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Title page

Laparoscopic vs Open approach for transverse colon cancer. A systematic review and meta-analysis of short and long term outcomes

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Abstract

Background: Transverse colon malignancies have been excluded from all randomized controlled trials comparing laparoscopic against open colectomies, potentially due to the advanced laparoscopic skills required for dissecting around the middle colic vessels and the associated morbidity. Concerns have been expressed that the laparospopic approach may compromise the oncological clearance in transverse colon cancer. This study aimed to comprehensively compare the laparoscopic (LPA) to the open (OPA) approach by performing a meta-analysis of long and short term outcomes.

Methods: Medline, Embase, Cochrane library, Scopus and Web of Knowledge databases were interrogated. Selected studies were critically appraised and the short-term morbidity and long term oncological outcomes were meta-analyzed. Sensitivity analysis according to the quality of the study, type of procedure (laparoscopic vs laparoscopically assisted) and level of lymphadenectomy was performed. Statistical heterogeneity and publication bias were also investigated.

Results: Eleven case control trials (1415 patients) were included in the study. There was no difference between the LPA and the OPA in overall survival [Hazard Ratio (HR)=0.83 (0.56, 1.22); P=0.34], disease free survival (p=0.20), local recurrence (p=0.81) or distant metastases (p=0.24). LPA was found to have longer operative time [Weighted mean difference (WMD)=45.00 (29.48, 60.52);P<0.00001] with earlier establishment of oral intake [WMD=-1.68 (-1.84, -1.53);P<0.00001] and shorter hospital stay [WMD =-2.94 (-4.27, -1.62);P=0.0001]. No

difference was found in relation to anastomotic leakage (p=0.39), intra-abdominal abscess (p=0.25), lymph nodes harvested (p=0.17).

Conclusions: LPA seems to be safe with equivalent oncological outcomes to OPA and better short term outcomes in selected patient populations. High quality Randomized control trials are required to further investigate the role of laparoscopy in transverse colon cancer.

Highlights:

- 11 studies comparing the open to the laparoscopic approach were pooled
- The laparoscopic approach carries significant short term benefits with the same disease free and overall survival
- Laparoscopic high tie of the middle colic vessels appears to be a safe and feasible technique

Keywords: transverse colon cancer, laparoscopic, minimally invasive, neoplasia, surgery

Introduction

The laparoscopic technique in colonic cancer surgery has significant benefits compared to the open technique, such as shorter hospital stay, less post-operative pain and earlier return to normal activity with similar oncological outcomes[1-5]. All the randomized control trials[5,1,4,2,6] that compared open with laparoscopic colectomy for colon cancer though excluded cancers located in the transverse colon. The potential reason for this has been the perceived increased difficulty of laparoscopic lymph node dissection around the middle colic artery and vein, the potential for increased intraoperative complications because of the close proximity of the transverse mesocolon to structures such as the duodenum, the pancreas and the superior mesenteric artery, as well as the low incidence of transverse colon cancer[7,8]. A number of studies have suggested that the laparoscopic approach may compromise the oncological clearance of the tumour and provide a less radical dissection of the transverse mesocolon[9-11] especially when the aim is complete mesocolic excision at the transverse mesocolon.

Over the last few years the increasing experience in laparoscopic colonic resections among surgeons has led to the cumulative publication of several studies comparing the oncological outcomes of the open to the laparoscopic approach for transverse colon cancer. The aim of this study therefore was to systematically review the literature and identify all the studies comparing the open and the laparoscopic approach in the resection of transverse colon cancer, critically review all the available evidence and provide a comprehensive comparison of the laparoscopic to the open approach by comparing short and long term outcomes and compare high vs low tie in transverse colon cancer.

Methods

This systematic review and meta-analysis followed the PRISMA guidelines Supplementary Figure 1 [12]. A protocol was available to all the authors of the study.

Inclusion and exclusion criteria

All randomized or case control trials comparing the open to the laparoscopic colectomy techniques for histologically proven transverse colon adenocarcinoma were included in the study. Transverse colon cancer was defined as cancer involving the transverse colon excluding the hepatic and the splenic flexure. Studies that compared open with hand-assisted laparoscopic colectomies were excluded. For duplicate studies the most up to date study was included (see PRISMA flow chart).

The primary outcome of the study was 5 year overall survival. Outcomes such as 5 year disease free survival, anastomotic leakage, intraoperative blood loss, operating time, time to first oral intake, length of hospital stay, overall morbidity and mortality were also compared between the two groups.

Search Strategy

Medline, Embase, Cochrane library, Scopus and Web of Knowledge databases were searched by two independent authors for studies comparing open with the laparoscopic approach for transverse colon cancer from 1990 to July 2016. CAB abstracts (1990-2016) and Asco University libraries were also searched for abstracts. The following Mesh terms were used: “transverse

colon adenocarcinoma", "transverse colon neoplasia", "transverse colon malignancy", "transverse colectomy", "extended right hemicolectomy", "extended left hemicolectomy", "laparoscopy", "laparoscopic", "minimally invasive" and "open" with no language restrictions. The results of the electronic search were screened through the title, abstract and/or a full publication review.

Data abstraction and validity assessment

The data from the selected studies were extracted by two independent authors to predefined tables. The tables included but were not limited to independent variables, patient characteristics, paper statistics, short and long term outcomes quality assessment of included studies as per Cochrane Handbook[13] and Newcastle Ottawa Scale(NOS) [14].The quality assessment of the studies was performed independently by two authors.

Statistical Analysis

For continuous data weighted mean difference (WMD) and 95% confidence intervals (CI) were calculated. In studies that did not report mean and standard deviation values for their continuous data an estimate was calculated[15]. For dichotomous data an odds ratio (OR) and 95% CI were calculated. An OR of less than 1 favored the laparoscopic approach. HR was used for disease free survival and overall survival data. A hazard ratio (HR) of less than 1 favored the laparoscopic approach. For studies that did not report a HR an estimate was calculated from the Kaplan Meier curve[16,17]. Subgroup analysis was done for high and low quality studies, totally laparoscopic vs laparoscopically assisted and high versus low tie of the middle colic vessels. High quality studies were considered the studies scoring more than 8 in the NOS. Sensitivity analysis was performed excluding studies that reported a laparoscopically assisted technique, low quality studies and low tie. Meta-regression was not performed as the number of studies was low. I^2 and χ^2 were used to assess statistical heterogeneity. If it was found to be above 50% the random effect model was

used for the analysis. Publication bias was assessed by visual interpretation of the symmetry of the funnel plots.

