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Single incision *versus* standard multiport laparoscopic cholecystectomy: up-dated systematic review and meta-analysis of randomized trials

Short title: SILC *versus* MLC meta-analysis

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Key words: laparoscopic cholecystectomy, single incision, multiport, meta-analysis

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Abstract

Background and purpose. We aimed to compare single incision laparoscopic cholecystectomy (SILC) to the standard multiport technique (MLC) for clinically relevant outcomes in adults. **Methods**. Systematic review and random-effects meta-analysis of randomized trials. **Results**. We identified 30 trials (SILC N=1209, MLC N=1202) mostly of moderate-to-low quality. Operating time (30 trials): longer with SILC (WMD=12.4 min, 95%CI 9.3, 15.5; p<0.001), but difference reduced with experience – in 10 large trials (1321 patients) WMD=5.9 (-1.3, 13.1; p=0.105). Intra-operative blood loss (12 trials, 1201 patients): greater with SILC, but difference practically irrelevant (WMD=1.29 mL, 0.24-2.35; p=0.017). Procedure failure (27 trials, 2277 patients): more common with SILC (OR=13.9, 4.34-44.7; p<0.001), but overall infrequent (SILC pooled incidence 4.39%) and almost exclusively addition of a trocar. Post-operative pain (29 trials) and hospital stay (22 trials): no difference. Complications (30 trials): infrequent (SILC pooled incidence 5.35%) with no overall SILC vs. MLC difference. Incisional hernia (19 trials, 1676 patients): very rare (15 vs. 4 cases), but odds significantly higher with SILC (OR=4.94, 1.26-19.4; p=0.025). Cosmetic satisfaction (16 trials, 11 with data at 1-3 months): in 5 trials with non-blinded patients (N=513) in favor of SILC (SMD=1.83, 0.13, 3.52; p=0.037), but in 6 trials with blinded patients (N=719) difference small and insignificant (SMD=0.42, -1.12, 1.96; p=0.548). **Discussion**. SILC outcomes largely depend on skill, but irrespectively of it, compared to MLC, it requires somewhat longer operating time, risk of incisional hernia is higher (but overall very low) and early cosmetic benefit is modest. **Conclusion**. From the (in)convenience and safety standpoint, SILC is an acceptable alternative to MLC with a modest cosmetic benefit.

Introduction

Laparoscopic cholecystectomy is a widely accepted standard in treatment of benign gallbladder diseases.[1] Shortly after Mühe[2] had performed the first laparoscopic cholecystectomy in 1985 using a modified laparoscope, Mouret[3] performed the first video-assisted laparoscopic cholecystectomy in 1987. The procedure gained wide acceptance due to advantages of a smaller incision, less postoperative pain, shorter hospital stay and faster return to everyday living as compared to the traditional open approach.[4] To further enhance these benefits, even more minimally invasive techniques have been developed. These include needlescopic cholecystectomy, natural orifice transluminal endoscopic surgery (NOTES) cholecystectomy and single-incision laparoscopic cholecystectomy (SILC). The latter technique was first described in 1995[5]. Although it might not have enjoyed a widespread use, it has gained a fair share of popularity: we were able to identify 16 meta-analyses of randomized controlled trials (RCTs) comparing SILC to the standard multiport laparoscopic cholecystectomy (MLC) published by the mid 2013 (Table 1). The two largest reviews referred to 16[13] and 24[9] RCTs in adults (Table 1). Since further RCTs have been conducted in the meantime, we found it plausible to perform an up-dated literature search and a systematic review of RCTs comparing SILC to MLC.

Materials and Methods

This study followed methodological recommendations for systematic reviews as given in the PRIMSA statement[22] and Cochrane Handbook for Systematic Reviews.[23]

Literature search

Electronic databases [Pubmed MEDLINE, Ovid MEDLINE, EBM Reviews (all Cochrane Library), Scopus – Health Sciences, ISI Web of Knowledge, EBSCO (Academic Search Complete, CINAHL and ERIC) and Google Scholar] were searched till December 9, 2013. The strategy was designed to be sensitive, not specific: the search terms “laparoscopic“, “cholecystectomy“, “single port“, “single site“, “single incision“, “transumbilical“, “laparo-endoscopic“, “SILS“ and “SILC“ were used in combination with Boolean operators AND and OR (“all fields”). No limits, filters or restrictions were set. Reference lists of identified reviews/articles were also searched (Fig. 1).

Study selection and abstracting

Study inclusion criteria were: a) RCT, irrespective of language, country of origin, blinding or publication status; b) compared SILC to MLC for a benign gallbladder disease. We defined SILC as a laparoscopic cholecystectomy through a single skin incision either using multiport devices specifically designed for SILC or using conventional trocars introduced through separate fascial incisions. MLC was defined as a laparoscopic cholecystectomy through three or four skin incisions irrespective of their length and position; c) included adults ≥18 years of age; d) did not report duplicate data; e) provided data on at least one of the pre-defined outcomes. Exclusion of duplicate publications was computer-assisted (Reference Manager version 12, Thomson Reuters) (Fig 1). Study selection/abstracting were performed by two independent authors. Discrepancies were resolved through a consensus of all authors.

Study quality assessment

Two authors independently evaluated study quality using the Cochrane Collaboration recommended tool[23] that critically assesses selection, performance, detection, attrition, reporting and other potential biases. It categorizes risks (of bias) as “low” (explicit evidence of

measures to minimize the bias), "high" (explicit evidence of no measures to control the bias) and "uncertain". In the category of "other biases" we assessed the risk of differential expertise bias, i.e., a bias due to discrepancy in investigators' (in)experience with SILC relative to MLC. Different views have been expressed about the SILC learning curve – 5[24], 10[25] or 20 to 25[26] surgeries have been suggested as needed to reach the plateau. We chose the learning curve of 10 cases as a cut-off: when there was explicit evidence that before the trial investigators had performed <10 SILC procedures, the risk was assessed as "high"; when at least 10 procedures had been performed, the risk was assessed as "low"; otherwise the risk was assessed as "uncertain". Disagreements were resolved through a consensus of all authors.

Outcomes for quantitative review

We defined seven (co)primary outcomes of interest in order to comprehensively characterize SILC in relation to MLC: a) Intra-operative - duration of surgery; blood loss; procedure failure. For SILC, failure was defined as addition of an extra port (standard or needlescopic) or as conversion to open surgery or MLC (transabdominal sutures or wires for gallbladder retraction were acceptable). For MLC, failure was defined as addition of an extra port or conversion to open surgery or SILC; b) Peri- and postoperative - spontaneous abdominal pain at rest (quantitative data on pain perception); complications (biliary, wound-related and other complications excluding nausea/vomiting and non-specific mild adverse events); length of hospital stay; patient satisfaction with the cosmetic outcome.

Data extraction

Data were extracted independently by two authors and discrepancies were resolved through a consensus of all authors. A digitizing software Dagra (Blue Leaf Software, New Zealand) was

used to retrieve numerical values from graphs. For dichotomous outcomes, patient-level data (n/N) were extracted. A non-event was considered reported only when explicitly stated, otherwise a particular outcome was considered not reported. Validated methods were used to estimate means and standard deviations (SDs) from medians and ranges[27] or to input SDs[28] where needed. Most of the cosmetic scales assigned higher values to better outcomes hence inverse values were used in the case of scales with the opposite scoring systems.

Effect measures

Continuous outcomes quantified by different scales (cosmetic satisfaction, pain) were pooled as standardized mean difference (SMD), otherwise (weighted) mean difference (WMD) was used. For cosmesis, 15 different time points (day 3 to 1 year after surgery) were reported across the trials. They were collapsed into four postoperative periods: 1-21 days, 1-3 months, 6 months and 1 year post-surgery. For pain, 16 different time points (2 hours to 1 month after surgery) were reported. They were collapsed to 11 periods: up to 3 hours, 4 hours, 6-8 hours, 12 hours, 24 hours, 48 hours, 72 hours, 4-5 days, 7 days, 10-14 days and 1 month post-surgery. Time points not fitting into these periods and/or with data from <3 trials were omitted. When multiple time-point data within a period were reported, pooled mean and SD represented the respective time period. Dichotomous outcomes were summarized as odds ratios (OR).

Data analysis

Random-effects meta-analysis was employed. For repeated-measures outcomes, separate estimates for different time periods (no pooling) were produced. Heterogeneity was evaluated by the Q-test and I^2, and publication bias was assessed by inspection of the funnel plots, Egger's regression and trim-and-fill method. Conventional meta-analytical methods do not perform well

with sparse binary data (procedure failure, complications).[23,29,30] For convenience, they were summarized as Mantel-Haenszel (M-H) odds ratio (OR). However, zero frequency cell correction and omission of zero-event studies (inherent to the M-H method) can introduce bias. [23,29,30] Hence, we implemented methods that use all trials and do not employ corrections: a) a random-effects method for sparse dichotomous data by Shuster et al.[29] and b) random-effects analysis within the bivariate binomial-normal model (BN).[30] The latter provides estimates of event incidence for each treatment and of treatment difference (OR). Between-trial heterogeneity is indicated by: (i) across-trial variance (τ^2) of log(odds) by treatment; (ii) covariance between log(odds) for two treatments and (iii) across-trial variance of overall treatment effect [log(OR)].[30] We considered that the effect of surgical skill (SILC) on the SILC vs. MLC differences should be investigated. We assumed that trials with more SILC-treated patients came from more experienced investigators – a larger patient turn-over would result in more experience and possibility to enroll more patients, and a larger trial *per se* increases experience with the procedure (learning through the trial). Therefore, we evaluated the relationship between the number of SILC-treated patients and size of the effect. Other predefined factors in exploration of heterogeneity were: a) risk of differential expertise bias (pre-trial experience with SILC); b) other biases [e.g., risk of performance bias (blinding of participants) in the case of subjective outcomes (cosmesis, pain)]. Covariate effects were assessed by random-effects meta-regression with residual (restricted) maximum likelihood (REML) estimation. Explanation of heterogeneity is illustrated by reduction in τ^2 and by residual I^2.[31,32] We used CMA version 2.2 software (Biostat Inc., Englewood NJ, USA) and SAS 9.3 for Windows (SAS Inc., Cary, NC, USA) *proc nlmixed* (BN

method)[30], *proc mixed* (meta-regression)[33] and a SAS macro for sparse dichotomous data by Shuster[29] (available from http://ags.bwh.harvard.edu/).

Results

Characteristics and quality of the included trials

We identified 30 RCTs (Fig. 1) with 2411 patients (1209 SILC, 1202 MLC). Most trials (25/30) included ≤50 SILC-treated patients, follow-up varied considerably across the trials, whereas variations of patient demographics across treatments and trials were moderate (Table 2). Trials differed regarding the SILC technique and instruments (Table 3). One trial[43] included 2 MLC groups: 3-port and 4-port. Data were pooled into one MLC group for the following reasons: a) only 3 other trials used exclusively a 3-port MLC and two trials combined the 3-port and 4- port approaches not making a distinction. Therefore, there was too few data to compare SILC separately to a 3-port and a 4-port MLC; b) the results for the two MLC approaches in this one trial[43] were practically identical. Trials also varied regarding the gallbladder retraction methods in SILC, inclusion/exclusion criteria and analgesic strategies (not shown), and blinding (Table 4). In 11/30 trials, investigators had performed <10 SILC procedures before the trial, i.e, the risk of differential expertise bias was high and it was uncertain in further nine trials (Table 4). Other quality limitations were related mainly to the risk of attrition (high in 6/30, uncertain in 8/30 trials) and performance bias (high in 2/30, uncertain in 19/30 trials) (Table 4). Study quality and size did not appear related (Table 5).

SILC vs. MLC: Intra-operative outcomes

Operating time

Operating time (all trials) was longer with SILC by 12.4 minutes ($p<0.001$) with high heterogeneity (Fig. 2A). Heterogeneity was largely resolved in a meta-regression analysis accounting for differential expertise bias (pre-trial SILC experience) and the number of SILC-treated patients [21.3% heterogeneity explained, I^2 reduced from 87% (high) to 47.8% (moderate)] (Figure 2B). The SILC vs. MLC WMD in operating time was significantly lower in trials with a low risk of bias than in trials with a high risk (Δ WMD= -11.5 min, p=0.040) (Fig. 2B). Similarly, the SILC vs. MLC WMD was significantly lower in trials with >40 SILC-treated patients than in other trials (Δ WMD= -12.0 min, p=0.010) (Fig. 2B).

