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Robot-assisted laparoscopic pyeloplasty versus laparoscopic pyeloplasty for pelvi-ureteric junction obstruction in the paediatric population: a systematic review and meta-analysis

Samih Taktak, (DOliver Llewellyn, Mohamed Aboelsoud, Shahab Hajibandeh and Shahin Hajibandeh

Abstract

Background: Owing to the improved vision and instrument manipulation in robot-assisted procedures, we sought to evaluate the comparative outcomes of robot-assisted laparoscopic pyeloplasty (RALP) and laparoscopic pyeloplasty (LP) in a paediatric patients with pelvi-ureteric junction obstruction (PUJO).

Methods: We conducted a systemic literature search of online sources, including PubMed, MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials, and respective bibliographic reference lists. Success rate, operative time, hospital length of stay, postoperative complication rate and re-intervention rate were our primary outcomes. Combined overall effect sizes were calculated using fixed-effect or random-effects models. **Results:** We identified 14 observational studies reporting a total of 2254 paediatric patients with PUJO, who underwent LP (n = 1021) or RALP (n = 1233). Our analysis demonstrated that RALP was associated with a significantly higher success rate [odds ratio (OR) 2.51; 95% confidence interval (CI) 1.08–5.83, p = 0.03] and shorter length of hospital stay [mean difference (MD) –1.49; 95% CI –2.22 to –077; p < 0.0001] compared with LP. Moreover, nonsignificant reductions in postoperative complications (OR 0.61; 95% CI 0.36–1.02; p = 0.06) and re-intervention (OR 0.43; 95% CI 0.15–1.21; p = 0.11) were found in favour of RALP. There was no difference in procedure time between the two approaches (MD –0.15; 95% CI –30.22 to 29.93, p = 0.99].

Conclusions: Our meta-analysis of observational studies demonstrated that RALP is safe and may have higher success rate compared with the more traditional laparoscopic approach in a paediatric population. Moreover, it may be associated with lower postoperative complications and re-intervention rates. Evidence from randomized trials is required.

Keywords: laparoscopic pyeloplasty, paediatric, robot-assisted laparoscopic pyeloplasty

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Introduction

Pelvi-ureteric junction obstruction (PUJO) is a condition frequently encountered by urologists, both paediatric and adult, and describes an obstruction of urinary flow from the renal pelvis into the ureter.¹ It is the commonest cause of hydronephrosis in children, with around half of antenatal hydronephrosis diagnoses on screening

ultrasound being secondary to PUJO upon further investigation. The reported incidence of PUJO is around 1 in 500 live births.^{2,3}

The most commonly performed surgical intervention for PUJO in a paediatric population remains the open pyeloplasty, with an unrivalled success rate to date.⁴ Despite this, there has been

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a growing acceptance towards laparoscopic pyeloplasty (LP) in the past few decades, and more recently, robotic-assisted laparoscopic pyeloplasty (RALP), owing to their reported similar success rates, shorter hospital stays, and increased parental approval.⁵ Moreover, more precise suturing and a reduced learning curve have been reported associated with RALP compared with LP.6,7 The complexity of reconstructive procedures, such as pyeloplasty, which require challenging anastomoses, has further been aided by the robotic approach, negating the two-dimensional views and restricted instrument movements that can often cause difficulty.8 A minimally invasive approach, such as LP or RALP is often performed transperitoneally, with either three or four ports being placed into the abdomen. In RALP, one port allows access for the bedside assistant, with the remaining ports accommodating the robot arms. A similar surgical technique is subsequently used for both approaches.9

In 2014, a meta-analysis¹⁰ of comparative studies demonstrated shorter length of hospital stay and lower analgesia requirement associated with RALP compared with LP in children with PUJO. However, the number of included studies in that meta-analysis was limited. As several more comparative studies have been published since 2014, we aimed to conduct a comprehensive systematic review and meta-analysis to evaluate the comparative outcomes of RALP and LP in paediatric patients with PUJO.

Methods

Design and study selection

This review conformed to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards.¹¹ Our study selection, analysis methods and outcomes for investigation were specified prior to the study. We planned to include all comparative studies evaluating the outcomes of LP and RALP in paediatric populations. Patients of any sex aged less than 18 years were included.

The intervention of interest was RALP in children for PUJO, and this was compared against LP. Primary outcome measures were success rate (defined by either the resolution of symptoms, or radiologically by resolution or reduction of hydronephrosis on ultrasound scan, or improved drainage with or without differential renal Table A.1. Search Strategy.

	••
Search no.	Search strategy*
#1	pyeloplasty: TI, AB, KW
#2	paediatric: TI, AB, KW
#3	pediatric: TI, AB, KW
#4	child: TI, AB, KW
#5	#2 OR #3 OR #4
#6	MeSH descriptor: [laparoscopic] explode all trees
#7	laparoscop*: TI, AB, KW
#8	MeSH descriptor: [robotic] explode all trees
#9	robot*: TI, AB, KW
#10	#6 OR #7 OR #8 OR #9
#11	#1 AND #5 AND #10
*This sear	ch strategy was utilized on the following

alabases: PubMed, MEDLINE, EMBASE and Cochrane Control Register of Controlled Trials.

function on MAG-3 renogram, with or without resolution of symptoms), postoperative complications, length of hospital stay, procedure time and re-intervention rate.

Literature search strategy

Two authors (ST and OL) independently conducted a literature search utilizing: PubMed, MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials, with the final search on the 21 June 2018. The search strategy is listed in Table A.1. Bibliographic lists were also scrutinized for any further eligible studies.

Selection of studies

Two authors (ST and OL) independently assessed each study identified from the literature search. Full texts were obtained (MA), examined and at a study meeting, the eligibility criteria were selected. Discrepancies in study selection were resolved between the two authors following study selection and an independent third author (Shahin H) was consulted in the event of disagreement.

Data extraction and management

An electronic data extraction spreadsheet was created in line with Cochrane's data collection form for intervention reviews. This spreadsheet was pilot tested in randomly selected studies and tailored as necessary. The data extraction spreadsheet contained:

- Study data and design (first author, country of origin, and year and journal of publication);
- (2) Baseline demographics (age, sex, weight);
- (3) Primary outcomes data.

Two authors (ST and OL) independently collected and recorded all data in this spreadsheet. Disagreements were resolved between the two authors, and if no resolution achieved, an independent third author (Shahin H) was consulted.

Assessment of risk of bias

The methodological quality and risk of bias of the included studies were assessed independently by two authors (ST and OL) using the Newcastle–Ottawa Scale (NOS).¹² When discrepancies existed, a third author (Shahin H) was consulted.

Summary measures and synthesis

For dichotomous outcome measures (success rate, postoperative complications and re-intervention), the odds ratio (OR) was calculated as the summary measure and presented with the 95% confidence interval (CI). The OR was defined as the odds of an event in the RALP group compared with the LP group. An OR < 1 would favour the RALP group except in the analysis of the success rate, where the OR > 1 would favour the RALP group. For continuous outcome measures (length of hospital stay, procedure time), the mean difference (MD) was calculated between the RALP and LP groups.

The individual patient was used as the unit of analysis, with information regarding missing data evaluated, and if required, authors contacted.

The Review Manager (RevMan) 5.3 software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, 2014) for data synthesis¹³ was used. An independent author (Shahin H) entered the extracted data into the Review Manager, and this was independently checked by another author (Shahab H). Fixed-effect modelling was used as appropriate for the analysis, with the random-effects models applied when significant between-study heterogeneity existed. The results were reported in the forest plots with 95% CIs.

Heterogeneity among the studies was evaluated using the Cochrane Q test (χ^2). Inconsistencies were addressed by calculating I^2 and interpreted using the following guide:

- (1) 0-25% may not be important;
- (2) 25–75% may represent moderate heterogeneity;
- (3) 75–100% demonstrates considerable heterogeneity.

Additional analyses were performed to explore potential sources of heterogeneity, involving repeated primary analysis, and the effect of each study individually on the results, thereby assessing the robustness of our results.

Results

Literature searches via the databases identified 375 articles. Following further evaluation of the titles, abstracts and full text, 14 articles were deemed eligible for inclusion^{4,14-26} (Figure 1). These were one case-control study, one prospective cohort study, and 12 retrospective cohort studies, reporting a total of 2254 paediatric patients who underwent LP (n = 1021) or RALP (n =1233) for PUJO. In 11 articles,4,14-16,18,20,22-26 all LP and RALP cases were performed using a transperitoneal approach, with one¹⁹ only including cases that carried out a retroperitoneal approach. The RALP cases included in Franco and colleagues'26 study which adopted a standard laparoscopic technique to initiate exposure of the renal pelvis before completing with robotic assistance. The remaining two studies made no comment on the approach utilized.

Table 1 represents our studies, including their date and origin of publication, journal and study design, as well as the baseline demographic and clinical characteristics of the study population. All studies, except one, included patients with similar ages and weights in their treatment groups. Reporting of baseline clinical characteristics were variable, with nonsignificant difference between the groups in each study.



Figure 1. PRISMA study flow diagram.

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Methodological appraisal

Table 2 highlights the risk of bias assessment of the cohort studies, using the NOS. The risk of bias was low in 10 studies and moderate in 4.

Outcome synthesis

Outcomes are highlighted in Figures 2 and 3.

Success rate. Eleven studies reported success rate as an outcome. The success rate in the LP and RALP were 96.2% and 98.2%, respectively. Our pooled analysis of 1138 patients demonstrated that RALP was associated with a significantly higher success rate compared with LP. Low betweenstudy heterogeneity existed ($I^2 = 0\%$; p = 0.97).

Postoperative complications. Twelve studies (1721 patients) reported the incidence of their postoperative complications. There were 52 (8.0%) complications in the LP group and 43 (3.9%) complications in the RALP group. RALP was associated with lower postoperative complications than LP but the difference was not statistically significant (OR 0.61; 95% CI 0.36–1.02; p = 0.06). There was low heterogeneity among the included studies ($I^2 = 0\%$; p = 0.93).

Length of hospital stay. Six studies reported the length of hospital stay of their patients. Our analysis of 1791 patients showed that there was a significantly shorter length of hospital stay in favour of RALP (MD -1.49; 95% CI -2.22 to -077; p < 0.0001). There was considerable betweenstudy heterogeneity ($I^2 = 93\%$; p < 0.00001).

Procedure time. Although 10 studies reported their procedure time, only four studies were included in the pooled analysis as the rest of the studies did not report the procedure time as mean \pm standard deviation (SD) of their reported mean. The pooled analysis included 689 patient and did not find any significant difference in procedure time between LP and RALP (201.3 minutes *versus* 200.5 minutes, MD -0.15; 95% CI -30.22 to 29.93; p = 0.99). Considerable heterogeneity existed among the included studies ($I^2 = 86\%$; p < 0.0001).

