()	00 500 00 45.0000 00 122.0000 00 122.0000 00 297.0000 00 270.0000 00 270.0000 00 270.0000 00 212.0000 00 212.0000 00 212.0000 00 212.0000 00 212.0000 00 212.0000 00 297.0000 00 212.0000 00 297.0000 00 212.0000 00 297.0000 00 212.0000 00 297.0000 00 20 20 20 20 20 20 20 20 20 20 20 20 2		-300-200-100 C	0 100 20	-2 -1 -1 -1 0 300	26.00 52.00 -3.00 52.00 15.00 35.94 OR 5.09 0.43 7.07 0.16 0.70 0.71	[8.12 [-24.87 [-247.56 [-325.16 [-235.71 [-106.31 [-106.31 [.102; [0.11; [0.32; 1 [0.32; 1 [0.02; [0.17; [0.29;	2; 95.88] 3; 18.87] 3; -70.44] 5; 21.16] 5; 265.71] 7; 34.44] 25%-CI 25.49] 1.77] 58.49] 7.74] 1.07] 2.84] 1.74]	0.0% 0.0% 29.2% 31.9% 21.6% 11.0% 6.4% 100.0% Weight 14.9% 17.3% 5.8% 7.7% 12.2% 17.4% 24.7%
2002 Rosen 2007 Wang Ke Xin 2012 Xin Wang suppramasive 2012 Xin Wang suppramasive 2017 Tsamalaidze 2019 Xiangyu Sun Random effects model Heterogeneity: I ² = 81%, p < 0.01 D Study 2001 Targarona 2002 Rosen 2007 Wang Ke Xin 2012 Xin Wang massive 2012 Xin Wang supprama 2017 Tsamalaidze 2019 Xiangyu Sun Random effects model	31 16 8 11 27 46 139	376.00 138.00 63.00 113.00 10.00 230.00 _aparc Event 1	80.0000 26.0000 78.0000 110.7700 823.5000 s Tota 3 36 6 31 2 16 1 6 3 11 9 27 2 46 175	14 12 12 12 10 11 11 11 11 11 11 11 11 11	602.0 602.0 66.0 272.0 2162.0 215.0 C T 2 5 0 2 7 5 15	200 45.0000 20.0000 20.0000 297.0000 297.0000 270.00000 270.00000 270.00000 270.00000 2			0 100 20	-2 -1 -1 -1 0 300	26.00 52.00 59.00 59.00 52.00 15.00 35.94 OR 5.09 0.43 7.07 0.57 0.16 0.70 0.71 0.82	[8.12 [-24.87 [-247.56 [-325.16 [-235.71 [-106.31 [-106.31 [-100; [0.11; [0.32; 1 [0.04; [0.02; [0.17; [0.29; [0.36;]	2; 95.88] 3; 18.87] 5; -70.44] 5; 21.16] 5; 265.71] 7; 34.44] 25.49] 1.77] 58.49] 7.74] 1.07] 2.84] 1.74] 1.85]	0.0% 0.0% 29.2% 31.9% 21.6% 11.0% 6.4% 100.0% Weight 14.9% 17.3% 5.8% 7.7% 12.2% 17.4% 24.7%