Results

Selection and quality assessment

Eleven case control trials[8,7,18-26] fulfilled the inclusion and exclusion criteria including 652 patients in the open group and 763 patients in the laparoscopic group. Four studies were excluded two studies because they included tumours of the splenic flexure[27,28], one study because the comparative group included tumours of the descending colon[29] and one because a more up to date study by the same authors was published[30] Figure 1.A summary of the included studies is provided in Table 1. Overall survival, disease free survival were reported in 7 studies and recurrence data were reported in five studies[21,20,7,22,24] one of which was multicentric[21].

Most of the patients included in the studies were in their late fifties or early sixties apart from the patients in 3 studies [23,7,8]which were in their late sixties to early seventies. Six studies [21,22,24,7,8] [25]reported an American Society of Anesthesiologists Score. Patients with ASA III score ranged variably from 0% to 41.8%. Body Mass Index (BMI) was reported in seven studies[21,24,7,19,18,25,26] and the mean value ranged from 21.7 to 24.2 (Table 2).

The surgical approach in most studies included right extended hemicolectomy, transverse colectomy and left extended hemicolectomy for transverse colon cancer. In five of the studies [8,23,19,20,25] a small number of subtotal colectomies were performed. In the laparoscopic approach subtotal colectomies ranged from 1.3 to 11.7%. Only two studies[20,19] report a subtotal colectomy in the open approach and the percentage varied greatly from 4.3% to 23%.

Laparoscopic transverse colectomy varied between 2.9% and 59% of the cases. In seven studies[18,21,20,24,23,25,26] the authors performed high tie of the vessels routinely and in one study[22] high tie was only done for T3N1 disease. All the studies apart from two[23,22] reported their conversion rates which ranged from 1.9% to 16.7%. Four of the studies [18,8,7,26] reported on the experience of the surgeons that performed the procedure.

All the studies apart from one[18] provide data on the stage of the disease. Nine studies reported the stage according to the TNM and one study[8]according to the Dukes classification. In the laparoscopic group stage III disease ranged from 22% to 51.4%. Stage IV disease was reported in two studies. Mean follow up ranged from 33 to 71 months. Five of the studies[23,24,7,25,26] reported on the use of chemotherapy. Most of the reported outcomes were not clearly defined. The quality of studies (Newcastle Ottawa Score) can be found on Table 1. The studies were found to be sufficiently homogeneous to meta-analyze their results.

Meta-analysis

Funnel plot visual interpretation did not reveal any publication bias in any of the reported outcomes.

Mortality

Nine studies[21,20,23,22,24,19,18,7,26] reported their mortality data. Seven of the studies reported no mortality. No significant difference was found between the open and the laparoscopic approach [OR=1.36 (0.22, 8.44); P=0.74]. The incidence for the laparoscopic group was 0.4%(3/662) and 0.3% (2/605) for the open approach.

Anastomotic leakage

Anastomotic leakage was reported in all but one[25] of the studies. There was no statistical heterogeneity I^2=0 between the studies. No difference was found between the open and the laparoscopic approach [OR=0.72 (0.33, 1.53); P=0.39] (Figure 2).

Intra-abdominal abscess

Six of the studies [21,23,24,19,8,26] reported this outcome. No heterogeneity was present I^2=0. No statistical significant difference was found between the two groups [OR=0.60 (0.25, 1.42); P=0.25].

Wound infection

Six of the studies[21,23,24,19,8,18,26] reported this outcome. No heterogeneity was found between studies I^2=0. No statistical significant difference was found between studies [OR=1.15 (0.50, 2.64); P=0.74].

Operative time

Nine studies[21,20,22,24,7,19,18,26,25] reported this outcome. In all but one[7] the laparoscopic approach lasted longer. Significant heterogeneity was present (I^2 =93%). The random effect model was used. There was statistically significant difference between the two groups favoring the open approach [WMD=45.00 (29.48, 60.52); P<0.00001].

Time to oral intake

Eight studies[18,19,22,21,7,24-26] reported this outcome. In four[22,19,18,26] of them it was defined as time to liquid diet. In the other four [21,7,24,25] there was no clear definition. In two studies[26] [7] oral diet was started after passing flatus and in another[21] time to soft diet is reported. Time to liquid diet was significant shorter for the laparoscopic group with a [WMD=-1.23 (-1.48, -0.98); P<0.00001 but with high heterogeneity I^2=79%. When all the studies are included in the outcome there is still statistically significant difference between the two groups with a [WMD=-1.68 (-1.84, -1.53); P<0.00001] favoring the laparoscopic approach but with heterogeneity of I^2=93% (Figure 3).

Re-operation

Six of the studies [23,24,7,20,8,26] reported this outcome. There was no statistical heterogeneity between the studies I^2=0. No statistically significant difference was found [OR=0.71 (0.33, 1.52); P=0.38].

Length of hospital stay

All but one[8] of the studies reported this outcome. Significant heterogeneity was present with a I^2=81%. The random effect model was used. There was a statistical significant difference in favor of the laparoscopic approach with a [WMD=-2.94 (-4.27, -1.62); P=0.001] (Figure 4).

Lymph nodes harvest

All the studies reported this outcome. High degree of heterogeneity was present between studies (I^2=73%). The random effect model was used. No difference between the two groups was found but there was a tendency favoring the laparoscopic approach [WMD=-1.19 (-2.89, 0.50); P=0.17].

Overall Survival

Seven studies [21,20,22,24,7,25,26] reported this outcome. No statistical heterogeneity was present I^2=0. No statistically significant difference was found between the two groups [HR=0.83 (0.56, 1.22); P=0.34] (Figure 5).