Re-intervention. This outcome has been evaluated by nine studies (421 patients). The re-intervention rate in the RALP group was 1.7%, whereas 5.9% of the patients in the LP group had re-interventions. A nonsignificant reduction in re-intervention rate was associated with RALP compared with LP (OR 0.43; 95% CI 0.15–1.21; p = 0.11). There was low heterogeneity among the included studies ($I^2 = 0\%$; p = 0.79).

Sensitivity analysis. Using random-effect or fixedeffect models did not affect the pooled-effect size in any of the outcomes. The direction of pooledeffect size remained unchanged when the OR, RR, or RD was calculated.

Discussion

In light of current operative trends continually evolving in not only the urological field, but throughout the surgical world, it is imperative high-quality data are updated to give clinicians the resource to adapt, maintain and improve the care to their patients. As we enter an era whereby robotically assisted procedures are becoming the mainstay of tertiary urology centres, more and more data are extracted, highlighting promising results in a range of urological procedures. Despite this, current systematic reviews of the literature have highlighted a paucity of comparative trials in this field.27 Furthermore, controversy exists with regards to pyeloplasty in children, and the ideal approach to perform optimal reconstructive procedures in this population.28

In view of controversies with regards to pyeloplasty in children, and the ideal approach to perform optimal reconstructive procedures in this population, we conducted a comprehensive systematic

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Memoria farate 2013 Lapareentodes Re3 La Lapareentodes Lapareentodes <thlapareentodes< th=""> Lapareentodes</thlapareentodes<>	Tam ¹⁴	China	2018	J Laparoendosc Adv Surg Tech A	RCS	63	37	26	L:9.6 versus R:10.8	L:12 (3–15) <i>versus</i> R:18.5 (2–16)	USS & MAG3
Reinductive Damate Zand Jund. PCS 38 13 250 NR Ling (46-192) wrsus NR South South Morea 2017 PLOS One RC 40 US Ling (46-192) wrsus NR Ling (46-192) wrsus NR Above South Morea 2017 JPediatr Uncl RC 40 V US NR Ling (42-13) wrsus NR Above 2017 JPediatr Uncl RCS 67 40 US NR Ling (42-13) wrsus NR Above Bab 2016 JPediatr Uncl RCS 67 40 10 Ling (42-13) wrsus NR Above Bab 2016 Carbor RCS 67 28 30 NR Ling (42-13) wrsus NR Above Bab Deviat Uncl RCS 30 NR Ling (42-13) wrsus NR Ling (42-13) wrsus NR Above Bab Deviat RAD RCB 201 RCB RD R	Neheman ¹⁵	Israel	2018	J Laparoendosc Adv Surg Tech A	RCS	34	13	21	L6.29 v R5.8	L:9.1 versus R:7.5	MAG3
Gond* South Kons PLOS One RCS 40 301 L33.613.4.75.01 L33.613.4.75.01 L33.612.4-75.01 L33.612.4-75.01 <thl33.< th=""><th>Reinhardt¹⁶</th><th>Denmark</th><th>2017</th><th>Scand J Urol</th><th>PCS</th><th>38</th><th>13</th><th>25</th><th>NR</th><th>L:108 (48–192) <i>versus</i> R:120 (48–192)</th><th>MAG3</th></thl33.<>	Reinhardt ¹⁶	Denmark	2017	Scand J Urol	PCS	38	13	25	NR	L:108 (48–192) <i>versus</i> R:120 (48–192)	MAG3
Image: Control of the contro	Song ⁴	South Korea	2017	PLOS One	RCS	40	30	10	L:39.5 [13.4–75.0] <i>versus</i> R:40.1 [14.5–92.8] <i>p</i> = 0.240	L:126 [24–192] versus R:132 [48–216] <i>p</i> = 0.175	USS & MAG3
Peterlet Z016 Can Urot RCS 68 13 55 NR Le88 (22-138) versus W S13N* USA 2016 J Pediatr Urot RCS 575 390 185 L-33 versus R.47.1 L:103 versus R.94. M S13N* USA 2016 J Pediatr Urot RCS 575 390 185 L:103 versus R.94. M M Lu ¹ USA 2016 J Pediatr Urot RCS 37 28 L:103 versus R.94.7 M M Lu ² USA 2016 J Pediatr Urot RCS 37 28 L:103 versus R.94.7 M M Lu ² USA 2016 J Pediatr Urot RCS 37 28 M	Chan ¹⁷	NSA	2017	J Pediatr Urol	RCS	679	46	633	NR	L:91.5 (4–214) <i>versus</i> R:105 (2–215)	NR
itation 2016 Jerdiatr Urol RCS 575 390 183 L:33 versus R:47.1 L:103 versus R:32 W danute ²⁰ India 2015 World Urol RCS 47 28 193 L:37 versus R:32 W danute ²⁰ India 2015 World Urol RCS 47 28 W L:37 versus R:32 W duavity Usa 2014 Jediatr Urol RCS 47 28 W L:11 versus R:119 W M duavity Usa 2013 Jurol RCS 32 320 72 193 111 versus R:119 W duavity Usa Jurol RCS 64 18 123 1605 171 versus R:119 W duavity Usa Jurol RCS 64 18 123 1605 171 versus R:119 17 duavity W Liss versus R:33 Jurol RCS 24 18 173 173 174	Patel ¹⁸	NSA	2016	Can J Urol	RCS	68	13	55	NR	L:88 (22–138) <i>versus</i> R:88 (42–150)	USS
denote ²⁰ India 2015 World Urol RCS 47 28 19 L:10.85 versus R:125 L:27 versus R:32 W Lu ¹¹ US 2014 Uediatr Urol RCS 392 320 72 N L:11 versus R:13 N Lu ¹¹ US 2014 Urol RCS 392 320 72 N L:11 versus R:13 N Richy ¹² US 2013 Urol RCS 342 230 72 N L:11 versus R:135 N Richy ¹² US 2013 Urol RCS 64 13 L:30 versus R:105 N Subtriat US Juol RCS 64 23 23 N L:30 versus R:105 N Subtriat US Juol RCS 64 23 23 N L:30 versus R:105 N Subtriat US Juol RCS 46 L:32/15.8-01 p= 0.124 L:30 versus R:105 N Subi	Silay ¹⁹	NSA	2016	J Pediatr Urol	RCS	575	390	185	L:33 versus R:47.1	L:103 versus R:94	MAG3
Image: line line line line line line line line	Ganpule ²⁰	India	2015	World J Urol	RCS	47	28	19	L:10.85 versus R:12.5	L:27 versus R:32	USS & MAG3
Riachy ² USA 2013 Urol RCS 64 18 46 L:23.2 (5.9-71) versus, R:27 (5.8-90) ρ = 0.124 L:97 (3-216) versus, R:106 (5-264) ρ = 0.194 W Casella ²³ USA 2013 Urol RCS 46 23.7 (5.8-90) ρ = 0.124 R:106 (5-264) ρ = 0.194 W Casella ²³ USA 2013 Urol RCS 46 23 03 Urol RCS 46 23 0 N <th>Liu²¹</th> <th>NSA</th> <th>2014</th> <th>J Pediatr Urol</th> <th>RCS</th> <th>392</th> <th>320</th> <th>72</th> <th>NR</th> <th>L:111 <i>versus</i> R:119 (mean)</th> <th>NR</th>	Liu ²¹	NSA	2014	J Pediatr Urol	RCS	392	320	72	NR	L:111 <i>versus</i> R:119 (mean)	NR
CaseLla ²³ USA 2013 Urol RCS 46 23 23 NR L:83 versus R:102 N Subotic ²⁴ Switzerland 2013 Urol RCS 39 20 19 L:9(4-15) versus R:33 L:11(1-33) versus R:115 N Subotic ²⁴ Switzerland 2013 Urol RCS 39 20 19 L:9(4-15) versus R:33 L:11(1-33) versus R:115 N Kim ²⁵ USA 2008 JUrol CCS 142 58 N N N N Franco ²⁴ USA 2008 JUrol RCS 27 12 N L:120(72-240) versus U	Riachy ²²	NSA	2013	J Urol	RCS	64	18	46	L:23.2 $(5.9-71)$ versus R:27 $(5.8-90) p = 0.124$	L:97 [3–216] <i>versus</i> R:106 [5–264] <i>p</i> = 0.194	USS & MAG3
Subotic ³⁴ Switzerland 2013 Urediatr Urol RCs 39 20 19 L:9 (4-15) versus R:33 L:11 (1-33) versus R:115 U Kim ²⁵ USA 2008 J Urol CCS 142 58 84 NR N Franco ²⁴ USA 2007 J Urol RCS 27 12 15 NR L:120 (72-240) versus U	Casella ²³	NSA	2013	J Urol	RCS	46	23	23	NR	L:83 versus R:102 p = <0.215	NR
Kim ²⁵ USA 2008 J Urol CCS 142 58 84 NR NR NR N Franco ²⁴ USA 2007 J Urol RCS 27 12 15 NR L:120 (72-240) versus U	Subotic ²⁴	Switzerland	2013	J Pediatr Urol	RCS	39	20	19	L:9 (4–15) versus R:33 (17–51)	L:11 (1–33) <i>versus</i> R:115 (58–179)	USS & MAG3
Franco ²⁶ USA 2007 J Urol RCS 27 12 15 NR L:120 (72-240) versus U R:156 (48-216) R:156 (48-216) R:156	Kim ²⁵	NSA	2008	J Urol	CCS	142	58	84	NR	NR	NR
	Franco ²⁶	USA	2007	J Urol	RCS	27	12	15	NR	L:120 (72-240) versus R:156 (48-216)	NSS

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Table 2. Summary of study quality analysis using Newcastle-Ottawa Scale (NOS).

