Post-operative Complications in Patients Undergoing Early Closure Compared to Delayed Closure of Ileostomy: A Meta-Analysis

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Background: The objective of this study was to evaluate the post-operative outcomes of early ileostomy closure compared to delayed closure in adult patients that have undergone bowel surgery. Specific outcomes measured included wound infection, ileus, postoperative obstruction, anastomotic failure, total number of complications and mortality.

Methods: Online search was made through Medline, Cochrane, EBSCHost, and ClinicalKey databases up to June 2018 for randomized controlled trials comparing early (<4 weeks) and delayed (≥ 4 weeks) closure of ileostomy. Review Manager 5.3 was utilized for data analysis. The odds ratio was determined for each of the outcomes.

Results: Eight RCT's met the inclusion criteria, yielding 1126 patients (506 in early closure and 620 in delayed closure group). Statistical analysis showed no advantage of delayed closure over early closure of ileostomy in terms of post-operative complications (OR 1.13, 95% CI, 0.84-1.54, p=0.45), rate of anastomotic leakage (OR 0.96;95% CI, 0.55-1.66, p=0.54) and over-all mortality (OR 2.00;95% CI, 0.18-22.29, p=0.57). Early closure patients were found to be less likely to have post-operative ileus or obstruction when compared to delayed closure (OR 0.36;95% CI, 0.14-0.90, p=0.03). However, early closure was more likely to cause post-operative wound infection compared to delayed closure (OR 2.32;95% CI, 1.48-3.63, p=0.0002).

Conclusion: Early closure of ileostomy is beneficial in terms of development of less post-operative ileus. Delayed closure of ileostomy is advantageous in terms of less wound infections.

Keywords: early closure, late closure, reversal, defunctioning stoma, ileostomy, colon surgery, bowel surgery

Diverting ileostomies have been used by surgeons to mitigate anastomotic leak and minimize pelvic sepsis after bowel surgery.[1] Gastrointestinal continuity is restored after a period of 6-12 weeks but it can be longer if the patient is on adjuvant chemotherapy or due to low priority given to this procedure.[2] It has been proven by a few RCT's[3] and one unpublished meta-analysis[4] that early stoma closure (EC) within 4 weeks after proctectomy is feasible and has some advantages in selected patients. It was also stated that early closure of a temporary ileostomy after proctectomy at 4 weeks showed no significantly increased morbidity, except for an increased wound infection rate.[4,15]

In 21-28% of cases, defunctioning stomas are not reversed, becoming permanent.[5] Reasons for not reversing a stoma include advanced cancer stage and anastomotic leakage.[6] One study showed that delayed closure was associated with development of more post-operative complications.[7] Temporary diverting stomas were also associated with a negative impact on patient quality-of-life, as evidenced in global Quality of Life (QoL) scores.[8] In addition to this, temporary stomas are also associated to have a negative image on patient's body image and general feeling of well-being.[9]

Early closure of ileostomy is often defined in majority of trials as closure of stoma within 4 weeks after initial bowel surgery.[4] In one study, early closure was defined as early closure done after the 8th day of initial surgery.[3] Compared to traditional closure, early closure has only been in practice since the early 2000's as described by current available literature. The goal of this study was to compare post-operative complications of early versus late closure of ileostomy.

In this study, the authors compared the post-operative outcomes of early closure(less than 4 weeks after initial bowel surgery) against delayed closure(4 weeks or more from the initial bowel surgery) of ileostomy in adult patients that have undergone bowel surgery for both malignant and benign disorders of the colon.

They specifically would: 1) compare the complication rate, wound infection rate, incidence of ileus or obstruction and incidence of anastomotic failure between patients undergoing early closure of ileostomy and delayed closure of ileostomy; and 2) compare the total number of patient mortality between patients undergoing early closure of ileostomy and delayed closure of ileostomy within the immediate postoperative period (30 days after closure of ileostomy).

Methods

Studies included in this meta-analysis were obtained using Medline, Cochrane, EBSCHost, and ClinicalKey database up to June of 2018. The search conducted used the following MeSH terms: *Ileostomy Closure and [Takedown or Reversal] and [Late or Early] and [Post-operative Complications or Outcomes] and [Randomized Controlled Trial]*. Search was limited to English language only.