2002 Rosen 2007 Wang Ke Xin 2012 Xin Wang massive 2012 Xin Wang suppramasive 2017 Tsamalaidze 2019 Xiangyu Sun Random effects model Heterogeneity: / ² = 81%, p < 0.01 D Study 2001 Targarona 2002 Rosen 2007 Wang Ke Xin 2012 Xin Wang massive 2012 Xin Wang supprama 2017 Tsamalaidze 2019 Xiangyu Sun Random effects model Heterogeneity: / ² = 43%, p	31 16 8 11 27 46 139 L assive = 0.10	376.00 138.00 63.00 113.00 10.00 230.00 _aparc Event 1	80.0000 26.0000 78.0000 110.7700 823.5000 pscopic s Tota 3 36 6 31 2 16 1 6 3 11 9 27 2 46 175	14 14 10 10 10 10 11 111 111 11	602.0 602.0 66.0 272.0 2162.0 162.0 175.0 0 2 7 5 15	200 45.0000 20.0000 20.0000 297.0000 270.00000 270.00000 270.00000 270.00000 2		-300 -200 -100	0 100 20	-2 -1 -1 -1 0 300	26.00 52.00 59.00 59.00 52.00 15.00 35.94 OR 5.09 0.43 7.07 0.57 0.16 0.70 0.71 0.82	[8.12 [-24.87 [-247.56 [-325.16 [-235.71 [-106.31] [-106.31] [0.11; [0.12; [0.11; [0.32; 1 [0.32; 1 [0.32; 1 [0.29; [0.17; [0.29; [0.36;	; 95.88] ; 18.87] ; -70.44] ; 21.16] ; 265.71] ; 34.44] 25.49] 1.77] 58.49] 1.77] 2.849] 1.07] 2.849] 1.74] 1.85]	0.0% 0.0% 29.2% 31.9% 21.6% 11.0% 6.4% 100.0% Weight 14.9% 17.3% 5.8% 7.7% 12.2% 17.4% 24.7%
2002 Rosen 2007 Wang Ke Xin 2012 Xin Wang suppramasive 2012 Xin Wang suppramasive 2017 Tsamalaidze 2019 Xiangyu Sun Random effects model Heterogeneity: / ² = 81%, p < 0.01 D Study 2001 Targarona 2002 Rosen 2007 Wang Ke Xin 2012 Xin Wang massive 2012 Xin Wang supprama 2017 Tsamalaidze 2019 Xiangyu Sun Random effects model Heterogeneity: / ² = 43%, p =	31 16 8 11 27 46 139 L assive = 0.10	138.00 63.00 113.00 10.00 230.00	80.0000 26.0000 78.0000 110.7700 823.5000 s Tota 3 36 6 31 2 16 1 8 3 11 9 27 2 46 175	14 14 10 10 10 10 11 111 111 11	602.0 602.0 66.0 272.0 2162.0 215.0 C T 2 5 215.0 2 7 5 15	00 500 00 45.0000 00 122.0000 00 122.0000 00 297.0000 00 270.0000 00 270.0000 00 270.0000 00 122 14 20 10 10 12 45 131	0.01	-300-200-100 C	0 100 20 PR	-2 -1 -1 0 300	26.00 52.00 59.00 59.00 52.00 15.00 35.94 OR 5.09 0.43 7.07 0.16 0.70 0.71 0.71 0.82	[8.12 [-24.87 [-247.56 [-325.16 [-235.71 [-106.31 [-106.31 [-106.31 [-102; [0.11; [0.32; 1 [0.32; 1 [0.32; 1 [0.32; [0.17; [0.29; [0.36;	2; 95.88] 3; 18.87] 5; 21.16] 5; 265.71] 7; 34.44] 95%-Cl 25.49] 1.77] 58.49] 7.74] 1.07] 2.84] 1.74] 1.85]	0.0% 0.0% 29.2% 31.9% 21.6% 11.0% 6.4% 100.0% Weight 14.9% 17.3% 5.8% 7.7% 12.2% 17.4% 24.7%