Intra-operative blood loss

Data from 12 trials (1201 patients) indicated a slightly greater (WMD=1.29 mL, p=0.017) blood loss with SILC, with negligible heterogeneity (Fig. 3). The SILC vs. MLC difference was consistent across the subsets of trials regarding the risk of expertise bias or number of SILC-treated patients (not shown). The "one-trial-omitted" analysis indicated consistent treatment difference except in the case of removal of studies Cao 2011[39] or Lai 2011[44], when difference was reduced to ≤1.0 mL and was not statistically significant (not shown).

Procedure failure

Data were available from 27 trials (2277 patients), however 5 trials were with no events (26/54 treatment arms with no events), hence conventional meta-analysis used 22 trials and indicated higher odds of procedure failure with SILC vs. MLC with no heterogeneity (Figure 4A). The sparse data-specific methods (all 27 trials, no continuity correction) yielded much higher estimates of treatment difference (ORs around 8-13) (Fig. 4B). Overall, procedure failure was reported for 69/1142 SILC-treated patients (Fig. 4B), where 55 cases referred to addition of a

trocar, 2 to conversion to open surgery and 12 to conversion to MLC; whereas MLC failed in 6/1135 patients [1 addition of a trocar, 2 conversion to open surgery, 1 conversion to SILC[38] (due to the intra-abdominal condition) and 1 conversion from a 3-port to a 4-port procedure]. The BN method indicated a random-effects pooled incidence of failure with SILC of 4.39% with high heterogeneity (τ^2 =1.43, p=0.019) vs. 0.53% with MLC (no heterogeneity) (Fig. 4B). The SILC vs. MLC difference was consistent across the subsets of trials based on the risk of expertise bias and the number of SILC procedures (not shown), however experience with SILC apparently reduced the risk of procedure failure: in 17 trials with a high/uncertain risk of expertise bias estimated incidence of failure was 5.16% with high heterogeneity (τ^2=1.82), whereas in 10 trials with a low risk of bias it was 3.60% with no heterogeneity. Similarly, in 17 trials with up to 40 SILC procedures, estimated incidence of failure was 4.85% with high heterogeneity (τ^2= 1.73), whereas in 10 trials with >40 SILCs it was 3.30% and with lower heterogeneity (τ^2 =0.89).

SILC vs. MLC: Peri- and postoperative outcomes

Post-operative pain

Overall, 29 trials reported on post-operative pain but the number of trials/patients across the analyzed time periods varied being the largest at 24 hours after the surgery (Fig. 5A). No SILC vs. MLC difference was statistically significant although point-estimates were mostly mildly in favor of SILC, all with high heterogeneity (Fig. 5A). At 24 hours post-surgery the difference tended towards statistical significance (SMD -0.30, p=0.093) (Fig. 5B). Around 1/3 of the between-trial variance at 24 hours post-surgery was explained by accounting for the risk of performance bias (patients blinded or not) and the number of SILCs in the trial. In 8 trials with a low risk of bias (blinded patients), SILC vs. MLC SMD was small and insignificant (SMD -0.15, p=0.591), whereas

in other trials it was large and statistically significant (SMD=-0.64, p=0.003) (Fig. 5C). The SILC vs. MLC SMD became more negative (more in favor of SILC) with a larger number of SILCs in a trial, but only in trials with a high/uncertain risk of performance bias (Fig. 5C).

Complications

Data were available from all trials. Cumulative numbers of patients by individual reported complications are listed in Table 6. There were no events in 5 trials (16/60 treatment arms with no events), hence conventional meta-analysis used 25 trials indicating no difference between treatments and no heterogeneity (Fig. 6A). The sparse data-specific methods using all 30 trials indicated similarly small treatment effects, but with high between-trial heterogeneity (the BN method) (Fig. 6B). The estimated random-effects incidence of complications for SILC (103/1209) was 5.35% vs. 3.79% for MLC, both with high variance across trials (Fig. 6B). Treatment differences and incidence of complications with SILC were similar in trials with a smaller and a larger number of SILC-treated patients (not shown). In 10 trials with a low risk of expertise bias, SILC vs. MLC difference was the largest (OR=1.56, 95%CI 0.91-2.67, p=0.096) and the pooled incidence in the SILC arm was high (10.7%), whereas in 20 trials with a high/uncertain risk of expertise bias there was practically no SILC vs. MLC difference (OR=1.04, p=0.859) and incidence in the SILC arms was low (4.0%). Occurrence of incisional hernia was explicitly stated in 19 trials (1676 patients), but 12 were with no events (Table 7). Hence, conventional meta-analysis used only 7 trials indicating no difference between treatments (Table 7). The sparse data-specific methods, however, and particularly the preferred unweighted method by Shuster[29] clearly indicated a higher risk of incisional hernia with SILC (OR=4.94, p=0.025) (Table 7).

Hospital stay

Data from 22 trials (1864 patients) indicated no difference between the procedures and high heterogeneity (Fig. 7). The best explanation of heterogeneity was achieved in a meta-regression model accounting for attrition and detection (investigators blinded or not) bias: it explained 33.8% of the between-trial variance and the residual I^2 was 79.1%. In trials with blinded investigators, i.e., low risk of detection bias (12 trials, 536 patients SILC, 566 patients MLC), hospital stay was somewhat shorter with SILC and in trials with uncertain risk of bias (10 trials, 374 patients SILC, 388 MLC), it was somewhat longer: the difference between the two subsets (-0.28, 95% CI -0.57, 0.01; p=0.061) indicated a greater difference in favor of SILC when assessors were blinded.

Patient satisfaction with the cosmetic outcome

Overall, 16 trials reported cosmetic outcomes but the number of trials/patients at the analyzed time periods varied being the highest at 1-3 months post-surgery (Fig. 8A). All SILC vs. MLC differences (SMD) were statistically significantly in favor of SILC and all with high heterogeneity. Treatment difference apparently decreased at later time periods (6 months, 1 year post-surgery) (Fig. 8A). At 1-3 months post-surgery, the difference in favor of SILC was the largest (SMD=0.99, p<0.001) (Fig. 8B). Although the effect appeared particularly large in one trial (Pan 2013)[54], the "one-trial-omitted" analysis showed consistently significant difference in favor of SILC and consistently high heterogeneity. Heterogeneity at this time point was practically completely resolved by accounting for the risk of performance bias [I^2 reduced from 94.0% (high) to 35.0% (mild)] (Fig. 8C) – in trials with blinded patients (low risk of bias) the difference was small and insignificant (SMD=0.42, p=0.548), whereas in other trials it was large and significant (SMD=1.83, p=0.037) (Fig. 8C).

Discussion

Using MLC as an example, Allori *et al*.[65] emphasized the need for thorough appraisal of surgical innovations before they are accepted as safe and effective. We therefore reasoned that an updated evaluation of SILC based on trials comparing it to MLC would be a worthwhile effort.

Strengths and limitations of the present analysis

We find the following to be the strengths of the present analysis: a) identification of the largest number of RCTs in adults as compared to previous systematic reviews; b) comprehensive evaluation of the publication bias; c) systematic evaluation of trial quality; d) use of methods designed for sparse dichotomous data and investigation of heterogeneity. However, limitations inherent to any systematic review remain: a) existence of unpublished data cannot be excluded; b) all review and meta-analytical methods have limitations; c) quality and completeness of the source data cannot be influenced – it may not be possible to adjust for the flaws of individual trials at the meta-analytical level.

Amount and quality of the data

SILC does not introduce a new therapeutic concept but tends to improve the cosmetic outcome of MLC while being at least as practical and safe. Hence, 2411 patients in 30 RCTs should generally represent a reasonable basis for its evaluation. Obstacles to this effort are primarily due to incomplete reporting and quality of trials. Operating time and incidence of complications were the only outcomes addressed in all 30 trials[35-64]. Also, it is surprising that only 16/30 trials provided quantitative data on patient satisfaction with cosmesis. In most of these instances, incomplete reporting referred to the failure to explicitly state the lack of events. Next, failure to report basic patient characteristics reduced a possibility of exploration of heterogeneity (e.g.,

impact of sex ratio on the SILC-MLC differences in cosmetic outcome or pain). Finally, failure to report measures or to explicitly declare a lack of measures for controlling different biases left a high level of uncertainty. Overall, apart from two high-quality trials and one "very low quality" trial, the trials were of moderate to low quality considering the standard[23] parameters. We find three of those to be particularly relevant. If the objective is to evaluate the method *per se*, "mixing" of data from differently skilled surgeons (confounding of skill and method) is inappropriate. Therefore, failure to report one's own level of skill with the investigated method is a drawback. A further drawback is a failure to perform patient-blinded evaluation of subjective outcomes (pain, cosmesis). Finally, inappropriate handling of patient attrition may impact the results particularly in small trials. However, a fairly large number of identified trials allowed us to employ analyses that enabled a reasonably unbiased assessment of SILC.

Main findings

Operating time and procedure failure

In all but two trials (Fig. 2A), operating time was longer for SILC than for MLC by at least a few minutes. However, considering differences between trials (surgeons' experience, number of SILCs, surgical technique/instruments) the pooled estimate (12.4 minutes) tells little about a part that would be "inherent to the method". The present analysis emphasizes the importance of experience/skill with the method. The SILC vs. MLC differences in trials with low risk of expertise bias (investigators with ≥10 SILCs before the trial; 9.6 minutes) and those with >40 SILC-treated patients in the trial (5.9 minutes, p=0.106) suggest that skilled surgeons do not require relevantly (if at all) more time to complete SILC than they need for MLC. Since these differences were significantly lower (by around 11-12 minutes) than in smaller trials and in trials

with a high risk of expertise bias, they could be considered “inherent to SILC”. The present analysis indirectly indicates that experience with SILC and operating time (difference vs. MLC) are, at least in part, related “through” procedure failure. Procedure failure (almost exclusively a need for an additional trocar) was clearly more frequent with SILC but incidence was lower in larger trials and in trials with pre-trial SILC-experienced surgeons indicating the “learning effect”. The fact that even in trials with >40 SILC-treated patients (3.30%) or with pre-trial experienced surgeons (3.60%) incidence of procedure failure with SILC was higher than the overall estimate for MLC (0.53%) indicates that there might be some level of procedure failure that is “inherent to the method”.

Intra-operative blood loss

Present analysis indicates a significantly greater intraoperative blood loss with SILC vs MLC. However, the difference (1.29 mL) is small and practically irrelevant. It should be noted also that numerical values were in favor of SILC in 5/12 trials, in favor of MLC in 6/12 trials, while one trial reported no difference (Fig. 3). Considering the logic of the random-effects meta-analysis (estimates the mean of a distribution of individual effects), it seems plausible to conclude that the existing number of trials (n=12) is too small to illustrate the true “distribution of effects” – one further trial could greatly change the situation.

Post-operative pain

Two characteristics were evident regarding post-operative pain: a) use of different measurement tools; b) different analgesic strategies in different trials with only sporadically precisely defined timing of pain assessment relative to administration of analgesia. The former required SMD as a summary effect measure which is not very intuitive in a clinical sense. The

latter is an important issue since assessments under analgesia are biased towards a conclusion of "no difference". However, considering the number of trials and patients, it is reasonable to consider the pooled estimates as quite robust. The main present finding is that there is no "SILC-inherent potential" to reduce early postoperative pain (vs. MLC): a) pooled estimate at 24 hours post-surgery (adjusted for the number of SILCs, i.e., "surgeons' skill") of treatment difference when patients were blinded was close to 0 with no effect of trial size; b) when non-blinded assessment was performed, SILC yielded significantly less pain (SMD=-0.64, p=0.003), more so in trials with more SILC-treated patients. The difference between these two estimates could be denoted a "para-SILC effect" or "bias". Although it might be practically relevant (i.e., if patients feel less pain, the "reason" for that is of secondary interest), it apparently depends on surgeons' skill and might not be reproducible.

Complications

The present analysis focused on bile- and wound-related complications, but included also "other complications" apart from nausea/vomiting and minor non-specific adverse events (identified terms listed in Table 6). The problems with the analysis are related to different (across trials) or unknown periods of follow-up and failure to explicitly state non-events. These are study-level factors and it is difficult or impossible to control for the bias that they could introduce. As an example, 19/30 included trials explicitly referred to incisional hernia, 7 reporting at least one case, 12 explicitly stating "no events", but 11 made no reference to this complication. Although incisional hernia might not be a complication that would be underreported, it is methodologically erroneous to include such trials in the analysis.[23] The problem with less remarkable (potential) complications is even greater. Consequently, it is not feasible to

separately analyze individual complications (apart from the most remarkable ones), rather "overall complications" is an outcome of interest. The present analysis indicated no clear SILC vs. MLC difference in this respect. Apparently paradoxically, in trials conducted by the pre-trial SILC-experienced surgeons, SILC vs. MLC difference was greater (OR=1.56, p=0.096) and incidence of complications in the SILC arms was higher (10.7%) than in trials with a high/uncertain risk of expertise bias (OR=1.04, p=0.859; SILC pooled incidence 4.0%). Since the former trials were characterized by a negligible SILC vs. MLC difference in operating time, combined data suggest that SILC inherently is prone to somewhat more local complications (biliary, wound-related) than MLC, regardless of the experience with the method, but that this could be "leveled-off" by taking more time to complete the procedure. In particular, although the total number of events was low (15/839 SILC-treated and 4/837 MLC-treated patients in 19 trials), the present analysis strongly suggests that SILC is associated with an increased risk of incisional hernia (OR=4.94, 95%CI 1.26-19.4, p=0.025).