The search was conducted by the primary author and secondary author at the University of the East Ramon Magsaysay Memorial Medical Center Hospital on June of 2018. Figure 1 shows PRISMA flow chart summarizing the process for the identification of the eligible studies. Title and abstracts, when available, were reviewed in order to exclude irrelevant studies.
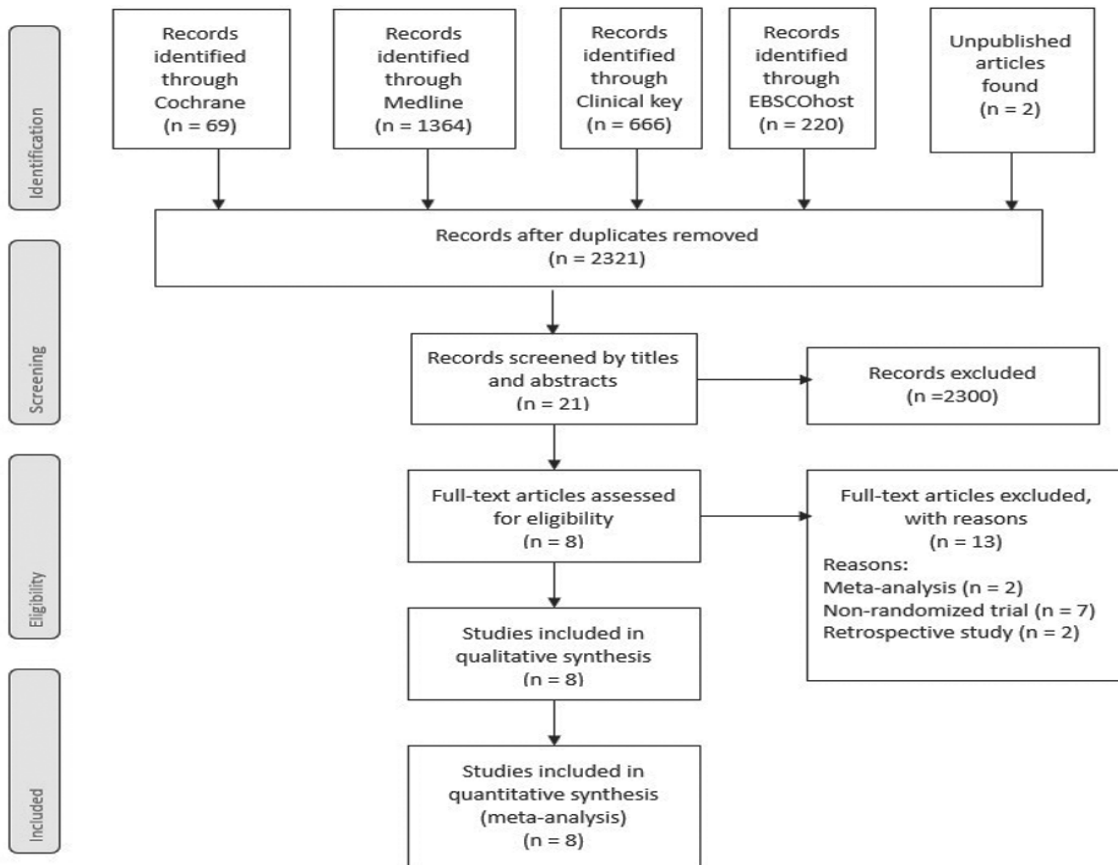

Figure 1. The PRISMA flow chart summarizing the process for the identification of the eligible studies.

Articles included in this study met the following inclusion criteria: 1) the study was a published randomized controlled trial, 2) early ileostomy closure was compared with delayed or late ileostomy closure, and 3) participants were adults of either gender, underwent bowel surgery for trauma, benign disorders or malignant disorders of the colon requiring diversion through ileostomy, 4) outcomes for the study compared post-operative outcomes and complications between the two groups. Exclusion criteria included: 1) Trials that included pediatric population, 2) Prospective non-randomized trials, 3) Ileostomy closure comparison utilized other outcomes.

All potential trials were selected for eligibility according to the abovementioned criteria. The quality of included studies was assessed using the Cochrane Handbook for Systematic Reviews of Interventions including random sequence generation, allocation concealment, blinding of the patient and the observer, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting.

The main comparison of Early and Delayed closure of ileostomy was done using the following determinants:
1. Total number of complications - defined as any adverse event within 30 days of closure of ileostomy
2. Wound infection - defined as surgical site infection noted within 30 days after closure of ileostomy
3. Overall mortality - defined as any mortality that occurred within 30 days after closure of ileostomy
4. Ileus or Obstruction - defined as any event within 30 days after the closure of ileostomy that caused mechanical obstruction or disorders motility
5. Anastomotic leakage - defined as failure of anastomosis or any form of extravasation of intraluminal contents that occurred within 30 days after the closure of ileostomy

Risk of bias was assessed using the Cochrane Collaboration's "Risk of Bias" tool.