Disease free survival

The same seven studies [21,20,22,24,7,26,25] as above reported this outcome. No statistical heterogeneity was found between the two groups (I^2=0). No statistically significant difference between the two groups was found HR= [0.82 (0.60, 1.11); P=0.20].

Local recurrence

Five studies [21,23,22,20,19] reported this outcome. No statistical heterogeneity was present I^2=0. No statistically significant difference was found between the two groups with an OR= [1.13 (0.42, 3.07); P=0.81]

Distant Metastases

The same studies [21,23,22,20,19] as above reported this outcome. As above there was no statistical heterogeneity. No statistically significant difference was found between the two groups I^2=0 with an OR=[0.70 (0.39, 1.26); P=0.24].

The subgroup analysis performed for high quality studies, totally laparoscopic studies and high tie did not alter the level of significance in any of the above results.

Discussion

Our study is the first to report meta-analytical data on overall survival, disease free survival, local recurrence and distant metastasis and to compare extended vs conventional lymphadenectomy in transverse colon cancer. The laparoscopic approach appears to retain its significant benefits seen in right and left colectomy techniques, such as shorter hospital stay and time to oral diet with equivalent overall and disease free survival. These benefits remain in the extended lymphadenectomy group. Equivalent local recurrence and metastatic disease development were also found between the two groups.

An extremely low mortality of 0.4% was reported overall in this group of studies, potentially an indicator of the high quality of surgery performed with only two of the studies reporting fatalities as the rest of the studies had reported a morality of zero. The low reported mortality though may also be an indicator of an inherent selection bias supported by the low BMI reported in seven [26,25,21,24,7,19,18] of the studies and the poor reporting of ASA score which can affect the external validity of the studies. Higher BMI levels usually found with North American and European patients may make the laparoscopic approach more difficult.

As expected laparoscopic resections were found to take longer time to complete, reflecting the difficulty of the laparoscopic dissection and the potential prolonged learning curve required to master this type of anatomical resection. Although there was high heterogeneity in relation to this outcome, part of it might be explained by the fact that in only one study [7] the laparoscopic procedures lasted the same time as the open. Conversion rates varied from 1.9% to 16.7% but in most of the studies the conversion rate was less than 5% which does not differ from what is expected from the literature [31,32], indicating a good level of experience of the laparoscopic surgeons involved in these studies.

There was no difference in the anastomotic leakage or in the intra-abdominal abscess rates between the two groups, with similar reoperation rates. None of the included studies reported on the use of an enhanced recovery protocol (ERP) or reported their discharge criteria raising the potential risk for observational bias. A further factor influencing the length of stay is the country in which the study was performed. Out of eleven studies nine [21,20,22,24,18,25,26] are of Eastern Asian origin and three[23,7,19] are from Europe. As previously described, [33] socioeconomic reasons may delay the decision of discharge in studies of Asian origin. These factors may have contributed to the high heterogeneity observed in the meta-analysis of the length of stay outcome. Furthermore, they can affect the external validity of the overall findings when related to countries employing ERPs with early discharge criteria. Within individual studies though reported data still indicated a shorter length of stay in the laparoscopic group.

The laparoscopic group had shorter time to oral intake but this outcome was again poorly defined as some studies reported the time to liquid diet, others the time to soft diet and some did not define it at all. Individually again most studies indicated earlier timings in the laparoscopic groups and is consistent with the faster discharge from hospital reported in this group of patients.

The number of lymph nodes harvested with the specimen is often used as a surrogate marker of surgical quality with a set standard of high quality care of at least 12 lymph nodes[34]. All the studies had a mean number of lymph nodes that exceeded this standard providing another surrogate marker of the quality of the laparoscopic resection. In all but three studies [19,7,8] the authors reported that they performed a high tie of the feeding vessels. In Japan D3 lymphadenectomy is the standard of care for stage II/III colon cancer[35]. A recent review has indicated that laparoscopic extended lymphadenectomy for colon cancer does not add in morbidity compared to the open approach and has similar long term outcomes[36]. Routine

laparoscopic dissection around central mesenteric vessels to achieve a high tie can prepare surgeons in gaining the advanced laparoscopic skills needed to perform lymph node dissection around the middle colic artery and the difficult mobilization of the transverse colon.

In relation to the oncological outcomes of overall survival and disease free survival reported results were excellent for both groups. The follow-up period beyond the 2 years with some studies reporting data on a 71-month period is also very good. The results though are weakened by the absence of reporting and potential control of the adjuvant treatment regimes employed in most studies which can have a direct influence on these outcomes, especially in patients with stage III disease.

The inclusion of non-randomized studies and the possible selection bias that these may introduce to the meta-analysis, even though this is the only level of evidence currently available should be considered as one of its limitations. Some of the outcomes were poorly defined and this may be one of the reasons that outcomes such as length of stay, time to oral intake and operative time indicated high heterogeneity, as already described. Calculation bias might be present in the overall and disease free survival outcomes as HRs were not reported in any of the studies but were calculated using statistical methods [16].

Overall, the reviewed evidence suggests that laparoscopic colectomy for transverse colon cancer is feasible and safe when performed by experienced surgeons. It also carries the benefits of other laparoscopic colonic resection techniques such as faster oral intake and discharge while having equivalent morbidity, mortality, overall and disease free survival when compared to the open approach (level IIIa evidence) [37]. Further higher level of evidence is required to support these findings, but in the current era and evidence in favor of the laparoscopic technique it would only

be ethical for these to be obtained through high quality prospective trials rather than randomized controlled trials.

Table & Figure legends.