Hospital stay

It has been suggested that SILC could be implemented as a day surgery[66], but none of the included reports[35-64] indicated that the "day surgery" concept was practiced. Under such conditions, the present analysis indicates no relevant SILC vs. MLC difference.

Patient satisfaction with cosmetic outcome

Considering the almost exclusive use of a 4-port MLC and a variety of small differences in port sizes (see Table 3), the existing published RCTs[35-64] do not allow for a pooled evaluation of SILC separately vs. the 3-port and 4-port MLC (or any of their variations), rather, the only feasible comparison is that of SILC vs. "MLC in general". The use of SMD allowed pooling of data

collected with different instruments [most commonly 4 - 11-point Likert scales (sometimes with inverse grading), or more complex specific instruments but with different (and even inverse) grading] but SMD is not clinically intuitive and this way of "data merging" is not sensitive to potential conceptual differences between different instruments. Finally, the overall amount of data for the long(er)-term post-surgical periods is still modest - 3 trials (N=390) provided data for 6 months and 4 trials (N=351) provided data for 1 year post-surgery. A common problem with long(er) trials is patient attrition. For example, the largest trial with 1-year data (Marks 2013)[51] experienced a 20% drop-out rate by this time, and there seems to be no remedy for this problem (and the bias that it could introduce) – the "last observation carried-forward" principle, that otherwise might help preserve the intent-to-treat analysis, could even further bias the results if the natural history of the cosmetic outcome was to show reduced SILC vs. MLC difference over time due to improvement in the MLC-treated patients. The amount of data for a short(er)-term period (1-3 months) appears reasonable (11 trials, 1232 patients). Numerically, all but one trial were in favor of SILC (Fig. 8) and the pooled estimate was highly statistically significant. Still, considering the design/conduct differences between trials and heterogeneity of treatment effects, it tells little about the effect that would be "inherent to the method". The major finding of the present analysis is that when patients were blinded (6 trials, 719 patients), difference in favor or SILC was not statistically significant. At the same time, in a similarly sized subset of trials (5 trials, 513 patients) with non-blinded patients, difference in favor of SILC was four times greater and statistically significant. The former could be considered a difference "inherent to SILC". Its size, expressed as SMD (0.42) is difficult for clinical interpretation, and it

would be so even if expressed in some scale units – unless a minimally important difference had been defined.

Conclusion

The present systematic review embraced 30 RCTs[35-64] comparing SILC to MLC in adult patients (N=2411), more than any of the previously published similar reports[6-21]. Despite the fact that the overall trial quality is "far from ideal", a fairly reasonable evidence-based assessment of SILC is possible. Only medium-term (1-3 months post-surgery) data are reasonably numerous regarding the main targeted objective of the procedure - a better cosmetic outcome. Although technical approach in SILC "promises" improvement over MLC, the present analysis suggests that a difference "inherent to SILC" is, at best, modest. In order to adequately assess its clinical relevance future trials should use standardized measurement tools and provide long-term data. Definition of a "minimally important difference" seems to be necessary. The risk of procedure failure, practically exclusively addition of a trocar, is clearly higher with SILC and it inherently requires somewhat more time for completion. Both aspects could be minimized with improved experience/skill. Since there is no evidence of SILC vs. MLC differences in pain or hospital stay, and that the difference in intraoperative blood loss is small and practically irrelevant, it is reasonable to state that SILC is acceptable from the (in)convenience standpoint. However, the present analysis strongly suggests that the risk of incisional hernia is relevantly higher with SILC. Fortunately, absolute numbers are low. Overall, although SILC has been discussed as a potential "new standard in cholecystectomcy"[54] the presently existing published RCTs comparing it to MLC suggest that it should rather be viewed as an acceptable alternative.

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Fig. 1 Prisma flow-chart of the study selection process.

* One trial (Marks 2013, see Table 2) was described also in a preliminary report.[34] Both papers were used to extract methodological particulars, but only the complete report (Marks 2013) was used for outcome extraction.

Fig. 2 Difference between single-incision (SILC) and standard multiport (MLC) laparoscopic cholecystectomy in operating time (minutes). **A**. Random-effects meta-analysis. Data are summarized as (weighted) mean differences (WMD), heterogeneity is illustrated by the Q-test and I^2 value. Inspection of the funnel plot, Egger's regression and trim-and-fill method did not indicate publication bias. The adjudicated levels of differential expertise bias [Diff.exp. (L=low, H=high, U=uncertain) are also shown. **B**. Meta-regression analysis of the SILC vs. MLC WMD with two independent variables: risk of expertise bias and number of SILC procedures in the trial. Explanation of heterogeneity is indicated by percent between-trial variance explained and residual I^2.

Fig. 3 Difference between single-incision (SILC) and standard multiport (MLC) laparoscopic cholecystectomy in intraoperative blood loss (mL) - random-effects meta-analysis. Data are summarized as (weighted) mean differences (WMD), heterogeneity is illustrated by the Q-test and I^2 value. Inspection of the funnel plot, Egger's regression and trim-and-fill method did not indicate publication bias. The adjudicated levels of differential expertise bias [Diff.exp. (L=low, H=high, U=uncertain) are also shown.

Fig. 4 Difference between single-incision (SILC) and standard multiport (MLC) laparoscopic cholecystectomy in incidence of procedure failure. **A**. Conventional random-effects (Mantel-Haenszel, M-H) meta-analysis. Data are summarized as odds ratios (OR), heterogeneity is illustrated by the Q-test and I^2 value. Inspection of the funnel plot, Egger's regression and trim-and-fill method did not indicate publication bias. The adjudicated levels of differential expertise bias [Diff.exp. (L=low, H=high, U=uncertain) are also shown. **B**. Pooled estimates (OR) generated by methods specifically designed for sparse dichotomous data (no continuity correction, use all trials): the bivariate binomial-normal (BN) method[30] and method by Shuster[29] with unweighted (recommended) and weighted estimation. The BN method provides random-effects estimates of incidence by treatment and of variance across trials within treatment, and also variance across trials between treatments (τ^2) with a formal t-test for heterogeneity (p-values indicated).

Fig. 5 Difference between single-incision (SILC) and standard multiport (MLC) laparoscopic cholecystectomy in post-operative pain. **A**. Pooled random-effects estimates of treatment difference (standardized mean difference, SMD) at different times after the surgery (indicated time-points, number of trials and patients). Heterogeneity is illustrated by the Q-test and I^2 value. Inspection of the funnel plot, Egger's regression and trim-and-fill method did not indicate publication bias at any point. The largest number of trials reported on 24 hours post-surgery (bolded). **B**. Random-effects meta-analysis at 24 hours post-surgery. The adjudicated levels of differential expertise and performance bias [Exp., Perf. (L=low, H=high, U=uncertain)] are also shown. **C**. Meta-regression analysis of the SILC vs. MLC SMD at 24 hours post-surgery with independent variables: risk of performance bias, number of SILC procedures in the trial and their interaction. Explanation of heterogeneity is indicated by percent between-trial variance explained and residual I^2.

Fig. 6 Difference between single-incision (SILC) and standard multiport (MLC) laparoscopic cholecystectomy in incidence of complications. **A**. Conventional random-effects (Mantel-Haenszel, M-H) meta-analysis. Data are summarized as odds ratios (OR), heterogeneity is illustrated by the Q-test and I^2 value. Inspection of the funnel plot, Egger's regression and trim-and-fill method did not indicate publication bias. The adjudicated levels of differential expertise and attrition bias [Diff.exp., Attrig. (L=low, H=high, U=uncertain) are also shown. **B**. Pooled estimates (OR) generated by methods specifically designed for sparse dichotomous data (no continuity correction, use all trials): the bivariate binomial-normal (BN) method[30] and method by Shuster[29] with unweighted (recommended) and weighted estimation. The BN method provides random-effects estimates of incidence by treatment and of variance across trials within treatment, and also variance across trials between treatments (τ^2) with a formal t-test for heterogeneity (p-values indicated).

Fig. 7 Difference between single-incision (SILC) and standard multiport (MLC) laparoscopic cholecystectomy in length of hospital stay (days) - random-effects meta-analysis. Data are summarized as (weighted) mean differences (WMD), heterogeneity is illustrated by the Q-test and I^2 value. Inspection of the funnel plot, Egger's regression and trim-and-fill method did not indicate publication bias. The adjudicated levels of differential expertise, attrition and detection bias [Diff.exp., Attrit., Detect., (L=low, H=high, U=uncertain) are also shown.

Fig. 8 Difference between single-incision (SILC) and standard multiport (MLC) laparoscopic cholecystectomy in patients' satisfaction with cosmetic outcome. **A**. Pooled random-effects estimates of treatment difference (standardized mean difference, SMD) at different times after the surgery (indicated are time-points, number of trials and patients). Heterogeneity is illustrated by the Q-test and I^2 value. Inspection of the funnel plot, Egger's regression and trim-and-fill method did not indicate publication bias at any point. The largest number of trials reported on 1-3 months post-surgery (bolded). **B**. Random-effects meta-analysis at 1-3 months post-surgery. The adjudicated levels of differential expertise, performance and attrition bias [Exp., Perf., Attrit. (L=low, H=high, U=uncertain)] are also shown. **C**. Meta-regression analysis of the SILC vs. MLC SMD with the risk of performance bias as an independent variable. Explanation of heterogeneity is indicated by percent between-trial variance explained and residual I^2.

Table 1 Main characteristics of published meta-analyses (by author) of clinical studies comparing single incision laparoscopic cholecystectomy and multiport laparoscopic cholecystectomy identified through December 9, 2013.

Author, year	Country	Included studies (N)	Included patients (N)
Arezzo 2013[6]	Italy	12 RCTs	996
Bingener 2013[7]	USA	5 RCTs	502
Garg 2012[8]	India	9 RCTs	659
Geng 2013[9]	China	25 RCTs (1 pediatric)	1841
Hao 2012[10]	China	15 RCTs	1113
Markar 2011[11]	United Kingdom	7 RCTs	375
Pisanu 2012[12]	Italy	12 RCT	892
Qiu 2013[13]	China	40 studies, 16 RCTs, 24 non-randomized	3711
Sajid 2012[14]	United Kingdom	11	858
Trastulli 2012[15]	Italy	13	923
Wang, D 2012[16]*	China	9	–
Wang, Z 2012[17]	China	5	264
Wu 2012[18]	China	9	755
Zehetner 2013[19]	USA	9	695
Zhang 2013[20]	China	11	859
Zhong 2012[21]	China	7	611

RCTs, randomized controlled trials

*Abstract form, number of subjects not declared.