Statistical Analysis

The odds ratio (OR) was the primary measure of treatment effect or adverse events, and 95 percent confidence interval (CI) for OR was calculated. Heterogeneity was assessed by chi square (χ2) and I-square (I^2) statistics.[9] The I^2 statistic indicates the percentage variability due to between-study or interstudy variability as opposed to within-study or intrastudy variability. An I^2 value greater than 50 per cent was classified as a substantial presence of heterogeneity.[9]

Studies were combined using the fixed-effects model when heterogeneity could be considered low and using the random-effects model described by DerSimonian and Laird when I^2 was greater than 50 percent.[17] Meta-analysis with forest plot was produced using Review Manager Version 5.3.

Results

In conducting this meta-analysis, a total of 2321 articles were generated after the search and the abstracts of these articles were reviewed and scrutinized by both investigators. Only 8 full text articles (Table 1) were found to be relevant to the review after methodological assessment.

The Risk of Bias table (Figure 2) showed that there is low risk of bias with regards random sequence generation. However, there appears to be high risk of bias with regards blinding of participants and personnel, blinding of outcome assessment, allocation concealment, incomplete outcome data and selective reporting.

All studies were randomized controlled trials comparing early closure of ileostomy against delayed or late closure in patients with temporary diverting ileostomy after bowel surgery. A total of 1126 patients who had bowel surgery with diverting ileostomy were included in this meta-analysis. Seven out of the 8 studies randomized patients into two groups. One study[13], randomized the participants to 3 groups, one group as early as 2 weeks after initial surgery and the subsequent groups 4 and 8 weeks, respectively. Taking the patients in the first two groups (2 weeks and 4 weeks post-bowel surgery), their results were combined into one group and added into the experimental population's data of this study and the remaining patients, into the control group. Henceforth, a total of 506 patients were randomized to the Experimental group, and these patient underwent closure of ileostomy as early as 6 days and late as 28 days (mean of 14 days) after initial surgery. The remaining 620 patients were

Table 1. Summary of the characteristics of 8 randomized controlled trials included in the meta-analysis.