Fig. 3 Meta-analysis of secondary aim. HALS versus LS. a Length of hospital stay, b operative time, c excess blood loss, d mortality, e conversion, f complications, g spleen weight, h spleen size

splenomegaly and prior abdominal operation [32]. It should also be noted that Huang et al. meta-analysis was conducted mainly in diseases that conferred portal hypertension, such as hepatitis B and C viral infection and clinical situation that are less prevalent in Western countries and preclude definitive comparison with our study.

When OS was compared with HALS, HALS showed the obvious clinical advantages.

F																		
–	Laparo	oscopic	_	Ope	n		C	R										
Study	Event	s Total	Events	Tota	al						OR	ç	95%-CI	Weight				
2001 Targarona		7 36	1	2	0		_				4 59	[0 52:	40 321	22.7%				
2002 Rosen		7 31	. 1	1	4		_	1			3.79	[0.42]	34.26]	22.2%				
2007 Wang Ke Xin		4 16	0	2	0			+ -		— 1·	4.76	[0.73; 2	298.01	11.9%				
2012 Xin Wang massive		0 8	0	1	0									0.0%				
2012 Xin Wang suppramasive		0 11	0	1	0									0.0%				
2017 Tsamalaidze		3 27	1	1	2				-		1.38	[0.13;	14.75]	19.1%				
2019 Xiangyu Sun		9 46	1	4	5					- 1	0.70	[1.30;	88.43]	24.1%				
Pandom offects model		175		13	1						1 02	[1 75.	13 801	100.0%				
Heterogeneity: $I^2 = 0\%$, $p = 0.70$		175		15	•			\vdash		л [.]	4.52	[1.75,	10.00]	100.070				
						0.01	0.1	1 10	0 1	00								
_																		
F																		
Lap	arosco	pic	HAI	LS			D-fi-		~ ~									
Study Eve	ents I	otal EV	ents lo	tai		Udds	Ratio		OR		5%- (U We	ignt					
Xi angvu sun	12	46	15	45			+		0.71	[0.29	: 1.7	41 38	.8%					
Rosen	6	31	5	14			<u> </u>		0.43	0.11	1.7	7 16	.0%					
Targarona	13	36	2	20			-	- :	5.09	[1.02;	25.4	9] 12	.2%					
Tsamaliadze	9	27	5	12			<u> </u>	(0.70	[0.17	; 2.8	4] 16	.2%					
Wang Ke- Xin	2	16	0	20					7.07	[0.32;	158.4	9] 3	.3%					
Xin Wang massive	1	8	2	10		-			0.57	[0.04	; 1.1	4j 4	.1%					
Xin wang suppramasive	3	11	1	10			Ī		0.16	[0.02	; 1.0	/] 8	.8%					
Fixed effect model		175	1	31		-	Ļ		0.78	[0.44:	1.3	71 100.	.0%					
Heterogeneity: $I^2 = 43\%$, $\tau^2 = 0$.4925, p	o = 0.10					I I			•		•						
				0.0	01 0.	1 .	1 10	100										
G																		
6		Lan	aroscon	ic						Moo	n diff	oronco						
Study	Total	Mear	n S	SD T	otal M	l ean	SD			Weat	ii uine	erence		MD		95%-	cı w	/eiaht
,																		g
2001 Targarona	36	1425.00	884.00	00	20 175	53.00 1	124.0000				\vdash			-328.00	[-899.0)1; 243.0)1] 3	34.6%
2002 Rosen	31				14													0.0%
2007 Wang Ke Xin	16	1185.00	536.00	00	20 134	16.00	735.0000							-161.00	-576.6	52; 254.6	62] 6	65.4%
2012 Xin Wang massive				·	•	•												0.0%
2012 Ain wang suppramasive	•			•	•	•												0.0%
2019 Xiangyu Sun	•			•	•	•												0.0%
2019 Xiangyu Gun	•			•	•	•												0.070
Fixed effect model	83				54						-	-	-	-218.84 [-554.8	7; 117.2	0] 10	00.0%
Heterogeneity: $I^2 = 0\%$, $p = 0.64$										500	1	5	1					
										-500	0	5	00					
Н																		
Studie	т		arosco	pic			HALS			Mea	n diff	erenc	e				14/-	
Study	10		an	30		lean	30							ND	:	5%-CI	we	ignt
2001 Targarona		36 25	.00 5.00	000	20 2	6.00	8.0000							-1.00	[-4.87	7: 2.871	3	.9%
2002 Rosen		00 20	.00 0.00	/00	20 2	.0.00	0.0000					1		1.00	[1.07	, 2.07]	ő	.0%
2007 Wang Ke Xin		. 16 24			20.2	. 00 7	7 0000					Ļ		-3.00	I_6 Q2	8· 0 031	3	8%
2007 Wang Ke Xin		8 21		000	10 2		1 0000				L	i		1 00	[-0.07	7. 1 Q31	67	.070 6%
2012 Xin Wang suppramas	ivo	11 32		000	10 2		3 0000				L			_ 1.00	10.01	, 1.90j) 8 001	2	.0 /0 6%
2012 All Wally Supplainas	IVE	27 24		200	10 2	0.00	4 0000			_				4.00	122	7, 0.00j 1. 2 241	7	.0 /0
		46 22	20 3.92	200	12 2	3.70	4.0000 5.4000					1		0.50	[-2.24	+, 3.24j): 1 201	12	.0%
2019 Alangyu Suli		40 22	.70 4.80	000	40 2	.5.50	0.4000				-	1		-0.00	[-2.90	, 1.30]	13	.2 /0
Fixed effect model	1	144			117									0 60	r_0 16	• 1 371	100	0%
Heterogeneity: $I^2 = 45\%$, $p = 1$	0 1 1								1			-		0.00	1-0.10	,		
- + 0.00, p =	0.11								-	5	0		5					
									_	-	0		ĩ					
Fig. 3 continued																		