Author	Selection				Comparability	Outcome			
	Representativeness	Selection	Ascertainment of exposure	Records outcome absence pre-intervention	Comparability of cohorts	Assessment of outcome	Appropriate follow-up period	Cohort follow up achieved	NOS total (out of 9)
Tam <i>et al.</i> ¹⁴	*	*	*	*	*	*	*	*	6
Neheman <i>et al.</i> ¹⁵	*	*	*	*	*	*	*	*	6
Reinhardt <i>et al</i> . ¹⁶	*	×	*	*	*	*	*	*	8
Song <i>et al.</i> ⁴	*	*	*	*	*	*	*	*	6
Chan <i>et al.</i> ¹⁷	*	*	*		*	* *			7
Patel <i>et al.</i> ¹⁸	*	*	*	*	*	*	*	*	8
Silay <i>et al.</i> ¹⁹	*	*	*	*	*	*	*	*	6
Ganpule <i>et al</i> . ²⁰	*	*	*	*	*	*	*	*	8
Liu <i>et al</i> . ²¹	*	*	*	*	*	*			6
Riachy <i>et al.</i> ²²	*	*	*	*	*	*	*	*	6
Casella <i>et al.</i> ²³	*	*	*	*	*				6
Subotic <i>et al.</i> ²⁴	*	*	*	*	*	*	*	*	8
Kim <i>et al.</i> ²⁵	*	*	*	*	*		*	*	7
Franco <i>et al.</i> ²⁶	*	*	*	*	*	*	*	*	8
Each item scored 1 noint his	ablighted by scterick scide f	rom comparabi	ity which scores maxim	num of 2 nointe					