Authors	Year	Time of recruitment	Major inclusion criteria and exclusion criteria	Outcomes	Follow up
Alves, et al.[3]	2008	2001-2004	Inclusion criteria: All patients were either male or female, 18 years and older, requiring surgery for benign or malignant disease requiring elective rectal resection with anastomosis Exclusion criteria: EC of the temporary loop ileostomy, such as signs of active infection or organ failure in the postoperative period, or radiological signs of anastomotic leakage evident at a water-soluble contrast examination through the temporary loop ileostomy performed 7 days after surgery	Early stoma closure is feasible in selected patients, with reduced hospital stay, bowel obstruction and medical complications, but a higher wound complication rate.	All patients were followed up at 1, 2, 3, 6 and 12 months after the initial bowel surgery
Danielsen, et al.[10]	2016	February 2011 to November 2015	Inclusion criteria: Patients that have undergone TME with ileostomy for rectal cancer Exclusion criteria: Suspected anastomotic leakage, unwillingness to participate, excluded due to medical reasons	It is safe to close a temporary ileostomy 8 to 13 days after rectal resection and anastomosis for rectal cancer in selected patients without clinical or radiological signs of anastomotic leakage.	12 months after initial bowel surgery
Khan, et al.[11]	2016	January 2005 to December 2009	Inclusion criteria: All patients above the age of 18 years with a temporary loop ileostomy presenting during follow-up were enrolled in our out-patient department Exclusion criteria: Those patients with postoperative stomas who had repeated complications of stoma or more than one stoma were excluded from the study. So were patients with large bowel stomas and permanent and end stomas excluded from the study.	Apart from wound infection the frequency of complication following early closure (4 weeks) of temporary loop stoma is similar to delayed closure. Thus delayed closure of stomae should be abandoned.	Final follow up done 30 days after the closure of ileostomy
Lasithiotakis, et al.[1]	2016	January 2004 to August 2007	Inclusion criteria: Patients all consecutive patients under a single colorectal consultant, having a defunctioning ileostomy during a low rectal or anal anastomosis, were considered eligible and offered to participate in the trial. Exclusion criteria: Patients currently on steroids, at high cardiorespiratory risk and those experiencing any postoperative complication.	In carefully selected patients, early reversal of defunctioning ileostomy is feasible, technically easier and has shorter operative time which can also lead to significant cost savings.	Up to 3 months After closure of ileostomy
Nelson, et al.[12]	2016	February 2014 to November 2015	Inclusion: All consecutive patients between the ages of 18 years and 70 years who underwent temporary stoma following bowel surgery both in elective and emergency setting, irrespective of the indication for primary surgery were included in the study. Exclusion criteria:Patients in whom emergency stoma revision was done for necrosis or gangrene, those with evidence of sepsis or organ failure in the postoperative course, any radiological signs of primary anastomotic leak evident on water soluble contrast examination before stoma closure, and patients with poor nutritional status (Hb <8 g%, Albumin <2.5 g%) were excluded from the study.	Early stoma closure does not carry an increased risk of postoperative complications, reduces cost towards stoma care, and leads to better a quality of life.	After 1 month and 3 months after closure of ileotomy
Shah, et al.[13]	2016	March 2008 to March 2014	Inclusion criteria: Adults of both genders who had undergone bowel surgery with loop enteric stoma. Exclusion criteria: Patients who needed a permanent stoma, patients with inflammatory bowel disease, major intra-abdominal sepsis or wound infection, poor nutritional state or patient with polytrauma, abdominal tuberculosis and unwillingness to participate.	Early stoma closure, preferably during the same admission is a safe, cost effective and an attractive technique.	After 1 month and 3 months after closure of ileotomy
Shahab, et al.[14]	2016	February 2010 to July 2010	Inclusion criteria: All ages in whom ileostomy or colostomy was made for both traumatic and non-traumatic reasons Exclusion criteria: Patients who required permanent stoma, having inflammatory bowel disease, abdominal tuberculosis and with poor general condition not fit for immediate surgical intervention	It was concluded that early stoma closure is a safe and effective method. The results of early stoma closure are superior to delayed stoma closure in experienced hands.	After 2 months after closure of ileostomy
Azizi, et al.[16]	2016	2014-2016	Inclusion criteria: Patients that had undergone bowel surgery with loop enteric stoma. Exclusion criteria: Patients who needed a permanent stoma, patients with inflammatory bowel disease, major intra-abdominal sepsis or wound infection, poor nutritional state or patient with polytrauma, abdominal tuberculosis and unwillingness to participate.	In selected patients, early closure and reversal of diverting ileostomy is feasible and helps patients to continue their chemotherapy with socioeconomical benefit of significant cost saving.	Unclear

subjected to traditional timing of closure for their ileostomies, which were more than 28 days after the initial surgery. Most studies stated this to be 2-3 months(mean of 64 days) or more after the initial surgery.

For the analysis of total number of post-operative complications, the results are shown in Figure 3. It was noted that LC had no advantage over EC. A total of 122 post-operative complications occurred in the experimental population (n=506) compared to 117 post-operative complications for control population (n=620). Heterogeneity for the eight studies was at 0 percent,

random effects was used giving an overall OR of 1.13 (95% CI, 0.84-1.54, p=0.45).

For total wound infections in between groups, results are shown in Figure 4. It was noted that LC was less likely to cause wound infection compared to EC. Of the 506 patients that underwent EC, 68 had postoperative wound infection, compared to only 32 of the 620 patients in the LC group. Odds ratio was 2.32 (95% CI, 1.48-3.63, p=0.82).

For the analysis of number of anastomotic leakages, results are shown in Figure 5. There was no difference with regards anastomotic leak rates between early and
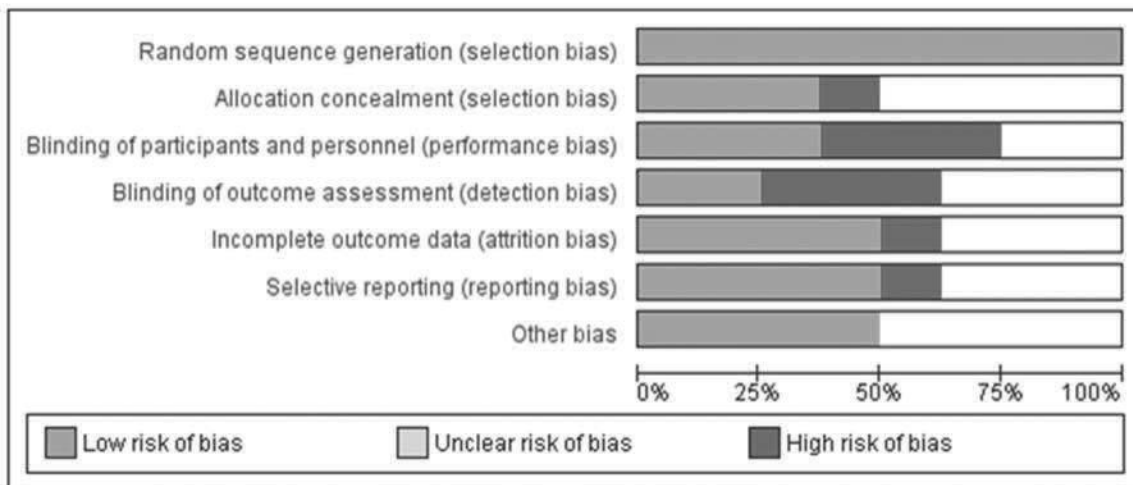