Table 1. Summary of studies investigating open versus laparoscopic colectomy for transverse colon cancer

Table 2. Studies' significant independent variables/external validity comparison

Figure 1. PRISMA 2009 Flow Diagram

Figure 2. Anastomotic leakage forest plot

Figure 3. Time to oral intake

Figure 4. Length of hospital stay forest plot

Figure 5 Overall survival forest plot

References

1. Guillou PJ, Quirke P, Thorpe H, Walker J, Jayne DG, Smith AM, Heath RM, Brown JM, Group mCT (2005) Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled trial. The lancet 365 (9472):1718-1726
2. Lacy AM, García-Valdecasas JC, Delgado S, Castells A, Taurá P, Piqué JM, Visa J (2002) Laparoscopy-assisted colectomy versus open colectomy for treatment of non-metastatic colon cancer: a randomised trial. The Lancet 359 (9325):2224-2229
3. Group COoSTS (2004) A comparison of laparoscopically assisted and open colectomy for colon cancer. N Engl j Med 2004 (350):2050-2059
4. Veldkamp R, Kuhry E, Hop W, Jeekel J, Kazemier G, Bonjer H, Haglind E, Påhlman L, Cuesta M, Msika S COlon cancer Laparoscopic or Open Resection Study Group (COLOR)(2005) Laparoscopic surgery versus open surgery for colon cancer: short-term outcomes of a randomised trial. Lancet Oncol 6 (7):477-484
5. Fleshman J, Sargent DJ, Green E, Anvari M, Stryker SJ, Beart Jr RW, Hellinger M, Flanagan Jr R, Peters W, Nelson H (2007) Laparoscopic colectomy for cancer is not inferior to open surgery based on 5-year data from the COST Study Group trial. Annals of surgery 246 (4):655-664
6. Group CCLoORS (2005) Laparoscopic surgery versus open surgery for colon cancer: short-term outcomes of a randomised trial. The lancet oncology 6 (7):477-484
7. Mistrangelo M, Allaix ME, Cassoni P, Giraudo G, Arolfo S, Morino M (2015) Laparoscopic versus open resection for transverse colon cancer. Surgical endoscopy 29 (8):2196-2202
8. Zmora O, Bar-Dayan A, Khaikin M, Lebeydev A, Shabtai M, Ayalon A, Rosin D (2010) Laparoscopic colectomy for transverse colon carcinoma. Techniques in coloproctology 14 (1):25-30
9. Gouvas N, Pechlivanides G, Zervakis N, Kafousi M, Xynos E (2012) Complete mesocolic excision in colon cancer surgery: a comparison between open and laparoscopic approach. Colorectal Disease 14 (11):1357-1364
10. West NP, Morris EJ, Rotimi O, Cairns A, Finan PJ, Quirke P (2008) Pathology grading of colon cancer surgical resection and its association with survival: a retrospective observational study. The lancet oncology 9 (9):857-865
11. Kontovounisios C, Kinross J, Tan E, Brown G, Rasheed S, Tekkis P (2015) Complete mesocolic excision in colorectal cancer: a systematic review. Colorectal Disease 17 (1):7-16
12. Moher D, Liberati A, Tetzlaff J, Altman DG (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Annals of internal medicine 151 (4):264-269
13. Higgins JP, Green S (2008) Cochrane handbook for systematic reviews of interventions, vol 5. Wiley Online Library,
14. Wells G, Shea B, O'connell D, Peterson J, Welch V, Losos M, Tugwell P (2000) The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses.
15. Hozo SP, Djulbegovic B, Hozo I (2005) Estimating the mean and variance from the median, range, and the size of a sample. BMC medical research methodology 5 (1):13
16. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR (2007) Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 8 (1):16
17. Goel M, Khanna P, Kishore J (2010) Understanding survival analysis: Kaplan-Meier estimate. International journal of Ayurveda research 1 (4):274
18. Akiyoshi T, Kuroyanagi H, Fujimoto Y, Konishi T, Ueno M, Oya M, Yamaguchi T (2010) Short-term outcomes of laparoscopic colectomy for transverse colon cancer. Journal of Gastrointestinal surgery 14 (5):818-823

19. Fernández-Cebrián J, Gil Yonte P, Jimenez-Toscano M, Vega L, Ochando F (2013) Laparoscopic colectomy for transverse colon carcinoma: a surgical challenge but oncologically feasible. Colorectal Disease 15 (2):e79-e83
20. Kim WR, Baek SJ, Kim CW, Jang HA, Cho MS, Bae SU, Hur H, Min BS, Baik SH, Lee KY (2014) Comparative study of oncologic outcomes for laparoscopic vs. open surgery in transverse colon cancer. Annals of surgical treatment and research 86 (1):28-34
21. Kim JW, Kim JY, Kang BM, Lee BH, Kim BC, Park JH (2016) short-and long-term outcomes of laparoscopic surgery vs open surgery for transverse colon cancer: a retrospective multicenter study. OncoTargets and therapy 9:2203
22. Sheng W, Zhang B, Chen W, Gu D, Gao W (2015) Laparoscopic colectomy for transverse colon cancer: comparative analysis of short-and long-term outcomes. International journal of clinical and experimental medicine 8 (9):16029
23. Storli KE, Eide GE (2016) Laparoscopic Complete Mesocolic Excision versus Open Complete Mesocolic Excision for Transverse Colon Cancer: Long-Term Survival Results of a Prospective Single Centre Non-Randomized Study. Digestive surgery 33 (2):114-120
24. Zeng W-g, Liu M-j, Zhou Z-x, Hou H-r, Liang J-w, Wang Z, Zhang X-m, Hu J-j (2015) Outcome of laparoscopic versus open resection for transverse colon cancer. Journal of Gastrointestinal Surgery 19 (10):1869-1874
25. Kim MK, Won D-Y, Lee J-K, Kang W-K, Kye B-H, Cho H-M, Kim H-J, Kim J-G (2015) Laparoscopic Surgery for Transverse Colon Cancer: Short-and Long-Term Outcomes in Comparison with Conventional Open Surgery. Journal of Laparoendoscopic & Advanced Surgical Techniques 25 (12):982-989
26. Zhao L, Wang Y, Liu H, Chen H, Deng H, Yu J, Xue Q, Li G (2014) Long-term outcomes of laparoscopic surgery for advanced transverse colon cancer. Journal of Gastrointestinal Surgery 18 (5):1003-1009
27. Okuda J, Yamamoto M, Tanaka K, Masubuchi S, Uchiyama K (2016) Laparoscopic resection of transverse colon cancer at splenic flexure: technical aspects and results. Updates in surgery 68 (1):71-75
28. Nakashima M, Akiyoshi T, Ueno M, Fukunaga Y, Nagayama S, Fujimoto Y, Konishi T, Noaki R, Yamakawa K, Nagasue Y (2011) Colon cancer in the splenic flexure: comparison of short-term outcomes of laparoscopic and open colectomy. Surgical Laparoscopy Endoscopy & Percutaneous Techniques 21 (6):415-418
29. Yamamoto M, Okuda J, Tanaka K, Kondo K, Tanigawa N, Uchiyama K (2012) Clinical outcomes of laparoscopic surgery for advanced transverse and descending colon cancer: a single-center experience. Surgical endoscopy 26 (6):1566-1572
30. Kim H, Lee I, Lee Y, Kang W, Park J, Oh S, Kim J, Kim Y (2009) A comparative study on the short-term clinicopathologic outcomes of laparoscopic surgery versus conventional open surgery for transverse colon cancer. Surgical endoscopy 23 (8):1812-1817
31. Yamamoto M, Okuda J, Tanaka K, Kondo K, Asai K, Kayano H, Masubuchi S, Uchiyama K (2013) Effect of previous abdominal surgery on outcomes following laparoscopic colorectal surgery. Diseases of the Colon & Rectum 56 (3):336-342
32. Moghadamyeghaneh Z, Masoomi H, Mills SD, Carmichael JC, Pigazzi A, Nguyen NT, Stamos MJ (2014) Outcomes of conversion of laparoscopic colorectal surgery to open surgery. JSLS: Journal of the Society of Laparoendoscopic Surgeons 18 (4)
33. Yamamoto S, Inomata M, Katayama H, Mizusawa J, Etoh T, Konishi F, Sugihara K, Watanabe M, Moriya Y, Kitano S (2014) Short-term surgical outcomes from a randomized controlled trial to evaluate laparoscopic and open D3 dissection for stage II/III colon cancer: Japan Clinical Oncology Group Study JCOG 0404. Annals of surgery 260 (1):23-30