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		RAL	Р	LP			Odds Ratio			Odds Ratio	
(a)	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Year		M-H, Fixed, 95% Cl	
	Franco 2007	15	15	12	12		Not estimable	2007			
	Kim 2008	83	84	56	58	10.3%	2.96 [0.26, 33.48]	2008			-
	Subotic 2011	19	19	20	20		Not estimable	2011			
	Riachy 2013	46	46	19	19		Not estimable	2013		1	
	Ganpule 2015	17	19	25	28	27.9%	1.02 [0.15, 6.77]	2015			
	Patel 2016	52	55	11	13	12.7%	3.15 [0.47, 21.15]	2016			_
	Silay 2016 Reinbordt 2017	184	185	381	390	17.4%	4.35 [U.55, 34.56]	2010		-	
	Song 2017	20	10	26	20	9.3%	3 57 (0 19 72 10)	2017			
	Tam 2018	25	26	34	37	14.1%	2.21 [0.22, 22,48]	2018			
	Neheman 2018	20	21	12	13	9.3%	1.67 [0.10, 29.18]	2018			
	Total (95% CI)		505		633	100.0%	2.51 [1.08, 5.83]				
	Total events	496		609							
	Heterogeneity: Chi ²	= 1.35, df:	= 6 (P =	0.97); l² =	= 0%				0.01	0,1 1 10	100
	Test for overall effec	t Z = 2.14	(P = 0.0	(3)						Favours [LP] Favours [RALP]	
		DAI	в	1.0			Odde Patio			Odde Patio	
(b)	Study or Subgroup	Events	Total	Events	Total	Weight	M-H. Fixed, 95% CL	Year		M.H. Fixed, 95% Cl	
(-)	Franco 2007	0	15	0	12	Weight	Notestimable	2007			
	Subotic 2011	4	19	5	20	10.0%	0.80 (0.18, 3.57)	2007			
	Casella 2013	0	23	ŏ	23	10.070	Not estimable	2013			
	Riachy 2013	2	46	2	19	7.0%	0.39 [0.05, 2.97]	2013			
	Ganpule 2015	0	19	0	28		Not estimable	2015			
	Silay 2016	6	185	30	390	48.4%	0.40 [0.16, 0.98]	2016			
	Patel 2016	2	55	0	13	2.0%	1.26 [0.06, 27.85]	2016			
	Song 2017	0	10	4	30	5.8%	0.28 [0.01, 5.68]	2017			
	Reinhardt 2017	1	25	0	15	1.5%	1.90 [0.07, 49.60]	2017			_
	Chan 2017	19	633	1	46	4.7%	1.39 [0.18, 10.64]	2017			
	Tarri 2018 Nebeman 2019	4	20	0	37	0.9%	0.94 [0.24, 3.73]	2018			
	Nelleman 2010	5	21	4	15	3.070	0.70 [0.15, 5.51]	2010			
	Total (95% CI)		1077		646	100.0%	0.61 [0.36, 1.02]			•	
	Total events	43		52							
	Heterogeneity: Chi ²	= 3.13, df:	= 8 (P =	0.93); l ² =	= 0%				0.01		100
	Test for overall effec	t: Z = 1.90	(P = 0.0)	6)					0.01	Favours (RALP) Favours (LP)	100
(c)	Chuche or Culturoum	RA	LP CD Tot	al Maar	LP	Total	Mean Differ	ence		Mean Difference	
(\mathbf{c})	Study of Subgroup	mean	1 10	al Mean	0 14	20	16.6% 2.60 L2.4	95% C	1	IV, Random, 95% CI	
	50ng 2017	3.2		10 5.0	5 1.4	30	15.5% -2.60 [-3.4	0,-1.80	1	-	
	Silay 2016	21	21 1	R5 41	6 24	390	181% -250628	9 -7 11			
	Silay 2016 Ganpule 2015	2.1 3.52	2.1 1 1.5	85 4.0 19 5.04	0 2.4 1.56	390 28	18.1% -2.50 [-2.8] 14.8% -1.52 [-2.4]	9,-2.11 10.63]]		
	Silay 2016 Ganpule 2015 Liu 2014	2.1 3.52 1.96	2.1 1 1.5 0.1 3	85 4.6 19 5.04 16 2.86	6 2.4 4 1.56 3 0.55	390 28 71	18.1% -2.50 [-2.8] 14.8% -1.52 [-2.4] 18.9% -0.92 [-1.0]	9,-2.11 1,-0.63 5,-0.79]		
	Silay 2016 Ganpule 2015 Liu 2014 Tam 2018	2.1 3.52 1.96 3.1	2.1 1 1.5 0.1 3 0.3	85 4.0 19 5.04 16 2.80 37 4	5 2.4 4 1.56 3 0.55 4 2.1	390 28 71 26	18.1% -2.50 [-2.8] 14.8% -1.52 [-2.4] 18.9% -0.92 [-1.0] 15.3% -0.90 [-1.7]	9, -2.11 1, -0.63 5, -0.79 1, -0.09]		
	Silay 2016 Ganpule 2015 Liu 2014 Tam 2018 Chan 2017	2.1 3.52 1.96 3.1 1.8	2.1 1 1.5 0.1 3 0.3 1 1.3 6	85 4.0 19 5.04 16 2.88 37 4 33 2.4	6 2.4 4 1.56 3 0.55 4 2.1 4 1.7	390 28 71 26 46	18.1% -2.50 [-2.83] 14.8% -1.52 [-2.4] 18.9% -0.92 [-1.0] 15.3% -0.90 [-1.7] 17.4% -0.60 [-1.1]	9, -2.11 1, -0.63 5, -0.79 1, -0.09 0, -0.10]]]		
	Silay 2016 Ganpule 2015 Liu 2014 Tam 2018 Chan 2017	2.1 3.52 1.96 3.1 1.8	2.1 1 1.5 0.1 3 0.3 1.3 6	85 4.6 19 5.04 16 2.86 37 4 33 2.4	6 2.4 4 1.56 3 0.55 4 2.1 4 1.7	390 28 71 26 46	18.1% -2.50 [-2.8] 14.8% -1.52 [-2.4] 18.9% -0.92 [-1.0] 15.3% -0.90 [-1.7] 17.4% -0.60 [-1.1]	9, -2.11 1, -0.63 5, -0.79 1, -0.09 0, -0.10]]]		
	Silay 2016 Ganpule 2015 Liu 2014 Tam 2018 Chan 2017 Total (95% Cl)	2.1 3.52 1.96 3.1 1.8	2.1 1 1.5 0.1 3 0.3 1.3 6 120 120	85 4.6 19 5.04 16 2.88 37 4 33 2.4	6 2.4 4 1.56 3 0.55 4 2.1 4 1.7	390 28 71 26 46 591	18.1% -2.50 [-2.8] 14.8% -1.52 [-2.4] 18.9% -0.92 [-1.0] 15.3% -0.90 [-1.7] 17.4% -0.60 [-1.1] 100.0% -1.49 [-2.22]	9, -2.11 1, -0.63 5, -0.79 1, -0.09 0, -0.10 2, -0.77]]]]		
	Silay 2016 Ganpule 2015 Liu 2014 Tam 2018 Chan 2017 Total (95% CI) Heterogeneity: Tau ² .	2.1 3.52 1.96 3.1 1.8 = 0.71; Ch	2.1 13 1.5 1.5 1.5 1.3 1.3 1.3 120 120 120 120 120 120 120 120	85 4.6 19 5.04 16 2.88 37 4 33 2.4 00 00, df = 5 (6 2.4 4 1.56 3 0.55 4 2.1 4 1.7 (P < 0.0	390 28 71 26 46 591	18.1% -2.50 [-2.8] 14.8% -1.52 [-2.4] 18.9% -0.92 [-1.0] 15.3% -0.90 [-1.7] 17.4% -0.60 [-1.1] 100.0% -1.49 [-2.2] = 93%	9, -2.11 1, -0.63 5, -0.79 1, -0.09 0, -0.10 2, -0.77	 -4		- <u> </u>
	Silay 2016 Ganpule 2015 Liu 2014 Tam 2018 Chan 2017 Total (95% CI) Heterogeneity: Tau ^{2,} Test for overall effect	2.1 3.52 1.96 3.1 1.8 = 0.71; Ch t: Z = 4.06	2.1 1 1.5 0.1 3 0.3 1.3 6 12 1 ² = 76.8 (P < 0.0)	85 4.6 19 5.04 16 2.86 37 4 33 2.4 00 00, df = 5 6 001)	6 2.4 4 1.56 3 0.55 4 2.1 4 1.7 (P < 0.0	390 28 71 26 46 591 0001); I²	18.1% -2.50 [-2.8] 14.8% -1.52 [-2.4] 18.9% -0.92 [-1.0] 15.3% -0.90 [-1.7] 17.4% -0.60 [-1.1] 100.0% -1.49 [-2.2] = 93%	9, -2.11 1, -0.63 5, -0.79 1, -0.09 0, -0.10 2, -0.77]]] -4	Favours [RALP] Favours [LP]	
(4)	Silay 2016 Ganpule 2015 Liu 2014 Tam 2018 Chan 2017 Total (95% CI) Heterogeneity: Tau ^a Test for overall effect	2.1 3.52 1.96 3.1 1.8 = 0.71; Ch t: Z = 4.06	2.1 13 1.5 1 0.1 3 0.3 1 1.3 6 12 12 12 12 12 12 12 12 12 12 12 12 12	85 4.6 19 5.04 16 2.86 37 4 33 2.4 00 00, df = 5 6 001)	6 2.4 4 1.56 3 0.55 4 2.1 4 1.7 (P < 0.0	390 28 71 26 46 591 00001); I ²	18.1% -2.50 F2.8 14.8% -1.52 F2.4 18.9% -0.92 F1.0 15.3% -0.90 F1.7 17.4% -0.60 F1.7 10.00% -1.49 F2.22 = 93%	9, -2.11, 1, -0.63 5, -0.79 1, -0.09 0, -0.10 2, -0.77 ce]]] -4	Favours [RALP] Favours [LP] Mean Difference	4
(d)	Silay 2016 Ganpule 2015 Liu 2014 Tam 2018 Chan 2017 Total (95% CI) Heterogeneity: Tau ² : Test for overall effect Study or Subgroup	2:1 3:52 1:96 3:1 1:8 = 0.71; Ch t: Z = 4:06 RAL Mean	2.1 13 1.5 0.1 3 0.3 1.3 6 1.3 6 1.3 6 120 P < 0.00 P SD Tota	85 4.6 19 5.04 16 2.86 37 4 33 2.4 00 00, df = 5 (001) al Mean	6 2.4 4 1.56 3 0.55 4 2.1 4 1.7 (P < 0.0 LP SD	390 28 71 26 46 591 0001); I² <u>Fotal We</u>	18.1% -2.50 [-2.8] 14.8% -1.52 [-2.4] 18.9% -0.92 [-1.0] 15.3% -0.90 [-1.7] 17.4% -0.60 [-1.1] 100.0% -1.49 [-2.2] = 93% Mean Differentight ight IV, Random, 9	9, -2.11, 1, -0.63 5, -0.79 1, -0.09 0, -0.10 2, -0.77 2, -0.77 2, -0.77)]] -4 Year	Favours (RALP) Favours (LP) Mean Difference IV, Random, 95% Cl	
(d)	Silay 2016 Ganpule 2015 Liu 2014 Tam 2018 Chan 2017 Total (95% Cl) Heterogeneity: Tau ² Test for overall effect Study or Subgroup Franco 2007	2.1 3.52 1.96 3.1 1.8 = 0.71; Ch : Z = 4.06 RAL <u>Mean</u> 223.1 4	2.1 17 1.5 $-$ 0.1 3 $-$ 0.3 $-$ 1.3 $-$ 1.3 $-$ 1.3 $-$ 1.3 $-$ 1.2 $-$ 1.3 $-$ 1.2 $-$ 1.3 $-$ 1.2 $-$ 1	85 4.6 19 5.04 16 2.84 37 4 33 2.4 00 00, df = 5 00 00, df = 5 001) al <u>Mean</u> 5 263.5 0 467.4	6 2.4 4 1.56 3 0.55 4 2.1 4 1.7 (P < 0.0 LP <u>SD</u> 24.1 107	390 28 71 26 46 591 00001); I ²	18.1% -2.50 [-2.8] 14.8% -1.52 [-2.4] 18.9% -0.92 [-1.0] 15.3% -0.92 [-1.7] 17.4% -0.60 [-1.7] 100.0% -1.49 [-2.2] = 93% Mean Differentive (M. Random, 9) 1.2% -0.40.40 [-67.60]	9, -2.11, 1, -0.63 5, -0.79 1, -0.09 0, -0.10 2, -0.77 2, -0.77 2, -0.77 2, -0.77	1]]] <u>-4</u> <u>Year</u> 2007	Favours (RALP) Favours (LP) Mean Difference IV, Random, 95% Cl	4
(d)	Silay 2016 Ganpule 2015 Liu 2014 Tam 2018 Chan 2017 Total (95% Cl) Heterogeneity: Tau ² Test for overall effect <u>Study or Subgroup</u> Franco 2007 Ganpule 2015 Silay 2016	2.1 3.52 1.96 3.1 1.8 = 0.71; Ch : Z = 4.06 : Z = 4.06	2.1 17 1.5 $-$ 0.1 3 0.3 $-$ 1.3 6 120 P = 76.8 (P < 0.00) P SD Tota 5.5 1 5.9 1 0.7 18	85 4.0 19 5.0-1 16 2.84 37 - 4 33 2.4 00 00, df = 5 1 00 00, df = 5 1 00 00 10, df = 5 1 00 00 10 10 10 10 10 10 10 1	$b^{2} = 2.4$ 4 = 1.56 3 = 0.55 4 = 2.1 4 = 1.7 $(P \le 0.0$ LP SD = 1 24.1 49.7 55.2	390 28 71 26 46 591 00001); I ² 12 24 28 23 390 29	18.1% -2.50 [2.8] 14.8% -1.52 [-2.4] 18.9% -0.92 [-1.0] 15.3% -0.90 [-1.7] 17.4% -0.60 [-1.1] 100.0% -1.49 [-2.2] = 93% Mean Differen ight V, Random, 9 1.2% -40.40 [-67.60, -] 1.2% -10.16 [-40.29] 1.2% -10.16 [-40.29]	9, -2.11, 1, -0.63, 5, -0.79, 1, -0.09, 0, -0.10, 2, -0.77, 2, -0.77, 2, -0.77, 2, -0.77, 13,20, -1, 13,20, -1, 15,49, -1, 8,43, -1, 8,43, -1,	year 2007 2015	Favours [RALP] Favours [LP] Mean Difference IV, Random, 95% Cl	4