Figure 2. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.
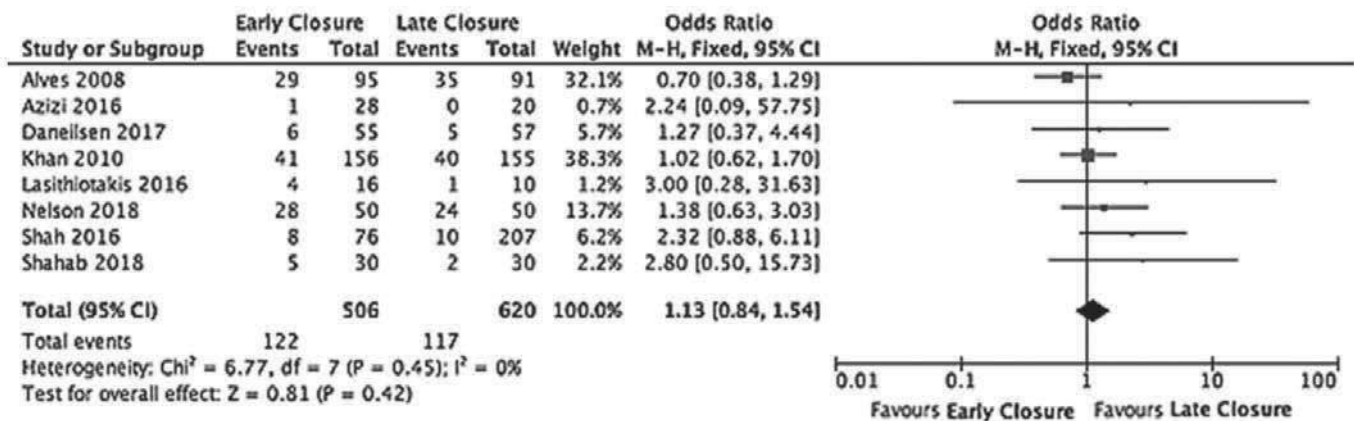

Figure 3. Total post-operative complications per group analysis for EC versus LC.

delayed closure of ileostomy. A total of 23 patients had anastomotic leakage occurred in the experimental population (n=506) compared to 30 postoperative complications for control population (n=620). Heterogeneity for the eight studies was at 0 per cent, a fixed effects model was used giving an overall OR of 0.96 (95% CI, 0.55-1.66, p=0.88).

For the analysis of total number of post-operative ileus or obstruction, results are shown in Figure 6. It was noted that EC group had a lower risk of developing ileus over the LC group. A total of 6 patients had ileus or obstruction in the experimental population (n=506) compared to 17 for control population (n=620). Odds ratio of 0.36 (95% CI, 0.14-0.90, p=0.15).
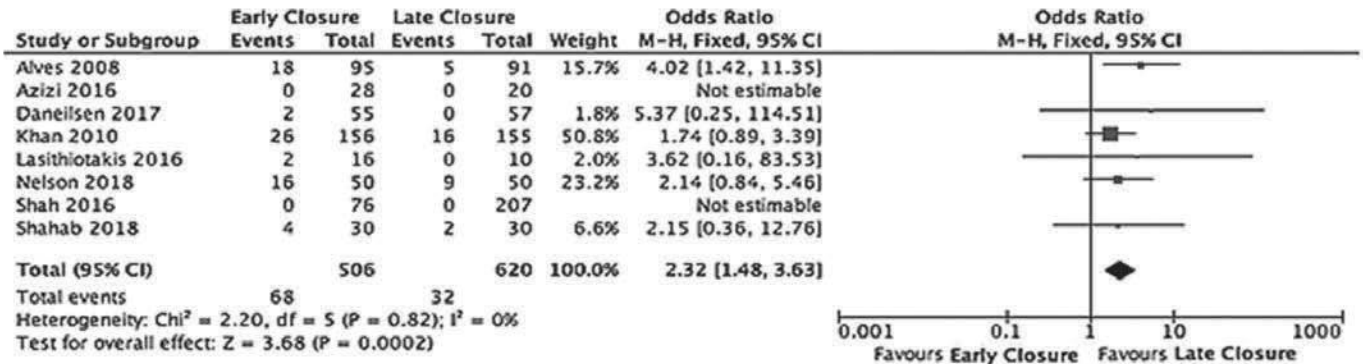
Study or Subgroup	Early Closure Events	Total	Late Closure Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Alves 2008	18	95	5	91	15.7%	4.02 [1.42, 11.35]
Azizi 2016	0	28	0	20		Not estimable
Daneilsen 2017	2	55	0	57	1.8%	5.37 [0.25, 114.51]
Khan 2010	26	156	16	155	50.8%	1.74 [0.89, 3.39]
Lasithiotakis 2016	2	16	0	10	2.0%	3.62 [0.16, 83.53]
Nelson 2018	16	50	9	50	23.2%	2.14 [0.84, 5.46]
Shah 2016	0	76	0	207		Not estimable
Shahab 2018	4	30	2	30	6.6%	2.15 [0.36, 12.76]
Total (95% CI)		506		620	100.0%	2.32 [1.48, 3.63]
Total events	68		32			