34. McDonald JR, Renehan AG, O'Dwyer ST, Haboubi NY (2012) Lymph node harvest in colon and rectal cancer: current considerations. World J Gastrointest Surg 4 (1):9-19
35. West NP, Kobayashi H, Takahashi K, Perrakis A, Weber K, Hohenberger W, Sugihara K, Quirke P (2012) Understanding optimal colonic cancer surgery: comparison of Japanese D3 resection and European complete mesocolic excision with central vascular ligation. Journal of Clinical Oncology 30 (15):1763-1769
36. Athanasiou C, Markides GA, Kotb A, Xia X, Gonsalves S, Miskovic D (2016) Open compared with laparoscopic complete mesocolic excision with central lymphadenectomy for colon cancer: a systematic review and meta-analysis. Colorectal Disease
37. Phillips B, Ball C, Sackett D, Straus S, Haynes B, Dawes M (2015) Oxford Centre for evidence-based medicine levels of evidence. Version 2009. June,

Table 1. Summary of studies investigating open versus laparoscopic colectomy for transverse colon cancer

Study	Design	Type of procedure	Outcomes that were defined In studies	Inclusion criteria	Exclusion criteria	Transverse colon cancer definition	OP (n)	LP (n)	Follow up	NOS S-C-O
Kim 2016	CCT-6-Korea	RH, LH ,TC	LR, SR, OS, DFS	Consecutive patients from 01/05-02/15	Recurrent cancer, FAP or HNPC, or stage 0 and IV , emergency or palliative colectomies	Between hepatic and splenic flexure	123	103	Lap: 46m OP: 54m	**4-1-3**
Storli 2016	CCT 1-Norway	ERH, TC, ELH, ST,	Mortality and oncological outcomes	Consecutive patients from 01/07- 05/14	Tumours in the flexures, not achieving CME	Between hepatic and splenic flexure	23	33	Lap: 46.1m (median) OP:79.5 m (median)	**3-1-2**
Kim 2015	CCT 1-Korea	RH, ERH, TC, LH, ELH, ST	ND	Consecutive patients from 04/96- 02/09	Stage 0/I/IV, emergency procedure, concurrent cancer, previous malignancy, staged operation, R1 resection, hereditary colon cancer	Between the hepatic and splenic flexure	23	79	Lap: 67.5m (median) OP: 132m (median)	**3-1-2**
Sheng 2015	CCT 1-China	ERH,ELH, TC	mortality	Histologically proven TCC, ECOG 0-1, clinical stage of cT1-3N0-1M0	Emergency and palliative resections	NA	59	59	(10-107m)	**4-2-2**
Zeng 2015	CCT 1-China	ERH, ELH, TC	DFS, OS	Consecutive patients from 01/06- 06/14	Emergency colectomies, stage IV disease, non-radical or multiple organ resections	Between hepatic and splenic flexure	122	156	Lap: 39 m (1–90 m) OP: 44 m (1–98 m)	**4-1-2**

Mistrangelo 2014	CCT 1-Italy	ERH, ELH, TC	ND	Consecutive patients (biopsy proven adenocarcinoma) from 04/98 and 04/ 11	Emergency colectomies for obstruction, perforation, acute bleeding, or unable to tolerate GA, invasion of adjacent organs (for the LAP group)	Between hepatic and splenic flexure	57	66	LP:67m (24–156) OP:71m (24–156)	**4-1-2**
Kim 2014	CCT 1-Korea	ERH, ELH, TC, ST	ND	Consecutive patients from 01/06 to 12/10 (pTNM stage I-III)	Previous malignancy, two primary cancer and those lost to follow-up (10 patient)	Between hepatic and splenic flexure	47	84	OC:58 m (10-85) LAP: 42 m (7-82)	**4-1-2**
Zhao 2014	CCT 1-China	ERH, ELH, TC	ND	Consecutive patients from 01/02 to 06/11	Stage 0/I/IV, recurrent disease, emergency colectomy, palliative surgery	Between hepatic and splenic flexure	83	74	OP:58m (median) LAP:54m (median)	**3-1-2**
Fernandez-Cebrian 2013	CCT 1-Spain	NR	Operative time, intra-operative blood loss	Consecutive patients from 03/98 to 12/09	Emergency colectomies, local invading tumours, simultaneous metastasectomy, non-curative resection, TNM Stage IV	NR	52	34	33 ±2.3 m	**4-1-2**
Akiyoshi 2010	CCT	RH, LH, TC	ND	Consecutive patients 07/05 to 10/09	Non-curative resection (19 patients) or with	Between hepatic and splenic	39	53	No follow up	**4-0-2**