(d)	Silay 2016 Ganpule 2015 Liu 2014 Tam 2018 Chan 2017 Total (95% Cl) Heterogeneity: Tau ² Test for overall effect Study or Subgroup Franco 2007 Ganpule 2015 Silay 2016 Song 2017	2.1 3.52 1.96 3.1 1.8 = 0.71; Ch : Z = 4.06 KAL Mean 223.1 4 155 46 173.1 5 254.1	2.1 17 1.5 \sim 0.1 3 \sim 0.3 \sim 1.3 6 1.3 6 \sim 120 \sim 76.8 (P < 0.0) P SD Tota 5.5 1 5.9 1 5.	85 4.0 19 5.0-1 16 2.84 37 - 4 33 2.4 00 00, df = 5 1 00 00, df = 5 1 00 00 01 10, df = 5 1 00 00 10, df = 5 1 00 10, df = 5 1 00 00 10, df = 5 1 00 00 10, df = 5 1 00 00 00 00 00 00 00 00 00 0	6 2.4 4 1.56 3 0.55 4 2.1 4 1.7 (P < 0.0 LP SD 1 24.1 49.7 55.2 38.9	390 28 71 26 46 591 00001); ² 12 24 28 23 390 22 390 22	18.1% -2.50 F2.8 14.8% -1.52 F2.4 18.9% -0.90 F1.7 17.4% -0.60 F1.7 17.4% -0.60 F1.7 100.0% -1.49 F2.22 = 93% Mean Differen IV, Random, 9 V, Random, 9 -2% -40.40 F67.60, - 1.9% -12.40 F40.29, -0.70 F4.9.3, 56 56 70 F24.97, 1	9, -2.11, 1, -0.63, 5, -0.79, 1, -0.09, 0, -0.10, 2, -0.77, 2, -0.77, 2, -0.77, 2, -0.77, 13,20, 13,20, 13,20, 15,49, 15,49, 38,43,	J]] Year 2007 2015 2016 2017	Favours (RALP) Favours (LP) Mean Difference IV, Random, 95% Cl	4
(d)	Silay 2016 Ganpule 2015 Liu 2014 Tam 2018 Chan 2017 Total (95% Cl) Heterogeneity: Tau ² Test for overall effect Study or Subgroup Franco 2007 Ganpule 2015 Silay 2016 Song 2017	2.1 3.52 1.96 3.1 1.8 = 0.71; Ch : Z = 4.06 KAL Mean 223.1 4 155 46 173.1 5 254.1	2.1 17 1.5 \sim 0.1 3 \sim 0.3 \sim 1.3 6 $^{2} = 76.8$ (P < 0.0) P SD Tot: 59 1 0.7 18 46 1	85 4.6 19 5.04 16 2.84 37 4 33 2.4 33 2.4 00 0, df = 5 6 001) al Mean 5 263.5 9 167.4 5 173.8 0 197.4	6 2.4 4 1.56 3 0.55 4 2.1 4 1.7 (P < 0.0 LP SD 7 24.1 49.7 55.2 38.9	390 28 71 26 591 00001); ² 12 24 28 23 390 29 30 22	18.1% -2.50 [2.8] 14.8% -1.52 [-2.4] 18.9% -0.92 [-1.0] 15.3% -0.90 [-1.7] 17.4% -0.60 [-1.1] 100.0% -1.49 [-2.2] = 93% Mean Differen N.Random.9 -2.2 -0.00 [-1.7] -0.60 [-1.1] 100.0% -1.49 [-2.2] = 93% Mean Differen N.Random.9 -0.70 [-9.3] .2% -40.40 [-67.60, -1] .3% -0.70 [-9.83] .6% 56.70 [24.97, 0]	9, -2.11, 1, -0.63, 5, -0.79, 1, -0.09, 0, -0.10, 2, -0.77] 2, -0.77] 2, -0.77] 2, -0.77] 5% CI 13.20] 15.49] 5.49] 5.43]	year <u>Year</u> 2007 2015 2016 2017	Favours [RALP] Favours [LP] Mean Difference IV, Random, 95% Cl	4
(d)	Silay 2016 Ganpule 2015 Liu 2014 Tam 2018 Chan 2017 Total (95% Cl) Heterogeneity: Tau ² : Test for overall effect Study or Subgroup Franco 2007 Ganpule 2015 Silay 2016 Song 2017 Total (95% Cl)	2.1 3.52 1.96 3.1 1.8 = 0.71; Ch : Z = 4.06 : Z = 4.06 Mean 223.1 155 46 173.1 5 254.1	2.1 1 1.5 0.1 3 0.3 1.3 6 1.3 6 1.3 6 P = 76.8 (P < 0.0) P SD Tot: 5.5 1 5.5 1 5.5 1 5.9 1 0.7 18 46 1 22	85 4.6 19 5.04 16 2.84 37 4 33 2.4 00 0, df = 5 6 001) al Mean 5 263.5 9 167.4 5 173.8 0 197.4 9	6 2.4 4 1.56 3 0.55 4 2.1 4 1.7 (P < 0.0 LP SD 2 24.1 49.7 55.2 38.9	390 28 71 26 591 00001); ² <u>Fotal We</u> 12 24 28 23 390 29 30 22 460 100	18.1% -2.50 [-2.8] 14.8% -1.52 [-2.4] 18.9% -0.92 [-1.0] 15.3% -0.90 [-1.7] 17.4% -0.60 [-1.1] 100.0% -1.49 [-2.2] = 93% Mean Differen WRandom, 9 -0.40 [-67.60, -1] 1.2% -0.40 [-67.60, -2] 9.3% -0.70 [-9.83] 8.8% 56.70 [24.97, i] 0.0% -0.15 [-30.22, 2]	9, -2,11 1, -0.63 5, -0.79 1, -0.09 0, -0.10 2, -0.77 2, -0.79 2,	year 2007 2015 2017 2017	Favours (RALP) Favours (LP) Mean Difference IV, Random, 95% Cl	
(d)	Silay 2016 Ganpule 2015 Liu 2014 Tam 2018 Chan 2017 Total (95% Cl) Heterogeneity: Tau ² Test for overall effect Study or Subgroup Franco 2007 Ganpule 2015 Silay 2016 Song 2017 Total (95% Cl) Heterogeneity: Tau ² =	2.1 3.52 1.96 3.1 1.8 = 0.71; Ch t: Z = 4.06 Mean 223.1 4 155 46 173.1 5 254.1 781.13; Ch	2.1 1: 1.5 $-$ 0.1 3: 0.3 $-$ 1.3 6: 1.3 6: 12: P = 76.8 ($P < 0.0$) P SD Tot: 5.5 1 5.5 1 5.5 1 5.9 1 0.7 18 4.6 1 22 P = 21.4	85 4.6 19 5.04 16 2.84 37 4 33 2.4 00 00, df = 5 1 00 10, df = 3 (F 9 10, df = 3 (F 10, df = 3 (F) 10, df = 3 (F 10, df = 3 (F) 10, df = 10, df =	$6^{\circ} 2.4$ $4^{\circ} 1.56$ $3^{\circ} 0.55$ $4^{\circ} 2.1$ $4^{\circ} 1.7$ (P < 0.0) LP 24.1 49.7 55.2 38.9 $2^{\circ} < 0.000$	390 28 71 26 46 591 0001); ² 70 12 24 28 23 390 20 390 20 30 22 460 100 01); ² = 86	18.1% -2.50 [2.8] 14.8% -1.52 [-2.4] 18.9% -0.92 [-1.0] 15.3% -0.90 [-1.7] 17.4% -0.60 [-1.1] 100.0% -1.49 [-2.2] = 93%	9, -2.11 1, -0.63 5, -0.79 1, -0.09 0, -0.10 2, -0.77 2, -0.79 2,	year 2007 2015 2016 2017	Favours [RALP] Favours [LP] Mean Difference N, Random, 95% Cl	
(d)	Silay 2016 Ganpule 2015 Liu 2014 Tam 2018 Chan 2017 Total (95% Cl) Heterogeneity: Tau ² Test for overall effect Study or Subgroup Franco 2007 Ganpule 2015 Silay 2016 Song 2017 Total (95% Cl) Heterogeneity: Tau ² = Test for overall effect; 3	2.1 3.52 1.96 3.1 1.8 = 0.71; Ch t: Z = 4.06 Hean 223.1 4 155 46 173.1 5 254.1 781.13; Ch Z = 0.01 (P	2.1 1: 1.5 $-$ 0.1 3: 0.3 $-$ 1.3 6: 1.3 6: 12($r^2 = 76.8$ (P < 0.0) P SD Tota 6.5 1 59 1 0.7 18 46 1 22 P = 21.4($r^2 = 0.99$)	85 4.6 19 5.04 16 2.84 37 4 33 2.4 00 0, df = 5 1 00 10, df = 3 (F 0, df = 3 (F) 0, df =	$5^{\circ} - 2.4$ $4^{\circ} - 1.56$ $3^{\circ} - 0.55$ $4^{\circ} - 2.1$ $4^{\circ} - 1.7$ (P < 0.0 LP 24.1 49.7 55.2 38.9 P < 0.000	390 28 71 26 46 591 0001); ² 70 12 24 28 23 390 25 390 25 30 22 460 100 01); ² = 86	18.1% -2.50 [2.8] 14.8% -1.52 [-2.4] 18.9% -0.92 [-1.0] 15.3% -0.90 [-1.7] 17.4% -0.60 [-1.1] 100.0% -1.49 [-2.2] = 93%	9, -2,11 1, -0.63 5, -0.79 1, -0.09 0, -0.10 2, -0.77 2, -0.77 2, -0.77 2, -0.77 13,20 13,20 13,20 13,20 13,20 13,20 13,20 13,20 13,20 13,20 13,20 14,	year 2007 2015 2016	Favours [RALP] Favours [LP] Mean Difference IV, Random, 95% Cl	
(d)	Silay 2016 Ganpule 2015 Liu 2014 Tam 2018 Chan 2017 Total (95% CI) Heterogeneity: Tau ² Test for overall effect Study or Subgroup Franco 2007 Ganpule 2015 Silay 2016 Song 2017 Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: :	2.1 3.52 1.96 3.1 1.8 = 0.71; Ch t: Z = 4.06 Mean 223.1 4 155 46 173.1 5 254.1 781.13; Ch Z = 0.01 (P: RAI	2.1 1: 1.5 $-$ 0.1 3: 0.3 $-$ 1.3 6: 1.3 6: 1.3 6: 1.24 P = 76.8 ($P < 0.01$ P SD Tota 6.5 1 59 1 0.7 18 46 1 22 P = 21.4(-) = 0.99) P	85 4.6 19 5.04 19 5.04 16 2.88 37 4 33 2.4 00 00, df = 5 0 00, df = 5 0 001) al Mean 5 263.5 9 167.4 5 173.8 0 197.4 9 0, df = 3 (F LP	6 2.4 4 1.56 3 0.55 4 2.1 4 1.7 (P < 0.0 LP 24.1 49.7 55.2 38.9 2 < 0.000	390 28 71 26 46 591 00001); ² 12 24 28 23 390 22 300 22 460 100 01); ² = 86	18.1% -2.50 [2.8] 14.8% -1.52 [-2.4] 18.9% -0.90 [-1.7] 17.4% -0.60 [-1.7] 17.4% -0.60 [-1.7] 100.0% -1.49 [-2.2] = 93% Mean Differen IV, Random, 9 -12.40 [-40.29, -0.70 [-9.83, 8% 56.70 [24.97, 4] 0.0% -0.15 [-30.22, 2] %	9, -2,11 1, -0.63 5, -0.79 1, -0.09 0, -0.10 2, -0.77 2, -0.77 2, -0.77 2, -0.77 13,20 13,20 13,20 13,20 13,20 13,20 13,20 13,20 13,20 13,20 13,20 14,	J]] 2007 2015 2016 2017	Favours [RALP] Favours [LP] Mean Difference IV, Random, 95% Cl	
(d)	Silay 2016 Ganpule 2015 Liu 2014 Tam 2018 Chan 2017 Total (95% Cl) Heterogeneity: Tau ² Test for overall effect Study or Subgroup Franco 2007 Ganpule 2015 Silay 2016 Song 2017 Total (95% Cl) Heterogeneity: Tau ² = Test for overall effect : Study or Subgroup	2.1 3.52 1.96 3.1 1.8 = 0.71; Ch : Z = 4.06 RAL <u>Mean</u> 223.1 4 155 46 173.1 5 254.1 761.13; Ch Z = 0.01 (P ² RAL Events	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	85 4.6 19 5.04 19 5.04 16 2.84 37 4 33 2.4 00 0, df = 5 0 00 0, df = 5 0 00 10, df = 5 0 00 10, df = 5 0 00 10, df = 5 0 00 0, df = 3 (F EVents	6 2.4 4 1.56 3 0.55 4 2.1 4 1.7 (P < 0.0 LP SD 1 24.1 49.7 55.2 38.9 < < 0.000 Total	390 28 71 26 46 591 00001); ² 12 24 28 23 390 26 30 22 460 100 01); ² = 86 Weight	18.1% -2.50 F2.8 14.8% -1.52 F2.4 18.9% -0.92 F1.0 15.3% -0.90 F1.7 17.4% -0.60 F1.7 17.4% -0.60 F1.7 100.0% -1.49 F2.22 = 93% Mean Differen <u>N</u> Randon, 9 -12.40 F40.29, -0.70 F9.83 56.70 [24.97, 4 0.0% -0.15 F30.22, 2 % Odds Ratio M-H, Fixed, 95% CI	9, -2,11 1, -0.63 5, -0.79 1, -0.09 0, -0.10 2, -0.77 2, -0.77 2, -0.77 13.20	year 2007 2015 2016 2017	Favours [RALP] Favours [LP] Mean Difference IV, Random, 95% CI	
(d) (e)	Silay 2016 Ganpule 2015 Liu 2014 Tam 2018 Chan 2017 Total (95% Cl) Heterogeneity: Tau ² : Test for overall effect Study or Subgroup Franco 2007 Ganpule 2015 Silay 2016 Song 2017 Total (95% Cl) Heterogeneity: Tau ² = Test for overall effect : Study or Subgroup Franco 2007	2.1 3.52 1.96 3.1 1.8 = 0.71; Ch : Z = 4.06 RAL Mean 155 46 173.1 5 254.1 781.13; Ch Z = 0.01 (P: RAL Events 0 0	2.1 1: 1.5 : 0.1 3: 1.3 6: 1.3 6: 1.3 6: 1.3 6: 1.3 6: P < 0.01 P SD Tote 6.5 1 6.5 1 59 1 0.7 18 46 1 222 P = 21.4(1 - 2) P Total 15	85 4.6 19 5.04 19 5.04 16 2.88 37 4 33 2.4 00 00, df = 5 00 00, df = 5 00 10, df = 5 00 00, df = 3 00, df = 3 0	6 2.4 4 1.56 3 0.55 4 2.1 4 1.7 (P < 0.0 LP SD 1 24.1 49.7 55.2 38.9 	390 28 71 26 46 591 00001); ² 12 24 28 23 390 26 30 22 460 100 01); ² = 86 Weight	18.1% -2.50 F2.8 14.8% -1.52 F2.4 18.9% -0.92 F1.0 15.3% -0.90 F1.7 17.4% -0.60 F1.7 17.4% -0.60 F1.7 100.0% -1.49 F2.22 = 93% Mean Differen N.Random, 9 1.2% -40.40 F6.760, - 3% -12.40 F4.029, 3.% -0.70 F9.83 5.6% 56.70 [24.97, 1 0.0% -0.15 F-30.22, 2 % Odds Ratio M-H, Fixed, 95% CI Not estimable	9, -2.11 1, -0.63 5, -0.79 1, -0.09 0, -0.10 0, -0.10 2, -0.77] (2, -0.77] (3, 20] (5, 49] (5, 49] (year 2007 2015 2016 2017	Favours (RALP) Favours (LP) Mean Difference IV, Random, 95% Cl Favours (RALP) Favours (LP) Mean Difference IV, Random, 95% Cl Gavours (RALP) Favours (LP) Odds Ratio M-H, Fixed, 95% Cl	