Table 2 Main study characteristics (by author). Data presented as in the original publications.[35-64]

Study	Country	Patients (N)		Age (years)		Sex ratio F/M		BMI (kg/m^2)		Follow-up
		SILC	MLC	SILC	MLC	SILC	MLC	SILC	MLC	
Aprea 2011*	Italy	25	25	45.5±9.4	44±10	16/14	19/6	25.9±5.8	23.7±4.6	NR
Bresadola 1999#	Italy	45	45	42±20	45±15	19/9	22/15	NR	NR	NR
Brown 2013	USA	40	39	42 (21-75)	43 (18-76)	29/11	21/9	27.9±4.3	30.3±6.9	4 weeks
Bucher 2011	Switzerland	75	75	42 (18-81)	44 (20-78)	NR	NR	26 (22-35)	25 (19-34)	1 month
Cao 2011	China	57	51	62.2±5.1	59.7±4.4	34/23	29/22	28.6±4.4	29.1±5.1	1 month
Chang 2012	Singapore	24	26	49.5±11.49	51.2±12.3	14/10	16/10	24.1±4.2	27.7±7.8	2 weeks
Ellatif 2012	Egypt	125	125	47.7±10.6	46.9±11.4	95/30	88/37	26.9±5.5	29.5±5.6	6 months
Herrero Fonollosa 2012	Spain	26	24	45±12	49±12	20/6	14/10	26±4	25±2	6 months
Khorgami 2013‡	Iran	30	60	43.8±12.7	41.6±11.1	22/8	41/19	27.9±4.3	27.6±4.2	1 year
Lai 2011	Hong Kong	24	27	51.7±13.3	54.3±12.0	16/8	16/11	25±3	24.4±2.8	3 months
Lee 2010	Taiwan	35	35	51.0±13.5	53.3±15.5	22/13	20/15	24.2±3.4	25.8±3.0	6 months
Leung 2012	USA	36	43	41.8±16.9	52.3±19.8	NR	NR	28.7±6.91	28.4±6.12	Mean: SILC 99, MLC 90 days
Lirici 2011	Italy	20	20	45 (26-63)	50 (24-67)	14/6	14/6	25 (18-29)	27 (18-30)	1 month
Luna 2012	Brazil	20	20	NR	NR	NR	NR	NR	NR	30 days
Ma 2011	USA	21	22	57.3±16	45.8±11.9	NR	NR	28.2±5.3	30.7±6.1	Mean: SILC 19, MLC 16 days
Madureira 2012	Brazil	28	29	50	56	NR	NR	27.5 (15.6-43.5)	25 (18-34)	5.92 months
Marks 2013	USA	119	81	45.8 (18-77)	44.0 (19-68)	91/28	57/24	29.0 (15-45)	30.9 (19-45)	1 year
Mehmood 2010	Pakistan	30	30	44.42±8.59	42.7±9.1	28/2	26/4	NR	NR	NR
Noguera 201	Spain	20	20	49±4	60±5	17/3	16/4	28±4	30±1	1 year
Pan 2013	China	49	53	43.8±14	45.2±11	26/23	31/22	24.3±6.0	25.1±5	2 months
Rašić 2010	Croatia	48	50	44±6	44±5.7	26/22	32/18	27±4	27±4	1 month
Saad 2012	Germany	35	35	45±17	49±14	7/28	9/26	25.4±2.5	25.4±3.1	1 year
Sasaki 2012	Japan	27	27	56.6±14.2	58.2±12.3	13/14	13/14	24.4±3.0	24.9±3.4	30 days
Sinan 2012	Turkey	17	17	48.5±8.9	48.7±14.3	13/4	9/8	27.3±3.1	27.2±2.9	Median: SILC 30, MLC 23 wks
Solomon 2012	USA	22	11	38.4±3.3	35.5±4.1	22/0	11/0	31.8±1.4	31.4±2.2	30 days
Tsimoyiannis 2010	Greece	20	20	49.2±16.9	47.9±9.8	15/5	19/1	NR	NR	NR
Vilallonga 2012	Spain, Turkey	69	71	43.2±14.6	42.6±14.6	38/31	36/35	NR	NR	Mean 7.3 months
Yilmaz 2013	Turkey	43	40	48.5±12	51.0±9.0	34/9	27/13	24.2±4.0	23.3±3.0	7 days
Zapf 2013	USA	49	51	44.2±16.2	50.9±18.2	42/7	34/17	29.1±6.5	30.0±6.3	Mean: SILC 16.4, MLC 16.2 m
Zheng 2011	China	30	30	43.6±11.3	46.8±14.4	17/13	14/16	24.7±3.4	25.9±4.1	Median: SILC 9.4, MLC 11.6 m

Data are counts, mean±SD, median (range), median±SD in Rašić 2010, mean (range) in Marks 2013 and mean±SE in Noguera 2013.

BMI, body mass index; SILC, single incision laparoscopic cholecystectomy; MLC, multiport laparoscopic cholecystectomy; NR, not reported

*Declared number of patients (intent-to-treat) *per* group was 25, but sex ratio in the SILC group was expressed as 16/14 without any explanation.

#Declared number of patients (intent-to-treat) *per* group was 45. Patients were excluded due to data incompleteness or procedure failure and were not considered regarding demographics.

‡Study included two MLC groups (3 or 4 ports), each with 30 subjects. Results were practically identical, hence groups were pooled.

Table 3 Surgical technique/instruments used (studies by author) as presented in the original publications.[35-64]

Author	Trocars in MLC	Trocars/ports in SILC	Instruments in SILC
Aprea 2011	3, 2x12-mm + 1x5-mm	TriPort LAD (Olympus); 2x5-mm + 1x12-mm	Conventional
Bresadola 1999	4,diameters not specified	1x10-mm + 1x5-mm, single supraumbilical skin incision	Conventional or roticulator
Brown 2013	4, 1x11-mm + 3x5-mm	1x10-mm + 2x5-mm through the same skin incision	Conventional
Bucher 2011	4, 2x10-mm + 2x5-mm	TriPort® (Advanced Surgical Concepts, Wicklow, Ireland)	Flexible
Cao 2011	3, 2x10-mm + 1x5-mm	1x10-mm + 2x5-mm, single umbilical skin incision	Conventional
Chang 2012	4, 1x10-mm + 3x5-mm	The Covidien (Norwalk, USA) SILS port	Articulating
Ellatif 2012	4, 2x10-mm + 2x5-mm	1x10-mm + 1x5-mm transumbilical ports	Conventional
Herrero Fonollosa 2012	4, 2x10-mm + 2x5-mm	SILS port, Covidien	Articulating
Khorgami 2013	3 or 4, 1x10-mm + 2 or 3x5 mm	1x10-mm + 2x5-mm through the same skin incision	Conventional
Lai 2011	4, 1x10-mm + 3x5-mm	SILS Port (Covidien Inc., Norwalk, CT)	Conventional
Lee 2010	4, 1x10-mm + 3x3-mm	QuadraPort® LAD (LAGIS, Taiwan); 1x10-mm, 2x5-mm + 1x3-mm	Conventional
Leung 2012	NR	NR	Articulating
Lirici 2011	4, 2x12-mm + 2x5-mm	TriPort® (Olympus America, Center Valley, PA); 1x12-mm + 2x5-mm	Conventional
Luna 2012	4, 2x10-mm 2x5-mm	SITRACC® device (EDLO, Rio Grandedo Sul, Brazil); 1x10-mm + 3x5-mm	Conventional and angulated
Ma 2011	4, 1x10-mm + 3x5-mm	ASC TriPort (Advanced Surgical Concepts, Wicklow, Ireland)	Articulating
Madureira 2012	4, 10-mm and 5-mm ports (n=?)	SITRACC® portal (Edlo S.A., Curitiba, Brazil), SILS™ Port (Covidien, Mansfield, MA); X-cone® (Karl Storz Endoskope, Tuttlingen, Germany)	Curved and conventional
Marks 2013	3 or 4, 2 or 3x5-mm, 1 or 2x10/12-mm	SILS™ Port (Covidien)	Conventional and roticulating
Mehmood 2010	4, 2x10-mm + 2x5-mm	SILS™ port	Conventional or articulating
Noguera 2013	3, 1x11-mm + 2x5-mm	SILS™ Port (Covidien)	Conventional and articulating
Pan 2013	3, 2x10-mm + 1x5-mm	2x10-mm (Kanger, Tong Lu, China); intraumbilical incision	Conventional
Rašić 2010	3, port size not specified	1x10-mm + 2x5-mm through the same skin incision	Roticulator
Saad 2012	4, 2x10-mm + 2x5-mm	SILS Port® (Covidien, Norwalk, CT, USA); 3x5 or 1x10 + 2x5-mm	Conventional
Sasaki 2012	4, 1x12-mm + 3x5-mm	SILS port (Covidien, New Haven, CT)	Roticulating and conventional
Sinan 2012	4, 2x5-mm + 2x10-mm	Single port designed for SILC (Covidien, New Haven, CT)	Roticulating
Solomon 2012	4, 1x11-mm + 3x5-mm	SILS™ Port (Covidien)	Roticulating and conventional
Tsimoyiannis 2010	4, 1x11-mm 3x5-mm	1x10-mm + 2x5-mm through the same skin incision	Conventional and roticulating
Vilallonga 2012	3 or 4, 1xJason + 1x11-mm + 1 or 2x5-mm	TriPort™ (Advanced Surgical Concepts, Wicklow, Ireland) and SILS™ Port (Covidien, Inc., Norwalk, CT)	Conventional and roticulating
Yilmaz 2013	4, 1x10-mm + 3x11-mm	SILS™ Port (Covidien)	Not reported

Zapf 2013	4, 1x12-mm + 3x5-mm	3 low-profile ports through the same skin incision	Articulating
Zheng 2011	3, 2x10-mm + 1x5-mm	Tri-port (Advanced Surgical Concepts, Wicklow, Ireland)	Conventional

MLC, multiport laparoscopic cholecystectomy; SILC, single incision laparoscopic cholecystectomy; LAD, laparoscopic Access Device

Table 4 Risk of bias: summary of included trials (by author).[35-64]

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants (performance bias)	Blinding of assessors (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Differential expertise bias (other biases)
Aprea 2011	?	+	–	?	+	+	–
Bresadola 1999	?	?	?	+	–	–	–
Brown 2013	?	?	+	?	+	–	?
Bucher 2011	+	?	?	+	+	+	+
Cao 2011	?	+	?	+	–	+	–
Chang 2012	?	?	+	+	+	+	–
Ellatif 2012	+	+	+	+	+	+	+
Herrero Fonollosa 2012	+	?	?	?	?	–	?
Khorgami 2013	+	?	+	+	?	+	?
Lai 2011	+	+	–	+	–	+	+
Lee 2010	?	+	?	+	+	+	+
Leung 2012	+	?	+	?	?	–	+
Lirici 2011	?	+	+	+	+	+	–
Luna 2012	?	?	?	?	+	+	–
Ma 2011	+	?	?	+	?	+	–
Madureira 2012	?	?	?	?	–	+	+
Marks 2013	+	+	+	?	?	+	+
Mehmood 2010	?	+	?	?	?	+	–
Noguera 2013	+	?	?	?	+	+	?
Pan 2013	+	+	?	?	–	+	?
Rašić 2010	+	?	?	?	+	–	?
Saad 2012	+	+	+	+	+	+	+
Sasaki 2012	+	?	?	?	+	+	?
Sinan 2012	+	?	?	+	+	+	?
Solomon 2012	?	?	?	?	+	–	+
Tsimoyiannis 2010	?	+	?	+	?	+	–
Vilallonga 2012	?	?	?	?	?	+	–
Yilmaz 2013	+	+	?	?	-	+	?
Zapf 2013	+	?	+	+	+	+	-
Zheng 2011	+	+	?	?	+	+	+

+, low risk of bias; **–**, high risk of bias; **?**, unclear risk of bias

Table 5 Ranking of trials[35-64] (highest to lowest quality) based on a combination of evidently low (primary criterion) or evidently high (secondary criterion) or uncertain risks (tertiary criterion) of the seven biases assessed in Table 4. Except for the definition of high-quality trials (all risks evidently low), categorization/ranking by quality is arbitrary and serves only as an illustrative summary.