	1-Japan				synchronous resection (17 patients)	flexure				
Zmora 2010	CCT 1-Israel	ERH, ST, TC, LC	ND	Lap: between 1999 and 2005 compared to patients from 1997 to 2000 in the open approach	NR	Between hepatic and splenic flexure	24	22	NR	**3-0-2**

RH: Right hemicolectomy, ERH: extended right hemicolectomy, ELH: extended left hemicolectomy, LH: Left hemicolectomy, TC: transverse colectomy, ST: subtotal colectomy, TCC: transverse colon cancer, LR: local recurrence, SR: systemic recurrence, ND: outcomes not well defined, GA: General anesthetic, pTNM: pathologic tumour, node and metastasis stage, CME: complete mesocolic excision, ECOG*:* Eastern Cooperative Oncology Group performance status, RCT: randomized control trial, case-control trial, CCT: case-control study, CS: case series, OP: open, LAP: laparoscopic, PE: primary endpoint, NR: not reported, FAP: familiar adenomatous polyposis, HNPC: Hereditary non polyposis colorectal cancer, m: month(s), d: day(s), NOS: Newcastle Ottawa, Scale, S-C-O: Selection-Comparability-Outcome/Exposure

Data reporting: mean ± standard deviation, Med: median (range), data in ( ): represent range

Table 2. Studies' significant independent variables/external validity comparison

Study	**Age**		**Gender M/F**		**ASA score**		**Pathological clinical stage**							
							T		**N**		**M**		**Stage**	
	OP	**LP**	**OP**	**LP**	**OP**	**LP**	**OP**	**LP**	**OP**	**LP**	**OP**	**LP**	**OP**	**LP**
Kim 2016	62.8 ± 14.0	65.6 ± 12.1	66/57	68/35	I 20 (16.4%)	20 (19.4%)	NR	NR	NR	NR	NR	NR	I 18 (14.6%)	26 (25.2%)
					II 80 (65.6%)	58 (56.3%)							II 58 (47.5%)	45 (43.3%)
					III 21 (17.2%)	24 (23.3%)							III 47 (38.5%)	32 (30.8%)
					IV 1 (0.8%)	1 (1.0%)								
Storli 2016	68.0 ± 13.3	73.0 ± 11.4	10/13	11/22	NR	NR	T1 3 (13.0%)	2 (6.1%)	NR	NR	NR	NR	I 4 (17.4%)	4 (12.1%)
							T2 3 (13.0%)	4 (12.1%)					II 11 (47.8%)	16(48.5%)

							T3 16 (69.6%)	26 (78.8%)					III 8 (34.8%)	13(39.4%)
							T4 1 (4.3%)	1 (3.0%)					IV: NR	NR
Kim 2015	56.0 ± 15.9	65.7 ± 10.0	16/7	45/34	I 15(66.2%)	39(49.4%)	I+II 0	0	0 15 (65.2 %)	48 (60.8 %)	0	0	I 0	0
					II 8 (34.8%)	39(49.4%)	III 21 (91.3%)	74 (93.7%)	1 6 (26.1 %)	24 (30.4 %)			II 15 (65.2%)	48 (60.8%)
					III 0 (0%)	1(1.3%)	IV 5 (6.3%)	2 (8.7%)	2 2 (8.7%)	7 (8.9%)			III 8 (34.8%)	31 (39.2%)
Sheng 2015	61 (43-72)	60 (41-75)	32/ 27	34/ 25	I 37(62%)	36(61%)	NR	NR	NR	NR	NR	NR	I 7(11%)	6(10%)
					II 20 (33%)	21(35%)							II 28(47%)	26(44%)
					III 2(3%)	2(3%)							III 24(40%)	27(45%)
Zeng 2015	med58 (26–85)	58 (26–84)	55/67	71/85	I 12 (9.8%)	21 (13.5%)	NR	NR	NR	NR	NR	NR	I 12 (9.8%)	19 (12.2%)
					II 57	67 (42.9%)							II 58	77

					(46.7%)								(47.5%)	(49.4%)
					III 51 (41.8%)	64 (41.0%)							III 52 (42.6%)	60 (38.5%)
					IV 2 (1.6%)	4 (2.6%)							IV: NR	NR
Mistrangelo 2014	med70 (49–90)	68 (37–90)	33 /24	32 /34	I 17 (29.8%)	21 (31.8%)	T1 2 (3.5%)	11 (16.7%)	NR	NR	NR	NR	I 9 (15.8%)	15 (22.7%)
					II 27 (47.4%)	34 (51.5%)	T2 7 (12.3%)	7 (10.6%)					II 26 (45.6%)	25 (37.9%)
					III 11 (19.3%)	10 (15.2%)	T3 31 (54.4%)	43 (65.2%)					III 13 (22.8%)	18 (27.3%)
					IV 2 (3.5%)	1(1.5%)	T4 17 (29.8%)	5 (7.6%)					IV 9 (15.8%)	8 (12.1%)
Kim 2014	59.7 ± 13.2	62.3 ± 11.6	27/20	45/39	NR	NR	NR	NR	NR	NR	NR	NR	I: 6 (12.7%)	28 (33.3%)
													II: 21 (44.7%)	37 (44.0%)
													III: 20 (42.6%)	19 (22.6%)