(d) (e)	Silay 2016 Ganpule 2015 Liu 2014 Tam 2018 Chan 2017 Total (95% Cl) Heterogeneity: Tau ² : Test for overall effect Study or Subgroup Franco 2007 Ganpule 2015 Silay 2016 Song 2017 Total (95% Cl) Heterogeneity: Tau ² = Test for overall effect : Study or Subgroup Franco 2007 Subotic 2011	2.1 3.52 1.96 3.1 1.8 = 0.71; Ch t: Z = 4.06 Mean 223.1 4 155 46 173.1 5 254.1 781.13; Ch Z = 0.01 (P RAL Events 0 0 0	2.1 1' 1.5 $(P < 0.0)$ 2.1 $(P < 0.0)$ 2.1 $(P < 0.0)$ 2.1 $(P < 0.0)$ 2.1 $(P < 0.0)$ 3.1 $(P < 0.0)$ 4.1 $(P < 0.0)$ 3.1 $(P < 0.0)$ 4.1 $(P < 0.0)$ 5.1 $(P < 0.0)$	85 4.6 19 5.00. 16 2.843 37 4 33 2.4 00 0, df = 5 0001) al Mean 5 263.5 9 167.4 5 173.8 0 197.4 9 0, df = 3 (F Events 0 0	6 2.4 4 1.56 3 0.55 4 2.1 4 1.7 (P < 0.0 (P < 0.0	390 28 71 26 46 591 10001); ² 12 24 28 23 390 25 30 22 460 100 01); ² = 86 Weight	18.1% -2.50 [2.8] 14.8% -1.52 [2.4] 18.9% -0.92 [-1.0] 15.3% -0.90 [-1.7] 17.4% -0.60 [-1.1] 100.0% -1.49 [-2.2] = 93% Mean Differen IV. Random, 9 12.% -40.40 [-67.60, -1 .0.% -0.15 [-30.22, 2] .0.% -0.15 [-30.22, 2] 0.045 Ratio M-H, Fixed, 95% CI Not estimable Not estimable	9, -2, 11 1, -0, 63 5, -0, 79 1, -0, 09 0, -0, 10 2, -0, 77 13, 20 5, -0, 77 13, 20 5, -0, 77 13, 20 5, -0, 79 13, -0, -0, 10 13, -0, -0, 10 14, -0, -0, 10 15, -0, 79 15,	Year 2007 2015 2016 2017	Favours [RALP] Favours [LP] Mean Difference IV, Random, 95% CI Favours [RALP] Favours [LP] Odds Ratio M-H, Fixed, 95% CI	
(d) (e)	Silay 2016 Ganpule 2015 Liu 2014 Tam 2018 Chan 2017 Total (95% CI) Heterogeneity: Tau ² Test for overall effect Study or Subgroup Franco 2007 Ganpule 2015 Silay 2016 Song 2017 Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: : Study or Subgroup Franco 2007 Subotic 2011 Riachy 2013	2.1 3.52 1.96 3.1 1.8 = 0.71; Ch : Z = 4.06 Mean 223.1 4 155 46 173.1 5 254.1 781.13; Ch Z = 0.01 (P ⁻¹ RAL Events 0 0 0 0 0	2.1 11.5 1.5 30.1 33 3 1.3 6 1.3 7 1.3 7 1.3 6 1.3 7 1.3 6 1.3 7 1.3 6 1.3 7 1.3 6 1.3 7 1.3 7 1.3 7 1.5 7 1	85 4.6 19 5.00. 16 2.843 37 4 33 2.4 00 0, df = 5 0001) 10, df = 5 0001) 167.4 5 263.5 9 167.4 5 263.5 9 167.4 9 0. 173.8 0 197.4 9 0, df = 3 (F Events 0 1 1	6 2.4 4 1.56 3 0.55 4 2.1 4 1.7 (P < 0.0 (P < 0.0	390 28 71 26 46 591 0001); I ² 0001); I ² 12 24 28 23 390 29 30 22 460 100 01); I ² = 86 Weight 17.9%	18.1% -2.50 [2.8 14.8% -1.52 [2.4 18.9% -0.92 [4.0 15.3% -0.92 [4.0 15.3% -0.92 [4.0 15.3% -0.90 [4.7 17.4% -0.60 [4.1] 100.0% -1.49 [-2.2] = 93% Mean Differen IV, Random, 9 1.2% -40.40 [-67.60, -7 1.3% -0.70 [-9.83, 1.3% -0.70 [-9.83, 1.3% -0.15 [-30.22, 2 % Odds Ratio M-H, Fixed, 95% CI Not estimable Not estimable 0.13 [0.01, 3.41]	9, -2, 11 1, -0, 63 5, -0, 79 1, -0, 09 0, -0, 10 2, -0, 77 55% C1 3, 201 3, 201 3, 201 3, 201 3, 201 3, 201 3, 201 2, 9, 93] Year 2007 2011 2013	Year 2007 2015 2016 2017	Favours [RALP] Favours [LP] Mean Difference IV, Random, 95% CI	
(d) (e)	Silay 2016 Ganpule 2015 Liu 2014 Tam 2018 Chan 2017 Total (95% Cl) Heterogeneity: Tau ² Test for overall effect Study or Subgroup Franco 2007 Ganpule 2015 Silay 2016 Song 2017 Total (95% Cl) Heterogeneity: Tau ² = Test for overall effect : Study or Subgroup Franco 2007 Subolic 2011 Riachy 2013 Ganpule 2015	2.1 3.52 1.96 3.1 1.8 = 0.71; Ch : Z = 4.06 RAL 223.1 4 155 46 173.1 5 254.1 781.13; Ch Z = 0.01 (P: RAL Events 0 0 0 1	2.1 11.5 1.5 10.1 33 1.3 6 1.3 6 1.5 1 1 1.2 7 1.5 1 1 1.5 1 1 1	85 4.6 19 5.0-1 16 2.88 37 4 33 2.4 00 0, df = 5 6 001) al Mean 5 263.5 9 167.4 5 173.8 0 197.4 9 0, df = 3 (F Events 0 1 1 1	6 2.4 4 1.56 3 0.55 4 2.1 4 1.7 (P < 0.0 (P < 0.0 LP <u>SD</u> 24.1 49.7 55.2 38.9 2 < 0.000 <u>Total</u> 12 20 19 28	390 28 71 26 46 591 ⁻ 00001); I ² 12 24 28 23 390 20 30 22 460 100 01); I ² = 86 Weight 17.9% 6.6%	18.1% -2.50 F2.8 14.8% -1.52 F2.4 18.9% -0.92 F1.0 15.3% -0.90 F1.7 17.4% -0.60 F1.7 17.4% -0.60 F1.7 100.0% -1.49 F2.22 = 93% Mean Differen ight M. Random, 9 -12.40 F67.60, - 12.% -40.40 F67.60, - 12.% -40.40 F67.60, - 12.40 F40.29, - 0.70 F9.83, 56.70 F4.93, - 0.0% -0.15 F30.22, 2 % Odds Ratio M-H, Fixed, 95% CI Not estimable Not estimable Not estimable 0.13 [0.01, 3.41] 1.50 [0.09, 25.55]	9, -2, 11 1, -0, 63 5, -0, 79 1, -0, 09 0, -0, 10 0, -0, 10 2, -0, 77 55% C1 13, 201 5, 49 13, 20 15, 49 13, 20 15, 49 13, 20 14 20 17 20 20 20 20 20 20 20 20 20 20 20 20 20	Year 2007 2015 2016 2017	Favours [RALP] Favours [LP] Mean Difference IV, Random, 95% Cl Favours [RALP] Favours [LP] Odds Ratio M-H, Fixed, 95% Cl	
(d) (e)	Silay 2016 Ganpule 2015 Liu 2014 Tam 2018 Chan 2017 Total (95% Cl) Heterogeneity: Tau ² : Test for overall effect Study or Subgroup Franco 2007 Ganpule 2015 Silay 2016 Song 2017 Total (95% Cl) Heterogeneity: Tau ² = Test for overall effect : Study or Subgroup Franco 2007 Subotic 2011 Riachy 2013 Ganpule 2015 Patel 2016	2.1 3.52 1.96 3.1 1.8 = 0.71; Ch : Z = 4.06 RAL Mean 223.1 4 155 46 173.1 5 254.1 781.13; Ch Z = 0.01 (P RAL Events 0 0 0 0 0 0 0 0 0 0 0 0 0	2.1 1.1 1.5 · .0.1 3 3 0.1 3 3 · .1.3 6. 1.21 P P SD Tott 0.5 1 1.59 1 0.7 18 Control 1 0.9 P Total 15 19 19 46 19 19 55	85 4.6 19 5.0-0 18 2.84 37 4 33 2.4 00 0, df = 5 0001) al Mean 5 263.5 9 167.4 5 173.8 0 197.4 9 0, df = 3 (F Events 0 0 1 1 1 1	6 2.4 4 1.56 3 0.55 4 2.1 4 1.7 (P < 0.0 (P < 0.0 (P < 0.0 (P < 0.0 1.7 24.1 49.7 24.1 49.7 24.1 49.7 24.1 49.7 24.1 49.7 24.1 49.7 24.1 49.7 24.1 49.7 24.1 49.7 24.1 49.7 24.1 12 20.0 12 20.0 12 20.0 12 20.0 12 21 12 20.0 12 21 12 20.0 12 21 21	390 28 71 26 46 591 00001); ² 12 24 28 23 390 26 30 22 460 100 01); ² = 80 Weight 17.9% 6.6% 20.4%	18.1% -2.50 (-2.8) 14.8% -1.52 (-2.4) 18.9% -0.92 (-1.0) 15.3% -0.90 (-1.7) 17.4% -0.60 (-1.1) 100.0% -1.49 [-2.2] = 93% Mean Differen 12.40 (-40.28, -0.70 (-9.83) -0.70 (-9.83) 1.6% 56.70 (24.97, -0.70 (-9.83) 0.0% -0.15 (-30.22, 2) 1% Odds Ratio M-H, Fixed, 95% CI Not estimable 0.13 (0.01, 3.41) 1.50 (0.09, 25.55) 0.88 (0.00, 1.95) 0.88 (0.00, 1.95)	9, -2.11 1, -0.63 5, -0.79 1, -0.09 0, -0.10 2, -0.77 5% CI 13.201 5.49 15.49 20.07 2011 2013 2015 2016 2016	year 1 1 2007 2015 2016 2017 ← ←	Favours (RALP) Favours (LP) Mean Difference IV, Random, 95% Cl Favours (RALP) Favours (LP) Mean Difference IV, Random, 95% Cl Gravours (RALP) Favours (LP) Odds Ratio M-H, Fixed, 95% Cl	
(d) (e)	Silay 2016 Ganpule 2015 Liu 2014 Tam 2018 Chan 2017 Total (95% Cl) Heterogeneily: Tau ² Test for overall effect Study or Subgroup Franco 2007 Ganpule 2015 Silay 2016 Song 2017 Total (95% Cl) Heterogeneity: Tau ² = Test for overall effect : Study or Subgroup Franco 2007 Subotic 2011 Riachy 2013 Ganpule 2015 Patel 2016 Song 2017	2.1 3.52 1.96 3.1 1.8 = 0.71; Ch : Z = 4.06 Mean 223.1 4 155 46 173.1 5 254.1 761.13; Ch Z = 0.01 (P RAL Events 0 0 0 0 0 0 0 0 0 0 0 0 0	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	85 4.6 19 5.0.0 19 5.0.0 10 5.0.0 33 2.4 33 2.4 33 2.4 30 0 0, df = 5 0 001) al Mean 5 263.5 9 167.4 5 173.8 0 197.4 9 0, df = 3 (F Events 0 0 1 1 1 4	5 2.4 4 1.56 3 0.55 4 2.1 4 1.7 24.1 4 9.7 55.2 38.9 < 0.000 Total 12 20 19 28 13 30	390 28 71 26 46 591 12 24 12 24 300 22 460 100 01); P = 80 Weight 17.9% 6.6% 20.4% 19.3%	18.1% -2.50 [-2.8] 14.8% -1.52 [-2.4] 18.9% -0.92 [-1.0] 15.3% -0.90 [-1.7] 17.4% -0.60 [-1.1] 100.0% -1.49 [-2.2] = 93% Mean Differen ight W, Random, 9 1.2% -40.40 [-67.60, -1.9] 1.2% -40.40 [-67.60, -1.9] 1.2% -0.15 [-30.22, 2] 1% Odds Ratio M.H. Fixed, 95% CI Not estimable 0.13 [0.01, 3.41] 1.50 [0.09, 25.55] 0.08 [0.01, 1.5.68] 0.28 [0.01, 5.68]	9, -2.11 1, -0.63 5, -0.79 1, -0.09 0, -0.10 2, -0.77 2, -0.	Year 2007 2016 2017 4 	Favours [RALP] Favours [LP] Mean Difference N, Random, 95% Cl Favours [RALP] Favours [LP] Odds Ratio M-H, Fixed, 95% Cl	