Robotic-assisted surgery has also been proposed in splenic surgery [33, 34], but data are scarce regarding the use of this technique in the case of splenomegaly. We found only one study that compared this approach with LS [28].

Some studies report splenomegaly according to the preoperative diameter. This is an objective measure that

may help to predict the outcome, but most studies report the postoperative spleen weight, which is an outcome result, and not available preoperatively. The EAES consensus thus recommends using the preoperative size rather than the postoperative weight. However, we found that spleen weight was the most commonly reported variable to define splenomegaly in most of the studies.



The main strength of this study is that it is the first metaanalysis to date to analyze LS in splenomegaly and compare it to classical OS. Furthermore, it analyzes other minimal invasive techniques such as HALS as secondary aims. The study also has several limitations. Most studies were graded as high quality according to NOS, but the majority were retrospective observational studies. There were only four prospective cohorts and few RCTs. An additional limitation is the lack of a standardized definition of splenomegaly (size versus weight). We found great heterogeneity in splenomegaly grading and definition.

Despite our efforts to perform a subanalysis with a clear cutoff regarding values of weight or size, we were unable to achieve this due to the lack of standardized terminology and the different cutoff measures used in each study. Moreover, to assure comparability between groups either by weight or spleen size, we conducted an individual metaanalysis for these two variables. We found no statistical difference in LS versus OS or in LS versus HALS groups. An additional weak point was the difficulty in analyzing the outcomes according to the intention-to-treat principle. This subanalysis would help us better understand the outcome of cases operated purely by a minimally invasive technique and assess the additional impact of conversion to open surgery.

In conclusion, the data obtained from this meta-analysis provide an overview regarding the safety and feasibility of surgical strategies for the treatment of splenomegaly. After analyzing pooled results, we conclude that LS may be performed safely and has advantages over OS in the case of splenomegaly, despite a longer operative time. HALS shows superiority to LS, with a lower conversion rate and a clear reduction in surgical difficulty. Authors should use terminology and stratification in accordance with current guidelines in order to facilitate data synthesis. Future prospective randomized studies with standardized spleen size report are warranted to obtain stronger evidence.

Acknowledgements Authors would like to acknowledge Victor Galindo De la Cruz for his valuable and constructive suggestions during the development of this research work, Carolyn Newey for English proofreading and review, and Mickaël Schaeffer for the statistical analysis.

Authors' contribution All the authors have participated in the design, data collection and interpretation, and drafting and revising of this manuscript.

Funding There are no sources of support to be reported (from any of the following organizations: National Institutes of Health (NIH); Wellcome Trust; Howard Hughes Medical Institute (HHMI); or others), and no grants were received for the present work.

Compliance with ethical standards

Conflict of interest Drs Rodriguez-Luna R, Balagué C, Fernández-Ananín S, Vilallonga R, and Targarona Soler E. have no conflicts of interest or financial ties to disclose.