Heterogeneity: Chi^2 = 2.20, df = 5 (P = 0.82); I^2 = 0%
Test for overall effect: Z = 3.68 (P = 0.0002)

Figure 4. Total wound infections per group analysis for EC versus LC.

Study or Subgroup	Early Closure Events	Total	Late Closure Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Alves 2008	5	95	4	91	14.9%	1.21 [0.31, 4.65]
Azizi 2016	1	28	0	20	2.1%	2.24 [0.09, 57.75]
Daneilsen 2017	0	55	1	57	5.6%	0.34 [0.01, 8.51]
Khan 2010	9	156	13	155	47.3%	0.67 [0.28, 1.61]
Lasithiotakis 2016	0	16	0	10		Not estimable
Nelson 2018	2	50	4	50	14.8%	0.48 [0.08, 2.74]
Shah 2016	6	76	8	207	15.2%	2.13 [0.71, 6.36]
Shahab 2018	0	30	0	30		Not estimable
Total (95% CI)		506		620	100.0%	0.96 [0.55, 1.66]
Total events	23		30			

Heterogeneity: Chi^2 = 4.08, df = 5 (P = 0.54); I^2 = 0%
Test for overall effect: Z = 0.15 (P = 0.88)

Figure 5. Anastomotic leakage per group analysis for EC versus LC.

Study or Subgroup	Early Closure Events	Total	Late Closure Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Alves 2008	3	95	15	91	87.3%	0.17 [0.05, 0.59]
Azizi 2016	0	28	0	20		Not estimable
Daneilsen 2017	1	55	0	57	2.8%	3.17 [0.13, 79.37]
Khan 2010	0	156	0	155		Not estimable
Lasithiotakis 2016	1	16	1	10	6.8%	0.60 [0.03, 10.82]
Nelson 2018	0	50	0	50		Not estimable
Shah 2016	1	76	1	207	3.1%	2.75 [0.17, 44.47]
Shahab 2018	0	30	0	30		Not estimable
Total (95% CI)		506		620	100.0%	0.36 [0.14, 0.90]
Total events	6		17			

Heterogeneity: Chi^2 = 5.35, df = 3 (P = 0.15); I^2 = 44%
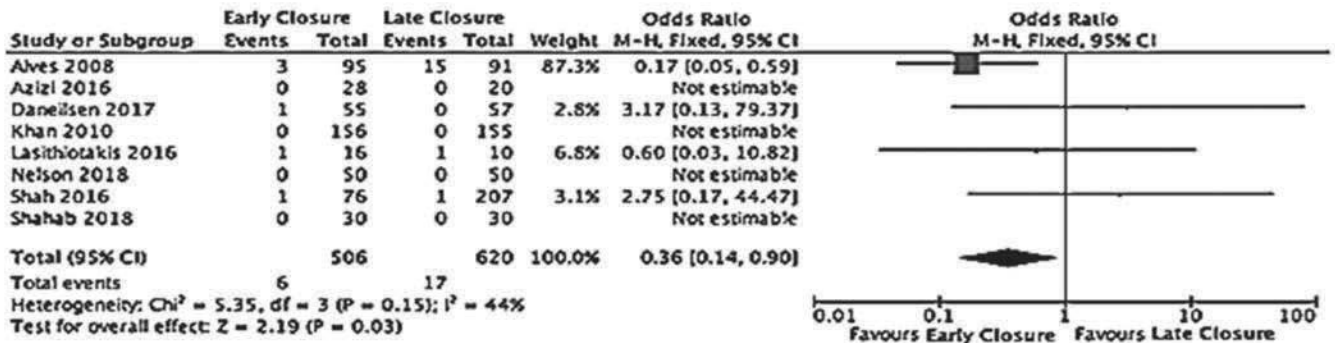Test for overall effect: Z = 2.19 (P = 0.03)