(d) (e)	Silay 2016 Ganpule 2015 Liu 2014 Tam 2018 Chan 2017 Total (95% Cl) Heterogeneity: Tau ² : Test for overall effect Study or Subgroup Franco 2007 Ganpule 2015 Silay 2016 Song 2017 Total (95% Cl) Heterogeneity: Tau ² = Test for overall effect ; Study or Subgroup Franco 2007 Franco 2007 Franco 2001 Riachy 2013 Ganpule 2015 Patel 2016 Song 2017 Reinhardt 2017	2.1 3.52 1.96 3.1 1.8 = 0.71; Ch t: Z = 4.06 Mean 223.1 4 155 46 173.1 5 254.1 781.13; Ch Z = 0.01 (P RAL Events 0 0 0 1 0 0 1 1 0 0 1 1 0 0 0 1 1 0 0 0 1 1 0 0 0 0 0 0 1 1 0 1 0 1 1 1 1 1 1 1 1 1 1 1 1 1	2.1 1: 1.5 \sim 0.1 3: 1.3 6: 1.3 7: 1.3 6: 1.3 6: 1.3 6: 1.3 6: 1.3 7: 1.4 6: 1.3 7: 1.4 6: 1.5 7: 1.5 7; 1.5 7; 1.5 7; 1.5 7; 1.5 7; 1.5 7; 1.5 7; 1.5 7; 1.5	85 4.6 19 5.0.0 16 2.843 37 4 33 2.4 00 0, df = 5 00 10 10 df = 5 00 10 10 df = 5 10 01 10 df = 3 0 197.4 9 LP Events 0 0 1 1 1 4 0 0	5 2.4 4 1.56 3 0.55 4 2.1 4 1.7 24.1 (P < 0.0 LP SD 24.1 49.7 55.2 38.9 12 24.1 24.1	390 28 71 26 46 591 00001); ² 70001); ² 70001); ² 8 20 460 100 11; ² = 80 Weight 17.9% 6.6% 20.4% 19.3% 5.3%	18.1% -2.50 [2.8] 14.8% -1.52 [2.4] 18.9% -0.92 [-1.0] 15.3% -0.90 [-1.7] 17.4% -0.60 [-1.1] 100.0% -1.49 [-2.2] = 93% Mean Differen Mean Differen 12.% -40.40 [-67.60, -1] 12.% -40.40 [-67.60, -1] 12.% -40.40 [-67.60, -1] 12.% -12.40 [-40.29, -1] 12.% -0.70 [-40.29, -1] 12.% -0.15 [-30.22, 2] 0.0% -0.15 [-30.22, 2] 0.0% -0.15 [-30.22, 2] 0.0% [0.00, 25.55] 0.28 [0.01, 5.68] 1.65 [0.06, 43.44] 1.50 [0.06, 43.44]	9, -2.11, 1, -0.63 5, -0.79 1, -0.09 0, -0.10 2, -0.77 3, 20 5, 49 3, 20 3, 20	Year 2007 2015 2017 2017 2016 2017	Favours [RALP] Favours [LP] Mean Difference IV, Random, 95% CI Favours [RALP] Favours [LP] Odds Ratio M-H, Fixed, 95% CI	
(d) (e)	Silay 2016 Ganpule 2015 Liu 2014 Tam 2018 Chan 2017 Total (95% Cl) Heterogeneity: Tau ² Test for overall effect Study or Subgroup Franco 2007 Ganpule 2015 Silay 2016 Song 2017 Total (95% Cl) Heterogeneity: Tau ² = Test for overall effect : Study or Subgroup Franco 2007 Subotic 2011 Riachy 2013 Ganpule 2015 Patel 2016 Song 2017 Teenhardt 2017 Tam 2018	2.1 3.52 1.96 3.1 1.8 = 0.71; Ch : Z = 4.06 Mean 223.1 4 165 46 173.1 5 254.1 781.13; Ch Z = 0.01 (P ⁻ RAL Events 0 0 0 1 0 1 1 0 1 1 1 1 1 1 1 1 1 1 1 1 1	2.1 11.5 .1.5 .1.1.5 .1.3 6: .1.3 6: .1.3 6: .1.3 6: .1.3 6: .1.3 6: .1.3 6: .1.3 6: .1.4 6: .1.5 1 .1.5	85 4.6 19 5.00. 16 2.843 37 4 33 2.4 00 0 0, df = 5 1 0001) al Mean 5 263.5 9 167.4 5 263.5 9 167.4 5 173.8 0 197.4 9 0, df = 3 (F Events 0 0 1 1 4 4 0 3 2 4 0 0 0 1 1 1 4 0 0 0 0 0 0 0 0 0 0 0 0 0	5 2.4 4 1.56 3 0.55 4 2.1 4 1.7 (P < 0.0 LP <u>SD</u> <u>SD</u> <u>SD</u> <u>SD</u> <u>24.1</u> 49.7 55.2 38.9 < 0.000 <u>Total</u> 12 20 13 30 55 23 30 55 20 50 50 20 50 20 50 20 50 20 50 20 50 20 50 20 50 20 20 20 20 20 20 20 20 20 2	390 28 71 26 46 591 12 24 28 23 390 22 460 100 01); F = 80 Weight 17.9% 6.6% 20.4% 5.3% 20.4%	18.1% -2.50 [2.8 14.8% -1.52 [2.4 18.9% -0.92 [1.0 15.3% -0.92 [1.0 15.3% -0.92 [1.0 15.3% -0.92 [1.7 17.4% -0.60 [1.1] 100.0% -1.49 [-2.2] = 93% Mean Differen IV, Random, 9 12.% -40.40 [-67.60, -1 13% -12.40 [-40.29, -0.70 [-9.33, -0.70 [-9.	9, -2.11, 1, -0.63 5, -0.79 1, -0.09 0, -0.10 0, -0.10 2, -0.77 13.20 1	Year 2007 2015 2016 2017 4 	Favours [RALP] Favours [LP] Mean Difference N, Random, 95% Cl Favours [RALP] Favours [LP] Odds Ratio M-H, Fixed, 95% Cl	
(d) (e)	Silay 2016 Ganpule 2015 Liu 2014 Tam 2018 Chan 2017 Total (95% Cl) Heterogeneity: Tau ² Test for overall effect Silay 2016 Song 2017 Total (95% Cl) Heterogeneity: Tau ² = Test for overall effect : Study or Subgroup Franco 2007 Subotic 2011 Riachy 2013 Ganpule 2015 Patel 2016 Song 2017 Reinhardt 2017 Tam 2018 Neheman 2018	2.1 3.52 1.96 3.1 1.8 = 0.71; Ch t: Z = 4.06 t: Z = 4.06 223.1 4 155 46 173.1 5 254.1 781.13; Ch Z = 0.01 (P: RAL Events 0 0 0 0 1 1 0 0 1 1 1	2.1 11 1.5 10.1 3 0.1 3 1.3 6 1.3 6 124 P P <u>SD Tott</u> P P <u>SD Tott</u> 16,5 1 1,559 1 10,7 18 46 1 222 2 ² = 21.44 = 0.99) <u>Tottal</u> 15 15 19 46 19 55 10 25 26 20 21	85 4.6 19 5.0-1 16 2.88 37 4 33 2.4 00 0, df = 5 6 001) al Mean 5 263.5 9 167.4 5 173.8 0 1 17.4 9 0, df = 3 (F Events 0 1 1 4 0 3 1	5 2.4 4 1.56 3 0.55 4 2.1 4 1.7 (P < 0.0 (P < 0.0	390 28 71 26 46 591 0001); ² 12 24 28 23 390 25 390 25 460 100 01); ² = 86 Weight 17.9% 6.6% 20.4% 19.3% 5.3% 20.4% 10.1%	18.1% -2.50 + 2.8 14.8% -1.52 + 2.4 18.9% -0.92 + 1.0 15.3% -0.90 + 1.7 17.4% -0.60 + 1.1 100.0% -1.49 + 2.22 = 93% Mean Differentime Mean Differentime M. Random, 9 .2% -40.40 + 67.60, -1 .2% -40.40 + 67.60, -1 .3% -0.70 + 9.83 .6% 56.70 + 24.97, 40 .0.0% -0.15 + 30.22, 2 % -0.15 + 30.22, 2 % -0.15 + 30.22, 2 % -0.15 + 30.22, 55 .0.8 + [0.09, 25.55] 0.08 + [0.00, 1.95] .0.8 + [0.01, 3.41] 1.50 + 0.33 + 44 .0.45 + [0.04, 4.62] 0.45 + [0.04, 4.62] .0.60 + [0.03, 10.51] -0.60 + 0.33 + 34	9, -2.11, 1, -0.63, 5, -0.79, 1, -0.09, 0, -0.10, 2, -0.77, 5%, C1, 13, 201; 15, 49, 18, 43, 2017, 2017, 2011, 2016, 2016, 2017, 2018, 2019, 2018	year 1 2007 2015 2016 2017 ↓ ↓ ↓	Favours (RALP) Favours (LP) Mean Difference IV, Random, 95% Cl Favours (RALP) Favours (LP) Odds Ratio M-H, Fixed, 95% Cl	
(d) (e)	Silay 2016 Ganpule 2015 Liu 2014 Tam 2018 Chan 2017 Total (95% Cl) Heterogeneity: Tau ² : Test for overall effect Study or Subgroup Franco 2007 Ganpule 2015 Silay 2016 Song 2017 Total (95% Cl) Heterogeneity: Tau ² = Test for overall effect : Study or Subgroup Franco 2007 Subotic 2011 Riachy 2013 Ganpule 2015 Patel 2016 Song 2017 Reinhardt 2017 Tam 2018 Neheman 2018	2.1 3.52 1.96 3.1 1.8 = 0.71; Ch : Z = 4.06 RAL 223.1 4 155 46 173.1 5 254.1 781.13; Ch Z = 0.01 (P RAL Events 0 0 0 0 0 1 1 1 1 1	2.1 1: 1.5 $-$ 0.1 3 3 1.3 6 1.3 6 1.3 6 1.3 6 1.3 6 1.3 7 1.3 7 1.3 6 1.3 7 1.3 6 1.3 7 1.3 6 1.3 7 1.3 7 1.3 6 1.3 7 1.3 7 1.3 7 1.3 6 1.3 7 1.3 6 1.3 7 1.3 7 1.5 7 1.3 7 1.5 7 1	85 4.6 19 5.0-0 16 2.84 37 4 33 2.4 00 0, df = 5 0001) al Mean 5 263.5 9 167.4 5 173.8 0 197.4 9 0, df = 3 (F Events 0 1 1 1 4 0 3 1	5 2.4 4 1.56 3 0.55 4 2.1 4 1.7 (P < 0.0 LP <u>55</u> .2 38.9 < 0.000 <u>Total</u> 12 20 19 28 13 30 13 13 185	390 28 71 26 46 591 12 24 28 23 390 22 460 100 01); P = 86 Weight 17.9% 6.6% 20.4% 19.3% 5.3% 20.4% 10.1%	18.1% -2.50 (-2.8) 14.8% -1.52 (-2.4) 18.9% -0.92 (-1.0) 15.3% -0.90 (-1.7) 17.4% -0.60 (-1.1) 100.0% -1.49 (-2.2) = 93% Mean Differen Mean Differen M. Random, 9	9, -2.11, 1, -0.63 5, -0.79 1, -0.09 0, -0.10 2, -0.77 2, -0.79 2, -0	year 2007 2015 2016 2017 ↓	Favours (RALP) Favours (LP) Mean Difference M. Random, 95% Cl Favours (RALP) Favours (LP) Mean Difference M. Random, 95% Cl Gravours (RALP) Favours (LP) Odds Ratio M-H, Fixed, 95% Cl	
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(d) (e)	Silay 2016 Ganpule 2015 Liu 2014 Tam 2018 Chan 2017 Total (95% Cl) Heterogeneity: Tau ² : Test for overall effect Study or Subgroup Franco 2007 Ganpule 2015 Silay 2016 Song 2017 Total (95% Cl) Heterogeneity: Tau ² = Test for overall effect : Study or Subgroup Franco 2007 Franco 2007 Subotic 2011 Riachy 2013 Ganpule 2015 Patel 2016 Song 2017 Reinhardt 2017 Tam 2018 Neheman 2018 Total (95% Cl) Total events	2.1 3.52 1.96 3.1 1.8 = 0.71; Ch t: Z = 4.06 Mean 223.1 4 155 46 173.1 5 254.1 781.13; Ch Z = 0.01 (P: RAL Events 0 0 0 1 1 1 4 = 3.14, df=	2.1 1: 1.5 $-$ 0.1 3: 1.3 6: 1.3 6: 1.3 6: 1.3 6: 1.3 7: 1.3 6: 1.3 6: 1.3 6: 1.3 6: 1.3 6: 1.3 6: 1.3 6: 1.3 7: 1.3 6: 1.3 7: 1.3 7: 1.5 7; 1.5 7; 1.5 7; 1.5 7; 1.5 7; 1.5 7; 1.5 7; 1.5 7; 1.5	85 4.6 19 5.0.0 16 2.843 37 4 33 2.4 00 0, df = 5 00 0, df = 5 00 1) al Mean 5 263.5 9 167.4 5 263.5 9 167.4 5 173.8 0 197.4 9 0 0, df = 3 (F Events 0 0 1 1 1 1 1 0 3 1 1 1 0.79); ² =	5 2.4 4 1.56 3 0.55 4 2.1 1.7 4 1.7 6 2 3 0.5 5 4 2.1 1.7 7 2 4 1.7 7 2 4 1.7 7 2 4 1.7 7 5 5 2 3 8 9 3 0 5 5 3 8 9 3 0 0 1 1 2 1 2 0 1 9 2 8 1 3 3 0 1 3 3 7 1 3 1 8 5 ≡ 0%	390 28 71 26 46 591 12 24 300 22 460 100 01); P = 80 Weight 17.9% 6.6% 20.4% 19.3% 5.3% 20.4% 10.1%	18.1% -2.50 (-2.8) 14.8% -1.52 (-2.4) 18.9% -0.92 (-1.0) 15.3% -0.90 (-1.7) 17.4% -0.60 (-1.1) 100.0% -1.49 (-2.2) = 93%	9, -2.11, 1, -0.63 5, -0.79 1, -0.09 0, -0.10 2, -0.77 3, 20 5% 5% 61 3, 20 3, 20, 20 3, 2	Year 2007 2016 2017 4 	Favours [RALP] Favours [LP] Mean Difference IV, Random, 95% CI Favours [RALP] Favours [LP] Odds Ratio M-H, Fixed, 95% CI	
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Figure 2. Forest plots comparing LP with RALP. Comparison of: (a) success rate; (b) postoperative complications; (c) length of hospital stay; (d) procedure time; and (e) re-intervention. The solid squares denote the odds ratios or mean difference. The horizontal lines represent the 95% confidence intervals (CIs), and the diamond denotes the pooled-effect size.