References

- Altaf AMS, Sawatzky M, Ellsmere J et al (2009) Laparoscopic accessory splenectomy: the value of perioperative localization studies. Surg Endosc 23:2675–2679. https://doi.org/10.1007/ s00464-008-0258-5
- Lemaire J, Rosière A, Bertrand C et al (2017) Surgery for massive splenomegaly. BJS Open 1:11–17. https://doi.org/10.1002/ bjs5.1
- Delaitre B, Maignien B (1992) Surgical workshop laparoscopic splenectomy. Br J Surg 79:1334
- Grahn SW, Alvarez J (2006) Trends in laparoscopic splenectomy for massive splenomegaly. Arch Surg 141:755. https://doi.org/10. 1001/archsurg.141.8.755
- Koshenkov VP, Németh ZH, Carter MS (2012) Laparoscopic splenectomy: outcome and efficacy for massive and supramassive spleens. Am J Surg 203:517–522. https://doi.org/10.1016/j.amj surg.2011.05.014
- Patel AG, Parker JE, Wallwork B et al (2003) Massive splenomegaly is associated with significant morbidity after laparoscopic splenectomy. Ann Surg 238:235–240. https://doi.org/10.1097/01. sla.0000080826.97026.d8
- Habermalz B, Sauerland S, Decker G et al (2008) Laparoscopic splenectomy: the clinical practice guidelines of the European Association for Endoscopic Surgery (EAES). Surg Endosc Other Interv Tech 22:821–848. https://doi.org/10.1007/s00464-007-9735-5
- Tsamalaidze L, Stauffer JA, Permenter SL, Asbun HJ (2017) Laparoscopic splenectomy for massive splenomegaly: does size matter? J Laparoendosc Adv Surg Tech 27:1009–1014. https:// doi.org/10.1089/lap.2017.0384
- 9. Moher D, Liberati A, Tetzlaff J, Altman DG (2009) Preferred reporting items for systematic reviews and meta-analyses: the

PRISMA statement. BMJ 339:332–336. https://doi.org/10.1136/ bmj.b2535

- Wells G, Shea B, O'Connell D The Newcastle–Ottawa Scale (NOS) for assessing the quality of non randomised studies in metaanalyses.
- Higgins JPT, Altman DG, Gøtzsche PC et al (2011) The Cochrane tool for assessing risk of bias in randomised trials. BMJ 343:1–9. https://doi.org/10.1136/bmj.d5928
- Terrosu G, Donini A, Baccarani U et al (1998) Laparoscopic versus open splenectomy in the management of splenomegaly: our preliminary experience. Surgery 124:839–843. https://doi. org/10.1016/S0039-6060(98)70006-6
- Targarona EM, Espert JJ, Cerdán G et al (1999) Effect of spleen size on splenectomy outcome. Surg Endosc 13:559–562. https:// doi.org/10.1007/s004649901040
- Boddy AP, Mahon D, Rhodes M (2006) Does open surgery continue to have a role in elective splenectomy? Surg Endosc 20:1094–1098. https://doi.org/10.1007/s00464-005-0523-9
- Owera A, Hamade AM, Bani Hani OI, Ammori BJ (2006) Laparoscopic versus open splenectomy for massive splenomegaly: a comparative study. J Laparoendosc Adv Surg Tech 16:241–246. https://doi.org/10.1089/lap.2006.16.241
- Feldman LS, Demyttenaere SV, Polyhronopoulos GN, Fried GM (2008) Refining the selection criteria for laparoscopic versus open splenectomy for splenomegaly. J Laparoendosc Adv Surg Tech 18:13–19. https://doi.org/10.1089/lap.2007.0050
- Zhou J, Wu Z, Cai Y et al (2011) The feasibility and safety of laparoscopic splenectomy for massive splenomegaly: a comparative study. J Surg Res 171:e55–e60. https://doi.org/10.1016/j.jss. 2011.06.040
- Wu Z, Zhou J, Pankaj P, Peng B (2012) Laparoscopic and open splenectomy for splenomegaly secondary to liver cirrhosis: an evaluation of immunity. Surg Endosc 26:3557–3564. https://doi. org/10.1007/s00464-012-2366-5
- Bo W, He-Shui W, Guo-Bin W, Kai-Xiong T (2013) Laparoscopy splenectomy for massive splenomegaly. J Invest Surg 26:154–157. https://doi.org/10.3109/08941939.2012.691604
- Shin RD, Lis R, Levergood NR et al (2019) Laparoscopic versus open splenectomy for splenomegaly: the verdict is unclear. Surg Endosc 33:1298–1303. https://doi.org/10.1007/s00464-018-6394-7
- Casaccia M, Sormani MP, Palombo D et al (2019) Laparoscopic splenectomy versus open splenectomy in massive and giant spleens: should we update the 2008 EAES guidelines? Surg Laparosc Endosc Percutaneous Tech 29:178–181. https://doi.org/ 10.1097/SLE.00000000000637
- 22. Swanson TW, Meneghetti AT, Sampath S et al (2011) Handassisted laparoscopic splenectomy versus open splenectomy for massive splenomegaly: 20-Year experience at a Canadian centre. Can J Surg 54:189–193. https://doi.org/10.1503/cjs.044109
- Barbaros U, Dinççağ A, Sümer A et al (2010) Prospective randomized comparison of clinical results between hand-assisted laparoscopic and open splenectomies. Surg Endosc 24:25–32. https://doi.org/10.1007/s00464-009-0528-x
- Sun X, Liu Z, Selim M., Huang Y (2019) Hand-assisted laparoscopic splenectomy advantages over complete laparoscopic splenectomy for splenomegaly. Surg Laparosc Endosc Percutan Tech 29:109–112. https://doi.org/10.1097/SLE. 000000000000640
- Rosen M, Brody F, Walsh M, Ponsky J (2002) Hand-assisted laparoscopic splenectomy (HALS) in cases of splenomegaly. Surg Endosc Other Interv Tech 16:426–430. https://doi.org/10. 1007/s00464-001-8104-z
- 26. Targarona EM, Balague C, Cerdán G et al (2002) Hand-assisted laparoscopic splenectomy (HALS) in cases of splenomegaly.