Study	Size	Rank	Quality	Description	Evidently low risks	Evidently high risks	Uncertain risks
Ellatif 2012	250	1	High	All risks evidently low	7	0	0
Saad 2012	70	1	High		7	0	0
Bucher 2011	150	2	Moderate		5	0	2
Lee 2010	70	2	Moderate		5	0	2
Marks 2013	200	2	Moderate	Evidently low risks clearly	5	0	2
Zheng 2011	60	2	Moderate	prevail over evidently high	5	0	2
Lirici 2011	40	3	Moderate	risks, uncertainty low	5	1	1
Zapf 2013	100	3	Moderate		5	1	1
Lai 2011	51	4	Moderate		5	2	0
Khorgami 2013	90	5	Modest		4	0	3
Sinan 2012	34	5	Modest		4	0	3
Chang 2012	50	6	Modest	Evidently low risks clearly	4	1	2
Noguera 2013	40	7	Modest	prevail over evidently high	3	0	4
Sasaki 2012	54	7	Modest	risks, uncertainty high	3	0	4
Leung 2012	79	8	Modest		3	1	3
Tsimoyiannis 2010	40	8	Modest		3	1	3
Yilmaz 2013	83	8	Modest		3	1	3
Aprea 2011	50	9	Low		3	2	2
Cao 2011	108	9	Low		3	2	2
Brown 2013	79	10	Low	Evidently low risks barely	2	1	4
Luna 2012	40	10	Low	prevail or are equally frequent	2	1	4
Ma 2011	43	10	Low	as evidently high risks,	2	1	4
Madureira 2012	57	10	Low	uncertainty high	2	1	4
Mehmood 2010	60	10	Low		2	1	4
Pan 2013	102	10	Low		2	1	4
Rašić 2010	98	10	Low		2	1	4
Solomon 2012	33	10	Low		2	1	4
Herrero Fonollosa 2012	50	11	Low		1	1	5
Vilallonga 2012	140	11	Low		1	1	5
Bresadola 1999	90	12	Very low	Evidently high risks prevail	1	3	3

* see footnote to Table 4

Table 6 Cumulative number of patients by type of reported complications in randomized controlled trials (N=30) comparing single incision laparoscopic cholecystectomy (SILC) and multiport laparoscopic cholecystectomy (MLC). Complications are listed by preferred terms used in the original reports.[35-64]

Complication type	SILC	MLC
Biliary complications		
Gallbladder perforation	11	12
Bile leakage	9	9
Retained bile duct stone	4	1
Bleeding in gallbladder bed	1	2
Biliary peritonitis	1	0
Cystic duct partial avulsion	0	1
Wound complications		
Contusion/hematoma/seroma	20	21
Infection	17	19
Incisional hernia	15	4
Erythema	5	0
Bleeding	1	3
Cellulitis	2	0
Other		
Urinary retention	1	2
Suture-related complication	2	0
Subphrenic abscess	2	0
Blood collection	2	0
Perforation of diaphragm	1	0
Liver dysfunction	0	1
Postoperative ileus	0	1

Table 7 Random-effects meta-analysis of the outcome "incidence of incisional hernia".*

	SILC		MLC		Effect	
Study	n	N	n	N	OR	95% CI
Bucher 2011	0	75	0	75	1.00	NE
Ellatif 2012	0	125	0	125	1.00	NE
Herrero Fonollosa 2012	0	26	0	24	0.93	NE
Khorgami 2013	0	30	1	60	0.65	NE – 78.0
Leung 2012	0	36	0	43	1.19	NE
Lirici 2011	0	20	0	20	1.00	NE
Luna 2012	0	20	0	20	1.00	NE
Ma 2011	1	21	0	22	3.29	0.03 - NE
Madureira 2012	0	28	0	29	1.04	NE
Marks 2013	10	119	1	81	7.34	0.92 – 58.5
Noguera 2013	0	20	0	20	1.00	NE
Pan 2013	0	49	0	53	1.80	NE
Rašić 2010	0	48	0	50	1.00	NE
Saad 2012	1	35	0	35	3.09	0.03 - NE
Sinan 2012	1	17	0	17	3.18	0.03 - NE
Solomon 2012	1	22	0	11	1.61	0.01 - NE
Vilallonga 2012	1	69	2	71	0.61	0.01 – 10.0
Zapf 2013	0	49	0	51	1.04	NE
Zheng 2011	0	30	0	30	1.00	NE
Conventional (trials used= 7)	15 / 313		4 / 297			
OR (95% CI), p-value	2.17 (0.75-6.33), 0.155					
Methods for sparse data (trials used= 19)	15 / 839		4 / 837			
BN method OR (95% CI), p-value	3.19 (0.87-11.72), 0.077					
Shuster weighted OR (95% CI), p-value	3.37 (0.94-12.10), p=0.063					
Shuster unweighted OR (95%CI), p-value	**4.94 (1.26-19.4), 0.025**					

NE – not estimable

*We followed the recommended procedure[29]: a) in trials with one or both zero-event arms, individual study odds ratio (OR) estimates are conditional exact, the remaining are conventional Mantel-Haenszel random-effects estimates (no continuity correction used in estimation); b) pooled effects are by the bivariate binomial-normal (BN) method[30], or by the study-size weighted or unweighted (*preferred*, bolded) method by Shuster[29].

Figure

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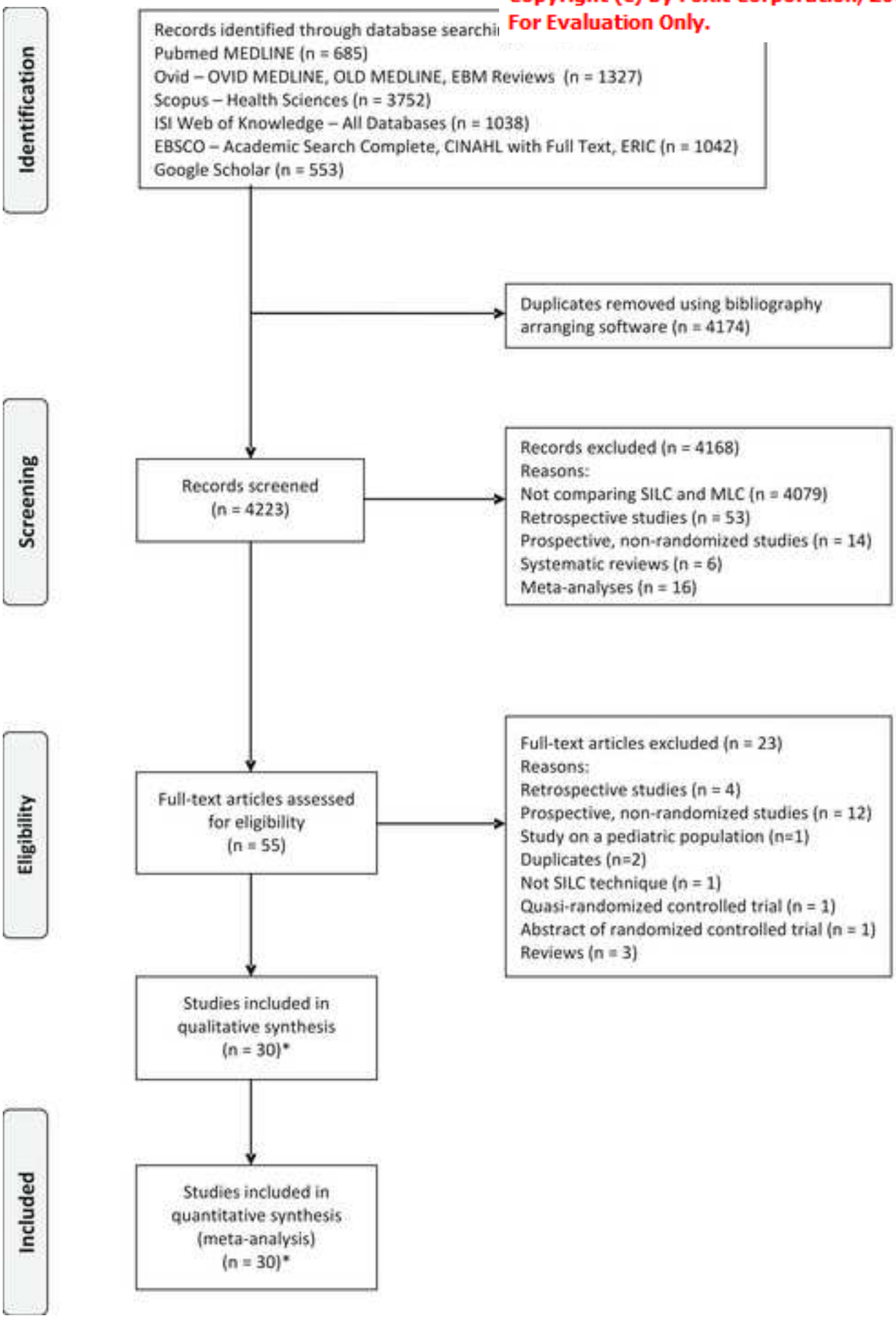

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Study	SILC			MLC			Statistics for each study				WMD (95% CI)	
	n	Mean	SD	n	Mean	SD	Δ means	LCL	UCL	p	Weight (%)	Diff. exp.
Aprea 2011	25	41.3	12.0	25	35.6	5.8	5.7	0.5	10.9	0.032	4.2	H
Bresadola 1999	45	94.0	29.0	45	85.0	33.0	9.0	-3.8	21.8	0.169	2.6	H
Brown 2013	40	57.0	29.5	39	47.0	15.3	10.0	-0.4	20.4	0.060	3.1	U
Bucher 2011	75	66.0	12.8	75	64.0	13.2	2.0	-2.2	6.2	0.346	4.3	L
Cao 2011	57	55.2	12.4	51	46.3	10.8	8.9	4.5	13.3	0.000	4.3	H
Chang 2012	24	76.0	33.7	26	61.1	33.7	14.9	-3.8	33.6	0.118	1.7	H
Ellatif 2012	125	62.7	10.2	125	55.3	8.9	7.4	5.0	9.8	0.000	4.6	L
Herrero Fonollosa 2012	26	54.0	21.0	24	48.5	17.0	5.5	-5.1	16.1	0.311	3.0	U
Khorgami 2013	30	63.7	9.8	60	53.0	13.5	10.1	4.5	15.7	0.000	4.1	L
Lai 2011	24	43.5	15.4	27	46.5	20.1	-3.0	-12.9	6.9	0.553	3.2	L
Lee 2011	35	71.7	11.6	35	48.4	10.5	23.3	18.1	28.5	0.000	4.2	L
Leung 2012	36	72.9	28.8	43	46.2	28.8	26.7	13.9	39.5	0.000	2.6	L
Lirici 2011	20	76.8	17.5	20	48.3	66.3	28.5	-1.6	58.6	0.063	0.9	H
Luna 2012	20	92.0	27.7	20	41.9	14.0	50.1	36.5	63.7	0.000	2.5	H
Ma 2011	21	88.5	40.4	22	44.8	40.4	43.7	19.5	67.9	0.000	1.2	H
Madureira 2012	28	60.3	21.0	29	51.3	21.0	9.0	-1.9	19.9	0.106	3.0	L
Marks 2013	119	56.8	21.1	81	45.3	21.1	11.5	5.5	17.5	0.000	4.0	L
Mehmood 2010	30	80.2	30.2	30	38.5	8.9	41.7	30.4	53.0	0.000	2.9	H
Noguera 2013	20	58.9	13.4	20	49.1	8.9	9.8	2.7	16.9	0.006	3.8	U
Pan 2013	49	41.8	17.0	53	38.5	22.0	3.3	-4.4	11.0	0.399	3.7	U
Rališ 2010	48	46.0	3.8	50	43.0	6.8	3.0	0.8	5.2	0.007	4.6	U
Saad 2012	35	45.7	10.9	35	35.0	14.0	10.7	4.8	16.6	0.000	4.0	L
Sasaki 2012	27	83.4	18.6	27	69.4	16.7	14.0	4.6	23.4	0.004	3.3	U
Sinan 2012	17	124.4	29.7	17	64.1	26.1	60.3	41.5	79.1	0.000	1.7	U
Solomon 2012	22	48.9	2.6	11	42.3	3.9	6.6	4.4	8.8	0.000	4.6	L
Tsimoyiannis 2010	20	49.7	9.0	20	37.3	9.2	12.4	6.8	18.0	0.000	4.1	H
Vilallonga 2012	69	63.9	23.9	71	58.4	20.8	5.5	-1.9	12.9	0.146	3.7	H
Yilmaz 2013	43	34.6	15.0	40	39.3	11.0	-4.7	-10.4	1.0	0.106	4.1	U
Zapf 2013	49	63.5	21.0	51	43.8	24.2	19.7	10.8	28.6	0.000	3.4	H
Zheng 2011	30	55.6	25.7	30	42.7	18.6	12.9	1.5	24.3	0.026	2.9	L
POOLED	**1209**			**1202**			**12.4**	**9.3**	**15.5**	**0.000**		

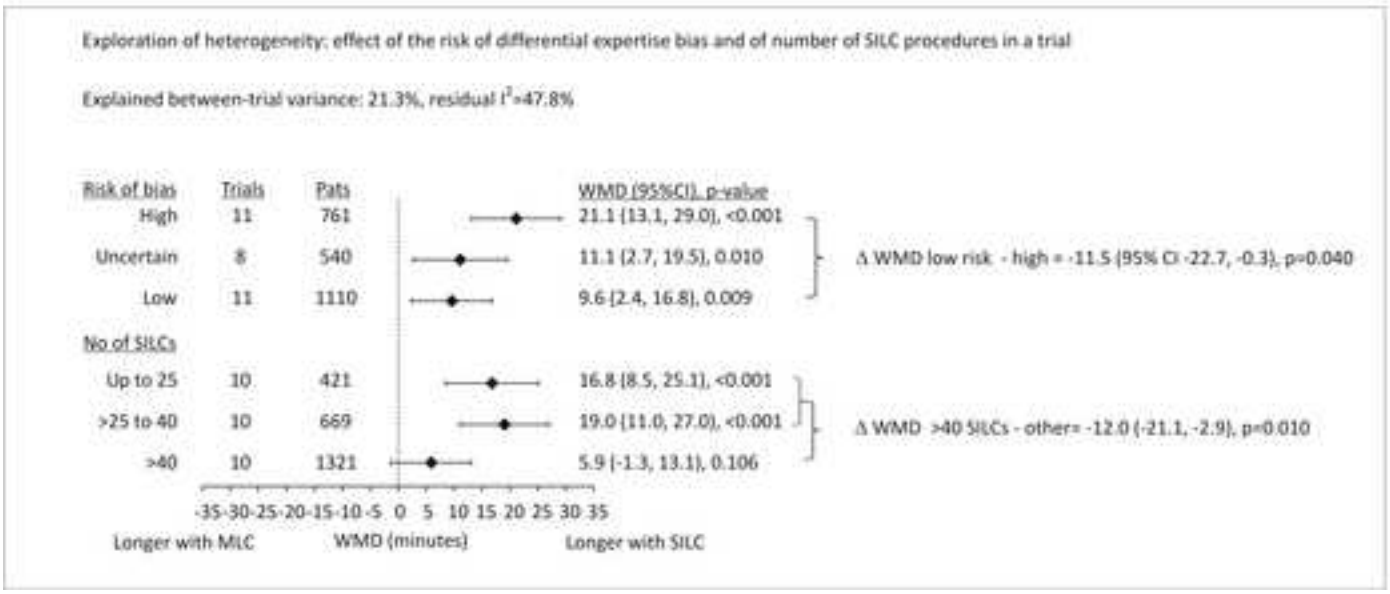
Overall: Trials N= 30; Effect: z=7.829, p<0.001