LP, laparoscopic pyeloplasty; M-H, Mantel Haenszel test; RALP, robot-assisted laparoscopic pyeloplasty; SD, standard deviation.



Figure 3. Funnel plots comparing outcomes. Comparison of: (a) success rate; and (b) postoperative complications.

OR, odds ratio; SE, standard error of the mean.

review and meta-analysis to compare the outcomes of LP and RALP in children with PUJO and identified 13 cohort studies (1 prospective and 12 retrospective) and a case-control study reporting a total of 2254 paediatric patients [LP (n = 1021) or RALP (n = 1233)]. Our outcome analysis demonstrated that RALP was associated with a significantly higher success rate and shorter length of hospital stay compared with LP. Moreover, it was associated with a nonsignificant reduction in postoperative complications, and re-intervention rate. Nevertheless, our analysis did not find any difference in procedure time between the two groups. The between-study heterogeneity was low in the analyses of success rate, complications and reintervention, suggesting that our conclusions regarding these outcome measures may be robust. However, there was considerable between-study heterogeneity in the analysis of length of hospital stay and procedure time, indicating a variability in reporting by the included studies.

Our findings from this meta-analysis indicate that an increased success rate using a robotic-assisted

approach to paediatric pyeloplasties exists compared with the laparoscopic approach. This was determined utilizing imaging to determine a resolution of the PUJO in patients, in the form of ultrasound scanning or MAG-3 renograms, or describing the resolution of symptoms in patients troubled previously. These findings may be related to the more technically challenging laparoscopic approach in children, considering the much smaller working space, and thus a robotic approach may be adequate to alleviate this, specifically due to the enhanced magnification, threedimensional vision and instrument dexterity associated especially when performing the more technically challenging elements.²⁹ An accelerated learning curve in robotic procedures has also been demonstrated, while maintaining safety and similar efficacies.30

The previous meta-analysis performed by Cundy and colleagues¹⁰ in 2014, found no significant differences in success rate between LP and RALP in a paediatric population. This is not consistent with our findings which demonstrated higher success rate associated with RALP. This may reflect that more widespread use of robotic surgery in recent years has positively influenced the surgeons' learning curve, leading to higher success rate of robotic procedures. Nevertheless, no study quantified the learning curve of RALP to date. Therefore, we believe that our meta-analysis may demonstrate more realistic comparison of the RALP and LP.

We did find reduced postoperative complications and re-intervention rates in the children who underwent a robotically assisted procedure, and despite this not being clinically significant, it may still reinforce the better visualisation, access and approach associated with using the robot for paediatric pyeloplasty operations.

Our study does have some limitations. Namely, we were unable to identify any randomized-controlled trials despite their gold-standard status in comparative studies, with the majority being retrospective cohort studies. This will undoubtedly subject our studies to a degree of selection bias. Considering that an ideal meta-analysis should be a meta-analysis of randomized studies, findings of our metaanalysis of nonrandomized studies should be interpreted in context of its limitation. Furthermore, the risk of bias was moderate or high in most of the included studies, which may subject our finding to bias. Moreover, there remains an inconsistency in

Table 5. Deminitions of operative time in included studies	Table 3.	Definitions	of o	perative	time	in	included	studies
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Study	Definition of operative time
Tam <i>et al.</i> ¹⁴	Skin incision to the end of skin closure
Reinhardt <i>et al.</i> ¹⁶	Skin port incision to end of skin closure
Patel <i>et al</i> . ¹⁸	Included cystoscopy and retrograde pyelogram for LP and patient positioning; robot docking and undocking for RP
Ganpule <i>et al</i> . ²⁰	Start of abdominal insufflation to placement of last skin suture
Riachy et al. ²²	Start of incision for port placement to first trocar incision closure
Casella <i>et al.</i> ²³	Start of cystoscopy to closure of skin incision
Subotic <i>et al.</i> ²⁴	LP: from cystoscopy to dressings on; RP: skin incision to dressings on
LP. laparoscopic pveloplasty: RP. robo	tic pyeloplasty.

definition of operative time, which, through the included studies, can range from commencing at the initial incision or from the initial cystoscopy performed, as highlighted in Table 3. Finally, the included studies heterogeneously reported their follow-up period which was not comparable within and between the included studies. This, undoubtedly, subjects our findings to bias.

We encourage future studies to focus more on stent and drain placement. The psychological impact of drain insertion or living with and removing a II stent, as an infant and for family members, is an important comparative outcome that can be assessed through accurate and reliable reporting in cohort studies. Song and colleagues⁴ suggested that the use of a robotically assisted approach requires less need for JJ stent insertion, comparatively. The use of patient- and familyrelated outcomes measures for this should be included in future studies. Consideration for future research with longer follow up for these patients, into adult life, and a consistent approach in reporting may be necessary to ensure that robust conclusions can be made in favour of an intervention.

Conclusion

Our meta-analysis demonstrated that RALP is safe and may have higher success rate compared with the more traditional laparoscopic approach in a paediatric population. Moreover, it may be associated with lower postoperative complications and re-intervention rates. Considering the ever-increasing exposure to robotically assisted procedures, especially in urological practice, it is imperative that high-quality randomized trials with longer follow up and adequate sample sizes are rolled out worldwide to improve the reliability of conclusions formulated, and the recommendations made for children requiring intervention to last them into their adult life.

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Samih Taktak and Oliver Llewellyn equally contributed to this research and first authorship is shared.

Conception and design: ST, OL

Literature search and study selection: ST, OL, MA

Data collection: ST, OL Analysis and interpretation: ST, OL

Writing the article: ST, OL

Critical revision of the article: All authors Final approval of the article: All authors

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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