Surg Endosc Other Interv Tech 16:426–430. https://doi.org/10. 1007/s00464-001-8104-z

- 27. Wang KX, Hu SY, Zhang GY et al (2007) Hand-assisted laparoscopic splenectomy for splenomegaly: a comparative study with conventional laparoscopic splenectomy. Chin Med J (Engl) 120:41–45. https://doi.org/10.1097/00029330-200701010-00008
- Cavaliere D, Solaini L, Di Pietrantonio D et al (2018) Robotic vs laparoscopic splenectomy for splenomegaly: a retrospective comparative cohort study. Int J Surg 55:1–4. https://doi.org/10. 1016/j.ijsu.2018.05.012
- Cordera F, Long KH, Nagorney DM et al (2003) Open versus laparoscopic splenectomy for idiopathic thrombocytopenic purpura: clinical and economic analysis. Surgery 134:45–52. https:// doi.org/10.1067/msy.2003.204
- Pietrabissa A (2011) Laparoscopic treatment of splenomegaly. Arch Surg 146:818. https://doi.org/10.1001/archsurg.2011.149
- Huang Y, Wang XY, Wang K (2019) Hand-assisted laparoscopic splenectomy is a useful surgical treatment method for patients

with excessive splenomegaly: a metaanalysis. World J Clin Cases 7:320–334. https://doi.org/10.12998/wjcc.v7.i3.320

- Ailawadi G, Yahanda A, Dimick JB et al (2002) Hand-assisted laparoscopic splenectomy in patients with splenomegaly or prior upper abdominal operation. Surgery 132:689–696. https://doi.org/ 10.1067/msy.2002.127686
- 33. Maeso S, Reza M, Mayol JA et al (2010) Efficacy of the da vinci surgical system in abdominal surgery compared with that of laparoscopy: a systematic review and meta-analysis. Ann Surg 252:254–262. https://doi.org/10.1097/SLA.0b013e3181e6239e
- Bodner J, Kafka-Ritsch R, Lucciarini P et al (2005) A critical comparison of robotic versus conventional laparoscopic splenectomies. World J Surg 29:982–985. https://doi.org/10. 1007/s00268-005-7776-2

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.