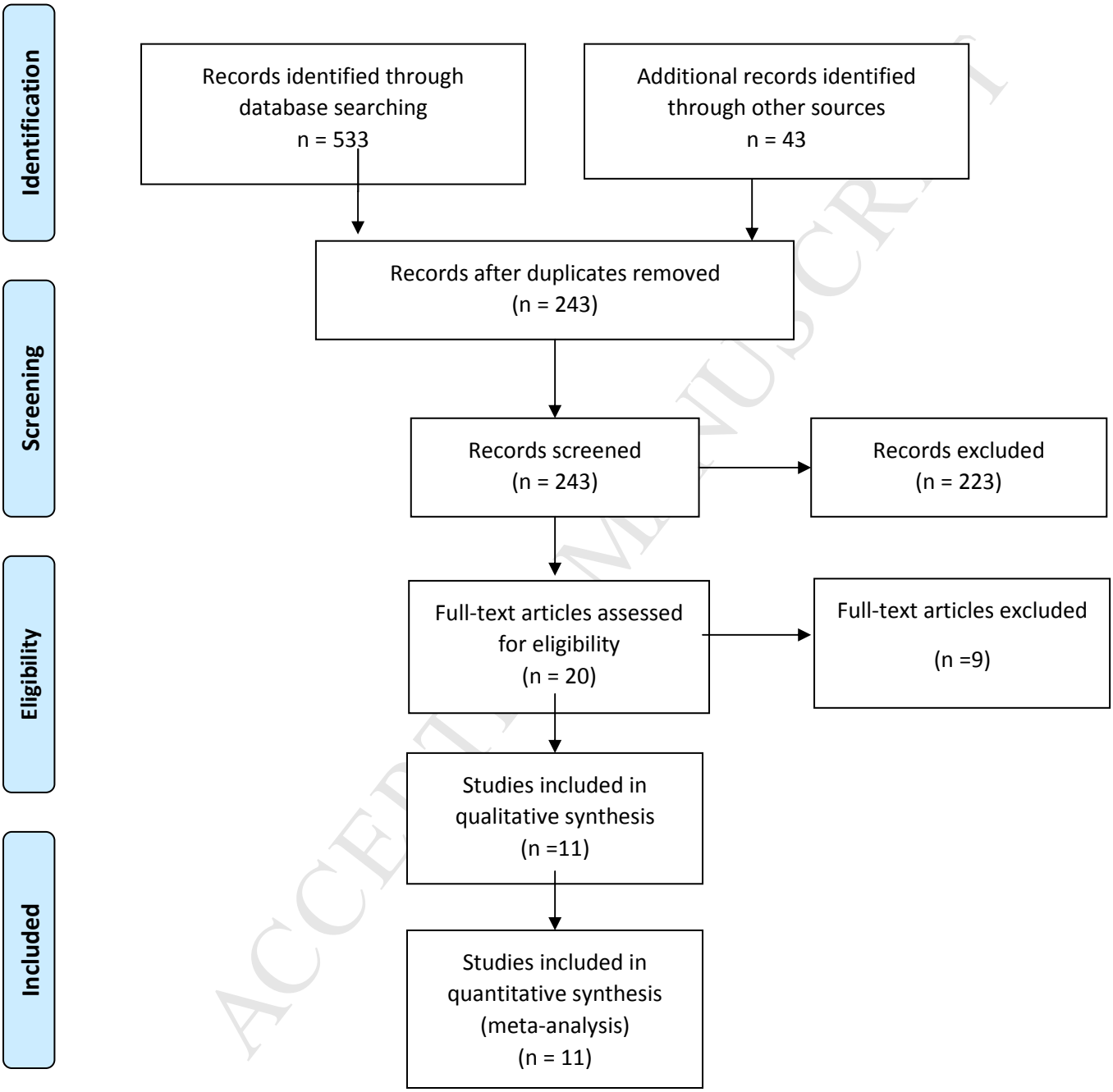
Zhao 2014	55.7 ± 14.8	54.0 ± 14.8	48/35	43/31	NR	NR	NR	NR	NR	NR	NR	NR	II 45 (54.2%)	36 (48.6%)
													III 38 (45.8%)	38 (51.4%)
Fernandez-Cebrian 2013	62.4± 6.8	60.3 ±8.1	25/27	21/13	NR	NR	NR	NR	NR	NR	NR	NR	I 7 (13.4%)	5 (14.7%)
													II 24 (46.1%)	13 (38.2%)
													III 21(40.4%)	16 (47%)
Akiyoshi 2010	62 (24–86)	66 (36–88)	21/18	32/21	NR	NR	Is 0 T1: 0	3 (6%) 10 (19%)	0: 22 (56%)	33 (62%)	NR	NR	NR	NR
							T2 3 (8%)	15 (28%)	1:13 (33%)	15 (28%)				
							T3 29 (74%)	11 (21%)	2: 4 (10%)	5 (9%)				
							T4 7 (18%)	14 (26%)						
Zmora 2010	70.5	68	12/12	14/8	2.5(mean ASA)	2.1(mean ASA)	NR	NR	NR	NR	NR	NR	***Dukes***	
													A 1 (4%)	2 (9%)

													B 14 (58%)	13 (59%)
													C 8 (33%)	5 (23%)
													D 1 (4%)	2 (9%)

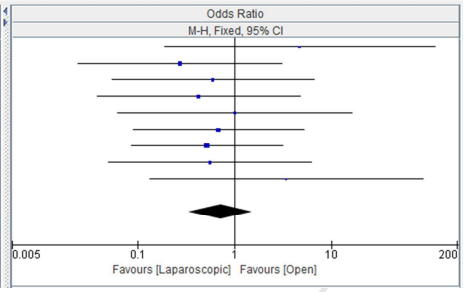
M: male, F: female, ASA: American Society of Anaesthesiology score, NR: not reported, NA; not applicable, Is: in situ

Data reporting: mean ± SD, Med ( ): median (range), N ( ): number and percentage, Stage reported as TNM unless otherwise specified