Heterogeneity: Q=223.9, df=29, p<0.001; I^2=87.0%

-80.0 -40.0 0.00 40.0 80.0

Longer with MLC — Longer with SILC

B



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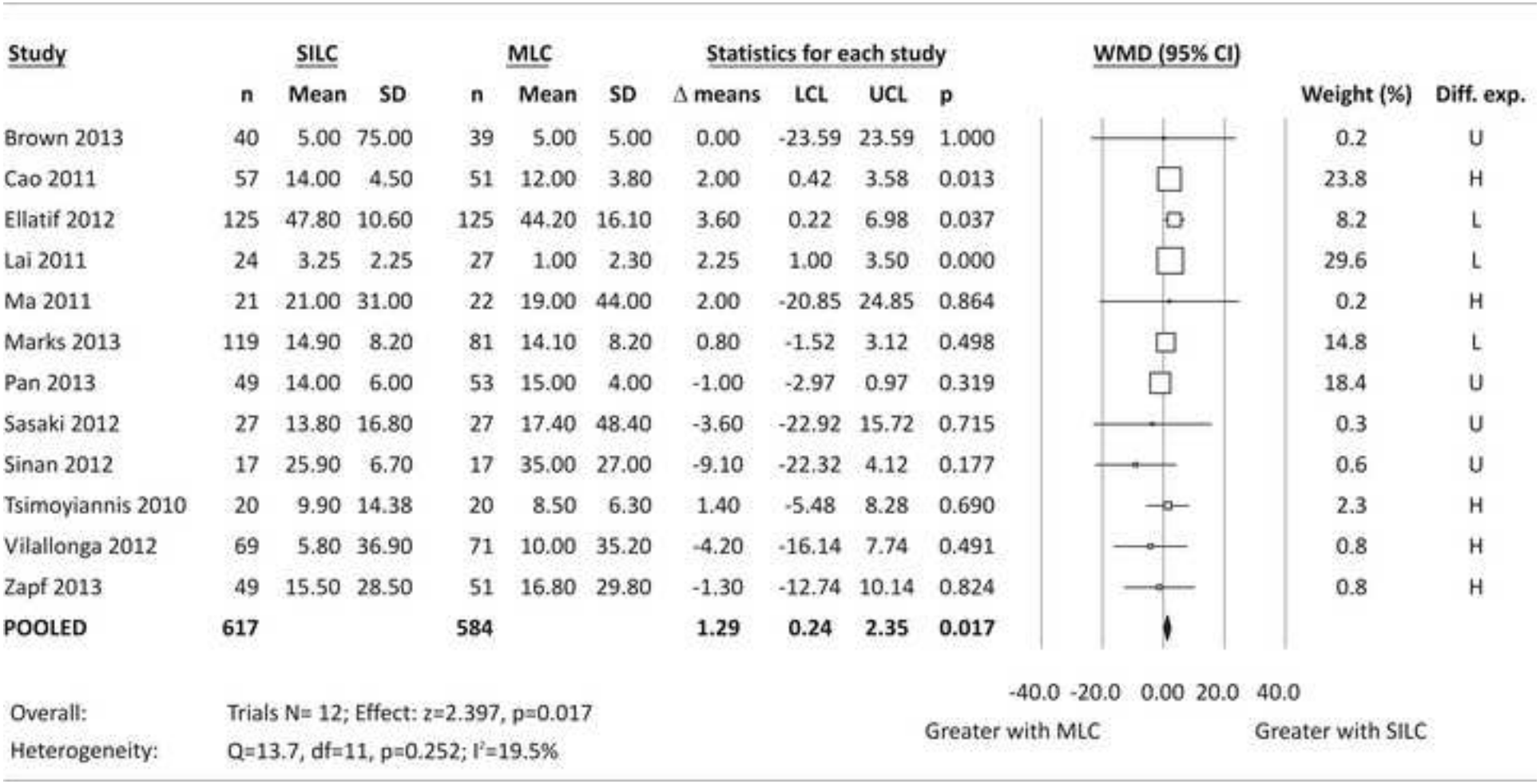

Overall: Trials N= 12; Effect: z=2.397, p=0.017

Heterogeneity: Q=13.7, df=11, p=0.252; I^2=19.5%

Figure

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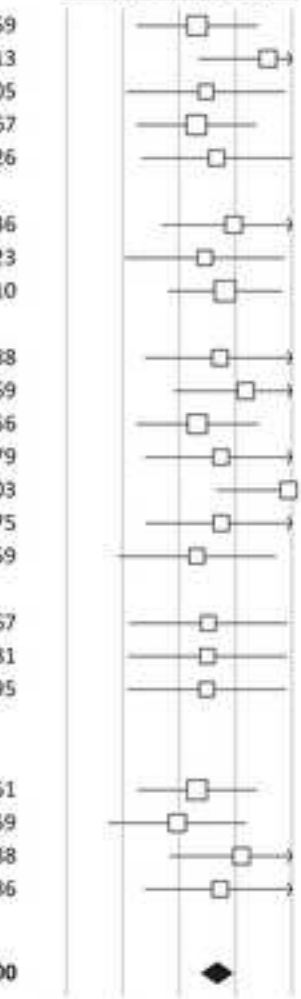
A

Study	SILC n/N	MLC n/N	M-H OR	LCL	UCL	p	Weight (%)	Diff. exp.
Aprea 2011	2 / 25	1 / 25	2.09	0.18	24.61	0.559	6.1	H
Bresadola 1999	13 / 45	0 / 45	37.80	2.17	658.95	0.013	4.6	H
Brown 2013	1 / 40	0 / 39	3.00	0.12	75.90	0.505	3.6	U
Bucher 2011	2 / 75	1 / 75	2.03	0.18	22.85	0.567	6.4	L
Cao 2011	2 / 57	0 / 51	4.64	0.22	98.95	0.326	4.0	H
Chang 2012	0 / 24	0 / 26	------ Not estimable ------					H
Ellatif 2012	4 / 125	0 / 125	9.30	0.50	174.51	0.136	4.4	L
Herrero-Fonollosa 2012	1 / 26	0 / 24	2.88	0.11	74.21	0.523	3.5	U
Khorgami 2013	3 / 30	1 / 60	6.56	0.65	65.95	0.110	7.0	U
Lai 2011	0 / 24	0 / 27	------ Not estimable ------					L
Lee 2011	2 / 35	0 / 35	5.30	0.25	114.47	0.288	4.0	L
Leung 2012	5 / 36	0 / 43	15.19	0.81	284.81	0.069	4.4	L
Lirici 2011	2 / 20	1 / 20	2.11	0.18	25.35	0.556	6.1	H
Luna 2012	2 / 20	0 / 20	5.54	0.25	123.08	0.279	3.9	H
Ma 2011	14 / 21	0 / 22	87.00	4.61	1642.09	0.003	4.3	H
Madureira 2012	2 / 28	0 / 29	5.57	0.26	121.27	0.275	3.9	L
Marks 2013	1 / 119	0 / 81	2.06	0.08	51.28	0.659	3.6	L
Noguera 2013	0 / 20	0 / 20	------ Not estimable ------					U
Pan 2013	1 / 49	0 / 53	3.31	0.13	83.17	0.467	3.6	U
Rašić 2010	1 / 48	0 / 50	3.19	0.13	80.23	0.481	3.6	U
Saad 2012	1 / 35	0 / 35	3.09	0.12	78.41	0.495	3.6	L
Sasaki 2012	0 / 27	0 / 27	------ Not estimable ------					U
Solomon 2012	0 / 22	0 / 11	------ Not estimable ------					L
Vilallonga 2012	2 / 69	1 / 71	2.09	0.19	23.59	0.551	6.4	H
Yilmaz 2013	1 / 43	1 / 40	0.93	0.06	15.36	0.959	4.8	U
Zapf 2013	5 / 49	0 / 51	12.73	0.68	236.68	0.088	4.4	H
Zheng 2011	2 / 30	0 / 30	5.35	0.25	116.31	0.286	3.9	L
Trials N= 27; Used n= 22								
POOLED	**69 / 1025**	**6 / 1024**	**4.73**	**2.57**	**8.72**	**0.000**		

Statistics for each study

M-H OR (95% CI)



Overall: Effect: z=4.980, p<0.001

Heterogeneity: Q=11.6, df=21, p=0.952; I^2=0.0%

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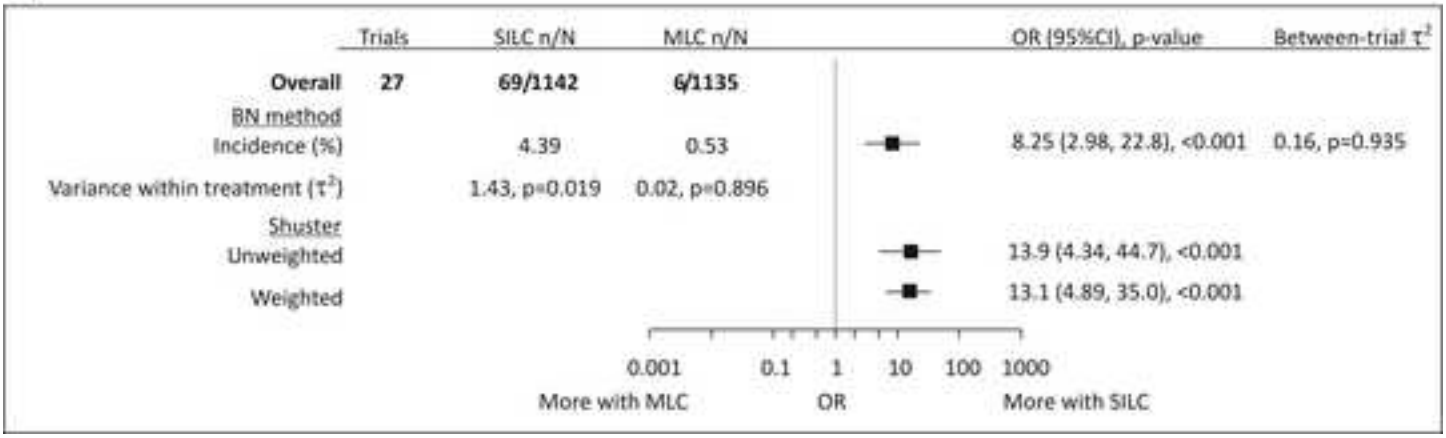

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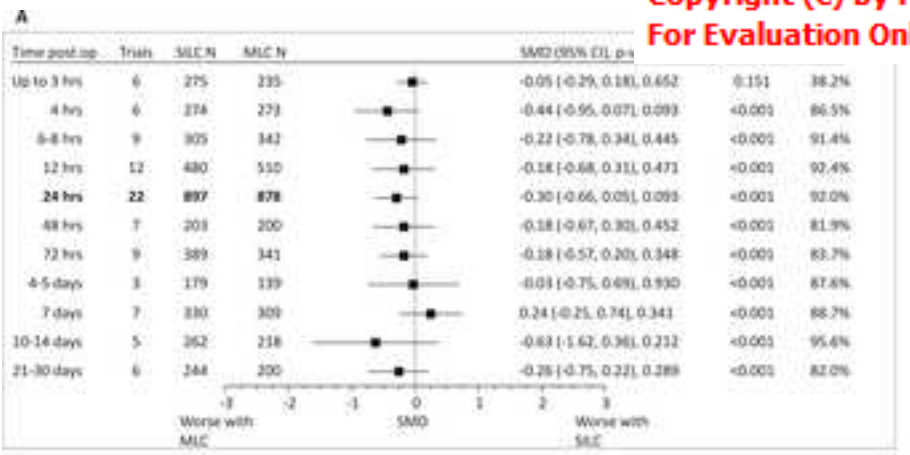