Figure 6. Post-operative ileus/obstruction per group analysis for EC versus LC.

For the analysis post-operative mortality, results are shown in Figure 7. It was noted that EC group had no advantage over LC. A total of 2 patients expired in the experimental group (n=506) compared to 1 patient in the control population (n=620). Odds ratio for this analysis is at 2.00 (95% CI, 0.18-22.29, p=0.57). It is also noted that only 1 study out of the 8 studies had patient mortalities documented in their results.

Discussion

In this meta-analysis, the 8 studies included have all concluded that late closure of ileostomy was not superior to early closure of ileostomy in terms of number of total complications, overall mortality, rate of ileus and anastomotic leakage. EC postop patients were less likely to have ileus or obstruction. On the other hand, LC was associated with less post-operative wound infections, compared to EC.

In reviewing the above mentioned studies, EC was beneficial in terms of cost-effectiveness[1] and quality of life.[12] Khan, et al. even stated that delayed closure of ileostomy may be abandoned completely.[11] Aside from the 8 RCT's analyzed for this study, current review of literature also revealed two meta-analysis[4,15] attempting to summarize these findings. One unpublished study[4] concluded that early closure of a temporary ileostomy after proctectomy at 4 weeks shows no significantly increased morbidity, except an increased wound infection rate. Another meta-analysis done suggested that EC of a defunctioning loop ileostomy is effective and safe in carefully selected patients without increasing overall post-operative complications.[15] Both study protocols were based on the same 3 RCT's[1,3,10] and included 4-5 retrospective papers. Although faulty in design, the study stated the same conclusion and promoted early closure over late closure.

In analyzing data obtained from the 8 RCT's, one may conclude that in terms of post-operative morbidity or complications, there is no difference between both groups and in terms of safety, early closure may be done as early as 4 weeks after the initial bowel surgery. Clinical outcomes between both groups are similar. In 2008 the study done by Alves, et al.[3] concluded that early stoma closure is feasible in selected patients and, in addition to lesser incidence of bowel obstruction, is associated with reduced hospital stay as well. Alves conducted his study with all the participants under the experimental group undergo early closure as early as 8 days after the initial bowel surgery. In his study, proctectomy and anastomosis was done 7 cms above the anal verge. In concluding his study results were comparable in terms of post-operative morbidity when compared to the delayed reversal group (reversal of ileostomy in this group was done at 60 days after the initial OR).
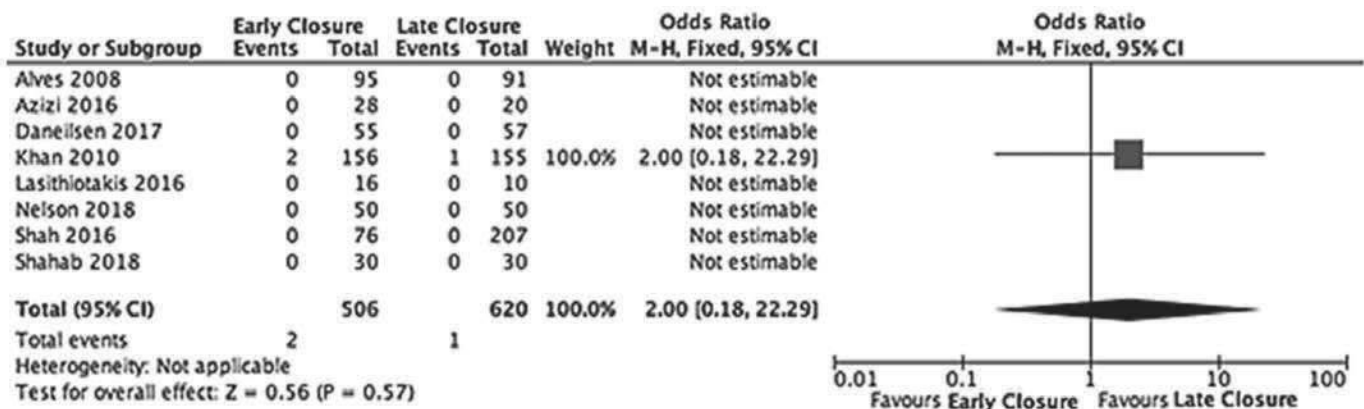