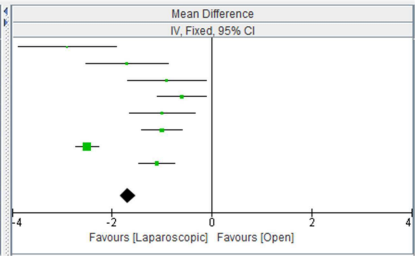
Figure 1. PRISMA 2009 Flow Diagram



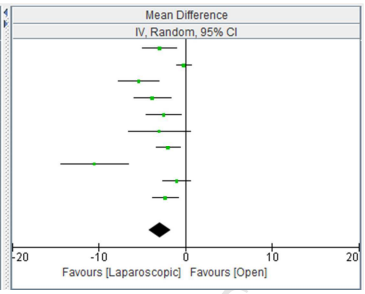
Study or Subgroup	Laparoscopic Events	Laparoscopic Total	Open Events	Open Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Fernandez Cebrian 2013	1	34	0	52	2.4%	4.70 [0.19, 118.83]
Kim 2014	1	84	2	47	16.2%	0.27 [0.02, 3.07]
Kim 2016	1	103	2	123	11.5%	0.59 [0.05, 6.64]
Mistrangelo 2014	1	66	2	57	13.5%	0.42 [0.04, 4.79]
Sheng 2015	1	59	1	59	6.3%	1.00 [0.06, 16.37]
Storli 2016	2	33	2	23	14.1%	0.68 [0.09, 5.19]
Zeng 2015	2	156	3	122	21.2%	0.52 [0.08, 3.13]
Zhao 2014	1	74	2	83	11.9%	0.55 [0.05, 6.25]
Zmora 2010	1	22	0	24	2.9%	3.42 [0.13, 88.40]
Total (95% CI)		631		590	100.0%	0.72 [0.33, 1.53]
Total events	11		14			
Heterogeneity: Chi² = 3.24, df = 8 (P = 0.92); I² = 0%						
Test for overall effect: Z = 0.86 (P = 0.39)						



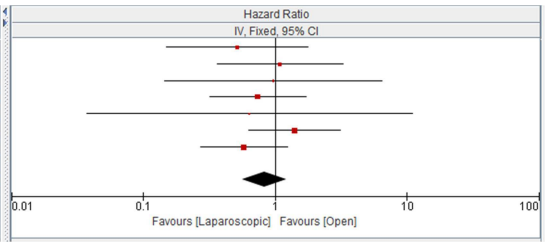
Study or Subgroup	Laparoscopic			Open			Weight	Mean Difference
	Mean	SD	Total	Mean	SD	Total		IV, Fixed, 95% CI
Akiyoshi 2010	2.4	1.75	53	5.3	2.75	39	2.5%	-2.90 [-3.88, -1.92]
Fernandez Cebrian 2013	2.1	0.3	34	3.8	3	52	3.5%	-1.70 [-2.52, -0.88]
Kim 2015	4.5	1.2	79	5.4	1.8	23	3.9%	-0.90 [-1.68, -0.12]
Kim 2016	6	1.6	103	6.6	2.2	123	9.6%	-0.60 [-1.10, -0.10]
Mistrangelo 2014	4	1.25	66	5	2.25	57	5.5%	-1.00 [-1.66, -0.34]
Sheng 2015	5	1.25	59	6	1	59	14.3%	-1.00 [-1.41, -0.59]
Zeng 2015	3	1	156	5.5	1	122	42.4%	-2.50 [-2.74, -2.26]
Zhao 2014	3.5	0.7	74	4.6	1.5	83	18.4%	-1.10 [-1.46, -0.74]
Total (95% CI)			624			558	100.0%	-1.68 [-1.84, -1.53]
Heterogeneity: Chi² = 98.67, df = 7 (P < 0.00001); I² = 93%								
Test for overall effect: Z = 21.39 (P < 0.00001)								



Study or Subgroup	Laparoscopic			Open			Weight	Mean Difference
	Mean	SD	Total	Mean	SD	Total		IV, Random, 95% CI
Akiyoshi 2010	12	5.75	53	15	3.75	39	10.4%	-3.00 [-4.94, -1.06]
Fernandez Cebrian 2013	7.1	2.2	34	7.3	1.6	52	12.7%	-0.20 [-1.06, 0.66]
Kim 2014	9.1	4.4	84	14.5	7.5	47	9.5%	-5.40 [-7.74, -3.06]
Kim 2015	12.1	4.2	79	15.9	4.8	23	9.9%	-3.80 [-5.97, -1.63]
Kim 2016	13.2	5.6	103	15.7	9.7	123	10.2%	-2.50 [-4.53, -0.47]
Mistrangelo 2014	7	3.25	66	10	13.5	57	6.8%	-3.00 [-6.59, 0.59]
Sheng 2015	11	3	59	13	4.5	59	11.7%	-2.00 [-3.38, -0.62]
Storli 2016	5	6.25	33	15.5	8	23	6.2%	-10.50 [-14.40, -6.60]
Zeng 2015	9	7.16	156	10	6.5	122	11.2%	-1.00 [-2.61, 0.61]
Zhao 2014	10.3	3.7	74	12.6	6	83	11.4%	-2.30 [-3.84, -0.76]
Total (95% CI)			741			628	100.0%	-2.94 [-4.27, -1.62]
Heterogeneity: Tau² = 3.41; Chi² = 48.57, df = 9 (P < 0.00001); I² = 81%								
Test for overall effect: Z = 4.35 (P < 0.0001)								



Study or Subgroup	log[Haza	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
Kim 2015	-0.66	0.63	10.0%	0.52 [0.15, 1.78]
Kim 2016	0.09	0.56	12.7%	1.09 [0.37, 3.28]
Mistrangelo 2014	-0.03	0.97	4.2%	0.97 [0.14, 6.50]
Sheng 2015	-0.3	0.43	21.5%	0.74 [0.32, 1.72]
Storli 2016	-0.45	1.45	1.9%	0.64 [0.04, 10.93]
Zeng 2015	0.34	0.41	23.6%	1.40 [0.63, 3.14]
Zhao 2014	-0.54	0.39	26.1%	0.58 [0.27, 1.25]
Total (95% CI)			100.0%	0.83 [0.56, 1.22]
Heterogeneity: Chi² = 3.41, df = 6 (P = 0.76); I² = 0%				
Test for overall effect: Z = 0.95 (P = 0.34)				



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Please state any conflicts of interest

No conflict of interest to declare

Please state any sources of funding for your research

No funding

Please state whether Ethical Approval was given, by whom and the relevant Judgement's reference number

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Author contribution

Please specify the contribution of each author to the paper, e.g. study design, data collections, data analysis, writing. Others, who have contributed in other ways should be listed as contributors.

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Guarantor

The Guarantor is the one or more people who accept full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Georgios Markides