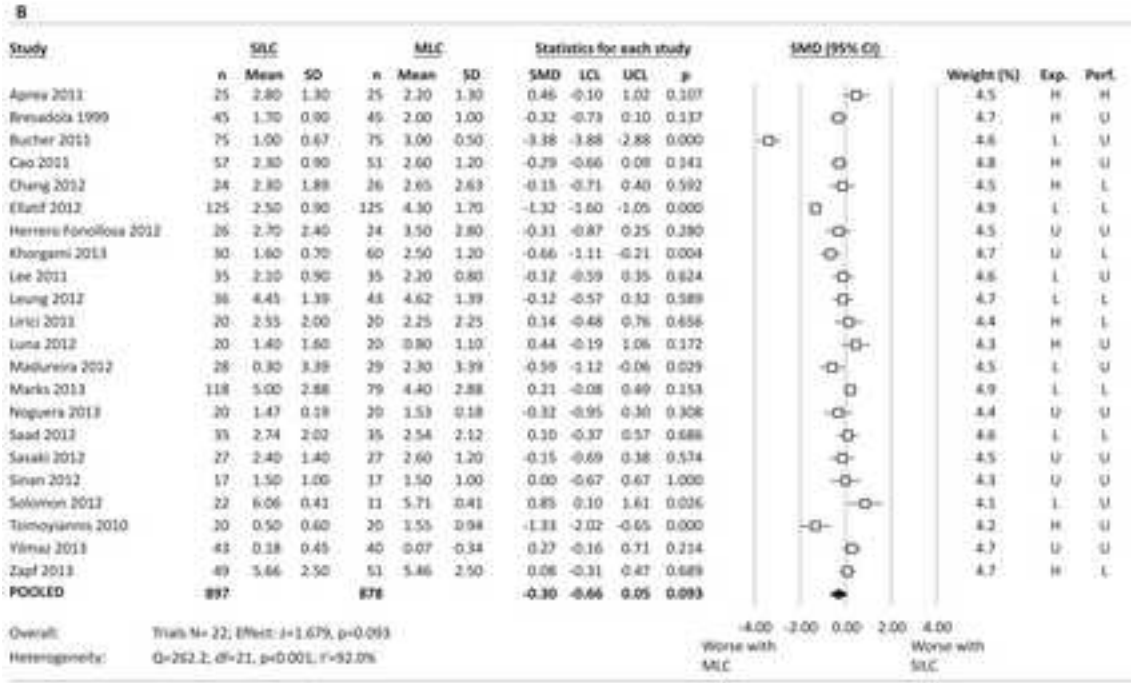

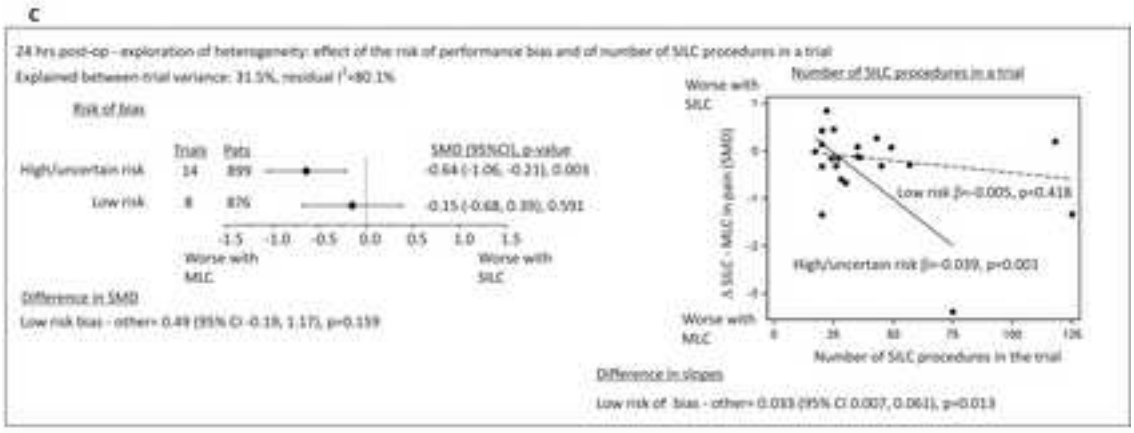

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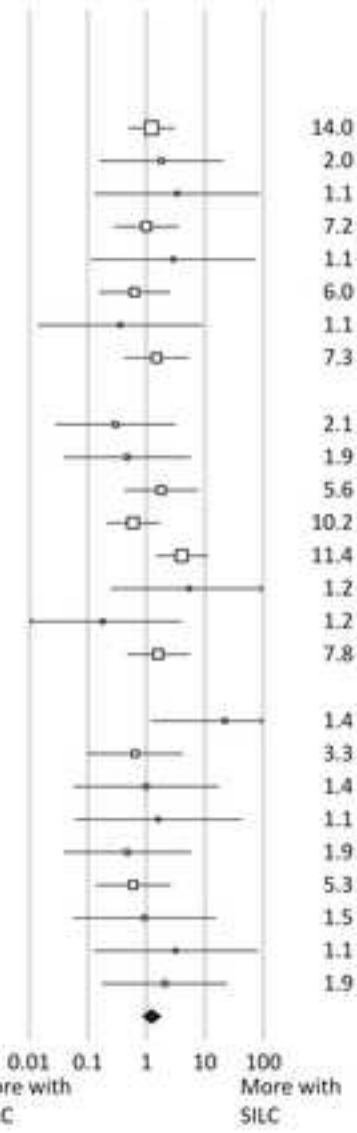
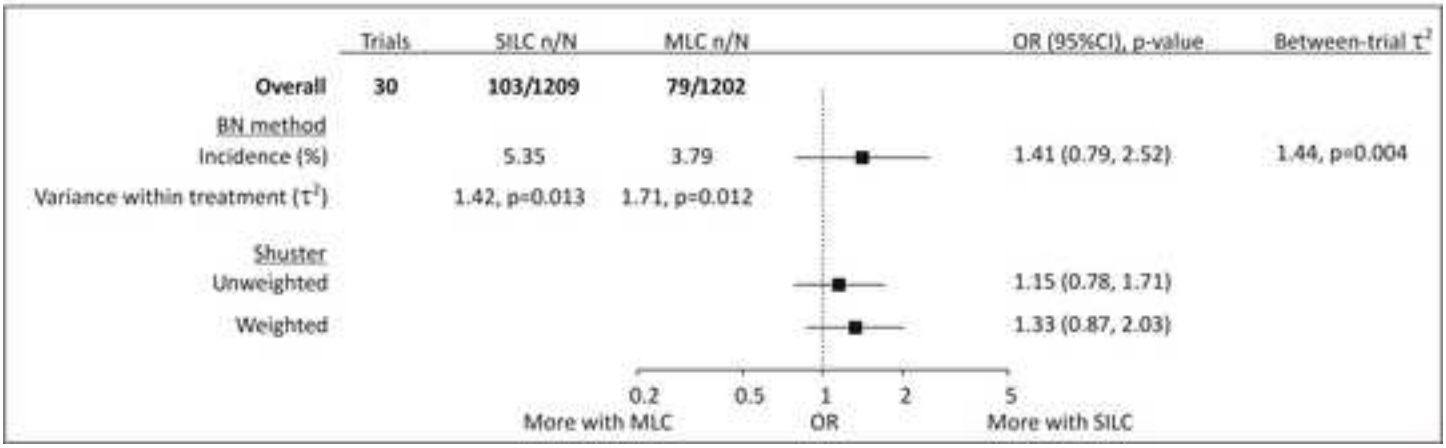
Study	SILC n/N	MLC n/N	M-H OR	LCL	UCL	p	Weight (%)	Diff. exp.	Attrit.
Aprea 2011	0 / 25	0 / 25	Not estimable					H	L
Bresadola 1999	0 / 45	0 / 45	Not estimable					H	H
Brown 2013	0 / 40	0 / 39	Not estimable					U	L
Bucher 2011	12 / 75	10 / 75	1.24	0.50	3.07	0.645	14.0	L	L
Cao 2011	2 / 57	1 / 51	1.82	0.16	20.67	0.630	2.0	H	H
Chang 2012	1 / 24	0 / 26	3.38	0.13	87.11	0.462	1.1	H	L
Ellatif 2012	5 / 125	5 / 125	1.00	0.28	3.54	1.000	7.2	L	L
Herrero-Fonollosa 2012	1 / 26	0 / 24	2.88	0.11	74.21	0.523	1.1	U	U
Khorgami 2013	3 / 30	9 / 60	0.63	0.16	2.52	0.513	6.0	U	U
Lai 2011	0 / 24	1 / 27	0.36	0.01	9.27	0.538	1.1	L	H
Lee 2011	7 / 35	5 / 35	1.50	0.43	5.28	0.528	7.3	L	L
Leung 2012	0 / 36	0 / 43	Not estimable					L	U
Lirici 2011	1 / 20	3 / 20	0.30	0.03	3.15	0.314	2.1	H	L
Luna 2012	1 / 20	2 / 20	0.47	0.04	5.69	0.556	1.9	H	L
Ma 2011	6 / 21	4 / 22	1.80	0.43	7.59	0.423	5.6	H	U
Madureira 2012	10 / 28	14 / 29	0.60	0.21	1.72	0.338	10.2	L	H
Marks 2013	25 / 119	5 / 81	4.04	1.48	11.06	0.007	11.4	L	L
Mehmood 2010	2 / 30	0 / 30	5.35	0.25	116.31	0.286	1.2	H	U
Noguera 2013	0 / 20	2 / 20	0.18	0.01	4.01	0.279	1.2	U	L
Pan 2013	7 / 49	5 / 53	1.60	0.47	5.42	0.450	7.8	U	H
Rašić 2010	0 / 48	0 / 50	Not estimable					U	L
Saad 2012	8 / 35	0 / 35	21.95	1.21	396.97	0.037	1.4	L	L
Sasaki 2012	2 / 27	3 / 27	0.64	0.10	4.17	0.641	3.3	U	L
Sinan 2012	1 / 17	1 / 17	1.00	0.06	17.41	1.000	1.4	U	L
Solomon 2012	1 / 22	0 / 11	1.60	0.06	42.63	0.777	1.1	L	L
Tsimoyiannis	1 / 20	2 / 20	0.47	0.04	5.69	0.556	1.9	H	U
Vilallonga 2012	3 / 69	5 / 71	0.60	0.14	2.61	0.496	5.3	H	U
Yilmaz 2013	1 / 43	1 / 40	0.93	0.06	15.36	0.959	1.5	U	H
Zapf 2013	1 / 49	0 / 51	3.19	0.13	80.09	0.481	1.1	H	L
Zheng 2011	2 / 30	1 / 30	2.07	0.18	24.15	0.561	1.9	L	L
Trials N= 30; Used n= 25									
POOLED	**103 / 1015**	**79 / 1000**	**1.23**	**0.88**	**1.73**	**0.224**			