Study or Subgroup	Early Closure Events	Total	Late Closure Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Alves 2008	0	95	0	91		Not estimable	
Azizi 2016	0	28	0	20		Not estimable	
Daneilsen 2017	0	55	0	57		Not estimable	
Khan 2010	2	156	1	155	100.0%	2.00 [0.18, 22.29]	
Lasithiotakis 2016	0	16	0	10		Not estimable	
Nelson 2018	0	50	0	50		Not estimable	
Shah 2016	0	76	0	207		Not estimable	
Shahab 2018	0	30	0	30		Not estimable	
Total (95% CI)		506		620	100.0%	2.00 [0.18, 22.29]	
Total events	2		1				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.56 (P = 0.57)							

Figure 7. Mortality per group analysis.

One advantage of LC of ileostomy identified by this study is that wound infection rate was lower than in patients undergoing EC of ileostomy. This conclusion was also reported by the studies done by Khan[11] and Alves.[3] Although this may be a nuisance for most patients and concomitantly, the surgeons that treat them, this may not be entirely a life-threatening entity on its own and may pose little threat to the patient's well-being. Apart from this negative outcome, other measured parameters between EC and LC proved no statistical advantage between that two and that EC had a statistical advantage with regards to post-operative ileus/obstruction. It was also identified by the aggregate of results from all 8 RCT's that overall complication rate and mortality rate between the two groups are comparable.

The patients under the experimental group for the studies included in this meta-analysis were subjected to early closure of ileostomy as early as 6-8 days after initial bowel surgery and as late as 28 days. The mean number for days for closure of ileostomy after bowel surgery for this group was 14 days. Late closure group had patients undergoing delayed closure within 60-90 days after the initial bowel surgery with a mean of 64 days. In applying these numbers to future patients as candidates for early closure of ileostomy, this meta-analysis has concluded that closure done during 14-28 days after bowel surgery may be comparable to closure done 60-90 days after surgery.

Of the 5 parameters reviewed and studied, the only one with heterogenous data was post-operative ileus/obstruction which had an I^2 of 44 percent. Heterogeneity was not assessed in mortality as only one study had reported it.

One identifiable source of bias is selection bias since the populations included in some studies had different indications for diverting ileostomy. Two studies[13,14] included a large number of patients that had traumatic bowel injuries(blunt abdominal trauma and penetrating abdominal trauma) that warranted diversion through ileostomy. Compared to the other 6 studies that had patients undergo diversion for malignant or benign(non-traumatic) disorders of the bowel. This may affect results as decision making to terminate the ileostomy and when to terminate the ileostomy may be affected by other injuries, for trauma patients and schedule/

prioritization of chemoradiation for patients with malignancy.

To summarize, one may arrive at the conclusion that early closure of ileostomy may be substituted for late or delayed closure in that EC is more beneficial since it is associated with less post-operative ileus/obstruction, and there is no statistical data that it is less safe than late closure in terms of complication rates during the post-operative period. The findings of this study may suggest that both are comparable in terms anastomotic leakage failure. LC was associated with fewer wound infections post-operatively. Taking all of this into consideration, it may be up to the surgeon to decide whether it would be an acceptable risk in exchange for a shorter post-operative course afforded by early closure of ileostomy.

Limitations

This study's limitation is that it does not determine the cause of increased wound infection after early closure of ileostomy. Patients were not also grouped as to what warranted the bowel diverting ileostomy (whether due to obstruction, malignancy or trauma, etc). The above-mentioned limitations may be avenues for further study. Another limitation noted is ileus or obstruction in the abovementioned studies were not defined in each study and were treated as one entity.

Conclusion

In this meta-analysis, the authors concluded that late closure of ileostomy had no advantage over early closure of ileostomy with regards to occurrence of total postoperative complications, and may be comparable in terms of rate of anastomotic leakage. However, patients that have underwent EC of ileostomy were more likely to encounter wound infection post-operatively. An identified advantage for early closure is patients were associated with a lower incidence of post-operative obstruction or ileus compared to patients undergoing traditional timing of closure. This meta-analysis suggests that early closure of an ileostomy had almost similar

post-operative outcomes compared to late closure and may be done safely in selected patients.

Acknowledgements

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