Overall: Effect: z=1.216, p=0.224

Heterogeneity: Q=20.8, df=24, p=0.648; I^2=0.0%

B



Figure

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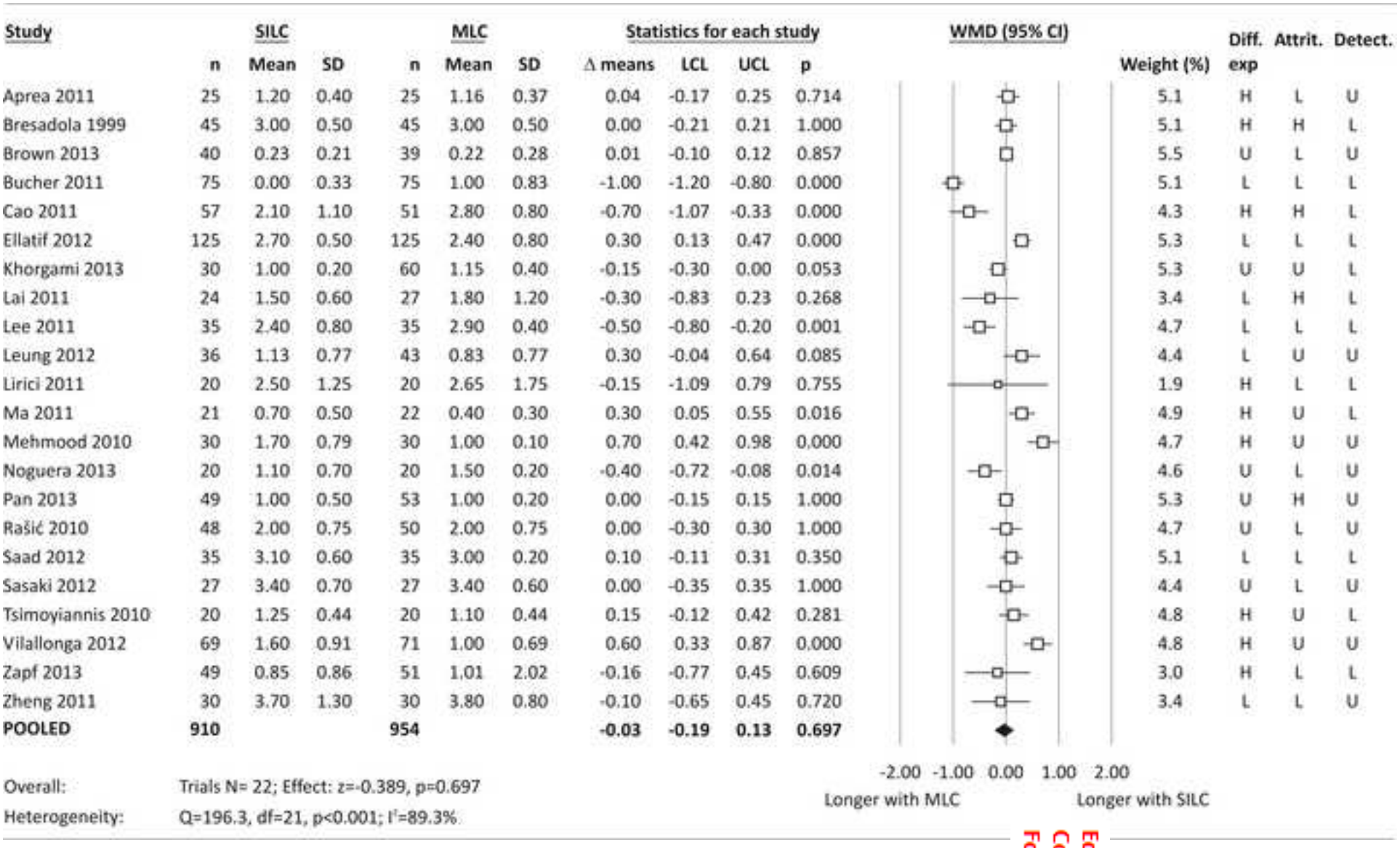

Study	SILC			MLC			Statistics for each study				WMD (95% CI)	Weight (%)	Diff. exp	Attrit.	Detect.
	n	Mean	SD	n	Mean	SD	Δ means	LCL	UCL	p					
Aprea 2011	25	1.20	0.40	25	1.16	0.37	0.04	-0.17	0.25	0.714		5.1	H	L	U
Bresadola 1999	45	3.00	0.50	45	3.00	0.50	0.00	-0.21	0.21	1.000		5.1	H	H	L
Brown 2013	40	0.23	0.21	39	0.22	0.28	0.01	-0.10	0.12	0.857		5.5	U	L	U
Bucher 2011	75	0.00	0.33	75	1.00	0.83	-1.00	-1.20	-0.80	0.000		5.1	L	L	L
Cao 2011	57	2.10	1.10	51	2.80	0.80	-0.70	-1.07	-0.33	0.000		4.3	H	H	L
Ellatif 2012	125	2.70	0.50	125	2.40	0.80	0.30	0.13	0.47	0.000		5.3	L	L	L
Khorgami 2013	30	1.00	0.20	60	1.15	0.40	-0.15	-0.30	0.00	0.053		5.3	U	U	L
Lai 2011	24	1.50	0.60	27	1.80	1.20	-0.30	-0.83	0.23	0.268		3.4	L	H	L
Lee 2011	35	2.40	0.80	35	2.90	0.40	-0.50	-0.80	-0.20	0.001		4.7	L	L	L
Leung 2012	36	1.13	0.77	43	0.83	0.77	0.30	-0.04	0.64	0.085		4.4	L	U	U
Lirici 2011	20	2.50	1.25	20	2.65	1.75	-0.15	-1.09	0.79	0.755		1.9	H	L	L
Ma 2011	21	0.70	0.50	22	0.40	0.30	0.30	0.05	0.55	0.016		4.9	H	U	L
Mehmood 2010	30	1.70	0.79	30	1.00	0.10	0.70	0.42	0.98	0.000		4.7	H	U	U
Noguera 2013	20	1.10	0.70	20	1.50	0.20	-0.40	-0.72	-0.08	0.014		4.6	U	L	U
Pan 2013	49	1.00	0.50	53	1.00	0.20	0.00	-0.15	0.15	1.000		5.3	U	H	U
Rašić 2010	48	2.00	0.75	50	2.00	0.75	0.00	-0.30	0.30	1.000		4.7	U	L	U
Saad 2012	35	3.10	0.60	35	3.00	0.20	0.10	-0.11	0.31	0.350		5.1	L	L	L
Sasaki 2012	27	3.40	0.70	27	3.40	0.60	0.00	-0.35	0.35	1.000		4.4	U	L	U
Tsimoyiannis 2010	20	1.25	0.44	20	1.10	0.44	0.15	-0.12	0.42	0.281		4.8	H	U	L
Vilallonga 2012	69	1.60	0.91	71	1.00	0.69	0.60	0.33	0.87	0.000		4.8	H	U	U
Zapf 2013	49	0.85	0.86	51	1.01	2.02	-0.16	-0.77	0.45	0.609		3.0	H	L	L
Zheng 2011	30	3.70	1.30	30	3.80	0.80	-0.10	-0.65	0.45	0.720		3.4	L	L	U
POOLED	**910**			**954**			**-0.03**	**-0.19**	**0.13**	**0.697**					

Overall: Trials N= 22; Effect: z=-0.389, p=0.697

Heterogeneity: Q=196.3, df=21, p<0.001; I^2=89.3%

Figure

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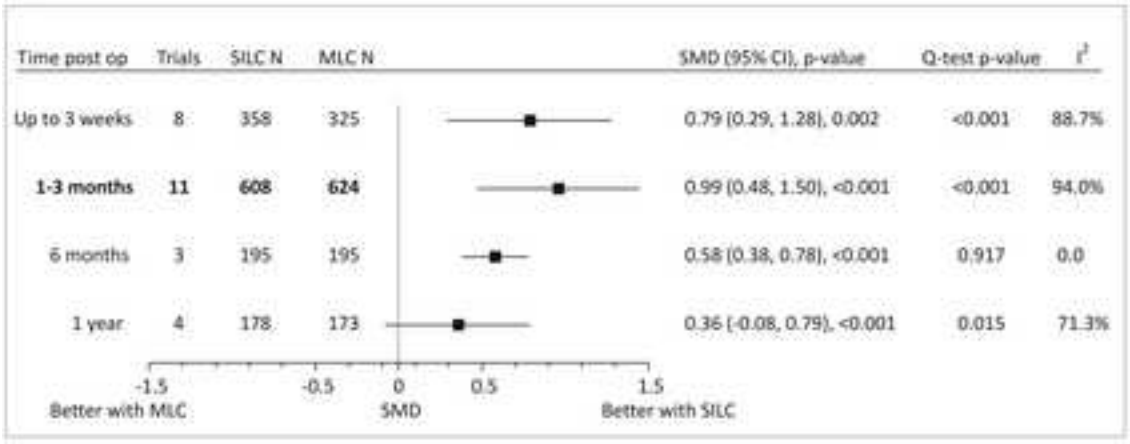

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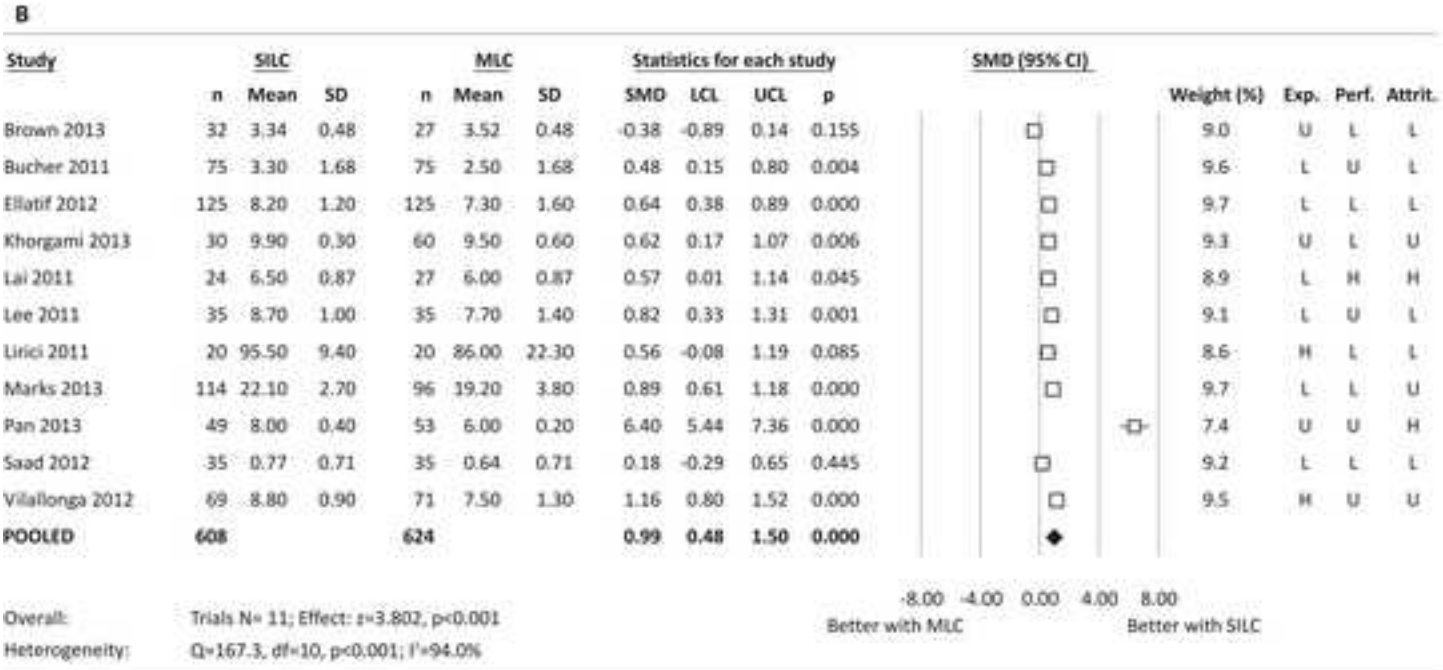

Study	SILC			MLC			Statistics for each study				Weight (%)	Exp.	Perf.	Attrit.
	n	Mean	SD	n	Mean	SD	SMD	LCL	UCL	p				
Brown 2013	32	3.34	0.48	27	3.52	0.48	-0.38	-0.89	0.14	0.155	9.0	U	L	L
Bucher 2011	75	3.30	1.68	75	2.50	1.68	0.48	0.15	0.80	0.004	9.6	L	U	L
Ellatif 2012	125	8.20	1.20	125	7.30	1.60	0.64	0.38	0.89	0.000	9.7	L	L	L
Khorgami 2013	30	9.90	0.30	60	9.50	0.60	0.62	0.17	1.07	0.006	9.3	U	L	U
Lai 2011	24	6.50	0.87	27	6.00	0.87	0.57	0.01	1.14	0.045	8.9	L	H	H
Lee 2011	35	8.70	1.00	35	7.70	1.40	0.82	0.33	1.31	0.001	9.1	L	U	L
Lirici 2011	20	95.50	9.40	20	86.00	22.30	0.56	-0.08	1.19	0.085	8.6	H	L	L
Marks 2013	114	22.10	2.70	96	19.20	3.80	0.89	0.61	1.18	0.000	9.7	L	L	U
Pan 2013	49	8.00	0.40	53	6.00	0.20	6.40	5.44	7.36	0.000	7.4	U	U	H
Saad 2012	35	0.77	0.71	35	0.64	0.71	0.18	-0.29	0.65	0.445	9.2	L	L	L
Vilallonga 2012	69	8.80	0.90	71	7.50	1.30	1.16	0.80	1.52	0.000	9.5	H	U	U
POOLED	**608**			**624**			**0.99**	**0.48**	**1.50**	**0.000**				

Overall: Trials N= 11; Effect: z=3.802, p<0.001

Heterogeneity: Q=167.3, df=10, p<0.001; I²=94.0%

C